PET and SPECT in Psychiatry

Rudi A. J. O. Dierckx
Andreas Otte
Erik F. J. de Vries
Aren van Waarde
Editors

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Second Edition

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Foreword

2nd Edition: 2020

PET and SPECT in Neurology

PET and SPECT in Psychiatry

PET and SPECT of Neurobiological Systems

Editors: Rudi A.J.O. Dierckx, Andreas Otte, Erik F.J. de Vries, Klaus L. Leenders, Iris E.C. Sommer, Adriaan A. Lammertsma, and Aren van Waarde

When in 2014 the Editors published the first edition of this three-volume series, dedicated to the use of PET and SPECT in the CNS, a major undertaking saw the light in print. These were significant multi-authored books, providing the most comprehensive review of this challenging field at the time.

Now in 2020, a second edition is launched, demonstrating the success of this initial endeavor. With a further major effort, over 50% of the numerous chapters are either entirely novel or rewritten anew, by an impressive list of international contributors. The team from Groningen deserve warm congratulations for this achievement.

In 2004, PETMR had just emerged as a novel imaging modality, and the medical applications of machine learning, or artificial intelligence, had hardly surfaced. PET imaging of Tau had just made it.

Now in 2020, amazing progress in the understanding of the brain is being made, and even dedicated brain PET and PETMR imaging instruments are in development (Catana, C. JNM, 60, 1044, 2019). Yet, with its hundred billion neurons, the brain keeps its mystery and continues to engage and stimulate our enquiry.

Little by little progress is being made, from decoding consciousness (Nature 571, S2, 2019) to growing neurons from reprogrammed skin fibroblasts (Nature 569, 333, 2019). We now understand that protein deposits in the brain may precede clinical manifestations by years, great advances have been made in extracting quantitative data from such studies (as shown with PETCT and amyloid and tau numerical data) and that we can intervene effectively, inter alia, in receptor deficiencies and in deep brain stimulation. The brain connectome is unravelling, with it, greater understanding of, amongst other, pain and drug-induced addictions, the dementias, and the movement disorders. All of this and much more is being critically reviewed by 119 chapters spread into these three major volumes.

It is hence perfect timing that the second edition shines a new light at the significant progress made in PET and SPECT, describing and analyzing latest information from novel biological radionuclide probes, neuroreceptors, and the clinical progress achieved.

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Preface

Neuroscientists of today dispose of a powerful armament for functional, physiological, and molecular imaging that has never made more impressive advances than before, helping to better understand the mechanisms of diseases and to develop and design drug treatment options with a superior efficacy and safety profile. Among these instruments, positron emission tomography (PET) and single-photon emission computed tomography (SPECT) have become forerunners in the *in vivo* imaging arena, and for this reason, the present trilogy, now in its second, completely revised and supplemented edition, is dedicated to PET and SPECT. The volumes of this trilogy are *PET and SPECT in Psychiatry*, *PET and SPECT in Neurology,* and *PET and SPECT in Neurobiological Systems*. In all volumes, we have again assembled the combined expertise of the renowned authors of the first edition and expanded this by some new authors for the second edition, whose dedication to the investigation of psychiatric and neurological disorders or of neurobiological systems through nuclear medicine technology has achieved international recognition.

The editors, who are nuclear medicine specialists, radiochemists, and biologists with a strong exposure to neurosciences, have again invited experts from the psychiatry, neurology, and medical physics fields to enhance the editorial board as guest editors for each volume of the trilogy. For *PET and SPECT in Psychiatry*, this was Iris Sommer, professor of cognitive aspects of neurological and psychiatric disorders; for *PET and SPECT in Neurology*, it remained Klaus (Nico) L. Leenders, emeritus professor of neurology; and for *SPECT in Neurobiological Systems*, it was Adriaan A. Lammertsma, professor of medical physics and positron emission tomography.

We are very happy that our trilogy has become a state-of-the art compendium with top downloads already for the first edition. This is certainly also due to the production and distribution by one of the premier publishers in the field, guaranteeing a high quality of reproduction and allowing for the inclusion of many color figures, which is essential in the field of neuroimaging. We are intrigued by the enthusiastic response from contributors from all over the world who made this endeavor successful and are confident that the second edition continues to live up to this onus. Finally, we would like to thank Mrs. Gesa Frese from *Springer-Verlag* for her continuous help and support during the development of the second edition of this book series.

We sincerely hope that the new trilogy will still serve as a key tool not only for all physicians in nuclear medicine, psychiatry, neurology, or geriatrics, but also for all professionals working to understand or treat brain disorders. With today's ageing population, PET and SPECT imaging can provide new insights into the processes that may lead to unhealthy ageing of the brain. May this book series serve as a guide towards the present use of PET and SPECT in brain disorders and as a catalyst for future research. The progress achieved by PET and SPECT in the diagnosis of the many facets of diseases disposed in the neurosciences has been astounding. Nevertheless, in line with the Socratic paradox "*I know that I know nothing*," it seems that we are still at the beginning of understanding the brain. This book hopes to provide a renewed platform to further contribute to this quest, at the benefit of patients suffering from neurologic and psychiatric disorders.

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Offenburg, Germany — Andreas Otte
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Part I

Basics

Neuroimaging in Psychiatric Drug Development and Radioligand Development for New Targets

1

Akihiro Takano, Christer Halldin, and Lars Farde

Contents

Abstract

Positron emission tomography (PET) is an imaging modality used to measure physiological and biochemical markers in the brain. Neuroreceptors, transporters, or enzymes are visualized and quantified with appropriate PET radioligands. In the development of drugs for treatment of psychiatric disorders, there are three major applications of PET. First, PET microdosing is used for pharmacokinetic evaluation. By injection of minute amount of radiolabeled drug, information about brain exposure can be obtained already at the early phase of drug development. Another application is receptor occupancy studies. Here, the competition

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between a drug and a PET radioligand binding is examined at the target sites. The competitive effect is useful to have when selecting the doses tested in further clinical trials. The third application is to use imaging biomarkers for diagnosis or efficacy. To widen the use of PET, the development of PET radioligands for new targets is vital. Several criteria and characteristics such as binding affinity, selectivity, and lipophilicity are important when selecting new PET radioligand candidates for targets in the brain.

1.1 Introduction

Drug development requires considerable investments of time and money. Since the technique of binding assay was introduced in the late 1950s (Yalow and Berson 1959), numerous compounds have been selected based on in vitro affinity data, evaluated in preclinical models and subsequently tested for efficacy in psychiatric diseases such as schizophrenia and mood disorder. However, as the pathophysiology of psychiatric diseases has not been fully understood, the industrial drug projects have had an evident element of "trial and error." Lack of or insufficient efficacy is thus a major reason for attrition and adds to failure for safety reasons (Arrowsmith 2011a, b). In some drug projects, the failure may be related to difficulties with dose finding. In other words, the doses used in preclinical and clinical trials were too low or too high. The fundamental question is thus whether the drug failed due to suboptimal brain exposure and target engagement of the drug or whether the target was invalid.

Positron emission tomography (PET) is an imaging modality by which it is possible to measure physiological and biochemical markers in the brain by using appropriate radioligands. Most PET radioligands are labeled with radionuclides having a short half-life such as ^{11}C (half-life, 20.4 min) or ^{18}F (109.8 min). Following the successful introduction of PET for neuroreceptor imaging in the 1980s (Farde et al. 1986), the technique has been widely used to visualize and quantify drug target sites, mainly neuroreceptors, enzymes, and transporters in the human brain in vivo.

In this chapter, we will focus on the major applications of PET in drug discovery and development. The need for development of novel radioligands for new targets will be given particular attention.

1.2 PET Application for Drug Development

1.2.1 PET Microdosing for Pharmacokinetic Evaluation

After radiolabeling of the drug itself with short-lived radionuclides, such as ^{11}C or ^{18}F, the distribution of the drug can be examined in the living body. This approach has been referred to as "microdosing" (Lappin and Garner 2003). A "microdose" is defined as a dosage level less than 1/100 of the dose estimated to induce a pharmacological effect. In addition, a maximum dose has been set to 100 μg (EMEA 2003).

Due to effective radiosynthesis and high specific radioactivity, the dose administered in a PET study is usually less than 1 μg.

There are several other approaches for microdosing, such as accelerator mass spectrometry (AMS) and LC/MS/MS. AMS is an ultrasensitive methodology that can be used to quantify ^{14}C in biological samples such as blood, urine, or tissue biopsies. LC/MS/MS is a technique that can measure very low concentrations of unlabeled compounds in plasma, urine, or CSF. When compared with AMS and LC/MS/MS, PET has the advantage of extending the microdose concept from body fluids to organs in the whole body. In other words, AMS and LC/MS/MS technologies provide pharmacokinetic information based on the plasma levels of the compounds. PET extends traditional pharmacokinetics by providing information about drug concentration in the target organ or region. However, a limitation is that the short half-life of the PET radionuclides limits the time of data acquisition to about 2 h for ^{11}C-labeled drugs and 12 h for ^{18}F-labeled drugs.

Some failures in CNS drug development have been attributed to poor brain exposure of the drug (Taylor 2002). The PET-microdosing approach may thus be of particular importance in the development of CNS drugs since it has the potential to confirm sufficient brain exposure in early phase of drug development. The information is of particular value before investments are made into expensive phase II and III trials.

To efficiently translate small animal's results into human condition, microdosing PET study of nonhuman primate (NHP) is a useful intermediate since it can serve as a valid predictor of exposure of the candidate drugs in the human brain (Schou et al. 2013). In a comprehensive microdosing PET study, brain exposure of 12 commercially available drugs has been evaluated in NHPs (Schou et al. 2015). The brain exposure was highly variable and ranged from 0.01% to 6.2% of the injected dose. As the study suggests that a drug can be efficacious even at very low level of exposure, there is probably no clear threshold for acceptable minimal brain exposure. However, if several compounds are evaluated comparatively in a drug development project, compounds having high brain exposure should be preferred due to lower risk for side effects related to binding outside the brain.

In a wider perspective, though drugs used in the field of psychiatry target the CNS, whole-body PET measurements can provide useful information in relation to potential side effects and unexpected organ accumulation. For example, in a whole-body NHP PET study using [^{11}C]MePPEP, it has been shown that radioligand binding to the CB1 receptor was found not only in the brain but also in brown adipose tissue (BAT) (Takano et al. 2014). This observation was interesting by itself since the CB1 receptor in BAT is one of the potential therapeutic targets for obesity (Lahesmaa et al. 2018). A limitation of PET is that the radiolabeled drug will be metabolized in the living body. Measurement of radioactivity by PET machine can thus not differentiate the parent radiolabeled drug from radiolabeled metabolites. To overcome this problem, radiolabeling and administration of the metabolite only may provide additional information (Seneca et al. 2009).

Although the requirements for preclinical safety data for microdosing study have been reduced by regulatory authorities (Verbruggen et al. 2008), the radioligand

production has to follow good manufacturing practice (GMP) (US FDA Code of Federal Regulations Title 21 n.d.). This requirement has increased the costs of PET-microdosing studies in human subjects.

1.2.2 PET Receptor Occupancy to Demonstrate Target Engagement in Relation to Pharmacodynamics

A number of PET radioligands have been developed for several key targets related to neurotransmission (Table 1.1 and Fig. 1.1) (Halldin et al. 2001). Using these radioligands, it is possible to map and quantify the in vivo distribution of the target neuroreceptors or transporters. Details on quantification of the radioligand binding are described elsewhere in this textbook (Chap. 2).

The change of radioligand binding between baseline and after drug administration is used to calculate the drug occupancy at the target neuroreceptor, transporter, or enzyme (Figs. 1.2 and 1.3).

PET determination of receptor occupancy has been most extensively applied for antipsychotic drug binding to the dopamine D2 receptor (Farde et al. 1988). The relationship between in vivo dopamine D2 receptor occupancy and antipsychotic drug effect was early established. More than 65–70% of dopamine D2 receptor occupancy is required to obtain antipsychotic efficacy, but at more than 80% of occupancy, there is a high risk for extrapyramidal symptoms (Farde et al. 1986; Kapur et al. 2000). The atypical antipsychotic clozapine is an exception since this drug has antipsychotic effect at lower dopamine D2 occupancy (Farde et al. 1992; Nordström et al. 1995).

Table 1.1 Representative PET radioligands for neurotransmitter systems

Neurotransmitter system		PET radioligand
Dopamine	D1	[^{11}C]SCH23390
		[^{11}C]NNC112
	D2	[^{11}C]raclopride
		[^{11}C]FLB457
	Transporter	[^{11}C]PE2I
		[^{18}F]FEPE2I
5HT	1A	[^{11}C]WAY10065
	1B	[^{11}C]AZ10419369
	2A	[^{11}C]MDL100907
	Transporter	[^{11}C]MADAM
		[^{11}C]DASB
GABA-benzodiazepine		[^{11}C]Flumazenil
		[^{18}F]Flumazenil
		[^{11}C]Ro15-4513
Norepinephrine	Transporter	[^{18}F]FMeNER-D2
Cannabinoid	CB1	[^{11}C]MePPEP
		[^{18}F]FMPEP-d2

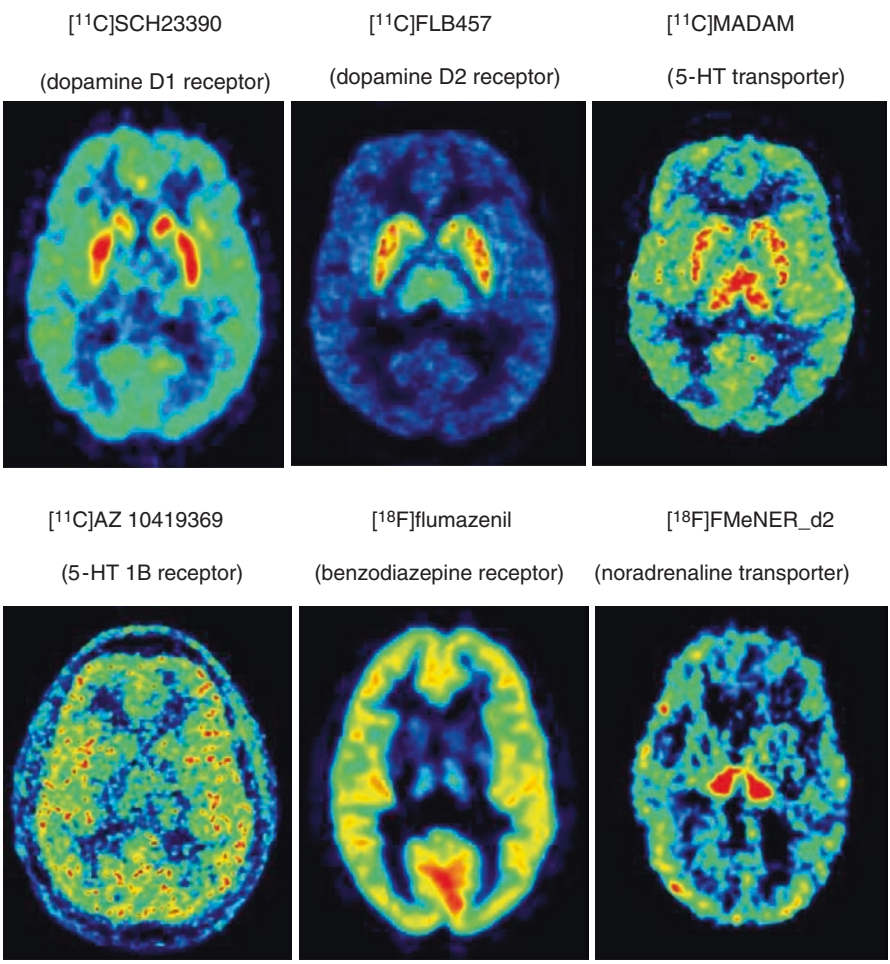

Fig. 1.1 Horizontal brain sections through the striatal level showing the regional distribution of the binding of commonly used PET radioligands. Images represent radioactivity summed after radioligand injection (9–51 min for [11C]SCH23390, 0–87 min for [11C]FLB457, 7–93 min for [11C]MADAM, 3–63 min for [11C]AZ10419369, 9–93 min for [18F]flumazenil, 90–210 min for [18F]FMeNER_d2)

The PET occupancy approach has now become widely applied to drug development and extended to several other targets including the serotonin and noradrenaline neurotransmission systems and enzymes such as monoamine oxidase B (Meyer et al. 2004; Hirvonen et al. 2009; Sekine et al. 2010). The target occupancy by a new candidate drug is usually estimated for different doses, so that the curvilinear relationship between dose/plasma level and occupancy can be established (Fig. 1.4). This key information will help efficient dose setting in phase II and III studies by avoiding doses that are too low or too high. For new targets, the relationship between

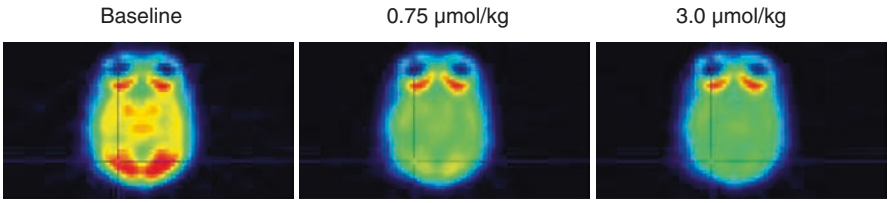

Fig. 1.2 Horizontal PET images showing [^{11}C]AZ10419369 binding to the $5HT_{1B}$ receptor at baseline and after AZD3483 i.v. administration in a cynomolgus monkey

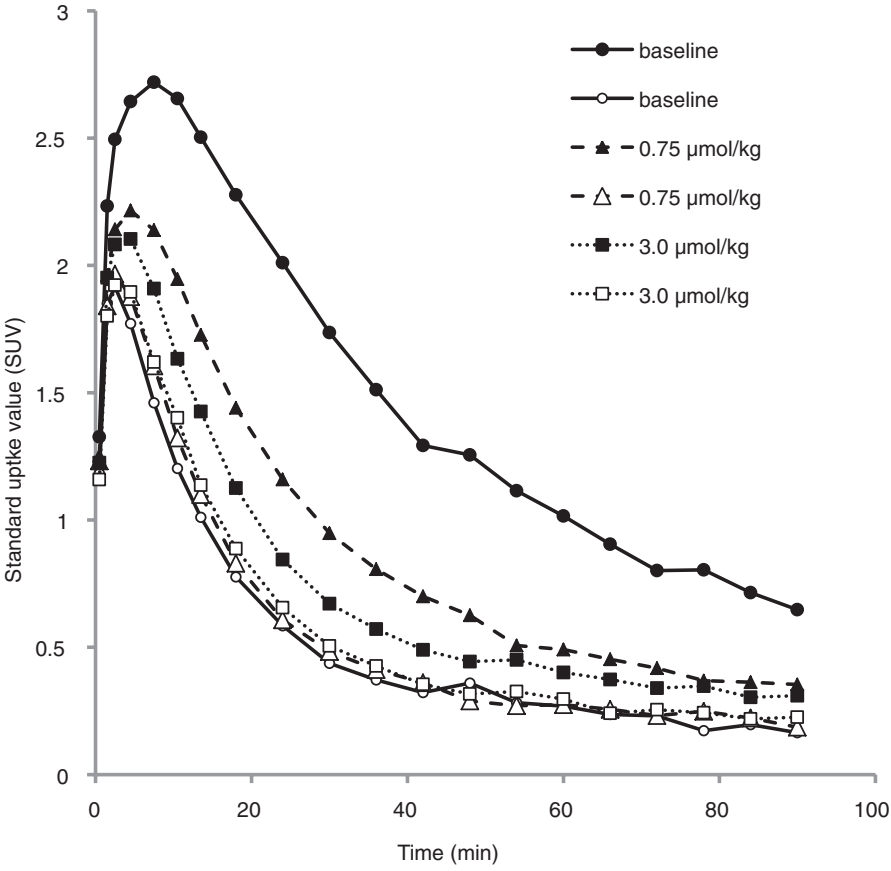

Fig. 1.3 Time-activity curves for the regional [^{11}C]AZ10419369 binding in a cynomolgus monkey illustrated in Fig. 1.2. *Filled marks* represent occipital cortex. *Open marks* represent the cerebellum

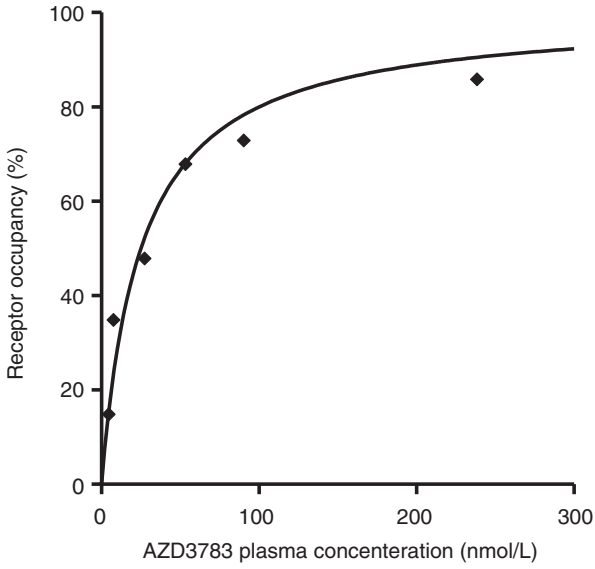

Fig. 1.4 The curvilinear relationship between plasma concentration of the $5HT_{1B}$ receptor antagonist AZD3783 and target receptor occupancy in cynomolgus monkeys (Modification of figure in Varnäs et al. 2011)

target occupancy and clinical efficacy or side effects may be insufficiently understood. In such cases, the relationship between occupancy and pharmacodynamics can only be established after phase II and III studies when clinical data becomes available.

A successful example of the occupancy approach is [^{11}C]AZ10419369, a PET radioligand for the serotonin 5HT1B receptor subtype (Figs. 1.2, 1.3 and 1.4). This radioligand was developed in a collaboration between Karolinska Institutet and AstraZeneca and has been used for the occupancy measurement by AZD3783, a candidate drug for treatment of depression (Pierson et al. 2008; Varnäs et al. 2011). The occupancy estimations were first performed in NHP and later in human subjects. The relationship between the dose and $5HT_{1B}$ occupancy by AZD3783 was similar between nonhuman primates and human subjects (Varnäs et al. 2011). Despite the value demonstrated for nonhuman primate studies of AZD3783 to predict binding in the human brain, some caution must be exercised whenever making such predictions for new drug targets.

In an optimal occupancy study, a wide range of doses are investigated, ideally covering the interval from 0 to 100%. However, in reality, due to the risk of side effects, the selection of the doses administered to human subjects is likely to be limited to lower doses. Due to a limited range of data, it may thus be difficult to confirm whether a maximal occupancy can be reached and whether the binding affinity estimates (Ki_{plasma} values (Karlsson et al. 1995)) are reliable.

For some drugs, a pharmacologically active metabolite having affinity for the target may contribute to occupancy at the target sites (Takano et al. 2011). In NHP,

the occupancy of the metabolite can be estimated by injection of the metabolite only. PET in NHP may thus provide additional useful information prior to the human PET study.

In a recent guideline for PET occupancy studies in drug development (Takano et al. 2016), key points for consideration are listed such as selection of radioligand and design of the study. The considerations are beyond the scope of this chapter but are described in detail in the article (Takano et al. 2016).

1.2.3 Pathophysiology Biomarkers for Diagnosis or Efficacy Studies

For most psychiatric disorders, there are not generally accepted biomarkers in spite of considerable efforts to reveal the pathophysiologies. The recent progress in neuroimaging of psychiatric disorders will be discussed in detail in other sections of this textbook.

A general approach applied in drug development is to use PET to measure physiological parameters such as cerebral blood flow or brain glucose metabolism using [^{15}O]H_2O or [^{18}F]FDG. Change in cerebral blood flow or brain glucose metabolism at drug treatment can thereby be detected, which indirectly serves to confirm a drug effect in the brain. The combined study of occupancy at a biochemical marker and a physiological biomarker has a promising potential to further confirm target engagement but has so far been utilized in a few studies only (Halldin et al. 2001).

In a back-translational approach, animal models for psychiatric disorders can be investigated using micro-PET (Higuchi et al. 2010; Klunk et al. 2004). As the animal does not have to be sacrificed after each PET measurement, longitudinal evaluation of chronic administration of the candidate drugs can be performed. Such translational approaches have potential to validate animal models in relation to the pathophysiology and clinical treatment of psychiatric disorders.

In the field of neurology, in vivo imaging of amyloid and tau have been added to the toolbox for diagnosis of Alzheimer's disease (AD). Indeed, several radioligands have been developed for each target in a short period (Klunk et al. 2004; Rinne et al. 2010; Jack Jr et al. 2011; Cselényi et al. 2012; Gelosa and Brooks 2012; Mathis et al. 2012; Maruyama et al. 2013; Okamura et al. 2013; Chien et al. 2013). Moreover, the literature includes comparisons of the radioligands (Maass et al. 2017; Schöll et al. 2019). Using the binding of such PET radioligands as a biomarker, stratification of patient samples with Alzheimer's disease and evaluation of disease progress are within reach in a clinical setting. It can be concluded that though depletion of amyloid has not proved to be a successful mechanism for the treatment of Alzheimer's disease, amyloid and tau imaging has a role for several purposes in drug development for Alzheimer's disease.

There is however no established biomarker for the diagnosis of psychiatric disorders based on pathological evaluation postmortem. Despite that, there might be some potential to develop imaging biomarker. PET imaging of the translocator protein (TSPO), which indicates activated microglia activity, has been intensively

investigated in schizophrenia. Initially, higher TSPO binding in schizophrenia was reported (van Berckel et al. 2008; Doorduin et al. 2009). However, the results were not confirmed in subsequent studies (Takano et al. 2010; Kenk et al. 2015; Van der Doef et al. 2016; Holmes et al. 2016; Coughlin et al. 2016; Hafizi et al. 2018). Indeed, recent reports have rather shown lower TSPO binding in schizophrenia (Collste et al. 2017; Notter et al. 2018; Selvaraj et al. 2018). Several conditions such as the heterogeneity of schizophrenia and numbers of episodes may contribute to the mixed results. Generally speaking, new imaging markers for the pathophysiology of major psychiatric disorders are needed to boost psychiatric drug development.

As discussed above, the discussed PET approaches can provide unique information to facilitate drug development. However, the success of a PET study depends on the development of appropriate PET radioligands. As shown in Table 1.1, the availability of PET radioligands is not yet sufficient. As the list of candidates for the drug development has expanded diversely, the need for novel PET radioligand development for new targets becomes critical.

1.3 Radioligand Development: Targeting Neurology and Psychiatry

The selection of radioligands for PET is initially guided by data obtained in vitro by using a tritiated radioligand or by displacing a reference radioligand with the unlabeled molecule. In vitro binding normally provides information regarding ligand *affinity* (e.g., the dissociation equilibrium constants K_d or K_i) and *selectivity* (i.e., the relative affinity to competing binding sites) as well as regarding the *concentration* of binding sites (B_{max}). The optimum affinity is closely related to the expected B_{max}. It is preferable if the B_{max} clearly exceeds the K_d of a ligand, i.e., if a binding site exists in vivo at nanomolar concentrations, a potentially successful radioligand ideally should have a subnanomolar affinity. Binding affinity is an important factor that determines the *ratio* of specific binding to nonspecific binding. The higher the ratio, the more sensitive the signal is likely to be to changes in available binding site concentration, caused by disease or drug occupancy.

Binding affinity (i.e., the fraction of dissociation rate constant, k_{off}, and association rate constant, k_{on}) usually governs the approach to be taken in the biomathematical modeling of the ligand-receptor interaction. If the binding of a radioligand is reversible over the timescale of a PET experiment (i.e., a "transient equilibrium" is attained), *equilibrium* approaches toward quantification can be utilized. On the contrary, irreversible ligands normally demand for *kinetic* modeling, wherein the transfer of radioligand between pharmacological compartments is described in terms of rate constants. This approach requires in most cases the determination of an *input function* (i.e., the time course of free radioligand in plasma), which makes the measurement of radiometabolites in arterial plasma necessary by radio-HPLC. Very high binding affinity of a radioligand in combination with a comparatively slow clearance from tissue can restrict its usefulness for PET, as the rate-limiting step of tracer retention may become the delivery—instead of the binding process.

A further important criterion for a radioligand is binding selectivity. Ideally, the affinity of a radioligand should be greatest for the site of interest by one order of magnitude. Lack of selectivity may be acceptable if nontarget sites are separated anatomically from the target binding sites. Most neurotransmitter receptors have now been found to exhibit multiple subtypes, and radioligands that were initially thought to bind to a single class of receptors truly display affinity toward several subtypes. Most benzamides are equipotent at the dopamines D_2 and D_3.

Another substantial consideration in the development of a new radioligand is estimation of *nonspecific binding*. This is an essentially non-saturable component of the total tissue uptake of a radioligand, usually attributed to adhesion to proteins and lipids. Nonspecific binding and its clearance in vivo is difficult to predict absolutely. Within a class of structurally related compounds, nonspecific interactions with tissue generally increase with increased lipophilicity. The logarithm of the partition coefficient between water and octanol (log *P*) is often taken as a useful index for the lipophilicity of a compound in the context of biological systems. But some degree of lipid solubility is needed for good passage over the blood–brain barrier, which is a prerequisite for satisfactory counting statistics. However, the lipophilic nature of a molecule might also favor binding to plasma proteins, thus reducing the available "free fraction" in the blood that is capable of diffusing through membranes. Taken together, it appears that there is an optimal—but rather narrow—"window" of lipophilicity for brain radioligands, which optimally should be 1.5–2.5.

PET measures the regional radioactivity concentration without being able to distinguish the chemical forms or environments in which the radioactivity resides. For a clearly interpretable signal, it is therefore necessary that radiometabolites do not contribute to specific binding. Thus, radioligands should be preferably resistant to rapid metabolism over the period of data acquisition. Furthermore, radiometabolites should not be taken up in the target area. This requirement may have important consequences concerning the elaboration of a radiolabeling strategy. In fact, the position of the radiolabel within a molecule might be crucial for the in vivo usefulness of a radioligand, as the major drawback for not useful radioligands is radiometabolites also penetrating the blood–brain barrier (BBB).

An important factor is the specific radioactivity (SA) of the radioligand. Too low SA may result in pharmacological side effects or toxicity of the radioligand. Moreover, low SA may saturate the biological system of interest; thus no tracer condition is achieved. For low-density binding sites, very high SA is essential in order to exclude a substantial occupation of target sites by unlabeled compound.

It has to be emphasized that any data extracted from in vitro experiments can only give a rough estimate of the situation to be encountered in vivo. Most in vitro assays use homogenized tissue, which does not reflect the tissue heterogeneity in the intact organ in vivo. Competition with endogenous ligands may lower the binding of a radioligand at a given site. It has to be kept in mind that neurotransmission systems in the intact body constitute part of a dynamic and communicating environment and that neural interaction may actually alter in vivo receptor binding.

If a potential candidate radioligand has been identified and a labeling technique developed, some preclinical evaluation, prior to PET in humans, needs to be

performed. Some useful information may be obtained by studies in rodents. Typically, the radioligand is injected intravenously into a series of rats or mice. These are then sacrificed at known times after injection and different organs are removed and counted, thus providing the distribution of the radiotracer in different organs over time. In addition to that, clearance of radioactivity from plasma and information on the appearance of plasma radiometabolites can be obtained. Specificity of binding may be demonstrated by using selective and potent unlabeled agents that act in a competing way at the site of interest. Small-animal PET devices are becoming increasingly available which promise to simplify radioligand evaluation. It should be noted, however, that species differences may be encountered and lead to different results between animals and human subjects.

A complementary tool in early radioligand development may be *autoradiography* experiments, wherein frozen slices of tissue obtained from the organ of interest such as the brain are mounted on glass slides and incubated for a given time with a buffered radioligand solution. These sections are exposed to radiation-sensitive film or preferably using a phosphor imager. Autoradiography may provide information if a radioligand is suitable for PET, especially regarding affinity, selectivity, and nonspecific binding. An advantage compared to in vitro homogenate binding assays is the use of intact tissue, which provides information in an anatomical manner. But, no data regarding the in vivo pharmacokinetics of the radioligand can be deduced from such an experiment. This lack of information can be compensated for by ex vivo autoradiography approaches, where the analysis is done in vitro after in vivo administration of the radioligand into small animals. Usually, autoradiography experiments are performed with ^{3}H-labeled compounds, but also molecules labeled with positron emitters can be used, although this lowers the spatial resolution. A superior method is using whole hemisphere autoradiography of the *postmortem* human brain.

The next step in radioligand development is normally PET in nonhuman primates – such as cynomolgus monkey. Analysis of plasma radiometabolites from venous blood samples provides useful information regarding clearance and metabolic pathways. Administration of potent and selective competing agents prior to radioligand injection (*pretreatment*) or during the time course of the PET experiment (*displacement*) can demonstrate the specificity and reversibility of radioligand binding.

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Brain PET Quantification in Neuropsychiatric Research

2

Jenny Ceccarini, Koen Van Laere, and Michel Koole

Contents

Abstract

Molecular PET neuroimaging in neuropsychiatry focuses on the quantification of brain PET data to assess group differences, short- and long-term effects of treatments or even to measure neurotransmitter levels in psychiatric conditions. In this chapter we introduce the main tracers used in neuropsychiatry, and starting from the basics of dynamic PET imaging, we present different methodologies to quantify PET imaging, including compartmental, graphical and semiquantitative approaches.

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We also present different approaches to measure changes in neurotransmitter levels induced by pharmacological or behavioural challenge. Finally, we conclude focusing on the potential use of hybrid PET/MRI in neuropsychiatric research.

2.1 Introduction

In the last 20 years, functional and molecular neuroimaging modalities have become an established and essential research tool for understanding the relationships between behavioural factors and pathophysiological mechanisms underlying neuropsychiatric disorders, such as schizophrenia (SCZ), major depressive disorder (MDD), bipolar disorder, substance use disorders (SUD), obsessive-compulsive disorders (OCD), post-traumatic stress disorder (PTSD), attention-deficit/hyperactivity disorder (ADHD) and personality traits (Hellwig and Domschke 2019). Among functional imaging modalities, functional magnetic resonance imaging (fMRI) allows to visualize task-dependent neuronal activation indirectly with high-spatial and temporal resolution. fMRI allows to also study specific alterations in the steady-state functional brain connectivity, which have been reported, for example, in MDD and SCZ (Kaiser et al. 2016; Zhang et al. 2018). Additionally, fMRI has been used to link neural stimulus-related signals to individual differences in behaviours and traits underpinning reward processing in SUD (Wang et al. 2016). On the other hand, molecular neuroimaging techniques such as positron emission tomography (PET) offer the unique ability to visualize and quantify functional and molecular physiological processes in vivo with great specificity and sensitivity. Specifically, brain PET enables the in vivo mapping of neurobiological functions such as blood flow (Fan et al. 2016), regional glucose metabolism, enzyme activity (Koole et al. 2017), neuroreceptor binding site density (Ceccarini et al. 2014; Leurquin-Sterk et al. 2018), endogenous neurotransmitter release (Ceccarini et al. 2012; Erritzoe et al. 2019; Turton et al. 2018), occupancy (Koole et al. 2019; Van Laere et al. 2012), synaptic dysfunction (Holmes et al. 2019; Matuskey et al. 2020), neuroinflammatory processes (Hellwig and Domschke 2019) and neuronal degeneration (Villemagne et al. 2017).

A typical PET study involves the injection of a compound, referred to as a PET radiotracer (a compound labeled with a radionuclide) into the venous bloodstream of a subject. This radiotracer is delivered to the brain by the arterial flow, and after crossing the blood–brain barrier (BBB), it might bind reversibly or irreversibly to neuroreceptors and transporter vesicles or be metabolized by endogenous enzymes. On the other hand, if the tracer is inert, it would diffuse across the BBB and would not be bound or trapped. In parallel to these biochemical processes, the radioisotope label will decay, emitting a positron that annihilates to emit diametrically opposed 511 keV photons. Part of these photon pairs will be detected by PET scanner within a predefined timing window (usually 6–10 ns) as a pair of coincidence detections. Therefore, PET is also being referred to as coincidence imaging. Over the total duration of the scan (usually 1–2 h), emission data are acquired, corrected for physical effects such as attenuation and scatter and binned into different time frames. The corrected data of each time frame are reconstructed using an analytical or iterative reconstruction algorithm to generate a three-dimensional image of the radiotracer distribution in the brain over various time intervals.

PET imaging has been used extensively to explore a variety of biochemical, physiological and pharmacological processes, to study aspects of the complex interaction of several neurotransmitter systems in the brain or to block studies using a drug or drug candidate. In this way, PET imaging has advanced understanding of a number of neurological and psychiatric conditions (McCluskey EJNMMI 2020). Recently, based on the increasing popularity of yoga worlwide, in association with several implicated physical and mental benefits, PET studies are also focusing on the neurobiology of yoga (van Aalst et al. 2020). Compared to MR-based techniques, PET has the particular advantage that it is highly sensitive and quantitative. Moreover, PET can quantify subpicomolar concentrations without any pharmacological or blocking effects at the target receptors. The amount of tracer injected is a trace amount and causes no changes in the physiology of the organism. In terms of PET tracer development for CNS targets, labeling the appropriate precursor is not the major obstacle since most candidate ligands contain carbon and hydrogen such that a positron-emitting nuclide can be incorporated as an isotopic variant or atomic substitute. An obvious requirement for a successful CNS PET tracer is the ability to accumulate within the CNS, a high affinity for target, high target selectivity and a relatively small window of an appropriate combination of lipophilicity, molecular weight and affinity (Pike 2016). Since each PET probe is characterized by its particular kinetic behaviour in the brain, understanding its dynamics and quantification is a critical component for designing PET imaging protocols, setting up clinical studies and interpreting results. Therefore the purpose of this chapter is to give a general overview of PET imaging quantification and of PET applications in neuropsychiatric research and to discuss how the use of hybrid PET/MR systems can pave the way for more comprehensive investigation of brain organization and pathophysiological mechanisms underlying neuropsychiatric disorders.

2.1.1 Types of Tracers Used in Psychiatry

A role for imaging and quantifying regional neuronal metabolism, dopaminergic, serotonergic and other neuroreceptor function has been suggested in the diagnosis of psychiatric disorders, such as SCZ, MDD, bipolar disorder, SUD, OCD and ADHD. Several radiolabeled molecules have been developed targeting specific receptor systems of interest in these debilitating psychiatric conditions.

In the last decades, PET imaging has been extensively used to investigate various key components of the dopaminergic system, involved in several neuropsychiatric disorders such as SCZ, MDD and SUD, both presynaptically, including dopamine transporters (DAT) (^{11}C-MP, ^{11}C-PE2I, ^{18}F-PE2I), dopamine synthesis capacity (^{18}F-DOPA), and postsynaptically, including dopamine $D_{2/3}$ receptors (with ^{11}C-raclopride, ^{18}F-fallypride, ^{11}C-PHNO, ^{11}C-FLB457 as radioligands). In MDD, the major pharmacological treatment target is inhibition of the serotonin (5-HT) transporter (SERT) (serotonin-selective reuptake inhibitors), which has prompted numerous studies of the role of SERT in the pathophysiology of MDD, mainly using the ^{11}C-DASB radioligand (Gryglewski et al. 2014). Recently, a novel 5-HT_{2A} receptor agonist radioligand, ^{11}C-CIMBI-36, has been used to measure serotonin release in the living human brain after a d-amphetamine challenge (Erritzoe et al.

2019). Next to the dopaminergic brain function, PET imaging of the glutamatergic system and the endocannabinoid system, considering their modulating effects on neurotransmission, has been reporting very interesting findings especially in relation to SCZ (Akkus et al. 2017; Ceccarini et al. 2013b) and SUD (Akkus et al. 2018; Ceccarini et al. 2019; Hirvonen et al. 2013; Martinez et al. 2014), by using ^{11}C-ABP688 and ^{18}F-FPEB, to quantify the metabotropic glutamate receptor 5 (mGluR5), and ^{18}F-MK9470, ^{11}C-OMAR and ^{18}F-FMPEP-d_2 to quantify the type-1 cannabinoid receptor (CB1R). Figure 2.1a and b. illustrates differences between healthy controls and alcohol-dependent patients in mGLuR5 (Leurquin-Sterk et al. 2018) and CB1R availability (Ceccarini et al. 2013a).

Besides synaptic targets, post-receptor signal transduction has gained interest since abnormalities in second messenger systems could play an important pathophysiological role in many psychiatric diseases. One of the major biochemical cascades in this context is the cyclic adenosine monophosphate (cAMP) signal transduction system. Recently, an antagonist PET tracer has been developed for the dual-substrate enzyme phosphodiesterase 10A (PDE10A) (Van Laere et al. 2013) which is part of this cascade system and has a restricted distribution, predominantly in the human brain and more specifically in medium spiny neurons (MSNs) of the striatum, substantia nigra, nucleus accumbens and the olfactory tuberculum. This enzyme mainly hydrolyzes the important second messengers cyclic adenosine monophosphate (cAMP) (Bender and Beavo 2006), regulating the excitability of MSNs and thereby acting on the postsynaptic dopaminergic neurotransmission. PDE10A can thus be seen as a key regulator of basal ganglia dopaminergic function (Wilson and Brandon 2014). Striatal binding potential (BP_{ND}) values of ^{11}C-Lu AE92686 (indicating PDE10A levels) have been recently related to striatal function and striato-cortical interaction in SCZ (Bodén et al. 2017; Persson et al. 2019). The ^{18}F-JNJ42259152 PDE10A PET radioligand has been recently used to show that PDE10A expression might be modulated by chronic dopamine-related treatment (Ooms et al. 2017) and by a chronic alcohol self-administration both in animals and in alcohol-dependent patients (Fig. 2.1c, Ceccarini, Van Laere et al., unpublished findings).

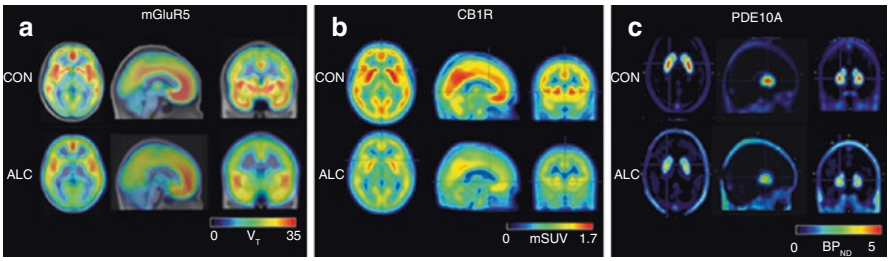

Fig. 2.1 Comparison within control subjects (CON) (top row) and alcohol-dependent patients (ALC) (bottom row) of (**a**) metabotropic glutamate receptor 5 (mGluR5) represented by ^{18}F-FPEB total distribution volume (V_T) (Figure adapted from Leurquin-Sterk et al. (2018)), (**b**) type-1 cannabinoid receptor (CB1R) represented by ^{18}F-MK9470 modified standardized uptake value (mSUV) (Figure adapted from Ceccarini et al. (2013a)) and (**c**) phosphodiesterase 10A (PDE10A) represented by ^{18}F-JNJ42259152 binding potential non-displaceable (BP_{ND}) (Ceccarini, Van Laere et al., unpublished findings)

Recent developments have provided evidence for the feasibility of imaging endogenous opioids, acetylcholine and 5-HT, and this is an area that has the potential of expanding into other neurotransmitter systems. The work gives an overview of all the existing approaches used to quantify neurotransmission with PET imagin. Moreover, recently the synaptic vesicle glycoprotein 2A (SV2A) protein has been identified as an interesting target not only in neurodegenerative disorders where synaptic loss is associated with cognitive impairment (Chen et al. 2018; Vanhaute et al. 2020) but also in MDD where lower synaptic density have been linked to network alterations and symptoms of depression (Holmes et al. 2019). Most of the work in this area has been performed with ^{11}C-UCB-J (Koole et al. 2019; Nabulsi et al. 2016) and ^{18}F-UCB-H (Warnock et al. 2014; Bastin et al. 2020), with both ligands demonstrating kinetics suitable for robust quantification of SV2A density.

Finally, inflammatory processes have been proposed to play a role in the initiation, progression and symptoms in different neuropsychiatric conditions such as SCZ, MDD, OCD and SUD (Attwells et al. 2017; Setiawan et al. 2015; Tyler et al. 2019). Although imaging neuroinflammation is not straightforward in terms of translocator protein (TSPO) quantification, which is upregulated on activated microglia, the most well-known TSPO PET radioligands are ^{11}C-PK11195, ^{11}C-PBR28, ^{18}F-DPA-714 and ^{18}F-FEPPA. Based on some TSPO confounds related to distinct high-/low-affinity binding genotypes, other promising targets for neuroinflammation have been recently investigated. One such target is the ionotropic purinoceptor P2X7 receptor (P2X7R). Recently the selective ^{11}C-JNJ54173717 PET radioligand has been shown to be suitable for quantifying P2X7R expression in human brain (Van Weehaeghe et al. 2019).

2.2 Quantitative PET Imaging

Three-dimensional PET images represent radioactivity concentration measured in the tissue: in each voxel the image intensity is determined by the radioactivity concentration. In vivo quantification of molecular targets with PET imaging is complicated due to the fact that tracers are administered intravenously and not directly applied to the target tissue. Therefore, delivery of the tracer to the brain is influenced by the local blood flow, free tracer concentration in the plasma and peripheral tracer clearance due to metabolization and excretion. Moreover, total brain activity is measured with PET brain imaging, while often tracer specifically bound to its intended target, tracer nonspecifically bound (temporarily and loosely bound to other entities within the tissue) and free intracellular tracer need to be separated to estimate the specific tracer signal. For the remainder, we assume that appropriate algorithms have been used to reconstruct a quantitative, accurate radiotracer distribution such that image values are proportional to the radiotracer concentration in brain tissue. We will focus on the accurate quantification of the particular neurobiological function targeted by the radiotracer. Therefore, three essential aspects should be considered. First, the kinetic behaviour of the PET tracer in brain tissue is characterized by *dynamic PET data*. Second, an *input function* is needed to describe the time-dependent amount of tracer that is delivered to the brain tissue. Third, relatively

complicated *mathematical (compartmental) analysis* will model the tracer kinetics on the basis of the dynamic PET data and an input function.

2.2.1 Dynamic PET Quantification

Dynamic PET image data are binned and reconstructed into various time frames and represent the radiotracer distribution in tissue at specific time points throughout the PET study. This temporal evolution of radiotracer concentration in individual voxels or regions of the image volume is called a time-activity curve (TAC) (see Fig. 2.2, right). These TACs form the basis for quantifying the physiological (e.g. blood flow) and/or pharmacological aspect (e.g. receptor binding site density, enzyme activity) of the system of interest.

To generate TAC for specific brain regions of interest, PET data can be aligned with corresponding MRI data by optimizing translation and rotation parameters (Van Laere et al. 2013). This way high-resolution anatomical MR information can be used to facilitate manual delineation of the appropriate volume of interest (VOI) (see Fig. 2.2b), especially when the PET data itself provide limited anatomical landmarks.

While manual delineation can be time-consuming and observer dependent, methodologies have been developed that allow automatic VOI generation (Svarer et al. 2005). These methods create an individualized VOI probability map on the basis of a database of several MRI datasets, where a VOI template has been defined manually on each MRI dataset. Nonlinear image registration between these MRI datasets and the MRI dataset of interest allows transfer of these individually defined VOI templates to the MRI dataset of interest. Based on the degree of overlap of the

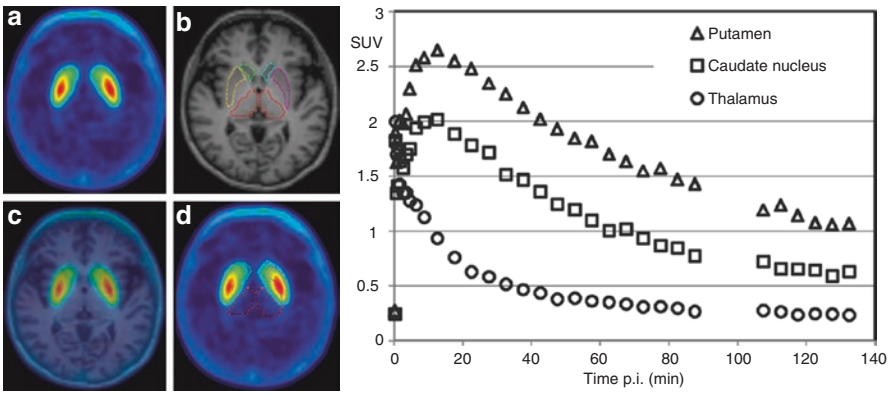

Fig. 2.2 Time-activity curves of a PET tracer targeting PDE10A (Van Laere et al. 2013) for the putamen, caudate nucleus and thalamus. (**a**) represents an average SUV image (averaged over 60–90 min interval), (**b**) the corresponding T1-weighted MRI dataset with delineated brain structures, (**c**) the co-registered MR and PET dataset and (**d**) the PET dataset with the brain structures transferred from the registered MR dataset

transferred VOI sets, a VOI probability map is created specifically for that particular PET dataset. When the generated VOI map is based on more than one template VOI set, VOI delineation proved to be better reproducible and showed less variation as compared to manual delineation or transfer of only a single VOI template. This methodology allows a fast, objective and reproducible assessment of regional brain PET values.

In addition, the latter methodology offers the possibility to correct for partial volume effects (PVEs) in brain PET imaging. Due to the limited resolution of PET imaging, a PET voxel is only partly composed of the target brain tissue which in most cases is a specific grey matter brain structure. Therefore, the PET signal actually reflects the activity concentration of different underlying adjacent tissue types like the grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). Because of differences in activity concentration between these tissue compartments, the PET signal of the target tissue (or VOI) is confounded (*spill-in* and *spill-out* effects of background activity into and from the VOI respectively). One can correct for this PVEs by using spatial distribution maps for the GM, WM and CSF generated from segmented co-registered MRI data. Taking into account the resolution of the PET system, it is possible to estimate the different underlying tissue fractions for each PET voxel and apply an appropriate correction and weighting of the PET signal (Rousset et al. 1998). This way, the actual tracer uptake per unit GM tissue can be determined. This especially applies when comparing healthy volunteers with elderly subjects or with patients suffering from psychiatric disorders where the presence of regional cerebral atrophy is suspected. For the present, there is an amount of studies focused on the clinical application of MRI-based PVC for PET images, mainly in the neurological applications, including different post-reconstruction PVC methods (divided into region-based and voxel-based methods) and within-reconstruction PVC techniques (Chen et al. 2019). However, since most PVC methods can provide different amounts of recovery due to different tissues, subject conditions and tracers (Shidahara et al. 2017), the utility of specific MRI-based PVC in brain PET imaging should be examined on the basis of an application-specific consideration (Minhas et al. 2018).

2.2.2 Input Functions

For the quantification of the pharmacological parameters, dynamic PET data need to be accompanied by time-dependent activity concentrations of the intact tracer in arterial plasma. Arterial plasma tracer concentrations represent the delivery of the radiotracer to the system of interest and are mandatory as input function for the kinetic modeling of this system. In general, arterial blood sampling is performed during the PET acquisition where blood samples are collected through an arterial puncture, plasma is separated from the cellular blood fraction, and radioactivity in the plasma is corrected for any radiotracer molecules that might have undergone metabolism by enzymes in the plasma or the liver. This way a time-activity curve of the free intact radiotracer in plasma is obtained. This traditional approach however

has a major drawback that drawing arterial blood samples is invasive for subjects and manual sampling requires substantial work for the PET personnel, although automatic sampling can also be considered in a discrete or continuous fashion by means of blood samplers (Alf et al. 2013). Errors in arterial sampling may propagate into the quantification of the system being studied. These errors can be due to incomplete or irregular sampling, sampling of small blood volumes yielding limited count statistics and irregular or unreliable metabolite analysis. Moreover, additionally cross-calibration between the sample detection setup and the PET system needs to be secured.

Efforts have been made to determine the input function from the PET data by isolating the PET signal from the carotid arteries. This noninvasive alternative to arterial sampling, denoted image-derived input function (IDIF), is however methodologically very challenging and has only been implemented successfully in clinical practice for a limited number of tracers (Sari et al. 2017). Indeed, feasibility of IDIF depends on tracer kinetics after bolus injection and more specifically on an adequate carotid to background ratio which affects the accuracy of the image-derived whole blood activity concentration. On the other hand, even an acceptable IDIF will typically show inaccuracies in peak estimation. Impact of these peak errors on the quantitative parameters depends on the kinetic model and needs to be assessed for each tracer separately.

Other important limitations of IDIF are that the parent compound cannot be distinguished from its radioactive metabolites and that the plasma radioactivity cannot be separated from the whole blood activity concentration. In general, a limited numbers of blood samples are still needed to estimate differences between the plasma and whole blood activity concentration and to calculate the percentage of intact parent tracer in plasma (Sanabria-Bohórquez et al. 2000). To avoid arterial blood sampling, venous blood samples can be considered. However, arterial tracer kinetics can differ from the venous one, while only at late time points of the PET acquisition the metabolite concentration reaches equilibrium between the arterial and venous compartment. Therefore, venous samples can be substituted for arterial samples but only for a limited time window that must be assessed individually for each tracer.

The tracer is also typically metabolized like any other administered exogenous compound, often resulting in a more hydrophilic compound unable to pass the blood–brain barrier (BBB). Therefore, since the radioactivity concentration in the blood may in part come from radiolabeled metabolites, the measured blood radioactivity needs to be corrected for metabolites and the ratio between free tracer in the plasma and whole blood radioactivity calculated. In terms of metabolization, most neuro-receptor tracers have a high metabolite fraction and will therefore not be easily amenable to integrate an individualized metabolite correction with IDIF. One could consider an average metabolite curve while using late venous blood samples to estimate the radio-metabolite concentration and to scale the metabolite curve (Backes et al. 2009). This type of metabolite correction is however not always possible and needs to be validated for every tracer.

Although with IDIF the number of arterial blood samples could at least be reduced, IDIF could only be used to its full extent for a limited number of PET tracers (Bastin et al, 2019; Zanotti-Fregonara et al. 2011a, b) and only rarely results in imaging procedures with reduced invasiveness for the patient. However, an IDIF approach allows to some extent to reduce the dependence of the quantification on reference devices such as well counter and dose calibrator. Therefore, this approach could prove more robust for possible incorrect cross-calibration with the PET system or be more sensitive to detect possible erroneous scaling. A promising development to the IDIF approach is to parameterize the IDIF and to estimate these parameters simultaneously with the kinetic parameters describing tracer kinetics of several brain regions (Sanabria-Bohórquez et al. 2012). However, in practice some blood samples could be needed to improve the parameter estimation.

An alternative approach to IDIF is the use of a population-based input function created by normalizing individual input functions from a population of subjects and appropriately scaling this standard input function using venous or arterial blood samples. This approach has been validated primarily for ^{18}F-FDG brain PET (Brock et al. 2005; Takagi et al. 2004), although this approach has been used for other tracers (Zanotti-Fregonara et al. 2011b). However, one needs to keep in mind that an average input function obtained for a population of healthy subjects may not apply for a patient population because the disease state or treatment may affect tracer metabolization.

2.2.3 Compartmental Analysis and Model Selections

In terms of mathematical analysis, brain uptake of a radioactive tracer is often described within the theoretical framework of compartments. Compartment modeling allows description of systems that vary in time but not in space as one of the assumptions for compartmental modeling is that there are no spatial concentration gradients within each compartment but only gradients in time. In fact, a compartment represents a unique state of the tracer and is defined as a space with separate uptake and clearance rate constants where the radioactive tracer concentration is assumed homogeneous. Rate constants for transfer between the compartments are indicated with k. Rate constants are assumed time invariant at least over the duration of the study and considered being representative for the steady state of the system and the properties of the ligand. A compartment may have a physical analogue such as interstitial fluid compartment but can also be considered as a tracer being in bound or unbound state. Once the exchange paths between compartments have been specified, the mass balance for each compartment can be described as a set of ordinary differential equations where one differential equation corresponds to an unknown tracer concentration. Tracer concentration in the vascular arterial compartment drives the model taking into account that tracer tissue concentrations are zero at the start of the PET study.

Figure 2.3 shows example of such box diagrams for the most commonly used models, the one-tissue compartment model (1TCM), the two-tissue compartment

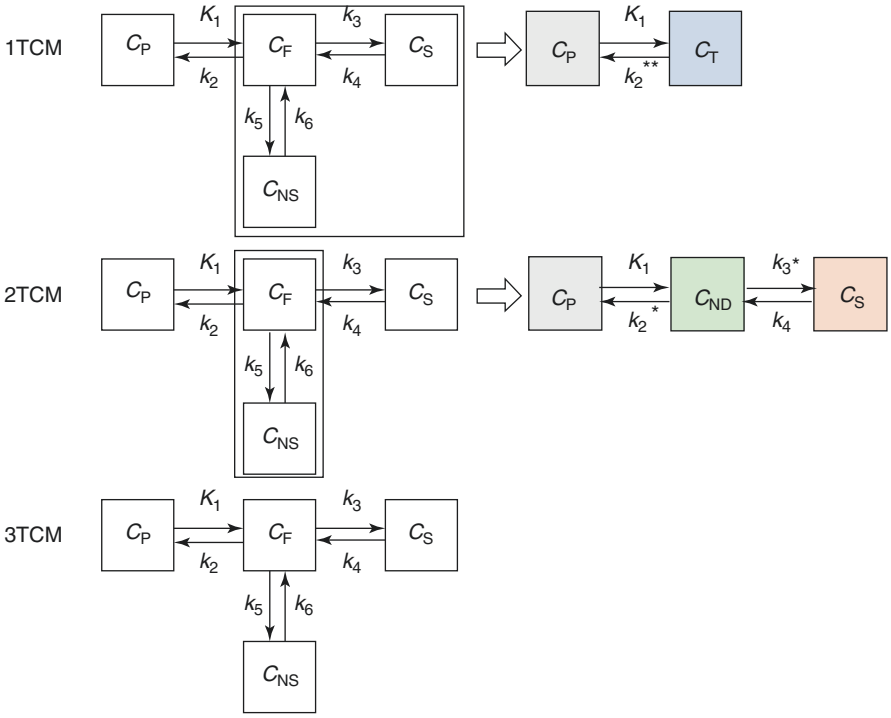

Fig. 2.3 Overview of the different compartment models: one-tissue compartment model (1TCM) with C_P the activity concentration in arterial plasma, C_T the tracer concentration in tissue and K_1 and k_2^{**} represent the transport rate constants between arterial plasma and brain tissue. A two-tissue compartment model (2TCM) with C_P the activity concentration in arterial plasma, C_{ND} the concentration of non-displaceable radioligand in tissue, C_S the concentration of tracer that is bound specifically, K_1 and k_2^{*} represent the transport rate constants between arterial plasma and brain tissue and k_3^{*} and k_4 represent the exchange rate constants between specific binding and the free and nonspecifically bound state. A three-tissue compartment model (3TCM) with C_P the activity concentration in arterial plasma, C_F the concentration of free radioligand in tissue, C_S the concentration of tracer that is bound specifically and C_{NS} the concentration of tracer that is bound nonspecifically, K_1 and k_2 represent the transport rate constants between arterial plasma and brain tissue, k_3 and k_4 represent the exchange rate constants between specific binding and the unbound state, while k_5 and k_6 represent the exchange rate constants between the free tracer and nonspecific binding

model (2TCM) and the three-tissue compartment model (3TCM). In addition to the tissue compartments, there is also a plasma compartment, representing the input function as previously mentioned, and the blood volume in tissue, although accounted for in the models, is not included in the box diagrams (C_P represents the activity concentration in arterial plasma).

2.2.3.1 One-Tissue Compartmental Model (1TCM)

The partition coefficient in the context of high extraction tracers can be defined more generally as the ratio of the steady-state concentrations between two

compartments and is numerically identical to the tissue volume of distribution V_T. V_T is often used in PET literature and is defined as the apparent volume a tracer would occupy, if the tracer were to adopt the same concentration in tissue as in the blood. In steady-state PET studies where tracer is delivered via constant infusion in order to maintain tracer concentration in the arterial blood at a constant level, the distribution volume is easily derived from constant concentration ratios in equilibrium.

In dynamic PET studies, however, we measure time-dependent concentrations. Assuming that the system is in steady state and the so-called tracer assumption is valid (that tracer concentration is negligible), the degree of substance exchange (such as transport through one or more membranes, enzymatic conversions or binding to specific sites) between kinetically defined 'compartments' is proportional to the concentration and can be quantified by rate constants, and rate constants between kinetic compartments are estimated. From these rate constants, the distribution volume can be derived as well. However, if we want to estimate the rate constants, we need to take into account that PET measures all activity present in the field of view, both intra- and extravascular. Thus, the total activity concentration measured by the PET system $C_{PET}(t)$ is given by

$$C_{PET}(t) = (1 - V_B) C_T(t) + V_B C_B(t). \tag{2.1}$$

V_B represents the blood fraction present in the field of view ($0 \leq V_B \leq 1$) and $C_B(t)$ the activity concentration in the whole blood, while $C_T(t)$ stands for the activity concentration in brain tissue.

Considering a one-tissue compartment model for describing the bidirectional flux of tracer between the blood and tissue, this model is characterized by the time-varying tracer concentration in tissue $C_T(t)$ and the arterial blood $C_A(t)$ and two first-order kinetic rate constants K_1 and k_2. This way the tracer flux from the blood to tissue is $K_1 C_A$, while the tracer flux from the tissue to blood is $k_2 C_T$. Therefore, the net tracer flux into tissue is describes as

$$\frac{dC_T(t)}{dt} = K_1 C_A(t) - k_2 C_T(t). \tag{2.2}$$

$C_T(t)$ represents the radioactivity concentration that is measured with PET in a given brain region, while blood samples may be drawn during the PET measurement in order to measure $C_A(t)$. K_1 is closely related to blood flow when the extraction fraction is large but is more related to permeability when the extraction fraction is low. Accordingly, the best tracers for studying blood flow have a large extraction fraction. For a freely diffusible tracer, K_1 equals perfusion, and the ratio $\frac{K_1}{k_2}$ equals the partition coefficient ρ. In a more general context, if we consider tracer concentrations in the blood and tissue in equilibrium, a state with no net transfer of tracer between the two compartments, the gradient $\frac{dC_T(t)}{dt}$ in (2.4) can be set to zero, and the following equation for the distribution volume V_T is valid:

$$V_T = \frac{C_T(t)}{C_A(t)} = \frac{K_1}{k_2}. \tag{2.3}$$

2.2.3.2 Two- and Three-Tissue Compartment Model (2TCM and 3TCM)

Partition coefficient ρ or distribution volume V_T can be considered as a potential quantitative endpoint of PET tracer uptake in the brain. However, for ligand-receptor PET studies, the law of mass action is applicable to ligand-receptor interaction, and under equilibrium conditions, the following equation is valid:

$$\frac{B}{F} = \frac{B_{max}}{K_d + F}. \tag{2.4}$$

In this equation, B represents the tracer concentration bound to the receptor, F denotes the free tracer concentration near the receptor, while B_{max} refers to the receptor density and $1/K_d$ to the ligand affinity for the receptor (K_d is ratio of the dissociation constant k_{off} over the association constant k_{on}). Since PET imaging typically involves the injection of a very limited amount of ligand mass dose, the concentration of free radiotracer is such that $F \ll K_d$, resulting in the following equation:

$$\frac{B}{F} = \frac{B_{max}}{K_d}. \tag{2.5}$$

This equation actually corresponds to the binding potential (*BP*) defined as the product of receptor density (B_{max}) and affinity ($1/K_d$). In terms of PET imaging, this means that *BP* can be estimated as the equilibrium ratio of specifically bound tracer to free tracer and can be considered as a quantitative endpoint for ligand-receptor studies.

For radioligands that pass the BBB by passive diffusion, one can reasonably assume that under equilibrium conditions, the concentration of free tracer in arterial plasma equals the concentration of free tracer in brain tissue. However, to estimate the concentration of specifically bound tracer, a 1TCM needs to be extended to a kinetic model containing multiple compartments. The most generalized kinetic model describing ligand-receptor kinetics consists of three-tissue compartments (3TCM) (see Fig. 2.3), taking into account the activity concentration in arterial plasma C_P, the concentration of free radioligand in tissue C_F, the concentration of tracer that bounds specifically C_S and the concentration of tracer that does not bound specifically C_{NS}, and therefore is not available for specific binding to the targeted receptor. In this context, K_1 and k_2 represent the transport rate constants between C_P and C_T through the BBB, k_3 and k_4 describe the rate of specific binding and target release of the tracer, while k_5 and k_6 represents the exchange rate constants between the free tracer compartment and nonspecifically bound compartment. For a 3TCM, the activity concentration in brain tissue $C_T(t)$ is given by

$$C_T(t) = C_F(t) + C_{NS}(t) + C_S(t). \tag{2.6}$$

If we formulate the differential equations for the unknown tissue concentrations $C_F(t)$, $C_{NS}(t)$ and $C_S(t)$, we get the following equations:

$$\frac{dC_F(t)}{dt} = K_1 C_P(t) - k_2 C_F(t) - k_3 C_F(t) + k_4 C_S(t) - k_5 C_F(t) + k_6 C_{NS}(t), \quad (2.7)$$

$$\frac{dC_S(t)}{dt} = k_3 C_F(t) - k_4 C_S(t), \quad (2.8)$$

$$\frac{dC_{NS}(t)}{dt} = k_5 C_F(t) - k_6 C_{NS}(t). \quad (2.9)$$

Considering the equilibrium condition where no net exchange between compartments is observed, gradients in (2.7), (2.8) and (2.9) can be set to zero, obtaining the following equations for the distribution volume of free tracer (V_F), specific bound tracer (V_S) and nonspecific bound tracer (V_{NS}):

$$V_F = \frac{C_F(t)}{C_P(t)} = \frac{K_1}{k_2}, \quad (2.10)$$

$$V_S = \frac{C_S(t)}{C_P(t)} = \frac{k_3}{k_4} V_F, \quad (2.11)$$

$$V_{NS} = \frac{C_{NS}(t)}{C_P(t)} = \frac{k_5}{k_6} V_F. \quad (2.12)$$

The total volume of distribution for brain tissue V_T can be written as

$$V_T = V_F + V_{NS} + V_S = \frac{K_1}{k_2}\left(1 + \frac{k_3}{k_4} + \frac{k_5}{k_6}\right). \quad (2.13)$$

If we consider equilibrium conditions for (2.8) and compare with (2.5), the following equation is valid:

$$\frac{k_3}{k_4} = \frac{V_S}{V_F} = \frac{C_S}{C_F} = \frac{B}{F} = \frac{k_{on} B_{max}}{k_{off}} = BP. \quad (2.14)$$

This means that BP can be estimated once the rate constants k_3 and k_4 are determined. Moreover, the rate constant k_3 is dependent on the density of available receptor sites and the ligand-receptor association constant k_{on}, while k_4 equals the ligand-receptor dissociation constant k_{off}.

When the transport rate constants k_5 and k_6 are high such that there is a fast equilibrium between the free tracer and nonspecifically bound tracer compartment, the

two compartments are kinetically indistinguishable and can be lumped together into one compartment representing the non-displaceable tracer concentration $C_{ND}(t) = C_F(t) + C_{NS}(t)$. This model reduction yields a two-tissue compartment model (2TCM) with the following differential equations describing this model:

$$C_T(t) = C_{ND}(t) + C_S(t), \tag{2.15}$$

$$\frac{dC_{ND}(t)}{dt} = K_1 C_P(t) - k_2^* \; C_{ND}(t) - k_3^* C_{ND}(t) + k_4 C_S(t), \tag{2.16}$$

$$\frac{dC_S(t)}{dt} = k_3^* C_{ND}(t) - k_4 C_S(t). \tag{2.17}$$

The corresponding tissue distribution volume is given by

$$V_T = V_{ND} + V_S = \frac{K_1}{k_2^*}\left(1 + \frac{k_3^*}{k_4}\right). \tag{2.18}$$

In this case the quantitative parameter of interest is the non-displaceable binding potential (BP_{ND}) defined as

$$BP_{ND} = \frac{C_S}{C_{ND}} = \frac{V_S}{V_{ND}} = \frac{k_3^*}{k_4}. \tag{2.19}$$

It is worthwhile noticing that BP_{ND} is defined relative to the C_{ND}, whereas the binding potential BP is defined relative to the concentration of free radioligand (Innis and Carson 2007). In cases where nonspecific tracer binding could be excluded, BP and BP_{ND} are identical. Model reduction to a 2TCM is usually necessary for the kinetic analysis of dynamic PET data. This way, the number of unknown variables is reduced, and more reliable estimates of the exchange rate constants can be achieved.

When the rate constants k_3^* and k_4 of a 2TC are high compared to transport rate constants K_1 and k_2^*, a fast equilibrium is achieved between the non-displaceable and specifically bound tracer compartment. In this case a further reduction to a 1TC is possible.

2.2.3.3 Reference Regions

The distribution of neuroreceptors varies across the brain, with some specific brain region devoid of receptors. In this case, the brain tissue of that region can be considered reference tissue and can be really used for PET quantification. For example, the cerebellum is considered as reference region in the quantification of dopamine PET radioligands, such as ^{11}C-raclopride and ^{18}F-fallypride. Recently, for the SV2A PET imaging, the white matter (centrum semiovale) region has been validated as

reference region for SV2A ^{11}C-UCB-J PET quantification (Koole et al. 2019; Mertens et al. 2019).

Consequently, BP_{ND} can be estimated for any target region using the tissue distribution volumes of reference (V_{R}) and target tissue (V_{T}) as follows:

$$\mathrm{BP}_{ND} = \frac{C_{\mathrm{S}}}{C_{\mathrm{ND}}} = \frac{C_{\mathrm{T}} - C_{\mathrm{R}}}{C_{\mathrm{R}}} = \frac{V_{\mathrm{T}} - V_{\mathrm{R}}}{V_{\mathrm{R}}}. \tag{2.20}$$

It is worthwhile noticing that in this context, $\frac{V_{\mathrm{T}}(t)}{V_{\mathrm{R}}(t)}$ is often termed the distribution volume ratio (DVR) such that $BP_{\mathrm{ND}} = \mathrm{DVR} - 1$. We need to point out that in the absence of a reference region, BP or BP_{ND} can be estimated numerically, but this estimate is often not reliable. The quantitative parameter that is used most frequently in the absence of reference tissue is the distribution volume V_{T} which can be estimated more reliably.

Equation (2.20) is valid if the tracer concentration in the reference region represents the non-displaceable tracer concentration and if the non-displaceable tracer concentration is the same for both reference and target region. If there is nonspecific tracer binding in the reference tissue and this nonspecific binding can again be assumed the same for both reference and target tissue, the binding potential BP_{ND} calculated from tissue distribution volumes will be biased. Taking into account the distribution volumes of both tissues, one gets the following equation:

$$BP_{\mathrm{ND}} = \frac{V_{\mathrm{T}} - V_{\mathrm{R}}}{V_{\mathrm{R}}} = \frac{V_{\mathrm{S}}}{V_{\mathrm{F}} + V_{\mathrm{NS}}} = \frac{BP}{\left(1 + \frac{V_{\mathrm{NS}}}{V_{\mathrm{F}}}\right)}. \tag{2.21}$$

However, besides estimating BP_{ND} from the DVR of the target region, BP_{ND} can also be estimated from a reference tissue model considering the reference region TAC as an indirect input function to the kinetic model of the target region. The most commonly used model for such estimations is the simplified reference tissue model (SRTM) (Lammertsma and Hume 1996), assuming tracer kinetics in both the target and reference region to be described adequately by a 1TCM. In addition to BP_{ND}, SRTM also provides an estimate of the relative tracer delivery R_1 (the ratio between K_1 for target and reference regions) and the target region k_2.

If we consider a 1TCM for target and reference region, we get the following equations (see (2.4)):

$$\frac{dC_{\mathrm{T}}(t)}{dt} = K_1 C_{\mathrm{P}}(t) - k_{2a} C_{\mathrm{T}}(t), \tag{2.22}$$

$$\frac{dC_{\mathrm{R}}(t)}{dt} = K_{1R} C_{\mathrm{P}}(t) - k_{2\mathrm{R}} C_{\mathrm{R}}(t). \tag{2.23}$$

$C_P(t)$ represents the plasma concentration of radioligand at time t, while $C_T(t)$ and $C_R(t)$ are instantaneous quantities denoting radioactivity concentration in the target and reference region, respectively. The subscript R refers to kinetic parameters of the reference region, while the subscript a refers to an 'apparent' kinetic parameter. By assuming that the distribution volume of the nonspecifically bound tracer is the same in the reference and target region, the following equations can be derived:

$$V_{ND} = \frac{K_1}{k_2} = \frac{K_{1R}}{k_{2R}}, \tag{2.24}$$

$$V_T = \frac{K_1}{k_2}\left(1 + BP_{ND}\right) = \frac{K_1}{k_{2a}}, \tag{2.25}$$

$$k_{2a} = \frac{k_2}{1 + BP_{ND}}. \tag{2.26}$$

If we define $R = \frac{K_1}{K_{1R}} = \frac{k_2}{k_{2R}}$, we get the following linear reference tissue model:

$$C_T(T) = RC_R(T) + k_2 \int_0^T C_R(t)\,dt - k_{2a} \int_0^T C_T(t)\,dt. \tag{2.27}$$

Expression (2.27) is similar as the multilinear reference tissue model (MRTM) (Ichise et al. 2003) and computationally efficient for voxel-wise estimation of BP_{ND} image data. On the other hand, BP_{ND} is the only achievable quantitative endpoint. Therefore, model validation using full kinetic modeling is essential, especially if non-displaceable tracer uptake could be affected by brain-penetrating radiometabolites or disease-related permeability changes of the blood–brain barrier. Selection of the appropriate reference tissue should be supported by histology data and in vivo preclinical imaging. PET imaging after pre-dosing with a blocking agent which selectively binds to the same target with high affinity and is nontoxic at higher doses can confirm the choice for a specific brain region as reference tissue and can verify whether non-displaceable tracer uptake is similar for reference and target regions.

2.2.3.4 Model Selections

The choice of a specific model configuration is governed by various factors including the properties of the tracer. To facilitate quantification, radiotracers need to have appropriate chemical characteristics (Pike 2016).

If the tracer is inert and does not interact with any receptor system or does not undergo any chemical change but simply diffuses into and back out of the cells, a 1TCM would be an appropriate model. If a 1TC is not appropriate, the reversibility of a tracer or in other words the retention of the tracer in the target tissue must be considered prior to choosing the model configuration. Reliable estimates of receptor levels in the brain require both uptake and washout phases of the tissue

TAC. Therefore, the tissue clearance of the tracer must typically be matched with the half-life of the radionuclide. This tissue clearance rate is in part determined by the affinity of the tracer and the receptor density. Ligands with higher affinity targeting a rather dense population of receptors tend to stick longer to the target molecules such that washout is delayed beyond the usable measurement time of the radionuclide. If the affinity is such that the radioligand shows very modest washout from the brain during the course of the PET measurement, then the washout rate cannot be determined reliably, and critical kinetic data are unavailable to calculate tissue macro-parameters distribution volumes V_T, BP or BP_{ND}. In terms of transport rate constants, known as micro-parameters, this means that a reliable estimation of the k_4 parameter describing the conversion from the tracer trapped in the bound state back to the nonspecific state is not feasible. In this case and in cases where the tracer is metabolized and the metabolized state is retained in the brain tissue, the tracer can be considered to bind irreversible, and k_4 can be set to zero. Instead of V_T, BP or BP_{ND}, the influx rate constant K_i, also named metabolic rate, trapping rate or accumulation rate constant, can be considered as an endpoint. K_i is defined as

$$K_i = K_1 \frac{k_3^*}{k_2^* + k_3^*}. \tag{2.28}$$

This assumption is, for instance, valid for measuring energy metabolism with 2-fluoro-2-deoxy-d-glucose labeled with the fluorine radioisotope ^{18}F (^{18}F-FDG). The substance is a glucose analogue that is trapped in brain tissue by being metabolized in the mitochondria to FDG-6-PO4 by the hexokinase enzymatic action. For a PET measurement time of less than 1 h postinjection, dephosphorylation (k_4) of the FDG-6-PO4 is not observed, and the assumption that $k_4 = 0$ is valid.

For radioligands with irreversible kinetic behaviour, late static scanning can be considered (as is common for ^{18}F-FDG PET), while these radioligands often provide high specific to nonspecific tracer concentration ratios. However, a high affinity in terms of a large k_3^* means that influx rate constant K_i becomes proportional to K_1 and thus dependent on tracer transport rate from the blood to the brain tissue. This way, K_i becomes less dependent of the parameter of interest k_3^* and therefore less sensitive to changes in binding site density. On the other hand, the slower equilibrium due to the slower irreversible kinetics of high-affinity tracers imposes longer PET acquisition times to quantify potential changes in binding density as accurate as possible. However, quantification can be confounded by radiometabolites entering the brain tissue. Many tracers currently used for imaging studies produce to some extent lipophilic metabolites. However, the quantities produced or their kinetics for passing the blood–brain barrier are such that they do not commonly confound the PET measurements. In cases where uptake and washout of the parent tracer are fast relative to the production and accumulation of radio-metabolites in plasma, their component of the total measured activity may be negligible during the imaging study. However, for longer PET acquisition times, lipophilic radiometabolites may enter the brain in sufficient concentration to confound the PET signal. In this context, preclinical micro-PET data of mice and rodents can provide

useful information about tracer characteristics in terms of metabolization, kinetics and nonspecific and (ir)reversible binding (De Laat et al. 2015) and prove to be a helpful tool in selecting the best possible tracer candidate for a specific target (Celen et al. 2010).

Although tracer characteristics can determine the compartmental model that best describes the in vivo process, biologically accurate models may not be practical. A model with higher complexity may be more accurate biologically but may have too many parameters, and hence it would be impossible to accurately estimate all of the model parameters. Some models might work when statistical noise is low but yield multiple solutions for high noise cases. Thus, model simplification may be required, and some bias in parameter estimates will need to be allowed in order to obtain better precision. A number of configurations might have to be tested before choosing an appropriate model.

2.2.4 Graphical Analysis Methods

As described before, coupled linear differential equations formalize the exchange of substances between the compartments. Kinetic parameters can be estimated by fitting an analytical solution of these differential equations to the measured dynamic PET data. However, nonlinear fitting procedures are needed which are quite time-consuming and therefore of limited use to estimate the kinetic parameters on a voxel-by-voxel basis. However, the coupled differential equations can be reformulated in a linear form by transforming the arterial plasma data and measured dynamic PET data. Using this approach the transfer rate constant is in general not estimated separately, but information is restricted to the level of distribution volume V_T or metabolic rate K_i. Both are rearrangements of the analytical solutions, resulting in a straight line after a certain time t^* where the slope is either V_T (for reversible tracers) using the Logan method (Logan et al. 1990) or K_i (for irreversible tracers) using the Patlak method (Patlak et al. 1983) (Fig. 2.4). On the x- and y-axes in the graph are different ratios of the measured radioactivity concentration in tissue and plasma and their integrals, depending on the method in question.

On the other hand, a linear mathematical model, meaning that there is direct proportionality between model variables and measured data, allows optimal estimates to be computed directly in one iteration using linear regression. Consequently, these linear least-squares fitting methods are computationally very efficient and therefore very convenient for generating voxel-wise parametric image data. Moreover, graphical methods rely on the area under the curve of the measured data. Since, for a bolus injection the peak contribution to the total area under the curve is limited while the tails of TACs are generally well estimated, these approaches are less sensitive to inaccuracies in peak estimation.

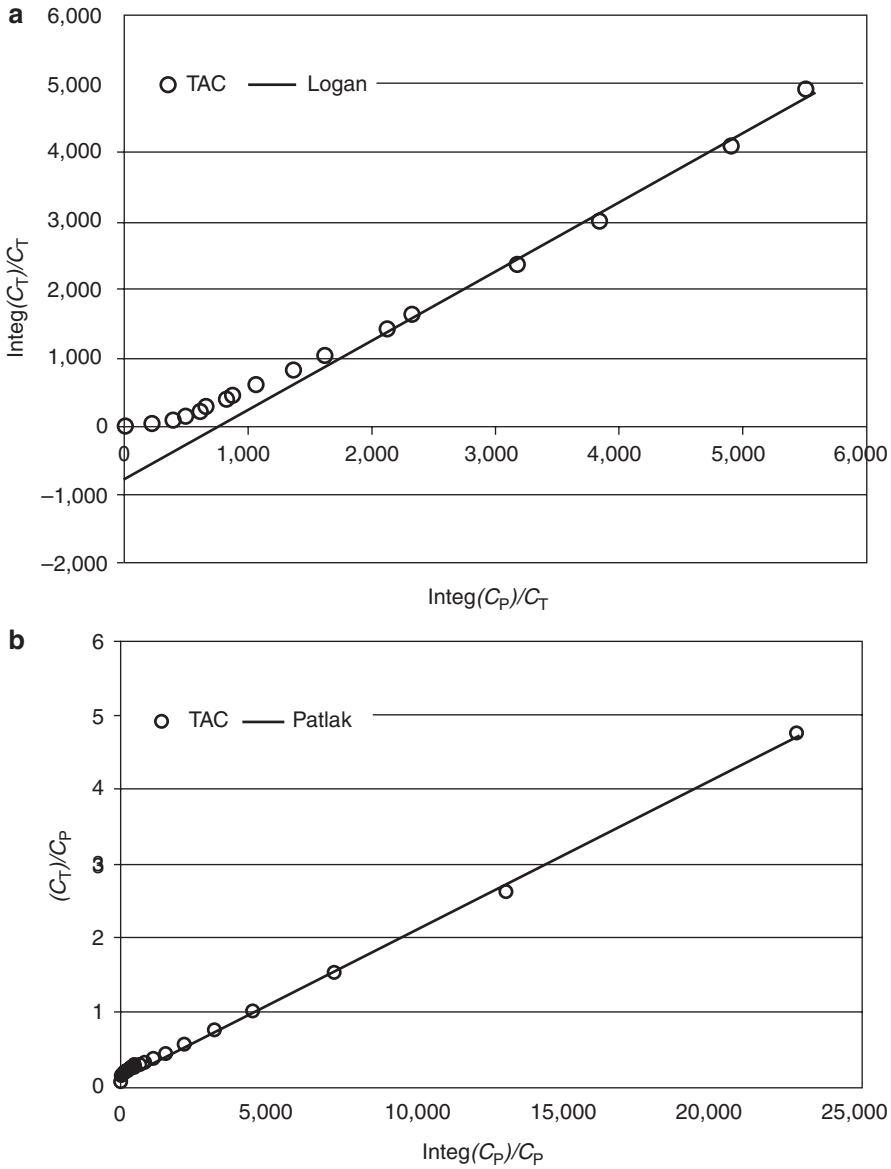

Fig. 2.4 (**a**) Logan plot for whole-brain TAC of [^{11}C]verapamil using an arterial input function corrected for metabolites. (**b**) Patlak plot for whole-brain TAC of [^{11}C]5-HTP in a rodent brain using an arterial input function corrected for metabolites

2.2.5 Semiquantitative Methods

The compartmental and graphical analysis methods so far discussed all required dynamic PET scanning, starting at the time of injection (Fig. 2.2b), in some case until to several hours. However semiquantitative estimates of the tracer uptake can be estimated using summation of time frames over a specified time window or for shorter time windows, resulting in a static image and representing an average radioactivity concentration over the summation window time interval. One approach is to normalize the measured radioactivity concentration to subject body weight and the amount of administered radioactivity, resulting in a standardized uptake value (SUV) (2.29) (Thie 2004), or when a reference region is available SUV ratio (SUVR), which essentially is the ratio of uptake in a target region (cortex) to uptake in a reference tissue (usually the cerebellum):

$$\mathrm{SUV}(T) = \frac{C_{\mathrm{PET}}(T)}{\dfrac{\text{Injected Dose}}{\text{Weight}}} \tag{2.29}$$

The SUVR may however be dependent on the time window for which it is estimated, if the target and reference regions do not exhibit the same tracer washout rate, and it is therefore crucial that it is properly validated against kinetic modeling before use (Lammertsma 2017). At a certain time point in the tracer kinetics, called the transient equilibrium, the SUVR is directly correlated with the BP_{ND} (Salinas et al. 2015), though this cannot be assumed to be the general case.

If, during a certain time interval of the dynamic PET data, the tracer concentration in brain tissue is in equilibrium with the tracer concentration in plasma, the SRTM can be further simplified, and the DVR of target tissue relative to reference tissue as index for specific binding can be approximated by the SUVR of the target region relative to the reference region:

$$DVR = \frac{V_{\mathrm{T}}}{V_{\mathrm{R}}} \cong \frac{C_{\mathrm{T}}(T)}{C_{\mathrm{R}}(T)} \cong \frac{C_{\mathrm{T,PET}}(T)}{C_{\mathrm{R,PET}}(T)} = \frac{\mathrm{SUV}_{\mathrm{T}}(T)}{\mathrm{SUV}_{\mathrm{R}}(T)} = \mathrm{SUVR}(T). \tag{2.30}$$

As an example, SUVR relative to the cerebellum have been used to quantify the brain retention of the amyloid ^{11}C-Pittsburgh compound B (Van Berckel et al. 2013). However, this approximation needs validation with full kinetic modeling for each tracer separately.

2.2.6 Neurotransmission Quantification

Recent developments have provided evidence for the feasibility of imaging endogenous neurotransmitters such as serotonin, opioid and dopamine release, and this is an area that has the potential of expanding into other neurotransmitter systems (Ceccarini et al. 2020). Neurotransmission responses encode important information

that may be relevant for understanding psychiatric disease such as schizophrenia and drug addiction. The theory relied on the hypothesis that a stimulus increases the firing rate of the involved neurons, leading to a release of endogenous neurotransmitter in the synaptic level with a measurable effect on the PET kinetics. The standard methodology to quantify neurotransmitter release is indexed as the fractional reduction in the radiotracer BP_{ND} following a specific (cognitive or pharmacological) stimulus (post-stimulus, BP_{NDpost}) compared to the baseline BP_{ND} (BP_{NDpre}) (2.31):

$$\Delta BP_{ND} = \frac{\left(BP_{NDpost} - BP_{NDpre}\right)}{BP_{NDpre}} \tag{2.31}$$

This approach has been normally used with ^{11}C-raclopride, ^{11}C-CIMBI-36 and ^{11}C-carfentanil PET, to quantify respectively endogenous dopamine (Wai et al. 2019; Zakiniaeiz et al. 2019), serotonin (Erritzoe et al. 2019) and opioid release (Turton et al. 2018) before and after the administration of drugs such as cannabis, methylphenidate and amphetamine. Traditional models that estimate BP_{ND} do not contain explicit functions to describe short-lived neurotransmitter responses.

In 1995, both Fisher et al. (Fisher et al. 1995) and Morris et al. (Morris et al. 1995) advanced the possibility to use dynamic PET data to detect dynamic changes in receptor binding or receptor occupancy occurring during pharmacological and activation studies. This idea was then extended to using PET to reveal transient alterations caused by endogenous or exogenous competing binding compounds, as long as the PET tracer fulfills the pharmacokinetic characteristics set forth by Morris et al. (Morris et al. 1995). Several methods have been proposed to analyse neurotransmission system under non-steady-state regime, such as the linear extension of the SRTM, called LSRTM or LSSRM (Alpert et al. 2003), and the linear parametric neurotransmitter PET (lp-ntPET) (Normandin et al. 2012), and used for the analysis of actual animal and human studies.

LSSRM is based on the MRTM expression (2.27), where R, K_2 and K_{2a} are time-dependent parameters. The α, β and γ parameters are linear terms in the model and were introduced to accommodate temporal changes in the R, K_2 and K_{2a} parameters, respectively, by assuming a time dependence form of $R + \alpha \cdot h(t)$, $k_2 + \beta \cdot h(t)$ and $k_{2a} + \gamma \ldots h(t)$. The coefficient γ represents the amplitude of the ligand displacement, and the function $h(t) = e^{-\tau(t-T)}$ describes the rapid change after task onset and dissipation over time, where τ controls the rate at which activation effects die away and T indicates the timing of stimulus initiation. Figure 2.5a shows a representative example of voxel-based parametric images of the kinetic parameters k_2, k_{2a}, R and γ directly fitted with LSSRM. In addition, the covariance image SD(γ) parametric images is used to generate voxel-wise T-statistic maps of γ parameter [$T = \gamma/\mathrm{SD}(\gamma)$] (see Fig. 2.5b). The LSSRM method has been applied to detect striatal and extrastriatal dopamine release in humans during stress and reward tasks (Ceccarini et al. 2012; Lataster et al. 2011, 2014). To characterize the time course of the competing compound, an extension of the LSSRM model (the lp-ntPET) was developed by using gamma variate functions spanning a wide range of feasible shapes, times of onset and duration (Normandin et al. 2012). Kim et al. revealed for the first time that

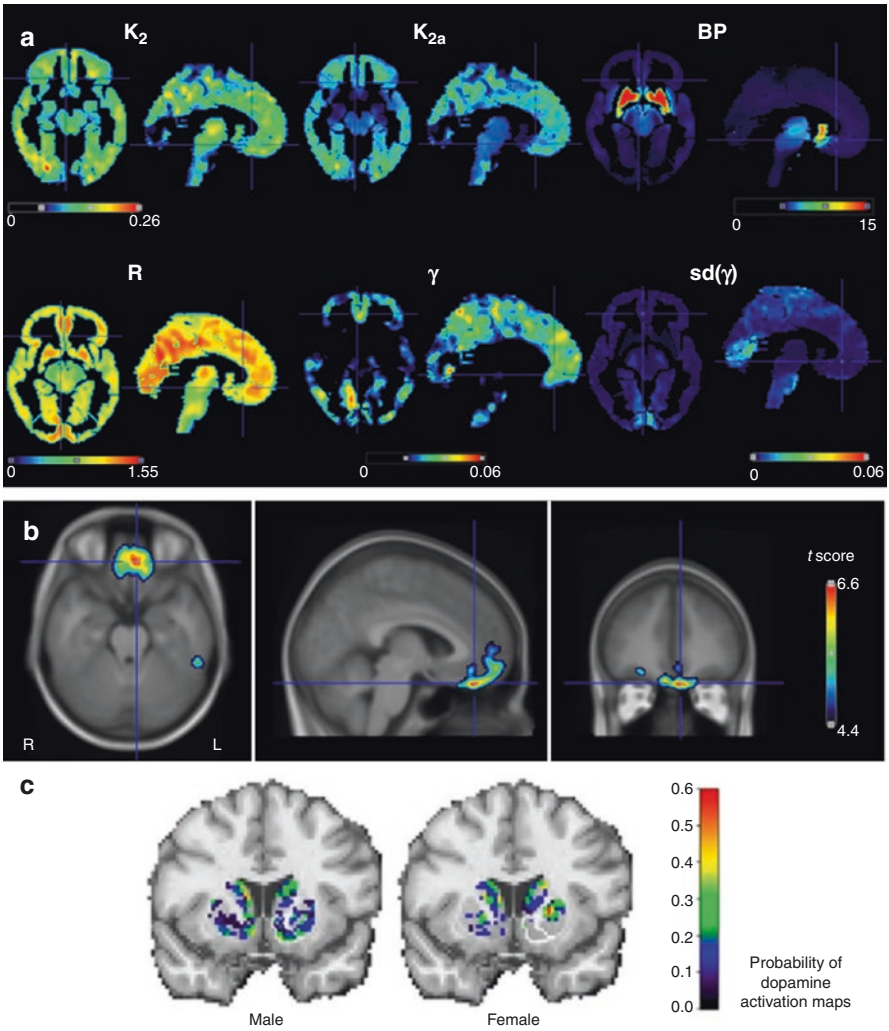

Fig. 2.5 (**a**) Example of k_2, k_{2a}, BP_{ND}, R, γ and SD(γ) parametric images calculated by LSSRM for an healthy control performing a reward task (Ceccarini et al. 2012). (**b**) Average statistical parametric T map of γ in transverse, coronal and sagittal sections overlaid on T1-weighted MRI template, showing significant bilateral reward-induced ^{18}F-fallypride displacement (hence dopamine release) in medial orbitofrontal cortex, ventromedial prefrontal cortex and dorsal anterior cingulate cortex (Ceccarini et al. 2012). (**c**) Probability of dopamine activation maps during smoking for male and female smokers calculated by lp-ntPET. Difference in activated voxels between male and female was observed in the right ventral striatum (modified from Cosgrove et al. (2014))

different temporal patterns were involved in the dopamine response to smoking using the more advanced lp-ntPET method to analyse ^{11}C-raclopride PET data of subjects smoking cigarettes during the acquisition (Cosgrove et al. 2014; Kim et al. 2014) (Fig. 2.5c).

2.3 News in Neuropsychiatric Research Using Hybrid PET/MRI

With the current availability of hybrid PET/MRI scanners, there is an increasing interest in the measurement of endogenous neurotransmitter release. These could potentially allow for simultaneous assessment of functional response using fMRI and neurotransmitter concentration changes using PET during activation paradigms, therefore providing a hitherto unprecedented possibility to study neurotransmission dynamics (Sander et al. 2019). Indeed, besides some of the more intuitive (methodological) advantages of simultaneous PET/MR acquisitions, such as PET motion and PVE correction, PET IDIF estimation, PET/MRI dosimetry, patient convenience and improved anatomical localization of PET data, there are biological considerations that favour simultaneous acquisitions of PET and MR-based signals (Cecchin et al. 2017; Streeter Barrett et al. 2019).

The real revolution and opportunity offered by PET/MRI consists in the possibility to investigate brain physiological rewarding processes unfold in space and time, hence in the same physiological or pharmacological conditions, well beyond the capability of each of the two modalities alone and reducing those factors that might increase interscan and intersubject variability obtained with two different scanning days. Dynamic changes in dopamine neurotransmission are also known to contribute to blood oxygenation level-dependent and cerebral blood volume (CBV) changes. Also, although MR is the most established imaging modality for in vivo investigating relationship between cerebral regions at different scales, the recent advent of hybrid PET/MRI scanners paved the way for more comprehensive investigation of the relationship of brain organization (connectivity) and physiological processes (Aiello et al. 2016). Different PET/MR studies have been recently performed to understand the dynamic contributions of neurotransmitter systems to the fMRI response using PET/MR (Sander et al. 2013). Much of Sander's group work has focused on establishing the contribution of the dopaminergic system to CBV and the fMRI response, suggesting that the haemodynamic response is directly linked to $D_{2/3}$ receptor occupancy by neurovascular coupling mechanisms. Subsequent studies have used this relationship to understand the mechanisms of dopaminergic receptor agonism (quinpirole) (Sander et al. 2015). In another study, Wey et al. (Wey et al. 2014) examined the opioidergic pain system using simultanoues fMRI/PET with ^{11}C-diprenorphine. Co-localized fMRI and PET signal changes in the thalamus were positively correlated suggesting that pain-induced changes in opioid neurotransmission contribute a significant component of the fMRI signal change in this region. In summary, while the use of simultaneous PET/MR to understand dynamic neurotransmitter changes during brain function is still in its infancy, preliminary results show great promise for the technique to inform comprehensive models of brain function beyond the traditional haemodynamic-based functional imaging methods.

In conclusion, in clinical (neuropsychiatric) research studies, neuroreceptor PET/(f)MRI will play an important role to elucidate the mechanisms underlying brain function and dysfunction in both health and disease condition, to characterize different drug-dosing effects and to investigate the functional effects of hyper- or hypo-neurotransmitters tone in neuropsychiatric disease.

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3 The Role of P-Glycoprotein at the Blood–Brain Barrier in Neurological and Psychiatric Disease

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Contents

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Abstract

P-glycoprotein, also known as ABCB1, is an efflux transporter located at endothelial cells of the blood–brain barrier and plays an important role in protecting the brain parenchyma from various neurotoxic substances. These substances are transported across the blood–brain barrier and are called 'P-gp substrates'. A broad range of P-gp substrates with a great degree of structural diversity exists. In this chapter we discuss the current state of knowledge about this interesting transporter with a special focus on the influence of P-gp on the tissue distribution of pharmaceuticals and drug resistance and the role of changes in P-gp function in psychiatric and neurological disorders.

Abbreviations

ABC transporters	ATP-binding cassette transporters
AD	Alzheimer's disease
ATP	Adenosine triphosphate
Aβ	Amyloid-beta
BBB	Blood–brain barrier
BCRP	Breast cancer resistance protein
CBF	Cerebral blood flow
CNS	Central nervous system
DDI	Drug–drug interactions
GIT	Gastrointestinal tract

JAM	Junctional adhesion molecules
LRP1	Low-density lipoprotein receptor-related protein-1
MRI	Magnetic resonance imaging
MRP	Multidrug resistance-associated protein
MSD	Membrane-spanning domain
NBD	Nucleotide-binding domain
NHP	Non-human primate
PET	Positron emission tomography
P-gp	P-glycoprotein (permeability glycoprotein)
SPECT	Single photon emission computed tomography
SUV	Standardized uptake value
TEER	Transepithelial/endothelial electrical resistance
V_T	Volume of distribution

3.1 Introduction

The human brain requires a strict homeostatic environment. The blood–brain barrier (BBB) protects the brain from neurotoxic substances and plays an important role in maintaining homeostasis as it functions as a biochemical and physical barrier (Hawkins and Davis 2005). The BBB was first described approximately 100 years ago by Paul Ehrlich, who discovered that a dye injected in the peripheral blood circulation did not reach the spinal cord and the brain (Ehrlich 1885) and concluded some sort of barrier between the peripheral circulation and the brain must exist. Later it was discovered that this 'sort of barrier' is a chemical and biochemical structure composed of the following five parts: endothelial cells, pericytes, immune cells, astrocytes and a basement membrane. These parts provide a robust barrier between the peripheral blood and the brain. Transport across the BBB is only possible through passive diffusion or through active efflux and influx which involve complex transport systems (Serlin et al. 2015). Three main subcategories of transporters at the BBB exist: carrier-mediated transporters, receptor-mediated transporters and active efflux transporters, including ATP-binding cassette transporters (ABC transporters). ABC transporters protect the brain against various lipophilic xenobiotics and other potential harmful compounds by ATP-dependent efflux across the endothelial cell membrane to the extracellular space. The seven known classes (A–G) of ABC transporters comprise a total of 48 different transporter proteins. P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and multidrug resistance-associated protein 1 (MRP1) are the main ABC transporters found at the BBB, and of these three, P-gp is the most studied and characterized.

In this chapter an overview of the main cell types and transporters of the BBB will be given. Subsequently, we will focus on the function of P-gp and other efflux transporters. It is possible to measure the function of P-gp in vivo using PET and SPECT imaging. The tracers used to evaluate the function of P-gp will be discussed and described. The role of P-gp in several psychiatric and neurological disorders as

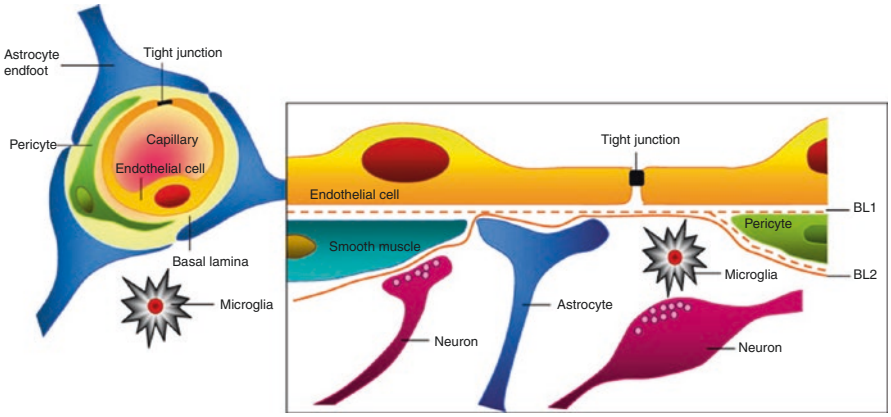

Fig. 3.1 The blood–brain barrier. Reprinted with permission from Abbott NJ, Patabendige AAK, Dolman DEM, Yusof SR, Begley DJ. Structure and function of the blood–brain barrier. Neurobiol Dis. 2010

schizophrenia, depression and Alzheimer's disease is not yet fully clear. In this chapter, an overview of recent and earlier literature will be presented.

3.2 Architecture of the BBB

3.2.1 Endothelial Cells

Brain endothelial cells are squamous epithelial cells that form the wall of cerebral blood vessels. Cerebral endothelial cells differ phenotypically of any other endothelial cells in the human body. They have some unique properties that allow them to strictly regulate the movement of ions, molecules and cells across the BBB. These properties and the presence of tight junctions, which are located between these cells, make free membrane diffusion across the BBB almost impossible (see Fig. 3.1) (Pardridge 1998).

3.2.2 Tight Junctions

The most unique feature of the BBB is the presence of tight junctions. Tight junctions can be found between the cerebral endothelial cells and are responsible for the high transendothelial electrical resistance and low paracellular permeability. They are formed by many different transmembrane proteins, such as junctional adhesion molecules (JAM-A, JAM-B, JAM-C), occludin and claudins (claudin-3, -5, and -12), as well as cytoplasmic proteins (Pereira et al. 2017). The function of tight junctions is regulated by modification, relocation and degradation of these proteins (Stamatovic et al. 2016). The claudins, for example, are responsible for the high transepithelial/

endothelial electrical resistance (TEER) of the BBB. Occludin plays a secondary role in regulating and supporting the tight junctions and is not essential for their formation (Wolburg and Lippoldt 2002).

3.2.3 Pericytes

Pericytes are mural cells embracing the brain micro-vessels and capillaries. They can be found close to astrocytes and neurons in the basement membrane and are involved in many vascular functions. They play as part of the neurovascular unit a role in angiogenesis, maintenance of the permeability of the BBB, regulation of blood flow in response to neuronal activity and trafficking of immune cells (Armulik et al. 2010). In various studies the involvement of pericytes in the formation of the BBB during development and the maintenance of its function in adulthood and ageing was demonstrated. Mouse embryos with a deficiency of pericytes could not form an intact BBB and showed an abnormal formation of tight junctions, an increase in endothelial cell vesicular trafficking and infiltration of immune cells in the central nervous system (Daneman et al. 2010; Armulik et al. 2011). Despite many studies concerning pericytes and their properties and function, there are still many remaining questions. For example, it is still unknown whether there are different subsets of pericytes that may have different functions. The identification of new pericyte-specific markers can possibly be helpful in answering this question (Jiang et al. 2018).

3.2.4 Astrocytes

Astrocytes are star-shaped glia cells that cover the exterior of the basement membrane and interact with pericytes and microvascular endothelial cells. They form the connection between neuronal signalling and the CNS vasculature. Astrocytes have specific anatomical structures, called astrocyte end-feet. These end-feet extend from the cell body and cover 80–99% of the basement membrane surrounding endothelial cells and pericytes of the CNS microvasculature, facilitating paracrine interactions between the cells (Herndon et al. 2017). The astrocyte end-feet also extend towards the neurons, which makes bidirectional signalling between neurons and the vasculature possible, leading to coordination of the blood flow with neuronal activity. One of the most important regulatory functions of astrocytes occurs in an inflammatory state. Through regulation of matrix metalloproteinase, they control breakdown of the basement membrane and make it possible for immune cells to cross the BBB and enter the brain (Cabezas et al. 2014).

3.2.5 Microglia

Microglia are related to monocytes and macrophages in morphological, immunophenotypical and functional ways. At the blood–brain barrier, two types of

microglia can be found: the perivascular cells enclosed in the basal lamina and the juxtavascular microglia, which represent the intraparenchymal resident microglia. They both play an important role in the immune response and in maintaining a homeostatic environment in the brain (Brioschi et al. 2019). As a key innate immune effector of the CNS, they can be found in 'resting' and 'active' state. The function of microglia in resting state and the factors that keep them in this state are still unknown. In response to injury, the microglia in resting state can rapidly convert to the active state, in which they can release various mediator substances, which also include cytotoxic compounds such as nitric oxide and inflammatory cytokines (Gehrmann et al. 1995).

3.2.6 Neurons

Neurons are cells of the CNS responsible for intracellular communication. They are able to make specific contacts with multiple other neurons. Connected neurons connected form so-called circuits into a neuronal network that transmits and processes information. Neurons are excitable cells, which means they generate electrical signals to communicate. Besides generating electrical signals, neurons also communicate via secretory products called neurotransmitters. Neurotransmitters are released in restricted regions of the extracellular space, called synapses (Daneman and Prat 2015).

3.2.7 Neurovascular Unit

The BBB is part of the so-called neurovascular unit (NVU), which is a dynamic structure regulated by pericytes, astrocytes and other additional regulatory cells such as neurons, microglia and peripheral immune cells (Hawkins 2005). The cells in the neurovascular unit maintain dynamic interactions with each other playing a significant role in cerebrovascular function (McCarty 2005; Ballabh et al. 2004). The most prominent function of the neurovascular unit is to regulate transport and diffusion properties of brain capillary endothelial cells, composing the BBB (Staddon and Rubin 1996). Understanding the function and the mechanisms of the neurovascular unit is an important key to the understanding of the function of the brain in physiological and pathophysiological conditions, and therefore there is a growing interest in exploring the NVU concept.

3.3 Transport across the BBB

There are two main pathways through which molecules can cross the BBB: the paracellular and the transendothelial pathway. The paracellular route, also called the junctional route, is restricted by interendothelial tight junctions with an estimated

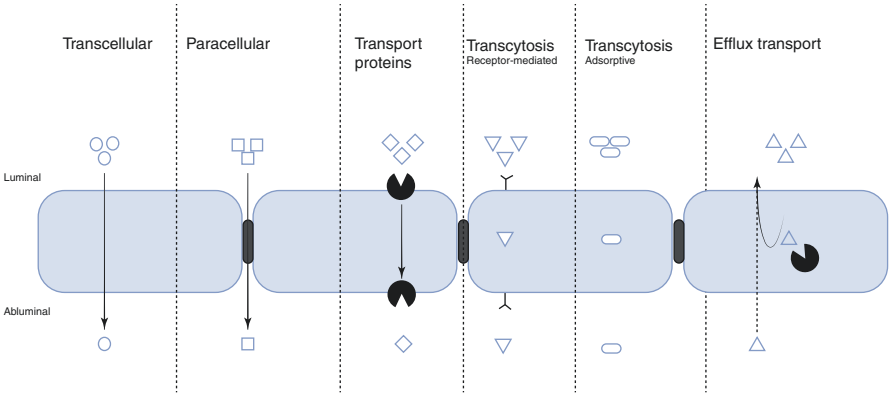

Fig. 3.2 Transport mechanisms across the BBB

gap size of approximately 1.4–1.8 nm (Furtado et al. 2018). This small gap size makes paracellular transport of BBB endothelial cells under physiological conditions almost impossible. The only exception is found in particles <1 nm in diameter, which may cross the BBB through water-filled intracellular spaces called 'pores'. Larger molecules must take some sort of transcellular or transendothelial route to cross the barrier. The transendothelial route, in which molecules cross the BBB through endothelial cells, consists of three distinct transport systems (see Fig. 3.2). Small lipid-soluble molecules can cross the brain endothelial cells through passive diffusion, when their molecular weight does not exceed 400 Da, and they can form less than eight hydrogen bonds (Pardridge 2012). For larger molecules diffusion is not possible, and transport is restricted to endogenous catalysed transport systems on the capillary membrane, e.g. carrier-mediated transport, receptor-mediated transport or active efflux as mediated by P-gp (Furtado et al. 2018).

3.3.1 Carrier-Mediated Transport

Carrier-mediated transport is a selective form of transport for small molecules and finds place through protein carriers expressed by the brain endothelial cells at the luminal side. The binding of the molecule to a protein carrier or transporter leads to a conformational change in the transporter, which is followed by transport of the compound to the other side of the membrane. Carrier-mediated transporters can be divided in two major groups, namely, the facilitated diffusion transporters that carry their compounds in the direction of the concentration gradient and active transporters, which transport their compound in the opposite direction against the concentration gradient. Besides this, transport can be either uni- or bidirectional. Examples of well-known carrier-mediated transporters include the GLUT1 transporter, the organic anion transporter OAT and the large neutral amino acid transporter (LAT1) (Pardridge 1998; Tsuji 2005).

3.3.2 Receptor-Mediated Transport

Although small nutrient molecules can use carriers and transporters to cross the BBB, this is not possible for larger macromolecules as growth factors, enzymes and plasma proteins. Such polypeptide ligands require binding at a specific receptor at the plasma membrane of endothelial cells to cross the BBB. The binding leads to uptake of the compound into a vesicle, which subsequently crosses the BBB by endocytosis or transcytosis. Endocytosis can occur via clathrin-mediated and caveolin-mediated pathways or via alternative routes, such as lipid raft internalization. Examples of receptors involved in receptor-mediated transport across the BBB are the insulin receptor, the transferrin receptor and the low-density lipoprotein receptor 1 and 2 (LRP 1 and 2). Since receptor-mediated transport makes it possible for macromolecules to cross the BBB, transport with the use of this kind of receptors seems to be a promising method of drug delivery to the brain.

3.3.3 Active Efflux Transporters

Active efflux transporters play an important role in preventing many (toxic) compounds from reaching the brain. They can be found at the luminal and at the abluminal side of the BBB endothelial cells. The most studied and best known group of active efflux transporters is the ATP-binding cassette transporters (ABC transporters) superfamily, which is primarily responsible for the ATP-dependent efflux of a large number of compounds. Among the transporters in this superfamily, P-gp, termed multidrug resistance protein 1 (MDR-1), is the best known and characterized and is the efflux transporter with the highest expression at the BBB.

3.3.4 Cerebrovascular Enzymatic Characteristics of the BBB

Although the BBB is composed of an almost impermeable barrier of endothelial cells and tight junctions, some exogenous molecules may cross this physical barrier and enter the brain. In those cases, cerebrovascular enzymes as monoamine oxidase and cytochromes P450 (CYP450s) are present to metabolize and inactivate those potentially neurotoxic compounds and prevent their accumulation in the brain. In addition to the cerebrovascular enzymes, the plasma membranes of endothelial cells, pericytes and astrocytes are covered with various peptidases, nucleotidases, cholinesterases and other ectoenzymes (Zlokovic 2011) that have protective functions.

3.4 P-Glycoprotein

P-gp, also known as multidrug resistance protein 1 (MDR1) or ABCB1, was the first ABC transporter described and is until now the most studied and characterized transporter of this family. It is located at the luminal side of endothelial cells in brain

capillaries, at the BBB and the blood-CSF barrier, and protects the brain from neurotoxic substances by facilitating the efflux of those substances back into the blood (Raaphorst et al. 2015a). P-gp was first described by Juliano and Ling in 1976, who found this glycoprotein in ovary cells of Chinese hamsters resistant to colchicine (Juliano and Ling 1976). Besides the localization in the brain, P-gp can be found at the barrier of the jejunum, the colon, the adrenal cortex and the liver (Thiebaut et al. 1987; Sugawara et al. 1988). P-gp has a very broad substrate specificity and transports hundreds of structurally divergent drugs and peptides. This efflux pump strongly affects the uptake of antidepressants and antipsychotic drugs in the brain (Linnet and Ejsing 2008). Its impressive capability to transport an extensive variety of structurally divergent compounds makes P-gp an interesting molecule.

3.4.1 Localization and Function of P-gp

P-gp is the product of the human MDR1 gene which is localized on chromosome 7q21. It is a 170 kD protein built of 1280 amino acids and is expressed as a single chain with two homologous parts (Ambudkar et al. 2003). At the intracellular side of these homologous parts, six transmembrane helices (TM) and two ATP nucleotide-binding domains (NBDs) encoded by a relatively hydrophilic intracytoplasmic loop are present (Aller et al. 2009). Translational and rotational motions find place during P-gp-mediated efflux. Once a substrate or inhibitor enters the different binding domains, changes of P-gp start at the nucleotide-binding site. Binding of ATP to the NBD and dimerization of NBD is thought to be responsible for the function of P-gp. The energy of ATP causes changes in the transmembrane helices. The subsequent efflux of the substrate through the TMD and lipid bilayer will also be catalysed by this energy. There are three models to describe the exact transport mechanism of P-gp (see Fig. 3.3). In the flippase model, the P-gp substrate interacts with the membrane before it interacts with the transporter (Higgins and Gottesman 1992). In the hydrophobic vacuum cleaner model, P-gp is able to efflux the substrate directly from the inner leaflet to the extracellular space (Raviv et al. 1990). In the pore model, the substrate interacts with P-gp in the cytosol, followed by efflux of the substrate via protein channels (Hoosain et al. 2015).

3.4.2 Avid and Weak Substrates of P-gp

Compounds interacting with P-gp can behave as substrate, inhibitor, inducer or activator. Substrates are compounds that are transported by P-gp. Inhibitors are able to decrease, and inducers and activators can increase the function of P-gp. A single chemical compound may exert different actions, depending on the administered dose.

P-gp is known to efflux various structurally different substrates. The mechanisms of substrate recognition by P-gp are still unclear. However, the molecules of all P-gp substrates have both hydrophilic and hydrophobic moieties (Liu 2019a). P-gp

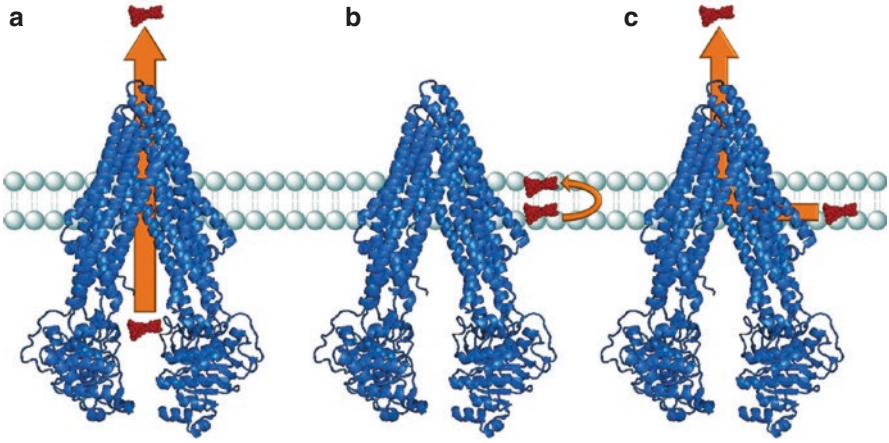

Fig. 3.3 Transport mechanisms of P-gp. (**a**) Hydrophobic vacuum cleaner model, (**b**) pore model and (**c**) flippase model. Reprinted with permission from Raaphorst R, Windhorst A, Elsinga P, Colabufo N, Lammertsma A, Luurtsema G. Radiopharmaceuticals for assessing ABC transporters at the blood–brain barrier. Clin Pharmacol Ther. 2015;97:362–371

substrates can be divided in weak and avid substrates. Since the major part of clinically used CNS-active pharmacotherapeutics are weak P-gp substrates, understanding brain distribution of weak substrates is an important topic of research. Since substrates of P-gp can be labelled with a radioactive compound and be used as PET tracer, there are tracers based on avid and weak substrates. The advantage of weak P-gp substrates as PET tracer is a higher uptake at baseline, which could make it possible to measure upregulation of P-gp function. [^{11}C]Metoclopramide was introduced and studied by Tournier et al. as a weak P-gp substrate for PET-imaging (Tournier et al. 2019a).

3.4.3 Inhibitors of P-gp

Bioavailability is an important parameter for the practical use of pharmaceuticals. Inhibition of intestinal and cerebral P-gp may improve the bioavailability of drugs that are P-gp substrates, which are used to treat epilepsy, depression and cancer. The action of P-gp can be inhibited by certain compounds in various ways. First, they can block the function of P-gp via disruption of the hydrolysis of ATP. Second, they can bind to P-gp at the drug-binding sites and may reversibly or irreversibly compete with substrates. Third, they can bind to an inhibitory site distinct from the substrate binding site. P-gp inhibitors are divided in three groups, first-, second- and third-generation inhibitors, depending on their specificity, affinity and toxicity (Liu 2019b). First-generation inhibitors are also P-gp substrates and, in order to inhibit the P-gp function, need to be administered in high concentrations. For this reason, side effects are frequent. Use of these substances as P-gp inhibitors in the clinic is

therefore undesirable. Second-generation inhibitors, on the other hand, demonstrate specific inhibition of P-gp, and their affinity for P-gp is higher. Third-generation inhibitors show an even higher specificity for P-gp compared with first- and second-generation inhibitors and also a lower toxicity. Most of the third-generation P-gp inhibitors have been tested in clinical trials, but unfortunately many of them failed for clinical use due to undesired drug–drug interactions, non-specific toxicity and high variability in response rate (Binkhathlan and Lavasanifar 2013). Since many of the third-generation P-gp inhibitors failed as therapeutic drugs, the aim in drug development is to search for a new, effective, non-toxic P-gp inhibitor that can be used in the clinic.

3.4.4 Inducers, Activators and Regulation of P-gp

An impaired function of P-gp can lead to accumulation of neurotoxic substances in the brain. Upregulation of P-gp could therefore be an interesting treatment method in brain diseases associated with accumulation of toxic proteins or other substances. In Alzheimer's disease, β-amyloid (Aβ) accumulates in the brain and plays a role in the pathogenesis. Since P-gp is known to be responsible for the transport of Aβ out of the brain, inducers of P-gp may play a significant role in the treatment of AD (Lam et al. 2001; Vogelgesang et al. 2002a; Jain et al. 2014). After exposure of mammals to toxic substances, upregulation of P-gp may prevent the accumulation of these substances in the brain (Silva et al. 2014a; Dinis-Oliveira et al. 2006). Many structurally different compounds were found to induce the expression of P-gp, including rifampicin, dexamethasone and St. John's wort (Silva et al. 2015). Inducers of P-gp cause alterations in the MDR1 gene, which consequently lead to an increased expression of P-gp. P-gp inducers can have many different chemical structures, since the transcription of MDR1 can be regulated by various routes and transcription factors, including pregnane X receptor (PXR), heat shock transcription factor 1, nuclear factor Y and early growth response protein 1 (EGR-1). The pregnane X receptor is a member of the orphan nuclear receptor subfamily acting as xenobiotic-sensing receptor (Kliewer et al. 2002). It is an important transcriptional regulator of P-gp which can be activated by diverse compounds including rifampicin, phenobarbital and mifepristone (Miller et al. 2008; Zhou 2008). Hartz and colleagues found that activation of PXR with pregnenolone-16α-carbonitrile in a mice model of AD restored the P-gp function, increased the transport activity and reduced Aβ levels in the brain (Hartz et al. 2010). Brenn and colleagues showed that the herbal compound St. John's wort (*Hypericum perforatum*) functions also as an inducer of P-gp and reduces Aβ accumulation in the brain of a transgenic AD mouse model (Brenn et al. 2014).

Upregulation of P-gp can also be caused by activators. An activator is a compound which binds to the P-gp transporter, leading to an alteration that stimulates transport of a P-gp substrate which is bound to another binding site (Silva et al. 2014b; Sterz et al. 2009). Shapiro and colleagues found by continuous fluorescence monitoring that Hoechst 33342 and rhodamine 123 are activators of P-gp (Shapiro

and Ling 1997). Since the activator mechanism increases the function of P-gp without alteration of protein expression levels, upregulation by activators occurs much more rapidly, compared to upregulation by P-gp inducers.

3.4.5 Non-P-gp-Mediated Efflux Transport at the BBB

P-gp is not the only member of the ABC-subfamily expressed at the blood–brain barrier. Other members of this family include multidrug resistance proteins (MRP1, -2, -4 and -5) and breast cancer resistance protein (BCRP), with a similar function and mechanism of action as P-gp (Zhang 2004). In humans, BCRP and MRP1 show high levels of expression at the BBB, which are nevertheless around 20-fold lower than the expression of P-gp (Slot et al. 2008).

3.4.6 BCRP

Similar to P-gp, the BCRP protein is an efflux transporter at the BBB which plays an important role in the transport of various compounds, including many pharmaceuticals. BCRP is located in many different tissues, such as the human intestine, liver, kidney, testis and placenta. BCRP is also expressed in breast and colorectal cell lines and in tumour tissue. BCRP seems to play a key role in neurodegenerative diseases as AD, ALS, epilepsy and PD. In a clinical study, a combined effect of P-gp and BCRP was noted in children suffering from lymphoblastic leukaemia treated with chemotherapy. The patients had an increased chance of encephalopathy when a specific combination of ABCB1 and ABCB2 polymorphisms was present, compared to patients who had a predisposing genotype for only one of the transporters (Erdilyi et al. 2008).

3.4.7 MRP Family and MRP-1

Transporters of the MRP family are localized at the blood–brain barrier and are ATP-dependent efflux proteins. The MRP transporters are less well-characterized than P-gp and BCRP, and their function is not yet totally unravelled, although it is known that the MRP family is responsible for the efflux of a diverse range of compounds among which are various xenobiotics and pharmaceuticals. Proteins in the MRP subfamily share common structural features, including multiple transmembrane helices in membrane-spanning domains (MSD) and intracellular NBDs for the binding of ATP. MRP-1 is the most studied and characterized MRP family member and is encoded by the ABCC1 gene on chromosome 16p13.1 In 1992, Cole and colleagues discovered that MRP1 has a role in multidrug resistance in a drug-selected human lung cancer cell line (Cole et al. 1992). Nowadays it is known that MRP1 does not only play a role in drug resistance but may also play a part in various inflammatory, immunological, cardiovascular and neurological diseases (Cole

2014). Because of its broad substrate specificity, MRP1 continues to be of considerable preclinical and clinical interest.

3.5 In Vivo Imaging of the P-gp Function

P-gp is thought to be involved in the pathogenesis of various neurodegenerative diseases and in drug resistance of various structurally different pharmaceuticals. Several research groups have studied the role of P-gp under physiological and pathophysiological conditions. To measure the function of P-gp in vivo, positron emission tomography (PET) and single-photon emission computed tomography (SPECT) can be used in combination with a radiolabelled substrate or inhibitor of P-gp, which will provide in vivo information about the functionality of P-gp (Kannan et al. 2009a). The first PET study to measure P-gp function was performed in 1998, and since then a range of radiopharmaceuticals have been developed and described in the literature (see Table 3.1) (Hendrikse et al. 1998a). Most of them are well-known substrates of P-gp, which are labelled with short-lived positron-emitting isotopes such as carbon-11 (half-life 20.4 min) or fluorine-18 (half-life 109.8 min). Besides substrates, inhibitors of the P-gp transporter can also be labelled and used as tracers for evaluation of P-gp function. However, a new P-gp tracer should meet the following criteria (Luurtsema et al. 2016; Kannan et al. 2009b):

- The ligand should be a selective substrate for P-gp and not a substrate for other ABC transporters (MRP1 or BCRP).
- The tracer should produce a good signal after blocking of the P-gp function.
- The tracer should generate none or only a few radioactive metabolites, which should not cross the BBB, since this will lead to a non-specific PET signal in the brain.
- The tracer should be sensitive enough to measure slight changes in P-gp function.
- The tracer should show a low binding potential to plasma proteins and blood cells.

After radiolabelling substrates or inhibitors of P-gp, the function of P-gp can be quantified in multiple manners: First, one can calculate the distribution volume (V_T) of the ligand, which will inversely reflect P-gp function. Further K_1, k_2 and the area under the curve (AUC) are parameters used to evaluate the function of P-gp. In physiological circumstances, the uptake of tracer in the brain will be low, since it will be directly transported out of the brain. In pathophysiological circumstances, when the function of P-gp is impaired, the uptake in the brain will be increased, since the tracer will be transported to a lesser extent out of the brain. In the clinic, PET imaging of ABC transporters may be important for the selection of medication in drug-resistant depression or schizophrenia and to identify subjects who are at risk of developing a (neurodegenerative) disease as, for example, Alzheimer's disease (Lubberink et al. 2007). In the next paragraph, existing tracers to measure P-gp function in vivo will be discussed.

Table 3.1 P-gp PET tracers

Tracer	Function	Studied
[^{11}C]Verapamil	Avid P-gp substrate	In vitro (Raaphorst et al. 2017) In vivo (mice, rats, NHP) (Hendrikse et al. 1998b; Toyohara et al. 2017; Syvänen et al. 2006, 2011) In humans (Bartels et al. 2010; Bauer et al. 2015; Ikoma et al. 2006a)
[^{11}C]Loperamide	Avid P-gp substrate	In vitro (Tournier et al. 2011) In vivo (mice, rats, NHP) (Damont et al. 2016; Zoghbi et al. 2008) In humans
[^{11}C] N-Desmethyl-loperamide	Avid P-gp substrate	In vitro In vivo (mice, rats, NHP) (Damont et al. 2016) In humans (Seneca et al. 2009; Kreisl et al. 2010)
[^{94m}TC]Sestamibi	Avid P-gp substrate	In vitro (Kannan et al. 2009c) In vivo (mice, rats) (Bigott et al. 2005; Piwnica-Worms et al. 2006) In humans (Piwnica-Worms et al. 2006)
[^{18}F]MC225	Weak P-gp substrate	In vitro (Raaphorst et al. 2017) In vivo (mice, rats, NHP) (Toyohara et al. 2017)
[^{18}F]Paclitaxel	Avid P-gp substrate	In vivo (mice, NHP) (Kurdziel et al. 2003a) In humans
[^{11}C]Laniquidar	P-gp inhibitor	In vivo (mice, rats) (Luurtsema et al. 2009a; Syvänen et al. 2013) In humans (Froklage et al. 2015)
[^{11}C]Tariquidar	P-gp inhibitor	In vitro (Bankstahl et al. 2013) In vivo (mice, rats, NHP) (Lozano et al. 2019) In humans (Lozano et al. 2019; Bauer et al. 2013)
[^{11}C]Phenytoin	Weak P-gp substrate	In vivo (mice, rats) (Verbeek et al. 2012a) In humans (Mansor et al. 2015)
[^{11}C]Elacridar	P-gp inhibitor	In vitro (Bankstahl et al. 2013) In vivo (mice, rats) (Dörner et al. 2009) In humans (Bauer et al. 2013)
[^{11}C]Metoclopramide	Weak P-gp substrate	In vitro (Pottier et al. 2016) In vivo (mice, rats, NHP) (Pottier et al. 2016; Zoufal et al. 2020; Auvity et al. 2018) In humans (Tournier et al. 2019a)

3.5.1 [^{94m}TC]Sestamibi

The first radiotracer used to image the function of P-gp was [^{99m}Tc]sestamibi, a positively charged lipophilic compound designed for SPECT imaging. Sestamibi was developed as an analog of K^+ for imaging of myocardial ischemia, but showed also potential as P-gp imaging tracer. After its use as SPECT tracer, it was labelled with ^{94m}Tc for the use in PET to measure overexpression of P-gp in multidrug-resistant cancer. Since [^{94m}Tc]sestamibi is a substrate of both P-gp and ABCC1 and produces a relatively weak PET signal, this agent is no longer in use, and other tracers were developed to measure the function of P-gp (Kannan et al. 2009c).

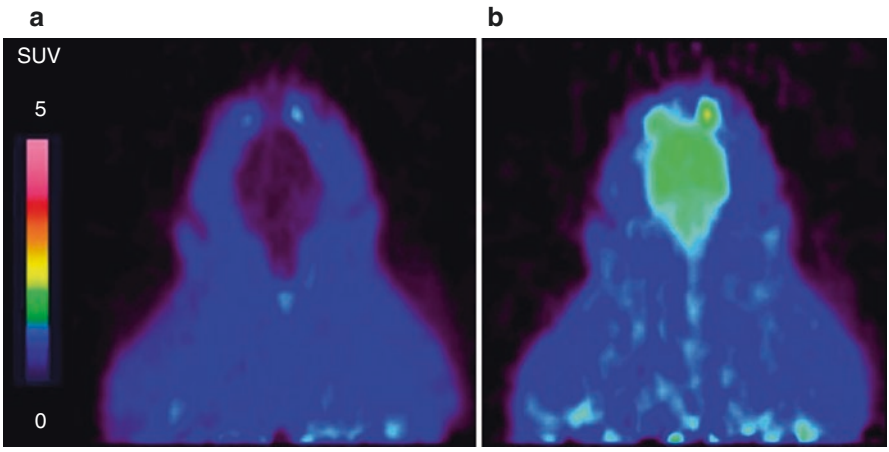

Fig. 3.4 [^{11}C]Verapamil PET images in rodents before and after inhibition show a significantly higher uptake when P-gp function is blocked with cyclosporine A 25 mg/kg. Reprinted with permission from 1. Syvänen S, Eriksson J. Advances in PET imaging of P-glycoprotein function at the blood–brain barrier. ACS Chem Neurosci. 2013;4:225–37, Copyright 2020 American Chemical Society

3.5.2 [^{11}C]Verapamil and (*R*)-[^{11}C]Verapamil

(*R*)-[^{11}C]Verapamil and racemic [^{11}C]verapamil are the most frequently used PET tracers to measure P-gp function and are considered to be the gold standard (see Fig. 3.4) (Hendrikse et al. 1998b; Elsinga et al. 1996). A great advantage of [^{11}C]verapamil is its specificity to P-gp (Römermann et al. 2013). Verapamil is an inhibitor of P-gp when it is administered in high dose, but at the ultra-low dose used in PET imaging, it is a substrate (Syvänen and Eriksson 2013). Although [^{11}C]verapamil is frequently used to measure P-gp function, it has several drawbacks: First of all, [^{11}C]verapamil is a strong substrate of P-gp and has a very low uptake at baseline, which makes it difficult to measure upregulation of P-gp (Wagner et al. 2009). Another drawback of [^{11}C]verapamil is the considerable amount of radioactive metabolites formed, which contribute to the PET signal and leads to complications in quantification of data. One of the metabolites generated by [^{11}C]verapamil is D617, which is also a P-gp substrate (Pauli-Magnus et al. 2000).

3.5.3 [^{18}F]MC225

Most of the tracers developed for measuring the function of P-gp are avid substrates. Those tracers can be used to detect an impaired function of P-gp, but their baseline uptake is too low to adequately measure upregulation of P-gp. Measuring upregulation of P-gp is useful in drug resistance, as well as for monitoring the effect of P-gp inducers. For this purpose, weak substrate tracers were developed with a

higher brain uptake at baseline. One of these weak substrates is [^{18}F]MC225, which has shown promising results in rodents and non-human primates (Toyohara et al. 2017; García-Varela et al. 2020). This tracer showed a much higher uptake at baseline than [^{11}C]verapamil. Besides a higher uptake at baseline, a lower amount of radioactive metabolites was formed from [^{18}F]MC225. The radioactive metabolites of [^{18}F]MC225 constituted only 11–24% of the total radioactivity 60 min post injection, compared to more than 50% in the case of [^{11}C]verapamil (Luurtsema et al. 2005). Last but not least, labelling with ^{18}F instead of ^{11}C gives [^{18}F]MC225 a longer half-life, which makes transport between hospitals possible. This makes [^{18}F]MC225 a suitable tracer for multicentre studies and facilitates the clinical use of this tracer in hospitals in which no cyclotron is present.

3.5.4 [^{11}C]Loperamide and [^{11}C]N-Desmethyl-Loperamide

Loperamide, sold over the counter under the name Imodium, is known for its antidiarrhoeal effects. In general it is used in the treatment of gastroenteritis and inflammatory bowel disease. Loperamide was first used as radioligand to measure the function of P-gp in 2008 by Passchier and colleagues to overcome the drawbacks of [^{11}C]verapamil (Passchier et al. 2008). After a few studies in mice and non-human primates using [^{11}C]loperamide, it was found that the main radioactive metabolite of [^{11}C]loperamide, [^{11}C]-*N-desmethyl*-loperamide, also behaves as a P-gp substrate and generates less radioactive metabolites in comparison to [^{11}C]loperamide (Seneca et al. 2009). In humans, [^{11}C]-*N-desmethyl*-loperamide showed a fourfold increase in uptake after inhibition with tariquidar, a selective P-gp inhibitor, which is a larger increase than was observed for [^{11}C]verapamil (Kreisl et al. 2010). The drawbacks of this tracer are its low brain uptake at baseline, which makes it difficult to measure an increase in P-gp function in, for example, multidrug resistance and epilepsy and the presence of radioactive metabolites which contaminate the brain PET signal (Seneca et al. 2010).

3.5.5 [^{18}F]Paclitaxel and [^{18}F]Fluoro-Paclitaxel

Paclitaxel is a chemotherapeutic drug used to treat several types of cancer, including ovarian cancer, lung cancer, melanoma, breast cancer and cervical cancer and is also a P-gp substrate. Paclitaxel was first labelled with ^{18}F to provide a quantitative method for evaluation of the P-gp transporter in the context of multidrug resistance (MDR) in oncology (Kiesewetter et al. 2003). Biodistribution of this tracer was successfully studied in NHPs after administration of a specific P-gp inhibitor (Kurdziel et al. 2003b). In humans, Kurdziel and colleagues performed [^{18}F]fluoro-paclitaxel scans in three healthy volunteers and three female breast cancer patients and noted that, although the mean tumour uptake was low, the tumour was visible against healthy breast tissue. They conclude the measured intratumoural distribution of [^{18}F]fluoro-paclitaxel may serve as surrogate marker for uptake of chemotherapeutic agents in evaluation of multidrug resistance in oncology (Kurdziel et al. 2011).

3.5.6 [^{11}C]Laniquidar

Laniquidar is a third-generation P-gp inhibitor and was first studied in clinical trials as a modulator of multidrug resistance transporters in cancer therapy. In 2009, Luurtsema and colleagues labelled laniquidar with carbon-11 to assess whether this compound could be used as a PET tracer for P-gp function. The first preclinical studies of this tracer did not show the expected uptake in the brain (Luurtsema et al. 2009b). This might be explained by an altered behaviour (as substrate instead of inhibitor) when laniquidar is administered in tracer concentrations. The dosimetry, kinetics and uptake of the tracer have been evaluated in healthy volunteers (Froklage et al. 2015; Dörner et al. 2011; Postnov et al. 2013). These studies showed that [^{11}C]laniquidar generates a high amount of radioactive metabolites that cross the blood–brain barrier. The metabolism of this tracer in humans is unexpectedly high compared to its metabolism in rodents.

3.5.7 [^{11}C]Tariquidar

Before tariquidar was used as PET tracer, this compound was already known as P-gp inhibitor. It was used in combination with anticancer drugs to overcome multidrug resistance (Patel et al. 2011; Fox and Bates 2007). In 2010, tariquidar was labelled with carbon-11 and was evaluated in rats to measure P-gp function (Bauer et al. 2010). In this study it was found that tariquidar acted as a substrate and not as an inhibitor of P-gp, when administered in ultra-low doses as PET tracer. Further studies showed that [^{11}C]tariquidar is not only a substrate for P-gp, but also for BCRP, which makes this tracer less valuable for measuring P-gp function. Despite these results in animal studies, the tracer was tested in humans to measure P-gp and BCRP density at the BBB. In this study, a low uptake of the tracer at baseline was observed, and after P-gp inhibition, no significant increase in brain-uptake was seen (Bauer et al. 2013).

3.5.8 [^{11}C]Phenytoin

Phenytoin is an antiepileptic agent. It is used for prevention of seizures and is given intravenously to patients in status epilepticus not responding to benzodiazepines. Phenytoin is a weak substrate of P-gp, and it was suspected to have a higher uptake at baseline compared with the gold standard [^{11}C]verapamil. In rats [^{11}C]phenytoin showed a two times higher brain uptake at baseline compared with [^{11}C]verapamil (Verbeek et al. 2012b). [^{11}C]Phenytoin was evaluated successfully in healthy volunteers (Mansor et al. 2015, 2017). The next step in evaluation of this tracer will be the verification of its kinetics under pathological circumstances in, for example, drug-resistant epilepsy patients with a higher P-gp function compared to healthy subjects.

3.5.9 [^{11}C]Metoclopramide

Metoclopramide is mostly used as anti-emetic medication and is known as a weak substrate of P-gp. Preclinical experiments showed that [^{11}C]metoclopramide might be a suitable PET tracer for measuring P-gp function, since only a negligible amount of radioactive metabolites cross the BBB and transport of the tracer was selective for P-gp over BCRP (Pottier et al. 2016). Further translational studies in rats, NHPs and humans demonstrated that the baseline uptake of [^{11}C]metoclopramide was significantly higher than that of *(R)*-[^{11}C]verapamil and [^{11}C]-*N*-desmethyl-loperamide, which can be explained by its behaviour as a weak substrate of P-gp (Pottier et al. 2016; Auvity et al. 2018; Tournier et al. 2019b). Zoufal and colleagues evaluated [^{11}C]metoclopramide in a beta-amyloidosis mouse model. In this animal model, induction of the P-gp function with a prototypical rodent pregnane X receptor (PXR) activator was detected with [^{11}C]metoclopramide. Thus, [^{11}C]metoclopramide is a suitable tracer to measure upregulation of P-gp (Zoufal et al. 2020).

3.6 Pharmacokinetic Modelling of P-gp PET Tracers

PET scanners can produce high-quality three-dimensional images after injection of a tracer into a patient. An appropriate reconstruction algorithm and proper corrections for undesirable physical effects as attenuation and scatter make it possible to obtain quantitatively accurate measurements of radioactivity concentration. The function of P-gp can theoretically be quantified in vivo with the use of standard compartmental models, but the modelling of PET tracers used for measuring the function of P-gp is complicated by the position of P-gp between the blood and the brain and the fact that the tracer is considered to be an substrate and therefore is transported by P-gp. For quantification of PET tracers used for the measurement of P-gp function, a single-tissue compartment model is generally used, in which K_1 represents the rate of influx across the BBB and k_2 the rate of efflux out of the brain to the blood (see Fig. 3.5). The change in kinetic parameters depends on the place of drug administration. If compounds are administered intracerebrally, k_2 will change, since P-gp is a known efflux transporter. However, in case of intravenous administration, K_1 will show the biggest change, since the transport of the compound across the BBB will be blocked by P-gp, and this will be measured as a decrease in K_1. The change in either k_2 or K_1, depending on the localization of drug administration, can be explained by the mechanism of P-gp to transport molecules in the lipid bilayer (Liow et al. 2009). In case of influx of those molecules across the BBB, the molecules are 'trapped' in the lipid bilayer and transported out of this layer before they can cross to the brain (Kannan et al. 2009b). Theoretically some P-gp substrates can cross the BBB, before being transported out of the brain by P-gp, which will lead to a decrease in K_1 and increase in k_2. Several studies concerning kinetic modelling of [^{11}C]verapamil showed that this tracer is such an avid P-gp substrate that increases of activity are mainly reflected by a decrease in K_1 (Ikoma et al. 2006b; Sasongko et al. 2005).

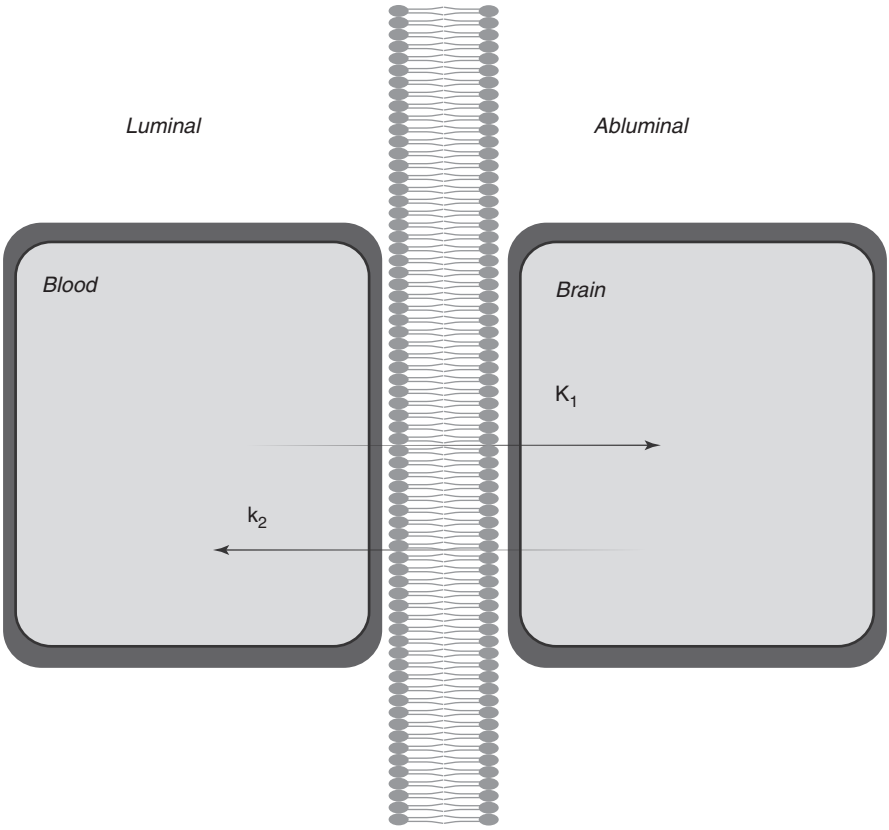

Fig. 3.5 Schematic representation of a simplified single tissue compartment model used to quantify P-gp function. The blood and brain are divided by a lipid bilayer on which P-gp is located. K_1 represents the influx rate of the radiolabelled P-gp substrate, and k_2 represents the efflux rate of the substrate from the tissue to the blood

3.7 Drug Resistance and Drug–Drug Interactions

Pharmaceuticals can cross the BBB and enter the brain via six main pathways depending on their size, lipophilicity and electrical charge: paracellular transport, passive transcellular diffusion, carrier-mediated transport, receptor-mediated transcytosis, adsorptive-mediated transcytosis and cell-mediated transport. For various diseases affecting the brain, the effect of treatment is limited because of drug resistance. For adequate drug distribution to the target-site, transport among various tissues and compartments is required. The distribution of pharmaceutics that have their target in the brain is dependent both on properties of the BBB and properties of the drug (Raaphorst et al. 2015a; Yamamoto et al. 2018). If drugs are transported by P-gp, this can have a great impact on their effect and distribution. P-gp may therefore play a role in multidrug resistance in the brain. Pharmaceuticals

transported by P-gp are structurally diverse and range from antidepressants and antipsychotics to drugs used in auto-immune conditions (see Table 3.2). Due to its ability to transport an extensive variety of structurally divergent pharmaceuticals, overexpression or hyperfunction of P-gp is considered as a possible mechanism of drug resistance in various pathological conditions (Aouali et al. 2005). Inhibition of P-gp could theoretically overcome resistance to pharmaceuticals that are substrates

Table 3.2 Pharmaceuticals affected by or affecting P-gp

Drug class	Pharmaceutical	Role
Analgesics	Morphine Methadone Fentanyl	Substrate, inducer[a] (Aquilante et al. 1999; Callaghan and Riordan 1993) Inhibitor (Zhou et al. 2007) Substrate, inhibitor[a] (Kim 2002; Wang et al. 2003)
Antibiotics	Erythromycin Rifampicin Clarithromycin Trimethoprim	Substrate, inhibitor[a] (Schuetz et al. 1998; Kim et al. 1999) Inducer (Schuetz et al. 1996) Substrate, inhibitor[a] (Kim 2002; Wang et al. 2003) Substrate (Taub et al. 2005)
Cytostatic	Doxorubicin Etoposide Paclitaxel Vincristine Vinblastine Imatinib Irinotecan	Substrate (Kim 2002) Substrate (Taub et al. 2005) Substrate, inducer[a] (Zhou et al. 2007) Substrate, inhibitor[a] (Kim 2002; Wang et al. 2003) Substrate, inducer[a] (Kim 2002; Wang et al. 2003) Substrate (Zhou et al. 2007) Substrate, inhibitor, inducer[a] (Zhou et al. 2007)
Anticoagulant	Dabigatran Clopidogrel	Substrate (Finch and Pillans 2014) Substrate (Zhou et al. 2007)
Antidepressants	Amitryptyline Nortriptyline Doxepin Venlafaxine Paroxetine Imipramine St. John's wort	Substrate, inhibitor, inducer[a] (Zhou et al. 2007; Kim 2002; Wang et al. 2003) Substrate (Kim 2002; Wang et al. 2003) Substrate (Kim 2002; Wang et al. 2003) Substrate, inducer[a] (Zhou et al. 2007; Kim 2002) Inhibitor (Kim 2002; Wang et al. 2003) Substrate, inhibitor[a] (Kim 2002; Wang et al. 2003) Inducer (Dürr et al. 2000)
Proton-pump inhibitor	Omeprazole	Substrate, inhibitor[a] (Zhou et al. 2007)
Antidiarrhoeal	Loperamide	Inducer, substrate, inhibitor[a] (Taub et al. 2005; Schinkel et al. 1996)
Anti-emetic	Ondansetron Domperidone	Substrate (Kim 2002; Wang et al. 2003) Substrate (Kim 2002; Wang et al. 2003)
Antiepileptic drugs	Topiramate Phenytoin Phenobarbital Carbamazepine	Substrate (Kim 2002; Wang et al. 2003) Substrate (Kim 2002; Wang et al. 2003) Inducer (Zhou et al. 2007) Substrate (Kim 2002; Wang et al. 2003)
Antihelmintic	Ivermectin Ketoconazole	Substrate, inhibitor[a] (Kim 2002; Wang et al. 2003) Inhibitor, inducer[a] (Taub et al. 2005)
Anaesthetic	Lidocaine	Inhibitor (Zhou et al. 2007)

Table 3.2 (continued)

Drug class	Pharmaceutical	Role
Cardiovascular	Simvastatin	Substrate, inhibitor (Zhou et al. 2007)
	Verapamil	Substrate, inhibitor[a] (Taub et al. 2005; Wang et al. 2003)
	Nifedipine	Inhibitor (Kim 2002; Wang et al. 2003)
	Diltiazem	Substrate, inhibitor[a] (Zhou et al. 2007)
	Digoxin	Substrate (de Lannoy and Silverman 1992)
	Quinidine	Inhibitor, substrate (Wang et al. 2003)
	Amiodarone	Inhibitor (Wang et al. 2003)
	Lovastatin	Substrate, inhibitor[a] (Kim 2002; Wang et al. 2003)
	Propranolol	Substrate, inhibitor[a] (Kim 2002; Wang et al. 2003)
	Atorvastatin	Substrate, inhibitor[a] (Zhou et al. 2007)
Corticosteroids	Dexamethasone	Substrate, inducer[a] (Taub et al. 2005; Ueda et al. 1992; Lin et al. 1999)
	Aldosterone	Substrate (Ueda et al. 1992)
	Cortisol	Substrate (Taub et al. 2005; Ueda et al. 1992)
Antiretroviral	Ritonavir	Substrate, inducer, inhibitor[a] (Zhou et al. 2007; Wang et al. 2003; Perloff et al. 2000)
	Indinavir	Substrate, inducer[a] (Wang et al. 2003)
	Saquinavir	Inducer (Perloff et al. 2000)
	Amprenavir	Substrate, inducer[a] (Perloff et al. 2000; Polli et al. 1999)
	Lopinavir	Substrate, inducer, inhibitor[a] (Zhou et al. 2007; Kim 2002; Wang et al. 2003)
	Nelfinavir	Inducer (Perloff et al. 2000)
Immunosuppressant	Cyclosporine A	Substrate, inhibitor[a] (Taub et al. 2005; Wang et al. 2003)
	Sirolimus	Substrate, inhibitor[a] (Kim 2002; Wang et al. 2003)
	Tacrolimus	Substrate (Zhou et al. 2007)
Other	Colchicine	Substrate (Taub et al. 2005; Wang et al. 2003)

[a]Dose-dependent

of P-gp (Taub et al. 2005). Although some of the inhibitors succeeded in modulation of drug resistance, others failed to show any effects (List et al. 2001; Lei et al. 2013). Measurement of the P-gp expression or function in patients could be useful to evaluate drug resistance in, for example, drug-resistant depression (Picchianti-Diamanti et al. 2014).

The ability to transport a great variety of compounds can lead in some cases to drug–drug interactions. Concomitant administration of another drug that acts on the P-gp transporter may lead to an increase or decrease of drug concentrations in the brain (Lund et al. 2017). Physicians should keep such interactions in mind when prescribing drugs that interact with the P-gp transporter, in order to prevent clinical side effects. The Food and Drug Administration and the European Medicines Agency (EMA) both have developed guidelines for the screening of drugs that could be responsible for transporter-mediated drug–drug interactions (DDI), which can be used in prescription (FDA 2020).

3.7.1 Polymorphisms and Genotyping

Variability in pharmacogenes can influence the metabolism, transport and elimination of drugs since genes encode for the expression of a protein. This makes the variability in pharmacogenes an interesting field of research, since the existence of pharmacogenes makes it in theory possible to alter the way patients respond to specific pharmaceuticals, in the sense of improving efficacy or preventing unwanted side effects. Polymorphisms in the ABCB1 gene have the ability to affect both the function and the expression of the P-gp transporter (Moreno et al. 2013). Since the function of P-gp significantly influences the uptake of many antidepressants in the brain, the question arises whether ABCB1 polymorphisms can predict therapy outcome. The hypothesis that variation in the ABCB1 gene encoding for P-gp is associated with antidepressant treatment outcome has been addressed in various clinical studies, and three major single nucleotide polymorphisms (SNP) at C3435T, G2677T and C1236T of ABCB1 are known to influence the efflux pump efficiency (Sakaeda et al. 2002; Ray et al. 2015). However, Breitenstein and colleagues found in a meta-analysis in which the association between ABCB1 polymorphisms and antidepressant treatment outcome was analysed that only SNP rs2032583 and rs2235015 have a significant influence, whereas other polymorphisms do not affect the therapy outcome (Breitenstein et al. 2015). In summary, despite the extensive number of studies performed, the question whether a predictive value of ABCB1 polymorphism can predict treatment outcome has not been unambiguously answered.

3.7.2 Intestinal P-gp Expression

A good bioavailability indicates that a pharmaceutical is able to reach the systemic circulation and therefore has a chance to reach its target tissue. The absorption of pharmaceuticals is influenced by the properties of the drug itself and by the physiology of the gastrointestinal tract (GIT) of the patient. Since P-gp is located both cerebrally and intestinally, uptake of pharmaceuticals in the brain is also affected by the function of intestinal P-gp (Takano et al. 2006).

Intestinal P-gp transporters can be found on the apical surface of the superficial columnar epithelial cells of the colon and the ileum. At lower levels also the jejunum, duodenum and stomach express P-gp. The function of intestinal P-gp can be inhibited by various compounds, which results in an increase in absorption of pharmaceuticals known to be P-gp substrates and consequently to a higher uptake of the pharmaceutical at the target site.

3.8 P-gp in Psychiatric Diseases

As mentioned in the previous paragraphs, P-gp plays an important role in maintaining brain homeostasis and the protection of the brain from neurotoxic substances. An altered function of P-gp could therefore lead to pathological conditions and drug

resistance. P-gp is an important player in the pathophysiology of depressive disorders and is involved in mechanisms of drug resistance. The next paragraph will focus on the role of P-gp in psychiatric diseases and on new insights in the role of the blood–brain barrier, the gut-brain axis and the hypothalamic-pituitary-adrenal axis (HPA axis) in the pathogenesis of various psychiatric disorders.

3.8.1 Depressive Disorder and Antidepressants

Major depressive disorder (MDD) is characterized by depressed mood and by feelings of hopelessness, guilt and worthlessness, causing a diminished interest or pleasure, thereby reducing quality of life. It is a relatively frequent psychiatric disease with a lifetime prevalence of 12%. Since major depression is a significant contributor to the global burden of disease, many studies in psychiatry are focussed on the pathophysiology and potential treatments of depression (Huot et al. 2013).

Although there is a wide range of antidepressants available, drug resistance remains a major problem in MDD. Only about 60–70% of patients diagnosed with a depressive disorder respond to their first described antidepressant; the remaining 30–40% do not reach an acceptable improvement with reasonable doses of medication. Ten percent of the patients do not achieve an adequate response to any of the prescribed antidepressants at all and are classified as 'treatment-resistant' (Fava 2003).

Several studies show an association between overexpression of the P-gp transporter and treatment-resistant depression. Antidepressant drugs are divided in various classes, based on their mechanism of action, including selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA) and tetracyclic antidepressants. Since drug resistance occurs in all of these groups, it is thought that the mechanism behind this resistance should be found in transport across the BBB. The BBB plays an important role in maintaining homeostasis in the CNS, by protecting the brain against toxic substances and regulating the uptake of endogenous molecules and xenobiotics (Zlokovic 2008). Most antidepressants are small, lipophilic compounds that can easily cross the BBB by passive diffusion. The underlying cause of treatment-resistant depression might therefore not be found in suboptimal influx but in excessive efflux of the pharmaceuticals. In order to test this hypothesis, de Klerk and colleagues performed a PET study and showed a lowered uptake (V_T) of [^{11}C]verapamil in the prefrontal cortex and temporal lobes of patients with MDD after long-term treatment with antidepressants. A reduced uptake of [^{11}C]verapamil reflects a higher P-gp function in those areas, which may provide an explanation for treatment resistance in this group (de Klerk et al. 2009). In other studies it was found that many antidepressant are interacting with the P-gp transporter in vitro and in vivo (O'Brien et al. 2012). Since genetic variants in the ABCB1 gene lead to different expression levels of P-gp, one way to overcome drug resistance might be the use of bio- and genetic markers to set up a personalized depression treatment plan after genotyping (Zheng et al. 2016).

3.8.2 Schizophrenia and Antipsychotics

Schizophrenia is a neurodegenerative disorder clinically characterized by positive (hallucinations, delusions) and negative (emotional dullness, social withdrawal) symptoms, leading to a significant impairment in daily life functioning. Despite various studies in this area, the underlying pathological mechanisms are still unknown. A few studies about P-gp and schizophrenia have been done with inconclusive results. Bernstein and colleagues studied post-mortem the expression of P-gp in 13 patients diagnosed with schizophrenia and found only a difference in P-gp expression in the habenular capillaries; other regions did not show any increase or decrease (Bernstein et al. 2016). Since this study was performed using immunohistochemistry, the *expression* of P-gp transporters was evaluated, and results of this study are difficult to compare with results of PET studies which focused on P-gp *function* and found an increase in ABCB1 activity in multiple brain regions including the temporal cortex, basal ganglia and amygdala (de Klerk et al. 2010).

The main treatment of schizophrenia is antipsychotic medication. However, in one third of the cases, patients do not response adequately to antipsychotics, and drug resistance persists despite the use of multiple pharmaceuticals. In the search for the underlying cause of drug resistance, multiple antipsychotics were found to show affinity for the P-gp efflux transporter which might affect uptake of these drugs into the brain (Moons et al. 2011; Summerfield et al. 2016).

3.8.3 The Hypothalamic–Pituitary–Adrenocortical (HPA) Axis and P-gp

The hypothalamic–pituitary–adrenal axis (HPA axis) is a hormonal system affecting many processes in the body, including the gastrointestinal, cardiovascular, immune, reproductive and central nervous system. P-gp is thought to affect the activity of the axis (Joseph and Whirledge 2017). The axis is composed of the paraventricular nucleus of the hypothalamus, the anterior part of the pituitary gland and the adrenal cortex, which all have their own role in the mechanisms by which the HPA axis affects multiple systems in the body. Activity of the HPA axis is controlled by the secretion of adrenocorticotrophic hormone (ACTH)-releasing factor and vasopressin from the hypothalamus. Those hormones activate secretion of ACTH from the pituitary gland, which leads to secretion of glucocorticoids from the adrenal cortex (Pariante 2009). Glucocorticoids, in the end, affect the previously mentioned target tissues and are involved in immunology, various metabolic processes, development and cognition. A part of these glucocorticoids enters the brain and mediates the negative feedback control of the HPA axis.

In psychiatry, affective disorders are associated with an altered response of the HPA axis. An increased function of the HPA axis is found in patients with depression or patients who are at risk for depression. This increase could be explained by the concept of ‘glucocorticoid resistance’, an altered feedback inhibition by endogenous corticoids. Through binding to glucocorticoid receptors, glucocorticoids give

negative feedback to the HPA axis, which leads to a decrease in synthesis and release of corticotrophin-releasing hormone (CRH) (De Kloet et al. 1998). In depression this feedback mechanism seems to be disturbed, which leads to less feedback and subsequently to an upregulated function of the HPA axis. In patients suffering from a psychotic disorder or healthy subjects at risk of developing psychosis, alternations of the HPA axis were found as well (Garner et al. 2005; Pariante et al. 2004).

The mechanism underlying the effect of P-gp on the HPA axis remains unclear, and results of studies in which the association between P-gp and the HPA axis was evaluated are contradictory and vary widely. Because of its ability to transport glucocorticoids across the BBB, it was thought P-gp could play an important role in the regulation of the HPA axis by the glucocorticoid feedback loop, and several in vitro and in vivo studies were set up. It was shown in vitro that mouse, rat and human P-gp can transport cortisol (Ueda et al. 1992; Pariante et al. 2003; Karssen et al. 2001; Uhr et al. 2002), which may imply a role for P-gp in the feedback mechanism of the HPA axis. In vivo studies in mice observed that P-gp could limit cortisol entry only at the location of the thalamus and not in other brain regions. This finding may be explained by a higher vascularization at the thalamus leading to a greater density in P-gp expression (Mason et al. 2008). Since much remains unknown about the HPA axis and the role of P-gp in negative feedback mechanisms, further studies are needed to evaluate the involvement of the axis in psychiatric diseases.

3.9 The Role of Ageing and Neurodegeneration in P-gp Functionality

During the normal ageing process, BBB functions may show a decline. This can lead to the onset and progression of neurodegenerative diseases and problems concerning pharmacotherapy in the elderly. Since ageing is the most important risk factor for the development of AD and P-gp is known as an efflux transporter of Aβ, there is an increasing interest in the function of P-gp in normal ageing and Alzheimer's disease. In 2002 Vogelgesang et al. studied brain tissue samples of 243 non-demented subjects and found an age-related decrease in P-gp in association with an inversely correlated amyloid deposition (Vogelgesang et al. 2002a). In addition to this histological study, a [^{11}C]verapamil PET imaging study was performed by Toornvliet and colleagues in which five young (21–27 years) and five elderly (59–68 years) subjects were scanned. The study showed a significant higher volume of distribution in the elderly group. Since tracer V_T is negatively correlated with P-gp activity, this suggests that P-gp function declines with increasing age (Toornvliet et al. 2006). Another study found also an increase in V_T, but only in men and not in women (Van Assema et al. 2012a). The underlying mechanism of a declined P-gp function in the elderly may be genetic. Gene transcription is believed to be altered during ageing by transcription events (Osgood et al. 2017). Besides a reduction in P-gp, there is also a reduction of the function of another efflux transporter at the BBB,

namely LRP-1. A decreased LRP-1 function and an increased RAGE (influx transporter) function was found in animal studies. This last increase could lead to increased influx of Aβ into the brain (Church et al. 2014).

3.9.1 Alzheimer's Disease and the Function of P-gp

The incidence of age-related neurodegenerative diseases rises significantly, as life expectancy of the population increases. Alzheimer's disease was first described in 1906 and is the most common form of dementia (Alzheimer 1906). Hallmarks of AD are the accumulation of neurotoxic beta amyloid (Aβ) plaques in the extracellular compartment of the brain, inflammation, accumulation of hyperphosphorylated tau in intracellular neurofibrillary tangles and neuronal loss (Zlokovic 2011). The exact pathogenesis of AD is still unclear. The accumulation of Aβ can be caused either by an overproduction of Aβ or by a reduced clearance of Aβ across the BBB. In familial AD the accumulation of Aβ is the result of Aβ overproduction in the brain due to mutations in the amyloid precursor protein (APP) gene, presenilin-1 (PSEN1) and presenilin-2 (PSEN2) (Dorszewska et al. 2016; Carter et al. 1992; Goate et al. 1991; Chartier-Harlin et al. 1991; Sherrington et al. 1996). However, in sporadic AD no genetic mutations or significant overproduction of Aβ are found, and the accumulation of Aβ in sporadic AD is considered to be a result of dysfunction in the degradation of aggregates and a decreased efflux of Aβ across the BBB (Mawuenyega et al. 2010; van Assema et al. 2012).

LRP-1, RAGE and P-gp are the most important transporters of Aβ across the blood–brain barrier (Ambudkar et al. 1999; Deane et al. 2003). LRP belongs to the low-density receptor family and is expressed in brain endothelial cells, pericytes, neurons and astrocytes (Herz and Bock 2002). It is a multifunctional scavenger receptor on the abluminal side of the blood–brain barrier, which regulates in collaboration with P-gp the transport of Aβ to the blood (Vogelgesang et al. 2002b). An in vivo study performed with the use of [^{11}C]verapamil showed a significant increase in binding potential of the tracer in patients suffering from mild AD, suggesting an impaired P-gp function (Van Assema et al. 2012b). Besides the accumulation of Aβ and hyperphosphorylated tau, cerebrovascular alterations are associated with AD (de la Torre 2017).

Mild cognitive impairment (MCI) refers in general to an impairment in cognition which is not severe enough to cause significantly impaired daily function as is the case in dementia due to Alzheimer's disease. The prevalence of MCI is 3–22% in people older than 65 years, prevalence rates depending on the demographics of the population that was studied (Ganguli et al. 2004; Hänninen et al. 2002; Sanford 2017a). Not every case of MCI proceeds to dementia, and it is difficult to predict the course of MCI (Sanford 2017b). Since in Alzheimer's disease a significant decrease in P-gp function was observed, future in vivo studies may be aimed at answering the question to what extent this also applies to MCI.

3.9.2 Gut–Brain Axis and P-gp

The gut–brain axis is described in literature as a bidirectional communication between the gut and the central nervous system, but the exact mechanisms and implications of the axis are poorly understood. Evidence from preclinical studies supports the hypothesis that microbiota in the GI modulate CNS functions via inflammation and the hypothalamic-pituitary-adrenal (HPA) axis and by changes in neurotransmission (Wang and Kasper 2014; Collins et al. 2012). The gut-brain axis concept arises from behavioural studies in microbiome-reconstituted mice, which show that the microbiome may play an important role in multiple neurodegenerative disorders as, for example, Alzheimer's disease. The pathogenesis of AD may be linked to bacterial infections and inflammation as potential etiology (Tremlett et al. 2017). To study the connection between the gut and the brain, the microbiome of AD patients was examined. Significant changes in microbiota of AD patients were found compared with non-AD patients and other dementia types (Zhuang et al. 2018; Vogt et al. 2017; Haran et al. 2019). Haran and colleagues noted that changes of the gut microbiota in AD patients could predict changes of P-gp levels (Haran et al. 2019). A current hypothesis states that the pathogenesis of AD is not only related to an imbalance in the microbiome of the gut but also originates there (Erny et al. 2015; Houser and Tansey 2017; Lin et al. 2019). The intestinal tract of healthy humans involves a dynamic balance between the immune response of the host and the population of bacteria in the gut, with a thin epithelial layer in between. This intestinal epithelium is responsible for the physical barrier to microbial penetration and provides also an important role as guard in the immune response.

The gut–brain axis seems to be also involved in the pathogenesis of affective disorders. Based on preclinical studies that showed that the gut microbiota influences many pathways which are involved in the development of depression, clinical and translational studies were set up. In those clinical studies, it was found that depression is associated with alterations in the gut microbiota and that this altered microbiota plays an important role in the pathophysiology of depression. In bipolar affective disorder patients, a decreased level of *Faecalibacterium* was found compared with healthy subjects (Evans et al. 2017). This finding was confirmed by another study which found a negative correlation between levels of *Faecalibacterium* and the severity of depressive symptoms in major depressive disorder (Jiang et al. 2015).

3.10 Concluding Remarks and Future Directions

In conclusion, changes of P-gp function are associated with several important psychiatric and neurological diseases, and their possible effects on the treatment of these diseases are a matter of ongoing study. Most pharmaceuticals used in treatment of psychiatric and neurological disorders are weak-, moderate- or high-affinity P-gp substrates or P-gp inhibitors. Besides its role in drug resistance, P-gp may also play a role in the pathogenesis of depression and psychotic episodes, since P-gp

function is decreased during neuroinflammatory events. The exact role of P-gp in psychiatric diseases is not yet fully clear. However, its importance in drug transport makes the P-gp protein a very interesting research target. As described above, some progress in identification of genetic polymorphisms and their effect on the function and expression of P-gp has been made. However, further pharmacogenetic studies are required to understand the complex mechanism of regulatory pathways involved in P-gp modulation. The development of a whole-body PET scanner, which makes it possible to scan the total human body at once, provides excellent opportunities to study the relationship of intestinal and BBB P-gp in diseased and healthy human subjects. Last but not least, many novel PET tracers for measurement of the function of P-gp are under development. The ideal tracer which can measure both up- and downregulation and that is sensitive enough to detect small changes in P-gp function is not yet available.

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Part II

Depression and Related Disorders

Molecular Imaging of Depressive Disorders

4

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Abstract

This chapter summarizes findings of a large number of molecular imaging studies in the field of unipolar and bipolar depression (BD).

Brain metabolism in depressed unipolar and bipolar patients is generally hypoactive in the middle frontal gyri, the pregenual and posterior anterior cingulate, the superior temporal gyrus, the insula, and the cerebellum, while hyperactivity exists in subcortical (caudate nucleus, thalamus), limbic (amygdala, anterior hippocampus), and medial and inferior frontal regions. Interestingly, after depletion of serotonin or noradrenalin/dopamine in vulnerable (recovered) major depressive disorder (MDD) patients, a similar response pattern in metabolism occurs.

Findings on the pre- and postsynaptic dopaminergic system show indications that, at least in subgroups of retarded MDD patients, presynaptic dopaminergic markers may be decreased, while postsynaptic markers may be increased. The findings regarding serotonin synthesis, pre- and postsynaptic imaging can be integrated to a presumable loss of serotonin in MDD, while this remains unclear in BD. This reduction of serotonin and dopamine in MDD was recently summarized in a revised version of the monoamine hypothesis, which focuses more on a dysfunction at the level of the MAO enzyme. This should be addressed further in future studies. Nevertheless, it should be acknowledged that the serotonergic and dopaminergic systems appear adaptive; therefore, it remains difficult to distinguish state and trait abnormalities. Therefore, future longitudinal molecular imaging studies in the same subjects at different clinical mood states (preferably with different tracers and imaging modalities) are needed to clarify whether the observed changes in transporters and receptors are compensatory reactions or reflect different, potentially causal mechanisms. Several suggestions for future developments are also provided at the end of this chapter.

4.1 Introduction

A depressive episode is characterized by lowered mood, anhedonia, sleeping and eating disturbances, psychomotor agitation and/or retardation, extreme fatigue, cognitive dysfunction, feelings of worthlessness, guilt, and suicidal ideation. Depressive

episodes occur as a mood episode in unipolar major depressive disorder (MDD) or bipolar disorder (BD); in the latter, depressive episodes are interspersed by manic episodes.

MDD and BD are disabling diseases with a lifetime prevalence of ≥20% and a high risk of recurrences after a first episode (Bockting et al. 2005; Geddes et al. 2003; Hollon et al. 2005; Rush et al. 2006; Ten Doesschate et al. 2010; Vittengl et al. 2007; Sim et al. 2015; Brouwer et al. 2019). In the adult population, MDD and BD have a year prevalence of 5 and 1%, respectively. Both disorders cause tremendous suffering. MDD is expected to be the second cause of disability in 2030 (Mathers and Loncar 2006; GBD collaborators 2017). Antidepressants (ADs) are often used for treatment of depressive episodes; mostly selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) are used (American Psychiatric Association 2000; Anderson et al. 2000; Kennedy et al. 2001; Mulrow et al. 1999; Cipriani et al. 2018), while monoamine oxidase inhibitors (MAOI) and electroconvulsive therapy (ECT) are used in treatment-resistant cases. For BD these ADs are routinely used in combination with mood-stabilizing drugs like lithium, antiepileptic agents, or atypical antipsychotics, although with less efficacy (Goodwin 2003; Nivoli et al. 2011; Yatham et al. 2009; Bowden and Singh 2016; Grande et al. 2016).

In the 1950s, the serendipitous finding that iproniazid (Crane 1956) and imipramine (Kuhn 1958) improved depressive episodes led to the monoamine hypothesis. The monoamine hypothesis stipulates that "depressive episodes are *caused* by a lack of serotonin, noradrenalin, and dopamine," which is an overt simplification (Ruhe et al. 2007). The monoamine hypothesis dominated research in MDD and BD for the past decades. In the field of nuclear medicine, many radioligands have been developed for the serotonergic and dopaminergic systems and more recently for the MAO-A enzyme, which is the major enzyme responsible for the breakdown of the monoamines. Noradrenergic ligands for the norepinephrine transporter (NET) have recently been developed to evaluate in vivo NET occupancy in the brain by psychotropic drugs, but have not yet been used often.

In this chapter we will summarize the outcomes of the efforts with molecular imaging techniques to clarify the pathophysiology of MDD and BD. Because imaging of cerebral blood flow and brain function is currently studied most by (functional) MRI, we will mainly focus on transporter and receptor imaging, as—to our opinion—this is most important in studying depression with molecular imaging techniques. For BD we will restrict ourselves to report findings about the depressed state. For a more thorough comparison of findings in depressed and manic states in BD, we refer to Chap. 7.

Despite large advances by research, to date the pathophysiology behind MDD and BD cannot be fully explained. This could be due to insufficient acknowledgment of the heterogeneity of the clinical phenotypes of depression and inclusion of comorbid disorders in small samples or indicate that other mechanisms must be investigated in addition, for which some new, interesting perspectives will be mentioned at the end of this chapter.

4.2 Metabolism and Cerebral Blood Flow

From the 1990s of the last century onward, the quantification of cerebral metabolism and blood flow by radioligands was also applied to MDD and BD. We will briefly summarize this literature and refer to the referenced reviews and meta-analyses for more in-depth reading.

In general, for MDD, studies of resting state metabolism revealed overactivity of limbic structures versus a decreased activity in the prefrontal cortex (cognitive, regulatory regions) (Drevets 1998, 2000; Drevets and Raichle 1992). The first meta-analysis comprised studies until 2006, including positron-emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) (all resting state and treatment studies were PET/SPECT studies) (Fitzgerald et al. 2008). The authors reported limited overlap across imaging paradigms, but in general found hypoactivity in bilateral middle frontal gyri (dorsolateral prefrontal cortex, DLPFC), the pregenual anterior cingulate cortex (ACC; pgACC), posterior ACC, left superior temporal gyrus, insula, and the cerebellum, while hyperactivity existed in subcortical (caudate nucleus, thalamus), limbic (amygdala, anterior hippocampus), and medial and inferior frontal regions. Treatment with SSRIs increases resting activity in the hypoactive regions (i.e., the DLPFC, dorsal, and posterior ACC) and decreases activity in hyperactive regions like insula, (para)hippocampus, pregenual ACC (pgACC), subgenual ACC (sgACC), and medial frontal regions (Fitzgerald et al. 2008). However, a more recent meta-analysis comprising four [^{18}F]FDG PET studies which used a data-driven whole-brain approach showed *increased* glucose metabolism in the (right) subgenual ACC and pgACC (Sacher et al. 2012b). Of note, these authors excluded studies with a region-of-interest approach, in their attempt to avoid publication bias, but vice versa they thus also limited the number of studies that contribute to the knowledge base. The apparent difference between these two meta-analyses regarding pgACC activity might reflect differences between included studies, e.g., differences in response rates between studied populations. In a more recent meta-analysis, including 10 whole-brain-based [^{18}F]FDG-PET studies with 188 MDD patients versus 69 controls, using an activation likelihood estimation analysis, in MDD patients a decrease in metabolism in the bilateral insula, left lentiform nucleus of the putamen, extra-nuclear, right caudate, and cingulate gyrus was found, while increased activation was seen in the right pulvinar (thalamus) and the anterior and posterior lobe of the cerebellum (Su et al. 2014).

In a meta-analysis increased pgACC activity was associated with increased chances of response to treatment (Pizzagalli 2011), but see Brody et al. (1999, 2001), Konarski et al. (2009), and Milak et al. (2009). Reductions of pretreatment [^{18}F]FDG glucose metabolism within the right posterior insula correlated with reductions in depression scores in 16 MDD patients receiving 16 weekly sessions of brief psychodynamic psychotherapy (Roffman et al. 2014). Regarding increased sgACC activity, especially after corrections for partial volumes (Drevets 1999), persistent increased sgACC metabolism has been reported especially in nonresponsive patients (Mayberg 2003). However, this could not be replicated in 33 drug-free

MDD patients scanned before 3 months of treatment with antidepressants (Milak et al. 2009). Higher activity of sgACC as measured with [^{18}F]FDG PET was associated with treatment response to accelerated high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) in 15 antidepressant-free unipolar, melancholic, treatment-resistant MDD patients, where clinical response was associated with a decrease in activity in the sgACC after the 2 weeks of treatment (Baeken et al. 2015). Based on the increased activity in sgACC metabolism in nonresponders (Mayberg 2003), this region has been targeted with deep brain stimulation (Lozano et al. 2008; Mayberg et al. 2005). Interestingly, during sad mood induction in healthy volunteers, also increases in activity in sgACC and insula have been described in combination with decreased activity in the DLPFC (Mayberg et al. 1999). These cingulate increases are not found in depressed patients after sad mood induction. Instead, unique dorsal ACC increases and medial and orbital frontal (OFC) decreases are reported (Mayberg 2003). Given these inconsistencies and the additional report that an index of the connectivity of the sgACC with the left anterior ventrolateral prefrontal cortex/insula, dorsal midbrain, and left ventromedial prefrontal cortex (measured with 7.5 min of resting state fMRI) showed differential predictive properties for treatment outcomes of cognitive behavioral therapy versus antidepressants (Dunlop et al. 2017), the search for prospective biomarkers for treatment response based on [^{18}F]FDG PET metabolism might better (and cheaper) be pursued with different (non-molecular) imaging modalities.

In BD in the depressed state, comparable dysfunction was found, although not consistently (Gonul et al. 2009). Globally reduced glucose metabolism was reported in depressed BD patients versus manic patients and controls. Region-wise, in the frontal cortex, metabolism was reduced in depressed BD, while the sgACC activity was increased, especially when measurements were corrected for smaller (partial) volumes (Drevets 1999), but again reports were not unequivocal (Gonul et al. 2009). Since abnormal ACC metabolism was also reported for manic and euthymic BD patients, this might represent more a trait marker for BD. For the caudate nucleus and thalamus, early PET/SPECT studies showed a reduced glucose metabolism, while later PET studies showed increased striatal activity in combination with increased activity of the amygdala and (para)hippocampus. Striatal and amygdala activity was linearly associated with depression severity. These findings can be interpreted as being indicative of a loss of inhibitory control by the PFC (Gonul et al. 2009).

4.3 Imaging of Monoamine Systems

4.3.1 Serotonin

The serotonergic system governs a multitude of normal psychophysiological functions such as sleep, appetite, stress responses, affective cognition, aggression, and impulsivity, many of which are disturbed during a depressive (or manic) episode. Serotonin in the brain is mainly synthesized in the raphe nuclei (Purves et al. 2001).

Serotonin has been associated with depression for decades, and this association was the basis for the monoamine hypothesis in depression. There is hardly any doubt that this system is important in the pathophysiology and treatment of depression, although the question remains how it contributes to depression symptomatology. Each and every serotonin receptor has its own unique distribution pattern in the brain and is involved in different physiological processes in the body. In relation to depression, almost all receptor subtypes seem to be involved in stress-related reactions or the efficacy of antidepressants. PET and SPECT can measure these receptor levels and in vivo processes in a noninvasive way.

4.3.1.1 Serotonin Synthesis

Serotonin is synthesized from the amino acid tryptophan. Tryptophan is transported over the blood–brain barrier (BBB) by the large amino acid transporter. Inside neurons, especially terminals, tryptophan is hydroxylated by tryptophan hydroxylase (TPH2) to 5-hydroxy-tryptophan (5-HTP). In turn, 5-HTP is decarboxylated to 5-hydroxy-tryptamine (5-HT), or serotonin, by aromatic amino acid decarboxylase (AADC). Produced 5-HT is taken up in vesicles by the monoamine vesicular transporter. These vesicles fuse with the synaptic membrane, and serotonin is released into the synaptic cleft. 5-HT can be taken up back into the neuron, by the serotonin transporter (SERT). Eventually, 5-HT is metabolized to 5-hydroxyindoleacitic acid (5-HIAA), which is extracted from the brain through the cerebrospinal fluid.

Besides being used for the production of 5-HT, tryptophan is used for the production of kynurenine by the enzyme indoleamine 2,3-deoxygenase (IDO). Increases in this process could reduce 5-HT synthesis, as tryptophan is used to produce kynurenine instead of 5-HT and tryptophan availability is rate limiting for 5-HT production.

Levels of 5-HT have been linked to the pathophysiology of depression and the efficacy of antidepressants. When tryptophan is artificially decreased by an amino acid drink, devoid of this precursor of 5-HT, people that are sensitive to developing depression experience a reduction in mood (Fusar-Poli et al. 2006; Ruhe et al. 2007; van Steenbergen et al. 2012).

The hypothesis of the involvement of serotonin in depression started with measurements of serotonin levels and its metabolites by Van Praag and Korf. Depressive patients appeared to have reduced 5-HT turnover levels in the brain. This was shown by performing the probenecid test, where 5-HIAA transport is prevented (van Praag and Korf 1974). However, another study showed contradictory results, where 5-HIAA levels, directly measured in the jugular vein, were actually increased, suggesting increased 5-HT turnover. This increase was greater in people carrying the low-expressing variant of the 5-HTTLPR gene compared to the high-expressing genotype, and the increase in turnover was abolished by SSRI treatment (Barton et al. 2008). As discussed further in Sect. 4.3.3, the increase in 5-HT turnover may also be explained by an increase in the enzyme MAO-A, increasing the degradation of 5-HT to 5-HIAA and thereby depleting the brain of 5-HT (Meyer et al. 2006a, 2009).

As results are contradictory, turnover rates do not necessarily reflect 5-HT synthesis and the measurement of 5-HT and 5-HIAA levels in CSF is invasive; a more sufficient way of measuring 5-HT synthesis is needed. With PET, direct measurements of synthesis rates could be obtained by labeling the precursors of 5-HT: tryptophan or 5-HTP. Currently, there are no SPECT tracers to measure 5-HT synthesis.

Nowadays, two radiotracers for measuring 5-HT synthesis are used; these are α-[^{11}C]methyltryptophan ([^{11}C]AMT) and 5-hydroxy-l-[β-^{11}C]tryptophan ([^{11}C]5-HTP). Most studies that measure 5-HT synthesis in the brain are performed with [^{11}C]AMT, while [^{11}C]5-HTP is additionally used to visualize pancreatic islet tumors. Notably, [^{11}C]AMT is a substrate for both AADC and IDO; therefore, it not only measures 5-HT synthesis rates but also the production of kynurenine (Batista et al. 2009). In relation to depression, this may also be interesting, as IDO activity is upregulated under inflammatory conditions; however, this tracer will not solely measure 5-HT synthesis rates. [^{11}C]5-HTP on the other hand is difficult to produce as the production involves enzymatic steps (Neels et al. 2006).

Only three imaging studies have been performed in patients with MDD, but most studies indicate a decrease in 5-HT synthesis rate in the prefrontal cortex and cingulate cortex (Agren et al. 1991; Agren and Reibring 1994; Rosa-Neto et al. 2004) (Table 4.1). In addition, one study studied the effects of treatment with the SSRI citalopram and augmentation with the beta-blocker and 5-HT$_{1A}$ antagonist pindolol on 5-HT synthesis in depressed patients (Berney et al. 2008).

The first [^{11}C]5-HTP study found a reduction in uptake of [^{11}C]5-HTP over the BBB in the whole brain. The most profound decrease was observed in the dorsolateral prefrontal cortex (effect size 0.83) (Agren et al. 1991). Thereafter, the same group of subjects was used to estimate AADC activity by using a reference tissue kinetic model. With this method, the authors found an opposite effect; the AADC activity was increased in the medial prefrontal cortex of MDD patients. This discrepancy might reflect a compensatory mechanism for the decrease in precursor uptake (Agren and Reibring 1994), but the reference tissue kinetic model is compromised as [^{11}C]5-HTP has no actual reference tissue.

With [^{11}C]AMT it was found that the 5-HT synthesis rate was reduced in MDD patients, mainly in the cingulate cortex, and this effect was more robust in women (Rosa-Neto et al. 2004). With this tracer it was additionally shown that the SSRI citalopram could elevate the 5-HT synthesis rate in patients with major depression in the medial prefrontal cortex, extending to the cingulate cortex (Berney et al. 2008). Increases were only seen after 24 days of treatment and could be accelerated by augmenting the effect with pindolol, a nonselective 5-HT$_{1A}$ antagonist. Interestingly, after 10 days, there was even a decrease in the right premotor area, which is in agreement with the inhibitory effects of SSRIs on 5-HT neurotransmission through 5-HT$_{1A}$ autoreceptor stimulation, causing inhibition of firing. Similar results were found with [^{14}C]AMT and autoradiography in a rat model for depression. Here acute citalopram increased synthesis rates in the terminal areas of olfactory bulbectomized rats, but decreased rates in the raphe nuclei, where the cell bodies of 5-HT neurons lie. Pindolol prevented this decrease and increased the rates in terminal areas even more (Nguyen et al. 2009). Recent in vivo molecular imaging

Table 4.1 Serotonin synthesis imaging studies (PET) in patients with major depression as compared to controls

Authors (year)	Pts/ controls	Radiotracer	MDD treatment	Change tracer trapping	Effect size (*d*)
Rosa-Neto et al. (2004)[a]	17 MDD (2 BD) 17 HC	[^{11}C]MTrp	Drug-free (>2 weeks)	Female:	
				Cingulate right: 18% ↓ K*	−1.09
				Cingulate left: 12% ↓ K*	−0.91
				Mesial temporal lobe right: 9% ↓ K* (ns)	−0.64
				Mesial temporal lobe left: 11% ↓ K*	−0.78
				Male:	
				Cingulate cortex right:3% ↓ K* (ns)	−0.21
				Cingulate cortex left: 9% ↓ K*	−0.58
Agren and Reibring (1994)[a,b]	6 MDD 8 HC	[^{11}C]5-HTP	Drug-free (>10 days)	Whole brain: 30% ↓ uptake	N/A[d]
				Medial prefrontal cortex lower level: 766% ↑ k_3-l_3[c]	4.84
				Medial prefrontal cortex upper level: 114% ↑ k_3-l_3[c]	2.59
Agren et al. (1991)[b]	6 MDD 8 HC	[^{11}C]5-HTP	Drug-free (>10 days)	Overall: 29% ↓ SUV	−0.93
				Dorsolateral prefrontal cortex: 27% ↓ SUV	−0.83
				Medial area: 26% ↓ SUV	−0.82
				Basal ganglia: 21% ↓ SUV (ns)	−0.54
				Caudate nucleus: 22% ↓ SUV (ns)	−0.57
				Lentiform nucleus: 15% ↓ (ns)	−0.38

The change in tracer trapping is estimated from several brain regions of depressive patients and compared to reported healthy control data
[a]Other statistical test than *t*-test used
[b]Same sample of patients
[c]New way of calculating vague (k_3-l_3)
[d]No individual data available to calculate the effect size

studies on serotonin synthesis in MDD are sparse, with no additional studies since 2004.

In summary, these studies indicate that 5-HT synthesis, mainly in the prefrontal cortex and cingulate cortex, probably plays a role in the pathophysiology of MDD and the efficacy of antidepressants. A decreased synthesis or an increased

breakdown of 5-HT would lead to lower levels of serotonin in the brain, putatively increasing the risk for MDD at least in some MDD subtypes. SSRIs increase 5-HT levels and may relieve some of the symptoms of depression; however, after acute administration a decrease in synthesis takes place through stimulation of autoreceptors. Blocking of 5-HT_{1A} receptors could lead to a faster and greater increase in 5-HT synthesis rates and possibly accelerate the efficacy of antidepressants. Imaging these 5-HT_{1A} autoreceptors with PET tracers is another important feature of molecular imaging in depression, which has been investigated with sustained effort as described in Sect. 4.3.1.3.

4.3.1.2 Serotonin Transporter (SERT) Imaging

The availability of the (nonspecific) SPECT tracer iodine-123-labeled 2β-carbomethoxy-3β-(4-iodophenyl)-tropane ([^{123}I]β-CIT) from 1991 onward (Innis et al. 1991) started the investigation of the SERT availability in affective disorders. [^{123}I]β-CIT and its analogue [^{123}I]nor-β-CIT (with a tenfold higher affinity to the SERT than β-CIT (Bergstrom et al. 1997a; Hiltunen et al. 1998)) do not bind selectively to SERT but also to the dopamine transporter (DAT) (Laruelle et al. 1993) and noradrenalin transporter (NET), and endogenous serotonin competes with binding (Heinz et al. 2004). Because of lower DAT density in the midbrain, binding there is considered to represent mainly SERT, while binding in the striatum will mainly represent DAT, because of the high density of DAT relative to SERT in this region (Pirker et al. 2000). Thereafter the selective PET ligand [^{11}C](+)McN5652 was developed, followed by [^{11}C]DASB. More recently the SPECT ligand [^{123}I]ADAM was developed which is also selective for SERT (Acton et al. 2001; Catafau et al. 2005; Frokjaer et al. 2008b). [^{11}C]DASB is now considered the gold standard for SERT imaging, due to its high ratio of specific to nonspecific binding (Szabo et al. 2002), although even this tracer is not perfectly suited for imaging cortical binding. [^{11}C](+)McN5652 and [^{123}I]ADAM yield slightly worse contrasts, especially in subcortical and cortical brain regions (Frankle et al. 2004; Szabo et al. 2002).

It remains unclear what pathophysiological mechanism the measurement of SERT availability exactly represents. First, SERT availability may simply represent a marker of axons/number of neurons with SERTs. From another perspective, increased SERT availability may represent more SERTs at the synaptic cleft which enhance clearance of serotonin from the synaptic cleft; reduced SERT may then result in the opposite (Meyer 2012). However, although not indisputable, SERT availability may also be influenced by the availability of intrasynaptic endogenous serotonin, with compensatory downregulation in case of reduced endogenous serotonin (Dewar et al. 1992; Frokjaer et al. 2009; Graham et al. 1987; Graham and Langer 1987; Meyer 2007; Rattray et al. 1996; Rothman et al. 2003).

Until December 2019, 30 separate studies investigated the SERT in unipolar MDD (Table 4.2A) and 4 in BP (Table 4.2B). Most studies were small (18 studies with less than 20 MDD patients), which generally limits the statistical power to detect differences with less than large effect sizes (<0.8). Eighteen studies used PET tracers ([^{11}C]DASB, 4-[^{18}F]ADAM, [^{11}C]-ZIENT, or [^{11}C](+)McN5652), and 16

Table 4.2 Results of serotonin transporter (SERT) imaging studies (PET/SPECT) in patients with unipolar major depressive disorder (A) or bipolar disorder (B) as compared to controls

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size[a]
A. Unipolar depression					
Ananth et al. (2018)	26 MDD 31 HC	[^{11}C]DASB	Drug-free (6 recently tapered); consecutively treated with 8 weeks of escitalopram 10–20 mg	Lower Amygd SERT binding in final remitters vs. controls (p = .03) but not in non-remitters vs. controls (p = .97), final remitters and non-remitters not significantly different (p = .06)[d]	–
				Differences in Midbr, Thal, dorsal putamen, Hippoc, ACC nonsignificant	
				No sign. association between baseline Amygd SERT and posttreatment HDRS-24 score (p = .39)	
Hahn et al. (2014) Sample also described in: Lanzenberger et al. (2012), Kraus et al. (2014)	20 MDD 20 HC	[^{11}C]DASB	Drug-free ≥3 months	Midbr: 1%↑ (p = .92) in MDD	0.03
				N accumbens: −6%↓ (p = .15) in MDD	−0.5
				Caudate: −6%↓ (p = .16) in MDD	−0.5
				Putamen: −5%↓ (p = .17) in MDD	−0.5
				Thal: −9%↓ (p = .03) in MDD	−0.7
				ACC: −9%↓ (p = .25) in MDD	−0.4
				Insula: −11%↓ (p = .04) in MDD	−0.7
				Amygd: −9%↓ (p = .10) in MDD	−0.5
				Hippoc: −2%↓ (p = .72) in MDD	−0.1
				Neg. associations of SERT availability and age in Thal, insula, medial PFC, middle/posterior ACC in controls and with insula and caudate in MDD patients (p < .001); not in Midbr or striatum. No associations with duration or treatment of MDD	

Yeh et al. (2014, 2015)	17 MDD (8 with suicide attempt) 17 HC	4-[^{18}F] ADAM	Antidepressant naive	Lower SERT in Midbr ($p < .001$), Thal ($p < .001$), Striat ($p = .005$)[d]	–
				SERT availability in Midbr and Thal especially lower in MDD patients with suicidal behavior	
				Significant correlation between lower Midbr SERT availability and higher HDRS score ($p < .05$) Significant correlation between higher SERT and decrease in HDRS at week 3 (but not week 6) in Thal ($p = .016$) and Striat ($p = .047$)	
Ho et al. (2013)	40 MDD 12 HC	[^{123}I]ADAM	Drug-free ≥4 months	Striat: −9%↓ ($p = .159$) in MDD	−0.3
				Thal: −24%↓ ($p = .036$) in MDD	−0.7
				Midbr: −12%↓ ($p = .139$) in MDD	−0.4
				Pons: −14%↓ ($p = .078$) in MDD	−0.5
				No association of SERT availability in any region with MDD severity (HDRS) or SLC6A4, STin2, age, gender	
Miller et al. (2013a)	51 MDD (15 with attempted suicide) 31 HC	[^{11}C]DASB	Drug-free ≥2 weeks (11 drug-naive)	Midbr: −11%↓ ($p = .025$) in MDD	−0.5
				Thal: −7%↓ ($p = .21$) in MDD	−0.3
				Amygd: −12%↓ ($p = .021$) in MDD	−0.5
				ACC: −14%↓ ($p = .06$) in MDD	−0.4
				Dorsal putamen: −7%↓ ($p = .07$) in MDD	−0.4
				Hippocampus: −11%↓ ($p = .15$) in MDD	−0.3
				MDD suicide attempters had lower Midbr binding than both MDD nonattempters ($p = .031$) and HC ($p = .0093$)	
				No relationship between age or depression severity (HDRS) and SERT availability across the six ROIs	

(continued)

Table 4.2 (continued)

Nye et al. (2013)	11 MDD + suicide attempt 10 HC	[^{11}C]ZIENT	Drug-free ≥6 weeks	Midbr/pons: −47%↓ (p = .03) in MDD	−1.4
				Putamen: −25%↓ (p = .04) in MDD	−0.6
				Amygd: 0%↓ (p = .50) in MDD	0
				Caudate: −23%↓ (p = .21) in MDD	−0.5
				Thal: −23%↓ (p = .08) in MDD	−0.6
				Frontal cortex: −20%↓ (p = .11) in MDD	−0.5
				Cingulate: 20%↑ (p = .89) in MDD	0.4
				No sign. effect of age on mean SERT availability, but because of differences between MDD and HC, used as covariate	
Newberg et al. (2012) Amsterdam et al. (2013)	20 MDD 10 HC	[^{123}I]ADAM	Drug-free ≥1 year (10 drug-naive)	Midbr: −9%↓ (p < .005) in MDD	−1.2
				Basal ganglia: −12%↓ (p < .0.03) in MDD	−1.0
				Temporal lobe: −15%↓ (p < .005) in MDD	−1.3
				No sign. effect of age, gender, illness duration, prior antidepressant drug exposure, or symptom severity on mean SERT availability After cognitive therapy, MDD patients had a sign. increase in SERT availability in Midbr and temporal lobes (p < .01), especially in responders	
Selvaraj et al. (2011)	12 MDD	[^{11}C]DASB	Drug-free ≥4 months (4 drug-naive)	Amygd: 0%↓ (p = .99) in MDD	0.0
	24 HC (males only)			ACC: −10%↓ (p = .31) in MDD	−0.3
				Midbr: −23%↓ (p = .00001) in MDD	−1.2
				Caudate: −23%↓ (p = .06) in MDD	−0.6
				PFC: −13%↓ (p = .30) in MDD	−0.4
				Hippoc: 7%↑ (p = .58) in MDD	0.2
				Insula: −4%↓ (p = .67) in MDD	−0.1

				Putamen: −14%↓ (p = .11) in MDD	−0.5
				Thal: −24%↓ (p = .01) in MDD	−0.8
				Possible (uncorrected) pos. correlation with age of onset (caudate, PFC + p < .05) and neg. association with severity (PFC; p = .02)	
Hsieh et al. (2010)	13 MDD 26 HC	[^{123}I]-ADAM	Drug-free >3 months	Midbr: 3%↑ (p = .76) in MDD	0.2
Ruhe et al. (2009a, c)	49 MDD	[^{123}I]β-CIT	Drug-free ≥4 weeks (34 drug-naive)	Midbr: 2%↓ (p = .73) in MDD	−0.1
	49 HC			Thal: 6%↑ (p = .27) in MDD	0.2
				Midbr male: 16%↓ (p = .09) in MDD[b]	−0.5
				Midbr female: 10%↑ (p = .37) in MDD[b]	0.3
				Thal male smoke +: 23%↓ (p = .01) in MDD[b,c]	−1.5
				Thal male smoke −: 13%↓ (p = .18) in MDD[b,c]	−0.6
				Thal Fem. smoke +: 5%↑ (p = .54) in MDD[b,c]	0.3
				Thal Fem. smoke − : 21%↑ (p = .003) in MDD[b,c]	1.0
				In winter in Midbr: 18%↑ SERT (p = .04)	
				No differences in Midbr, Thal SERT for 5-HTTLPR polymorphisms (Ruhe et al. 2009c)	
Lundgren et al. 2009	7 MDD	[^{123}I]-ADAM	Drug-free >3 weeks	Midbr: 18%↓ (p = .001) in MDD	−3.0
	6 NES (BDI <19)			L/R temp lobe: 15%↓ (p < .01) in MDD	−2.0
				L/R Bas. ganglia: 3%↓ (n.s.) in MDD	−0.2
Reimold et al. (2008)	10 MDD	[^{11}C]DASB	Drug-free >5 half-lives of previous drugs	Thal: 16%↓ (p = .005) in MDD	−1.1
	19 HC			Midbr: 6%↓ (p = .26) in MDD	−0.3
				Amygd: 1%↓ (p = .45) in MDD	−0.0

(continued)

Table 4.2 (continued)

				Thal SERT inversely correlated with anxiety (p = .02) and age, but not with depression severity (n.s.)	
Bhagwagar et al. (2007)	24 MDD (recovered)	[^{11}C]DASB	Drug-free >3 months (9 drug-naive)	No overall differences (p = 0.28)	
	20 HC (males only)			Amygd: 0%↑ (n.s.) in MDD	0.0
				ACC: 0%↑ (n.s.) in MDD	0.0
				Caudate: 9%↑ (n.s.) in MDD	0.3
				PFC: 5%↑ (n.s.) in MDD	0.2
				Hippoc: 7%↑ (n.s.) in MDD	0.3
				Insula: 0%↑ (n.s.) in MDD	0.0
				Thalamus: 4%↑ (n.s.) in MDD	0.1
				Dorsal raphe: 15%↑ (n.s.) in MDD	0.4
				No association with DAS scores	
Cannon et al. (2006b, 2007), Laje et al. (2010), Liu et al. (2011)	18 MDD	[^{11}C]DASB	Drug-free >3 weeks	Midbr: 8%↑ (n.s.) in MDD	0.4
	18 BD			Thal: 27%↑ (p = .0001) in MDD	1.4
	34 HC			Striat: 12%↑ (p = .04) in MDD	0.8
				Insula: 15%↑ (p=.02) in MDD	1.1
				PAG: 22%↑ (p = .009) in MDD	1.0
				pgACC: 16%↑ (p=.06) in MDD	0.7
				Negative correlation with MDD severity and Thal, insula, DCC SERT	
				Lower SERT in Thal associated with 5-HT$_{2A}$ rs7333412 AA polymorphism (Laje et al. 2010)	

				Increased SERT associated with galactose mutarotase polymorphism independent of diagnosis; replicated in another sample (Liu et al. 2011)	
Lehto et al. (2006, 2008b), Joensuu et al. (2007, 2010)	29 MDD	[^{123}I]nor β-CIT	Drug-naive	Midbr: 10%↓ (p = .0002) in MDD	−1.1
	19 HC			No correlation with MDD severity	
				Linear inverse correlation with atypical score (Lehto et al. 2006)	
	Subgroup: 8 MDD+ dysthymia vs. 11 MDD			In MDD in MPFC 26%↓ (p = .024) in SS vs. other genotypes; in Midbr 1%↓ (n.s.)	−1.2
				Midbr: 10%↓ (p = .004) in MDD	−1.0
				Midbr: 12%↓ (p = .004) in MDD + dysthymia (Lehto et al. 2008b)	−1.5
Miller et al. (2008, 2009b), Parsey et al. (2006a, b)	25 MDD	[^{11}C] McN5652	Drug-free ≥2 weeks (12 drug-naive)	BP ↓ (p < .02) over all regions in MDD	
	43 HC			Amygd: 19%↓ (p < .03) in MDD	−0.5
				Midbr: 21%↓ (p < .03) in MDD	−0.6
				No correlation with MDD severity. SERT↓ in ACC, Amygd, putamen, Hippoc, Midbr, and Thal (p < .046) in MDD with childhood abuse (Miller et al. 2009b)	

(continued)

Table 4.2 (continued)

				SERT↓ in Amygd, Midbr, and ACC in non-remitters (at 1 year; $p = .013$); higher Amygd SERT predicted lower final HDRS score ($p = .035$) (Miller et al. 2008)	
				No differences in any region for 5-HTTLPR polymorphisms (Parsey et al. 2006a)	
Staley et al. (2006)	32 MDD	[^{123}I]β-CIT	Drug-free	Females: Thal 22%↓ ($p = .005$) in MDD[b]	−1.0
	32 HC			Males: Thal 1% ≈ (n.s.) in MDD[b]	0.1
				Midbr: 1% ≈ (n.s.) in MDD (no interaction with gender)	0.0
				Age is neg. correlated with SERT; but pos. correlated with SERT in MDD females in the thalamus	
Herold et al. (2006)	21 MDD	[^{123}I]-ADAM	Drug-free	Midbr: 21%↑ ($p = 0.07$) in MDD	0.4
	12 HC			In MDD males < females (n.s.)	
				No correlation with MDD severity	
Catafau et al. (2006)	10 MDD	[^{123}I]-ADAM	Drug-free >6 months	Midbr: 4%↓ ($p = .52$) in MDD	−0.3
	10 HC			Thal: 11%↓ ($p = .09$) in MDD	−0.8
				Striat: 5%↑ ($p = .62$) in MDD	0.3
Uebelhack et al. (2006)	30 MDD (unknown number with schizo-affective disorder) 14 HC	[^{123}I]-ADAM	Drug-free >2 months (10 drug-naive)	Midbr: 9%↑ ($p = .51$) in MDD	0.2
Newberg et al. (2005)	7 MDD	[^{123}I]-ADAM	Drug-free >3 weeks	Midbr: 7%↓ ($p = .01$) in MDD	−1.4
	6 HC			Sign. correlation with MDD severity	
Meyer et al. (2004a)	20 MDD 20 HC	[^{11}C]DASB	Drug-free >3 months	MPFC, DLPFC, ACC, caudate, putamen, Thal, Midbr ≈ ($p > .24$)[d]	–

				Significant increase in SERT in patients vs. controls in all regions for 8 patients with high DAS scores. In MDD (but not HC) sign. correlations between increased DAS scores and increased SERT	
Meyer et al. (2004b)	37 MDD 35 HC	[^{11}C]DASB	Drug-free >1 month	Striat ≈ (p = .59) difference	0
Reivich et al. (2004)	4 MDD	[^{11}C](+) McN5652	Drug-free for	L PFC: 17%↑ (p = .013) in MDD	2.9
	4 HC		≥5 half-lives	R ACC: 24%↑ (p = .043) in MDD	1.9
				Thal: 17%↑ (n.s.) in MDD	0.4
				Midbr: 25%↑ (n.s.) in MDD	0.8
Ahonen et al. (2004)	10 MDD 14 HC	[^{123}I]-ADAM	Drug-free	Midbr: 7%↑ (n.s.) in MDD	0.5
Ichimiya et al. (2002)	7 MDD and 6 BD	[^{11}C](+) McN5652	Drug-free	Thal: 23%↑ (p = .002) in MDD/BD	1.0
	21 HC (males only)			Midbr: −2% ≈ (n.s.)	0.1
Meyer et al. (2001c)	13 MDD	[^{11}C]DASB	Drug-free (11 drug-naive)	Striat no differences (p = .82)[d]	–
	13 HC			Significant effect of age (p = .04)	
Dahlstrom et al. (2000)	31 MDD 10 non-MDD pts Children/adolescents	[^{123}I]β-CIT	Drug-naive	Midbr: 8%↑ in MDD at 1 h (p = .02), 9%↑ at 4 h (p = .08)	0.9 (1 h)
				PFC n.s.	0.8 (4 h)
				Thal n.s.	– –
Willeit et al. (2000)	11 SAD	[^{123}I]β-CIT	Drug-free ≥6 months	Midbr: 2%↑ (p = .95) in MDD (4 h)	0.2

(continued)

Table 4.2 (continued)

	11 HC			Thal: 7%↓ (p = .31) in MDD (4 h)	−0.6
				Midbr: 7%↓ (p = .39) in MDD (24 h)	−0.5
				Thal: 15%↓ (p = .026) in MDD (24 h)	−1.2
Kugaya et al. (2004), Malison et al. (1998b)	15 MDD	[^{123}I]β-CIT	Drug-free	Midbr: 18%↓ (p = .02) in MDD	−0.8
	15 HC			No correlation with MDD severity	
				Higher SERT predicted treatment response (Kugaya et al. 2004)	
B. Bipolar depression					
Chou et al. (2010)	24 BD (10 BP-I) (euthymic)	[^{123}I]-ADAM	Mood stabilizers and antipsychotics allowed; no SSRI/SNRI >1 year	Midbr: 8%↓ (p = .27) in BD-I+BD-II	−0.3
				Midbr: 25%↓ (p = .042) in BD-I	1.2
	28 HC			Midbr: 3%↑ (n.s.) in BD-II	0.1
				In BD-I SERT correlated inversely with duration of illness	
Oquendo et al. (2007)	18 BD (10 BP-I)	[^{11}C](+) McN5652	Drug-free ≥2 weeks (2 drug-naive)	Midbr: 27%↓ (p = .02) in BD[e]	−0.8[e]
	41 HC			Amygd: 26%↓ (p = .02) in BD	−0.6
				Hippoc: 23%↓ (p = .02) in BD	−0.7
				Thal: 23%↓ (p = .02) in BD	−0.8
				Putamen: 16%↓ (p = .02) in BD	−0.3
				ACC: 23%↓ (p = .02) in BD	−0.6
				No correlation with severity. No effect of 5-HTTLPR genotype	

Cannon et al. (2006b), Laje et al. (2010)	18 BD (5 BP-I)	[^{11}C]DASB	Drug-free ≥1 month (1 drug-naive)	Thal: 14% ↑ (p = .003) in BD	0.9
	37 HC			Insula: 13% ↑ (p = .015) in BD	0.7
				pgACC: 16% ↑ (p = .017) in BD	0.8
				sgACC: 9% ↑ (n.s.) in BD	0.4
				Striat: 8% ↑ (p = .06) in BD	0.5
				Midbr: 5% ↓ (n.s.) in BD	−0.4
				DCC: 19% ↑ (p = .004) in BD	0.8
				PCC: 14% ↑ (p = .05) in BD	0.6
				No correlation with severity. Pos. correlation between anxiety and SERT in insula and DCC	
				Comorbid OCD associated with increased SERT in insula and DCC; more pronounced differences in BD without previous mood stabilizers; lower SERT in midbrain of patients with attempted suicides	
				Lower SERT in Thal associated with 5-HT$_{2A}$ rs7333412 AA polymorphism (Laje et al. 2010)	
Ichimiya et al. (2002)	7 MDD and 6 BD	[^{11}C](+) McN5652	Drug-free	Thal 23%↑ (p = .002) in MDD/BD	1.0
	21 HC (males only)			Midbr −2% ≈ (n.s.)	0.1

Abbreviations: *5-HTTLPR* Serotonin transporter promoter region, *Amygd* Amygdala, *BDI* Beck Depression Inventory, *HDRS* Hamilton Depression Rating Scale, *Midbr* Midbrain, *ACC* Anterior cingulate cortex, *pg* Pregenual, *sg* Subgenual, *DAS* Dysfunctional Attitude Scale, *DCC* Dorsal cingulate cortex, *L* Left, *Midbr* Midbrain, *NES* Night eating syndrome, *PAG* Periaqueductal gray matter, *PCC* Posterior cingulate cortex, *PFC* Prefrontal cortex, *M* Medial, *DL* Dorsolateral, *R* Right, *SAD* Seasonal affective disorder, *Striat* Striatum, *Thal* Thalamus

Notes/remarks:

[a]The differences and effect sizes (vs. controls) have been estimated from tables and text (or graphs), based on specific binding potential relative to non-displaceable binding (BP_{ND}, V3″, or analogous measures), unless specified differently (Innis et al. 2007)

[b]Significant disease group by gender interaction ($p < .05$)

[c]Significant gender by smoking interaction ($p < .04$)

[d]Only statistics provided

[e]BP_P reported instead of BP_{ND}

studies used SPECT tracers ([^{123}I]β-CIT, [^{123}I]nor-β-CIT, or [^{123}I]ADAM). In most studies both males and females were included, although three studies (Bhagwagar et al. 2007; Ichimiya et al. 2002; Selvaraj et al. 2011) investigated males only. We will first summarize the findings of these studies for unipolar and bipolar depression separately and try to synthesize these thereafter.

Unipolar Depression

With PET, 295 MDD patients have been investigated in total versus 342 controls. All studies investigated drug-free depressed patients (of whom 55/271 were reported drug-naive), except one study which investigated remitted patients (of whom 9/24 were drug-naive) (Bhagwagar et al. 2007).

The PET ligand [^{11}C]DASB was used in ten studies (Bhagwagar et al. 2007; Cannon et al. 2007; Meyer et al. 2001c, 2004a, b; Reimold et al. 2008; Selvaraj et al. 2011; Miller et al. 2013a; Hahn et al. 2014; Ananth et al. 2018). Other PET ligands were 4-[^{18}F]ADAM (Yeh et al. 2014, 2015), [^{11}C]ZIENT (Nye et al. 2013), and [^{11}C]McN5652 (Ichimiya et al. 2002; Reivich et al. 2004; Miller et al. 2008, 2009b; Parsey et al. 2006a, b).

Many brain regions have been investigated: the thalamus, striatum, and midbrain (including the dorsal raphe) were investigated most, followed by more incidental reporting of SERT availability in the amygdala, anterior cingulate cortex (ACC; including the pre- and subgenual parts), caudate nucleus, putamen, prefrontal cortex (PFC; including the medial and dorsolateral parts), hippocampus, insula, and periaqueductal gray (PAG). The results are mixed.

In the midbrain five studies (n = 116 patients) reported a decrease in SERT availability (Parsey et al. 2006b; Selvaraj et al. 2011; Nye et al. 2013; Miller et al. 2013a; Yeh et al. 2014, 2015), and seven studies (n = 105 patients) reported no difference (Cannon et al. 2007; Ichimiya et al. 2002; Meyer et al. 2004a; Reimold et al. 2008; Reivich et al. 2004; Hahn et al. 2014; Ananth et al. 2018). One small study (n = 4 patients) was underpowered to distinguish an effect size of 0.8 *increase* in midbrain SERT availability (Reivich et al. 2004). Interestingly, three studies (n = 79 patients) reported that midbrain SERT availability was especially lower in patients with a history of suicide attempts (n = 34) (Nye et al. 2013; Miller et al. 2013a; Yeh et al. 2014, 2015).

In the thalamus, five studies (n = 70 patients) reported a decrease in SERT availability (Reimold et al. 2008; Selvaraj et al. 2011; Nye et al. 2013; Yeh et al. 2014, 2015; Hahn et al. 2014), while four studies (n = 101 patients) reported no difference (Meyer et al. 2004a; Reivich et al. 2004; Miller et al. 2013a; Ananth et al. 2018) and two studies (n = 25 patients) an increase (Cannon et al. 2007; Ichimiya et al. 2002).

In the striatum, five studies (n = 108) reported no difference in SERT availability (Meyer et al. 2001c, 2004a, b; Selvaraj et al. 2011; Ananth et al. 2018), three studies (n = 82 patients) reported nonsignificant lower SERT availability (Nye et al. 2013; Miller et al. 2013a; Hahn et al. 2014), while one study (n = 17 patients) reported significantly lower SERT availability in MDD (Yeh et al. 2014, 2015).

SERT availability in the amygdala was reported in seven studies (n = 130 patients), with no (significant) change in five studies (n = 67 patients) (Reimold

et al. 2008; Selvaraj et al. 2011; Nye et al. 2013; Hahn et al. 2014; Ananth et al. 2018) but significantly lower SERT availability in MDD in two studies (n = 76) (Miller et al. 2008, 2009b; Miller et al. 2013a). Interestingly, lower amygdala SERT availability was associated with remission of MDD after treatment with escitalopram (Ananth et al. 2018).

Age was negatively correlated with SERT availability in striatum (Meyer et al. 2001c; Hahn et al. 2014). In other regions only significant increases were reported in the right ACC (Reivich et al. 2004), PAG (Cannon et al. 2007), and insula (Hahn et al. 2014).

In remitted patients no differences in midbrain, thalamus, or striatal SERT availability were found, although for the midbrain and striatum, effect sizes of 0.4 and 0.3 (increased vs. controls) were reported (Bhagwagar et al. 2007). Another study of the same research group in another sample of depressed patients found a decrease in SERT availability in the midbrain and thalamus. These results are indicative of state-dependent changes in SERT availability in the course of MDD (Selvaraj et al. 2011).

Interestingly, Meyer et al. reported that in a subgroup of eight depressed patients with high dysfunctional attitude scores (DAS), an increased SERT availability in the midbrain, thalamus, striatum, PFC, and ACC existed (Meyer et al. 2004a). DAS scores also showed a significant correlation with SERT availability, which was not found in the remitted patients (Bhagwagar et al. 2007). Severity of depression was negatively correlated with SERT availability in the PFC (Selvaraj et al. 2011), thalamus, insula, dorsal ACC (Cannon et al. 2007), and midbrain (Yeh et al. 2014, 2015) (lower SERT, higher severity), which was not replicated in other PET studies. Of note is one study specifically investigating the effect of anxiety symptoms; this study demonstrated that more anxiety symptoms were associated with lower SERT availability in the thalamus (Reimold et al. 2008). Childhood abuse appeared to be associated with lower SERT availability in the midbrain, thalamus, ACC, amygdala, putamen, and hippocampus in a secondary analysis of 23 MDD patients (Miller et al. 2009b).

The original finding of Kugaya et al., who reported that higher SERT availability in the midbrain (measured by [^{123}I]β-CIT) appeared predictive of later response to antidepressants (Kugaya et al. 2004), was not replicated with PET (but see the association of lower SERT availability in the amygdala above (Ananth et al. 2018)). Some support that antidepressant treatment may depend on high SERT availability in the depressed state was found later: final non-remitters after 1 year of antidepressant treatment had lower SERT availability in the midbrain, ACC, and amygdala before follow-up (compared to final remitters), and higher amygdala SERT availability predicted lower posttreatment Hamilton (HDRS) scores (Miller et al. 2008). In addition, Lanzenberger et al. reported that the ratio of SERT binding in the amygdala/hippocampus complex, sgACC, and habenula relative to the SERT binding median raphe nuclei (MRN) was predictive for a response after ≥3 weeks of (es) citalopram (Lanzenberger et al. 2012). The higher the SERT binding in terminal regions in relation to the MRN SERT binding, the better the treatment outcome. If replicated and validated as a prognostic test, this study might herald the first

PET-based biomarker ([^{11}C]DASB binding in sgACC/habenula/amygdala–hippocampus complex relative to MRN) for the prediction of SSRI treatment outcome.

Despite the higher resolution in PET, many studies used the less expensive, easier to handle, alternative SPECT imaging, with a total of 318 MDD patients versus 230 healthy controls being scanned. All studies investigated depressed drug-free patients (of whom 114/318 were reported drug-naive). One study without healthy controls was omitted (Lundgren et al. 2009); one study included nondepressed patients as controls, but will be discussed further (Dahlstrom et al. 2000).

All studies with these SPECT ligands reported on SERT availability in SERT-rich regions of interest: mostly results were reported for the midbrain, sometimes for the thalamus/diencephalon, and occasionally for the MPFC (Joensuu et al. 2010) and temporal lobe (Newberg et al. 2012). Results are mixed, which might be explained by methodological issues. First, a ratio method overestimates SERT availability during a transient equilibrium, with the largest errors in high-binding regions. Second, the time point of (transient) equilibrium is later in regions with high binding. Third, plasma clearance rates may vary from subject to subject, and this may be even worse between patients and controls. For example, [^{123}I]ADAM studies in humans showed poor test–retest outcomes for the ratio method, with intrasubject variability of >13% (Frokjaer et al. 2008b).

In the midbrain, four studies ($n = 71$ patients) reported a decrease in SERT (Lehto et al. 2006; Malison et al. 1998b; Newberg et al. 2005; Newberg et al. 2012), and ten studies ($n = 247$ patients) found no (significant) difference (Ahonen et al. 2004; Catafau et al. 2006; Dahlstrom et al. 2000; Herold et al. 2006; Uebelhack et al. 2006; Hsieh et al. 2010; Ruhe et al. 2009a; Staley et al. 2006; Willeit et al. 2000; Ho et al. 2013) in direct comparisons of patients and controls. Of note is that four of the studies, which were poorly powered and reported no difference, in fact reported nonsignificant increases in SERT availability in MDD patients ($n = 92$ patients) (Ahonen et al. 2004; Dahlstrom et al. 2000; Herold et al. 2006; Uebelhack et al. 2006). One study reported a significant negative correlation between midbrain SERT and depression severity (Newberg et al. 2005). In one study MDD patients had a significant increase in SERT availability in midbrain (and temporal lobes; $p < .01$) after cognitive therapy, which was especially seen in responders (Newberg et al. 2012; Amsterdam et al. 2013).

In the thalamus, two studies ($n = 72$ patients) reported a decrease in SERT (Staley et al. 2006; Ho et al. 2013) and four studies ($n = 101$ patients) no difference (Catafau et al. 2006; Dahlstrom et al. 2000; Ruhe et al. 2009a; Willeit et al. 2000) in direct comparisons of patients and controls.

Importantly, two larger studies ($n = 81$ MDD patients) that reported no overall differences in direct comparisons between MDD patients and controls reported an interaction of gender by disease status (Ruhe et al. 2009a; Staley et al. 2006), albeit with opposite interaction effects. Staley et al. reported significantly lower thalamus SERT availability for depressed females versus controls and no difference in males (Staley et al. 2006). Both in the thalamus and midbrain, there was an age by gender interaction (lower SERT availability at higher age in males versus higher SERT availability in older females). In their sample no gender by disease status interaction

was found for midbrain SERT availability. However, Ruhe et al. reported a significant interaction of lower midbrain SERT availability in depressed males and an increase of SERT availability in depressed females (vs. controls). They also found an interaction of smoking by gender and gender by disease status for SERT availability in the thalamus. Relative to controls, smoking increased SERT availability in males, while this difference was not significant in females. In a recent study, in a mix of controls and a group of patients with different psychiatric disorders, smoking status significantly interacted with 5-HTTLPR genotype: active smoking was associated with reduced 5-HTT availability only in LL subjects but not in carriers of the S-allele (Smolka et al. 2019). Furthermore, like in the midbrain, SERT availability was lower in depressed males but higher in depressed females (Ruhe et al. 2009a).

Bipolar Depression

BP was investigated sparsely, with no additional studies since 2012, with three PET studies and one SPECT study (Table 4.2B). In total 56 BP patients were studied, of whom at least 25 were suffering from bipolar I disorder. One study did not report separate analyses for unipolar and bipolar subjects (Ichimiya et al. 2002), but found increased SERT availability in the thalamus. This was also found by Cannon et al., who also reported significantly increased SERT availability in the insula, pgACC, and DCC, with a trend for increased SERT in the striatum and no change in the midbrain (Cannon et al. 2006b). However, Oquendo et al. reported the opposite: lower SERT availability in the midbrain, thalamus, amygdala, ACC, putamen, and hippocampus in BD patients (Oquendo et al. 2007), although with a different tracer ([^{11}C](+)McN5652) and a different definition of the binding potential (BP_P). The authors reported no significant differences for BP_{ND}, but argue that the BP_P value is more precise due to differences in SERT availability in the cerebellum reference region between BD patients and controls. Finally, Chou et al. reported significantly reduced SERT availability, which correlated inversely with duration of illness (Chou et al. 2010), but only in bipolar I patients. No associations between SERT availability and SERT 5-HTTLPR polymorphisms were found nor with severity of depression, although Cannon et al. reported increased SERT availability in the insula and dorsal cingulate associated with anxiety and OCD comorbidity and lower SERT availability in the midbrain of patients with attempted suicide (Cannon et al. 2006b).

SERT Availability in Unipolar and Bipolar Depression

The inconsistencies in the reported studies have been discussed previously (Meyer 2012; Oquendo et al. 2007) and have also been meta-analyzed recently (Gryglewski et al. 2014; Kambeitz and Howes 2015; Nikolaus et al. 2016), but merit a further discussion here to synthesize the above findings. Possible explanations consist of differences in selectivity of ligands (with concomitant binding to DAT in the substantia nigra in the midbrain for [^{123}I]β-CIT) or artifacts by differential displaceable binding of (low) SERT availability in the reference region (cerebellum) as put forward by Oquendo et al. (2007) and Selvaraj et al. (2011). In order to overcome this problem, these authors suggest to measure BP in conjunction with arterial input modeling, which might increase the sensitivity of measurements.

Selection of studied patients (with or without anxiety or comorbid anxiety disorders (Cannon et al. 2006b; Meyer 2007; Reimold et al. 2008); early–late onset of the first episode (before/after 40 years of age) (Meyer 2012); previous use of antidepressants (Meyer 2012; Parsey et al. 2006b) or mood stabilizers (Cannon et al. 2006b); or suicidality (Cannon et al. 2006b; Nye et al. 2013; Miller et al. 2013a; Yeh et al. 2014, 2015)) or healthy controls (with/without screening for familial vulnerability for MDD (Ruhe et al. 2007)) might furthermore have influenced results.

Genetic polymorphisms might influence SERT availability. First, the well-studied 5-HTTLPR polymorphism (Risch et al. 2009) was not correlated with SERT availability in single studies of controls (Shioe et al. 2003; Van Dyck et al. 2004; Willeit et al. 2001), although the LL genotype was associated with more SERT availability in the raphe in one small study (Heinz et al. 2000) and associated with increased SERT availability in the putamen in a study by Praschak-Rieder et al. (most prominent in Caucasian participants) (Praschak-Rieder et al. 2007). Nevertheless, in a review Willeit et al. concluded that by genotyping the tri-allelic variant of the 5-HTTLPR, a small to moderate effect could be shown, with the L_A/L_A carriers having slightly higher cerebral [^{11}C]DASB SERT binding (Willeit and Praschak-Rieder 2010). Therefore, small genotype effects cannot be ruled out in the above comparisons between patients and controls. The effects of 5-HTTLPR were also studied in MDD and BD patients: Parsey et al. did not find an association between genotype and SERT availability in the midbrain, putamen, amygdala, thalamus, hippocampus, or ACC of unipolar patients (Parsey et al. 2006a). Ruhe et al. reported no differences in SERT availability by genotype in the midbrain and thalamus (Ruhe et al. 2009c), as did Ho et al. (2013) for the striatum, thalamus, midbrain, and pons. However, Joensuu et al. reported lower SERT availability in the MPFC, but not in the midbrain for the SS carriers (Joensuu et al. 2010). Oquendo et al. found no indication of differences in SERT availability in the midbrain, putamen, amygdala, thalamus, hippocampus, or ACC between genotypes in BD patients (Oquendo et al. 2007). Second, in the population originally studied by Cannon et al. (2007), lower SERT availability in the thalamus was associated with the AA variant of the 5-HT_{2A} rs7333412 polymorphism (Laje et al. 2010). This polymorphism was previously associated with nonresponse to citalopram treatment of MDD (McMahon et al. 2006). Third, in a genome-wide association study in the same population, SERT availability was independently associated with a polymorphism of galactose mutarotase (GALM; rs6741892; T-allele vs. AA homozygotes) in controls and patients with unipolar or bipolar depression, which was replicated in an independent sample (Liu et al. 2011). GALM might increase local serotonin release and membrane trafficking and N-glycosylation of SERT which are related to the surface expression of SERT. These genetic differences might very well have influenced the findings in the above (nonrandomized) studies and were not (but neither could be) taken into account in most analyses. Furthermore, gene–environment interactions (e.g., the association of the s/s SERT genotype with seasonal influence on SERT availability (Kalbitzer et al. 2010)) also have not been addressed in patient samples.

Finally, as an explanation of inconsistencies, confounding by the season when scans were obtained might also have obscured differences. Seasonal change in SERT availability was well demonstrated, with higher SERT availability when daylight is reduced (winter) (Buchert et al. 2006; Kalbitzer et al. 2010; Praschak-Rieder et al. 2008; Ruhe et al. 2009a). Furthermore, the observed gender by disease status interactions, although only reported for SPECT studies (Ruhe et al. 2009a; Staley et al. 2006), might have obscured differences between MDD patients and controls as well. These factors can only be reassessed when original data at a patient level is available.

Interestingly, in seasonal affective disorder (SAD), global SERT availability (measured with [^{11}C]DASB PET) was comparable between SAD patients and controls in summer, but in their symptomatic phase in winter, SERT availability was higher than in controls (Mc Mahon et al. 2016). In a comparable study, Tyrer et al. (2016a) also observed larger increases in SERT availability in winter in the PFC and ACC but also in the dorsal putamen, thalamus, striatum, midbrain, and hippocampus of (most severe) SAD patients. In both studies the seasonal change in SERT availability was positively correlated with increase of symptom severity. Treatment with light therapy reduced [^{11}C]DASB PET SERT availability (Tyrer et al. 2016b). Moreover, in people resilient for SAD, a decrease of SERT availability was observed in winter, suggesting an adaptation to winter in the healthy states (Mc Mahon et al. 2018).

Also in BP patients, the mixed results could at first be attributed to different radioligands and the method how SERT availability was measured, but in addition to the abovementioned confounders, also differences in duration of illness between the studied populations and type of BP patients might be explanative. Bipolar I patients in the study by Chou showed most spread in disease duration, with lower SERT availability in patients with longer disease duration (Chou et al. 2010). Patients in the study by Oquendo et al. (with 10/18 bipolar I patients) appeared more chronically ill (Oquendo et al. 2007) than patients in the study by Cannon et al., who also investigated mostly bipolar II patients (13/18) (Cannon et al. 2006b). Furthermore, with these small samples, no conclusions can be made about confounding by season nor about interactions of gender by disease or gender by smoking. Due to the limited number of studies in bipolar patients with conflicting results and a suggestion of different SERT availabilities between bipolar I and II subtypes, no definite conclusions regarding bipolar depression can yet be drawn.

Notwithstanding the abovementioned concerns, although, in general, the majority of studies in unipolar depressed patients reported no differences in SERT availability in the midbrain, when considering the number of patients investigated, there is an indication that the midbrain of MDD patients displays lower SERT availability. Indeed, the methodologically most appropriate and updated meta-analysis of 25 in vivo imaging (PET and SPECT) studies showed significantly lower SERT availability in the brain stem of MDD patients (pooled Hedges' g = −0.31 [95% CI −0.55 to −0.08] (Kambeitz and Howes 2015), which was also concluded by the earlier meta-analyses by Gryglewski et al. (2014), including18 studies, and Nikolaus et al. (2016), who identified 38 studies until 2015, but poorly described their methods

(e.g., pooling and handling of different study sizes). More equivocal changes (decrease, no difference, increase) appear from studies reporting about the thalamus, striatum, and amygdala. The meta-analysis by Kambeitz and Howes (2015) indicated no significant difference in SERT availability between MDD patients and controls in the thalamus (Hedges' $g = -0.31$ [95% CI −0.65 to 0.03]), but a significant reduction in SERT availability in MDD patients in the striatum (Hedges' $g = -0.39$ [95% CI −0.62 to −0.17]) and also amygdala (Hedges' $g = -0.34$ [95% CI −0.61 to −0.13]).

As noted, several underpowered studies in fact indicated an *increase* in SERT availability in the midbrain (Ahonen et al. 2004; Cannon et al. 2006b, 2007; Dahlstrom et al. 2000; Herold et al. 2006; Reivich et al. 2004), which was also reported in females as a result of the gender by disease status interaction (Ruhe et al. 2009a). Increases of SERT availability may result in enhanced clearance of endogenous serotonin from the synaptic cleft. In addition to this potentially increased SERT availability, Meyer et al. reported that increased SERT availability in the midbrain, thalamus, striatum, PFC, and ACC showed a significant correlation with more pessimistic DAS scores (Meyer et al. 2004a). This group also showed that in patients with higher DAS scores, 5-HT_{2A} receptor density was increased (Meyer et al. 2004b). Taken together with the fact that long-term depletion of serotonin increases 5-HT_{2A} receptor density in rats (Stockmeier and Kellar 1986), it might be concluded that increased SERT availability in specific patients might lead to decreased intrasynaptic serotonin, high depressive dysfunctional attitudes, and an upregulation of 5-HT_{2A} receptors (Meyer 2007, 2012).

From another perspective, decreases in SERT availability may reflect high competitive binding of endogenous serotonin with the tracer, a deficit of serotonergic neurons in the raphe nuclei, less projections from these neurons to various brain regions, and deficits in SERT in the synapses of these projections but also a compensatory response to lower intrasynaptic serotonin, as proposed by Miller et al. (2009b). Increased endogenous serotonin competitive binding is unlikely, because in humans reductions of serotonin did not affect binding of [^{11}C]-DASB (Praschak-Rieder et al. 2005; Talbot et al. 2005; Kambeitz and Howes 2015). The compensatory response to lower intrasynaptic serotonin is more probable since the observed differences in SERT availability in the midbrain and thalamus (and possibly also in the caudate nucleus/striatum) between depressed and euthymic patients and the observations in SAD patients (Mc Mahon et al. 2016; Tyrer et al. 2016a) suggest compensatory flexibility of the SERT expression (Bhagwagar et al. 2007; Selvaraj et al. 2011). However, it cannot be ruled out that the results in MDD patients (Bhagwagar et al. 2007; Selvaraj et al. 2011) are incomparable because of selection bias of the different groups under study. Furthermore, the compensatory hypothesis is not unequivocally supported by serotonergic manipulations in rats, with some studies showing no alteration (Dewar et al. 1992; Graham et al. 1987; Graham and Langer 1987; Meyer 2007) of SERT availability after prolonged depletion states, while others reported a downregulation of SERT availability (Rattray et al. 1996; Rothman et al. 2003). A recent study of (drug-naive) never-depressed co-twins with high familial risk for MDD (defined as MDD or BD in the other co-twin) showed a

decrease in DLPFC SERT availability, but no differences in SERT availability in the midbrain (Frokjaer et al. 2009). This finding could be interpreted as a compensatory modulation of SERT density in the nerve terminals in the DLPFC, keeping the serotonergic tone at a required level.

However, the findings that childhood abuse, like in macaques who were raised deprived of their mothers (Ichise et al. 2006), reduces SERT availability in a widespread manner, including the midbrain (Miller et al. 2009b), are suggestive of a deficit of serotonergic neurons in the raphe nuclei that might be programmed in interaction with the environment during brain maturation in early childhood. This, in combination with associations with poorer MDD treatment response in patients with childhood abuse, the observation that lower SERT availability (Kugaya et al. 2004; Miller et al. 2008) was associated with non-remission (but see Ananth et al. (2018)), and the reports of reduced midbrain SERT availability (Lehto et al. 2006; Malison et al. 1998b; Newberg et al. 2005; Parsey et al. 2006b; Selvaraj et al. 2011; Newberg et al. 2012; Nye et al. 2013; Miller et al. 2013a; Yeh et al. 2014, 2015), is suggestive of a subgroup of patients in whom a (potential) serotonergic deficit is present as a vulnerability factor. It would be interesting to investigate whether these patients could be identified by more specific clinical features (e.g., treatment resistance and/or past treatment with antidepressants,, longer duration of depressive episodes, severity of depression and/or suicidal ideation, higher levels of childhood adversity, high recurrence rates, early age of onset) and/or by being more susceptible for depressed mood after, e.g., tryptophan depletion (Ruhe et al. 2007). It would only be possible to assess this in the current studies when mega-analyses of individual patient data could be done, requiring (mostly) complete data on these features. Alternatively, future prospective studies with large and specifically sampled individuals to address these uncertainties would be necessary.

SERT Occupancy During Antidepressant Treatment

The SERT is the primary target for many serotonin reuptake inhibiting antidepressants. With the availability of SERT tracers, the measurement of SERT availability before and after antidepressant treatment provides a measure of the dynamics of SERT occupancy that is reached during antidepressant treatment. This was primarily used to establish specificity of ligands for the SERT in single-dose SSRI blocking experiments during tracer development (six studies in controls). However, thereafter 8 and 12 studies investigated the dynamics of short- and long-term (>2 weeks) treatment with antidepressants, respectively (Table 4.3). Most studies scanned patients before and after treatment, although five studies used BP_{ND} obtained in controls as a reference (Lundberg et al. 2012; Pirker et al. 1995; Suhara et al. 2003; Tauscher et al. 1999; Voineskos et al. 2007), and one study compared BP_{ND} in responders and nonresponders to antidepressants without occupancy measures (Cavanagh et al. 2006).

SERT occupancy is a nonlinear function of drug serum/plasma concentration described by an E_{max} curve (Fig. 4.1). The rapid increase in occupancy occurs at clinically (very) low doses of the antidepressants, while at therapeutic doses, a maximum occupancy is reached at around 80–90%. Initial studies with SSRIs reported

Table 4.3 Results of serotonin transporter (SERT) occupancy imaging studies (PET/SPECT) in healthy controls and patients with major depression during treatment

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]
Rominger et al. (2015)	19 MDD	[^{123}I]β-CIT	6 weeks EsCIT 10–20 mg	Occ EsCIT:
				Thal: 42.2%
				Midbr: 53.4%
				A significant negative correlation existed between Thal (but not Midbr) SERT occupancy and change in DAT-weighted striatal BP_{ND} ($R = -0.62$; $p = .005$)[d] No association with SERT occupancy and change in HDRS
Lundberg et al. (2012)	20 MDD 26 HC	[^{11}C] MADAM	≥2 months (13 patients >1 year)	Occ[b] putamen:
			AMI 30 and 67.5 mg ($n = 2$)	AMI + CLOM: 61% SSRI: 70%
			CLOM 40–100 mg ($n = 3$)	
			VLX 150–300 mg ($n = 3$)	
			CIT 20–60 mg ($n = 4$)	
			FLX 20–60 mg ($n = 3$)	
			SER 50–200 ($n = 4$)	
			MIR (30 mg)	
Smith et al. (2011)	7 MDD (geriatric)	[^{11}C]DASB	8–10 weeks CIT 20–40 mg	Occ[c] CIT:
				Striatum: 73%
				Thal: 76%
Ruhe et al. (2009b, c), Ruhé et al. 2014, Simoons et al. (2020)	42 MDD (32 randomized after 6 weeks)	[^{123}I]β-CIT	6 weeks PAR 20 mg	Occ (6 weeks PAR 20 mg):
			In 32 nonresponders after 6 weeks, PAR 20 mg was randomized to another 6 weeks placebo-*increase* (= PAR 20 mg) or PAR-*increase* (PAR 30–50 mg)	Midbr: 71.1%
				Thal: 61.3%
				Amygd: 59% ($n = 15$)

Table 4.3 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]
				Occ (placebo-increase PAR 20 mg):
				Midbr: 84.6%–>87.7%
				Thal: 72.2%–>66.4%
				Occ (PAR-increase PAR 30–50 mg):
				Midbr: 76.2%–>78.6%
				Thal: 64.3%–>66.2%
Voineskos et al. (2007)	12 MDD 12 HC	[^{11}C]DASB	>4 weeks VLX 225–450 mg, SER 150–200 mg, CIT 60–80 mg	Occ[b] VLX, SER, CIT:
				Striat: 85.8%, 85.8%, 85.4%
				Midbr: 99.5%, 98.2%, 95.7
				Thal: 77.6%, 76.3%, 82.2%
Kasper et al. (2009), Klein et al. (2007)	15 HC (males only)	[^{123}I]-ADAM	10 days EsCIT 10 mg or CIT 20 mg	Occ in Midbr EsCIT: 81.5%, CIT 64.0%
				Sign. lower binding by CIT after 10 days probably attributable to accumulation of R-enantiomer over time
Shang et al. (2007)	8 HC	[^{123}I]β-CIT	9 days VLX 150 mg (4 days stable dose)	Occ[d] in Thal: 52.5%
				Occ Midbr: 55.7%
Catafau et al. (2006)	10 MDD	[^{11}C] MADAM	4–6 weeks PAR 20 mg	Occ: Midbr 66.4%, Thal 63.0%, Striat 61.3%
Herold et al. (2006)	21 MDD	[^{11}C] MADAM	1 week CIT 10 mg	Occ in Midbr 61%
Kasper et al. (2009), Klein et al. (2006)	25 HC (males only)	[^{11}C] MADAM	Single-dose EsCIT (5, 10, 20 mg) or CIT (10 or 20 mg)	Occ in Midbr EsCIT: 60% (5 mg), 64% (10 mg), and 75% (20 mg). CIT: 65% (10 mg) and 70% (20 mg)

(continued)

Table 4.3 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]
Takano et al. (2006b)	15 HC (males only)	[^{11}C]DASB	Single-dose DLX (5, 20, 40, or 60 mg) (n = 12)	Occ Thal: 43.6% (5 mg), 71.3% (20 mg), 80.6% (40 mg), 81.8% (60 mg)
			DLX 60 mg for 7 days and then stopped (n = 3)	Occ Thal: 84.3% (7 days), 71.9% (9 days), 47.1% (11 days)
Takano et al. (2006a)	6 HC (males only)	[^{11}C]DASB	FLV 50 mg once	Occ: Thal 71.8%, Amygd 71.6%, Striat 70.5%, PFC 74.6%, Hippoc 75.9%
Cavanagh et al. (2006)	24 MDD	[^{123}I]β-CIT	Monotherapy (n = 17): VLX 75–300 mg, SSRIs 20–60 mg, tricyclic 150 mg, MIR 30 mg; combinations of 2 antidepressants, addition of lithium, valproate, carbamazepine, T3, or antipsychotics. Dosages unchanged for ≥2 weeks	No occupancy percentages available. No significant difference in SERT residual activity between responders and nonresponders. Wide range of SERT availability
Parsey et al. (2006c)	17 HC	[^{11}C]DASB	4–6 days SER 25, 50, and 100 mg (4 days at designated dose)	Occ average across 15 ROIs: max 106.8%
				Occ range: OFC 126.9% to Thal 79.3%; no exact data for separate ROIs provided
Erlandsson et al. (2005)	16 HC (males only)	[^{123}I]-ADAM	CIT at different dosages (10–60 mg) for different durations (2–7 days)	Occ Midbr: max 84%
				No mean occupancy for separate dosing regimens given

Table 4.3 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]
Meyer et al. (2004b)	29 MDD 16 MDD + anxiety disorder 37 HC	[^{11}C]DASB	4 weeks open treatment: CIT 20–60 mg, FLX 20–60 mg, SER 50–200 mg, PAR 20–60 mg, VLX 75–225 mg In HC: CIT 1–10 mg, FLX 1–10 mg, SER 5–25 mg, PAR 5–10 mg, VLX 2.4–37.5 mg	Mean CIT, FLX, SER, PAR, VLX Occ:
				Striatum: 81.4%, 76.2%, 85.0%, 84.5%, 83.7%
				Thal: 72.3%, 69.1%, 76.8%, 74.7%, 71.3%
				Midbr: 87.5%, 82.3%, 91.8%, 93.4%, 91.0%
				No relation between striatal occupancy and clinical remission or percentage change in Hamilton depression scores
Kugaya et al. (2003, 2004)	10 MDD	[^{123}I]β-CIT	6 weeks PAR 20 mg	Occ at 1–3 weeks: Midbr 36.5%, Thal 29.1%
				Occ at 6 weeks: Midbr 32.6%, Thal 23.4%
	9 HC		CIT 40 mg (8 days), CIT 40 mg + bupropion 100 mg (8–16 days)	Occ CIT (8 days): Midbr 51.4%, Thal 39.4%; no sign. change thereafter
				Bupropion did not sign. alter SERT Occ
Suhara et al. (2003)	10 MDD	[^{11}C] McN5652	CLOM 20–250 mg, FLV 25–200 mg (long term)	Occ[b] Thal: CLOM ≥61.3–100%; FLV ≥76.6–93.6%
	27 HC		CLOM 5–50 mg, FLV 12.5–50 mg (single dose)	Occ Thal: CLOM ≥83.9–100%; FLV ≥7.7–87.7%

(continued)

Table 4.3 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]
Meyer et al. (2001c)	12 MDD	[^{11}C]DASB	4 weeks open treatment: PAR 20 mg (n = 7), 10 mg (n = 1), or CIT 20 mg (n = 4)	Occupancy after PAR/CIT 20 mg:
	17 HC			Striat 83%/77%
				Thal 75–78%/65–70%
				CingA 76–77%/77–79%
				No relationship between HDRS score and occupancy level
				Striatal Occ increased with higher serum levels of paroxetine, with app. 85% Occ at serum levels of 28 µg/L
Parsey et al. (2000)	2 HC (males only)	[^{11}C] McN5652	PAR 60 or 80 mg single dose prior to 2nd scan	Occ PAR 60 mg (n = 1):
				Amygd 64.8%, Hip 46.0%, Thal 38.4%, Midbr 83.9%, CingA 26.4%
				Occ PAR 80 mg (n = 1): data not reported
Tauscher et al. (1999)	1 patient with MDD and bulimia	[^{123}I]β-CIT	FLX 60 mg (no baseline)	Occ[b] of app. 41% in Thal and Hypothal was estimated
Hiltunen et al. (1998)	5 HC	[^{123}I] nor-β-CIT	CIT 30 mg 3 h *prior* to injection (n = 1); CIT 20 mg (n = 1), VLX 37.5 mg (n = 1) 1 h *after* injection vs. untreated (n = 2)	CIT 30 mg 3 h *prior* to injection BP_{ND} midbrain 52% less than in untreated subjects. For venlafaxine and citalopram 20 mg, no data given

Table 4.3 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]
Pirker et al. (1995)	13 MDD 11 HC	[^{123}I]β-CIT	≥1 week CIT 20 mg (n = 5), 40 mg (n = 6), and 60 mg (n = 1); one untreated patient	CIT-treated patients showed sign. decrease in Thal, Hypothal, and Midbr BP_{ND} compared to controls[b]
				No difference in binding between CIT 20 and 40 mg

Abbreviations: *Amygd* Amygdala, *CIT* Citalopram, *CLOM* Clomipramine, *DLX* Duloxetine, *EsCIT* Escitalopram, *FLV* Fluvoxamine, *FLX* Fluoxetine, *Hypothal* Hypothalamus, *Midbr* Midbrain, *Occ* Occupancy, *OFC* Orbitofrontal cortex, *PAR* Paroxetine, *SER* Sertraline, *Thal* Thalamus/diencephalon, *VLX* Venlafaxine

[a]The change in binding ratios is estimated as the change in BP_{ND} after treatment relative to the before treatment scan unless stated otherwise

[b]No baseline scan; occupancy relative to BP_{ND} in untreated healthy controls

[c]Three different tracer kinetic models revealed similar outcomes

[d]Scans obtained 20–24 h after injection of radioligand

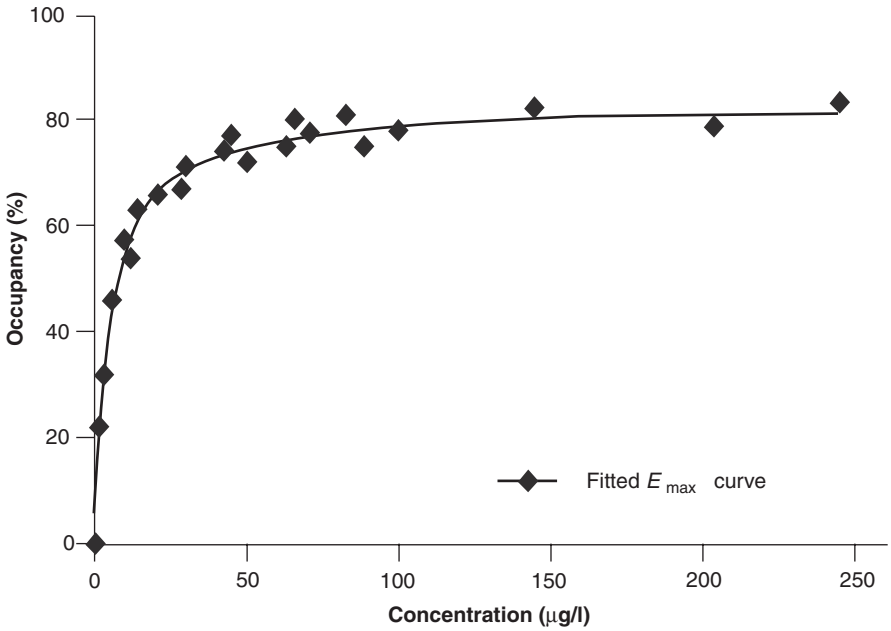

Fig. 4.1 Concentration–occupancy curve. This figure shows a hypothetical E_{max} curve. The curve is defined with the formula $y = (a*x)/(b + x)$, in which a represents the maximum binding (B_{max}) and b the concentration with 50% occupancy (EC_{50}). Here B_{max} = 82.8% ± 0.85 (SE) and EC_{50} = 5.09 µg/L ± 0.32 (SE)

that the lowest therapeutic doses of SSRIs were associated with ≥80% occupancy in the striatum, which was assumed to be necessary for a clinical response (Meyer et al. 2001c, 2004b; Suhara et al. 2003). However, later studies did not unequivocally replicate this finding (Catafau et al. 2006; Kugaya et al. 2004; Ruhe et al. 2009b, c; Smith et al. 2011; Rominger et al. 2015), which might also be attributable to the difference in radiotracers ([^{11}C]DASB versus [^{123}I]β-CIT) or an elderly population (Smith et al. 2011).

Clinical response was not associated with occupancy of SERT in the striatum, thalamus, or midbrain (Cavanagh et al. 2006; Meyer et al. 2004b; Ruhe et al. 2009b, c; Rominger et al. 2015). However, in a voxel-wise analysis in elderly patients, Smith et al. found significant associations of SERT occupancy with decrease in HDRS scores in the ACC; middle and inferior frontal, temporal, and parahippocampal gyrus; and cuneus. These regions also showed a change in glucose metabolism, which—in addition—was associated with decreases in HDRS scores (Smith et al. 2011). One study showed an association between SERT occupancy by the SSRI paroxetine (20 mg/day) and decrease in HDRS scores, but only in carriers of the L_A/L_A SERT promoter polymorphism. Higher occupancy was associated with more decrease in HDRS ($p < .001$) (Ruhe et al. 2009c). Previously, the L/L polymorphism had been associated with superior treatment effects (Serretti et al. 2007), while non-S/S carriers showed more favorable structural and functional anatomy of the amygdala–cingulate feedback circuitry (Pezawas et al. 2005). A possible explanation could be that the limbic–cortical network and the serotonergic innervations are developed more flexibly in non-S/S carriers. The significant association between higher SERT occupancy and increased reduction of symptoms in L_A/L_A carriers might be indicative for this broader range of regulation for the serotonergic system. Higher SERT occupancy might then result in more effects of serotonergic antidepressants in L_A/L_A carriers.

Our group also investigated the increase of SERT occupancy in a randomized, placebo-controlled dose-escalation study. This study showed that increasing the dose of paroxetine to 50 mg/day did not increase response rates nor improve changes in HDRS scores. Moreover, the SERT occupancy did not increase more after true dose escalation relative to the placebo dose escalation (Ruhe et al. 2009b). This study thus provided a rationale for the observed flat dose–response relationship for SSRIs (Adli et al. 2005; Corruble and Guelfi 2000; Ruhe et al. 2006). In the same study, we examined whether four polymorphisms of the ABCB1 gene coding for the P-glycoprotein efflux pump, responsible for the intracerebral concentrations of paroxetine and antidepressants in general (Cordon-Cardo et al. 1989), influenced SERT occupancy in 38 MDD patients after 6 weeks of paroxetine treatment (20 mg/day). Although we found significantly higher maximum SERT occupancies in the E_{max} curves for the rs1128503 and rs2032582 SNPs (C-carriers and G-carriers, respectively), this did not affect clinical responses (Simoons et al. 2020). Since previous meta-analyses showed equivocal or nonexisting associations of these SNPs with clinical response as well, the clinical relevance of our differences in SERT occupancy curves remains to be elucidated further (Breitenstein et al. 2015; Niitsu et al. 2013). In addition, in a smaller subsample ($n = 15$ patients) of this study, we showed

that higher SERT occupancy by paroxetine (20–50 mg/day) in both amygdalae was associated with greater attenuation of left amygdala activation by negative facial expressions as measured with fMRI (Ruhé et al. 2014). Given that the change in left amygdala activation was significantly correlated with (proportional) change in HDRS, this finding may provide a rationale for decreased limbic activity seen during treatment of MDD. It might also explain the rapid decrease in negative attentional bias and amygdala activation caused by SSRIs.

Finally, occupancy studies are increasingly used in the development and evaluation of the effects of antidepressants. First, several SERT occupancy studies indicated that the relationship between the in vitro affinity for SERT of SSRIs and their in vivo occupancy is poor. Therefore, with phase I occupancy studies, a minimal effective dose of new antidepressants might be determined better. Second, differences between isoforms of new antidepressants can be investigated. For example, Kasper et al. (2009) combined two occupancy studies (Klein et al. 2006, 2007) with an interesting approach: they compared the occupancy curves of citalopram and escitalopram (which contains only the S-enantiomer, while citalopram contains both the S-enantiomer and the pharmacologically inactive R-enantiomer) during acute and prolonged treatment and showed that although doses were equivalent, prolonged treatment for 10 days with escitalopram resulted in significantly higher occupancy values (81.5 ± 5.4%) than citalopram (64 ± 12.7%; $p < .01$). Furthermore, they observed a trend that, relative to acute single doses, after prolonged treatment the E_{max} of SERT occupancy by serum level curves increased in escitalopram, while it decreased for citalopram. This could be explained by the longer half-life of the R-enantiomer, which will accumulate over time and will compete more for binding to the SERT (despite its lower affinity relative to the S-enantiomer). Because the R-enantiomer binds to a low-affinity allosteric site on the SERT (Mansari et al. 2007), this will preclude binding of the S-enantiomer to the primary 5-HT binding site (but not the ligand), resulting in lower SERT blockade in the end.

In conclusion, occupancy studies are useful in the development of new tracers, in the study of the properties and dosing of new antidepressants, and in the study of the relationship between clinical and neurobiological effects of antidepressants.

4.3.1.3 Serotonin Receptor Imaging

5-HT_{1A}

The 5-HT_{1A} receptors are presynaptically localized on serotonergic cell bodies situated in the raphe nuclei in the midbrain and postsynaptically in terminal areas. These receptors are G-protein-coupled receptors that have an inhibitory influence on neuronal firing (Barnes and Sharp 1999). Therefore, antidepressants like SSRIs that increase synaptic 5-HT in the projection areas may inhibit 5-HT neuronal activity in early stages of treatment, and this inhibition can be prevented by administration of a 5-HT_{1A} antagonist like WAY-100635 (Gartside et al. 1997) or pindolol.

In vivo imaging of 5-HT_{1A} receptors by PET can therefore contribute to the understanding of the mechanisms of antidepressant drugs and elucidate underlying mechanisms of nonresponders to SSRIs and the involvement of desensitization of

autoreceptors. So far, mainly PET tracers for 5-HT_{1A} receptor have been developed (Passchier and van Waarde 2001). However, only [*carbonyl*-^{11}C]WAY-100635 (or [^{11}C]WAY-100635) has been used for studies which compare healthy controls to patients with MDD. WAY-100635 is a highly selective antagonist for the 5-HT_{1A} receptor; however, the synthesis of [^{11}C]WAY-100635 is technically challenging. Another 5-HT_{1A} antagonistic tracer used is [^{18}F]MPPF; this tracer has lower affinity for the 5-HT_{1A} receptor and lower brain uptake, probably because it is a substrate for P-glycoprotein, an efflux pump in the BBB. As the cerebellum is almost devoid of 5-HT_{1A} receptors, it was proposed that this region could be used as a reference region for kinetic analysis. Nevertheless, the outcome measures of the kinetic model used to analyze BP can differ depending on which activity measure is used as a reference: BP_{ND} (specific binding in respect to non-displaceable radioligand in tissue), BP_F (specific binding in respect to free radioligand in tissue), or BP_P (specific binding in respect to total parent radioligand in plasma) (Innis et al. 2007).

Twelve studies found an overall decrease in BP_{ND} or BP_P in several brain areas expressing postsynaptic 5-HT_{1A} receptors, and especially in the DRN, which expresses presynaptic 5-HT_{1A} receptors (Table 4.4A, B). In contrast six studies found an increase notably when BP_F was used as an outcome measure. One study did not detect an effect.

The most pronounced effects were found by Drevets et al. (effect size >1); this study also included patients with BD (Drevets et al. 1999, 2007). The largest decreases in BP_{ND} were found in the mesiotemporal cortex (−28%), hippocampus (−25%), and raphe nuclei (−42%). Another study in remitted MDD patients also found large effects in cortical areas, but no effect in the raphe nuclei (Bhagwagar et al. 2004). Sargent et al. also found that there is a reduction in 5-HT_{1A} binding in the medial temporal cortex, temporal pole, orbitofrontal cortex, anterior cingulate cortex, and insula cortex of MDD patients, which did not change when patients used antidepressants (Sargent et al. 2000). Similar results were found in MDD patients on SSRIs that additionally received electroconvulsive therapy. A reduction in BP_{ND} in the raphe nuclei was found in these patients, and this was not normalized after electroconvulsive therapy (Saijo et al. 2010). Hirvonen et al. found an overall decrease in BP_P, but not in BP_{ND}, and there was no significant difference in any individual brain region (Hirvonen et al. 2008a). In this same cohort, they tested the effect of the SSRI fluoxetine or psychotherapy on 5-HT_{1A} binding and found that psychotherapy increased BP_{ND} (with the cerebellum as reference tissue) compared to fluoxetine treatment and healthy controls. Fluoxetine did not induce any changes compared to healthy controls, although the clinical outcome was the same as in the patients treated with psychotherapy (Karlsson et al. 2010). Another study found only an effect on BP in the raphe nuclei (Meltzer et al. 2004). In postpartum depression (including patients with bipolar depression), there also seems to be a reduction of 5-HT_{1A} BP_{ND} in various cortical areas like the orbitofrontal, cingulate, temporal, and occipital cortex (Moses-Kolko et al. 2012). In addition a reduction in 5-HT_{1A} binding in the raphe nucleus was reported.

Table 4.4 Results of 5-$HT_{1A/B}$ imaging studies (PET) in patients with major depression as compared to controls

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Change 5-HT_{1A} binding	Effect size (*d*)
A. Unipolar depression 5-HT_{1A}					
Miller et al. (2013b)	21/51	[^{11}C] WAY-100635	Unmedicated	Raphe nuclei: 56% ↑ BP_F Amygdala: 37% ↑ BP_F Hippocampus: 29% ↑ BP_F Parahippocampal gyrus: 45% ↑ BP_F Temporal cortex: 39% ↑ BP_F Anterior cingulate: 28% ↑ BP_F Cingulate: 43% ↑ BP_F Dorsolat. prefront. cortex: 40% ↑ BP_F Medial prefrontal cortex: 26% ↑ BP_F Ventral prefrontal cortex: 38% ↑ BP_F Insula: 32% ↑ BP_F Occipital cortex: 44% ↑ BP_F Parietal cortex: 44% ↑ BP_F	1.33 1.02 0.94 1.37 1.19 1.20 1.33 1.15 0.99 1.15 1.06 1.26 1.24
Lothe et al. (2012)	6/18	[^{18}F]MPPF	Naive	Medial orbital cortex: 25% ↓ BP_{ND}	1.36
				Perigenual anterior cingulate cortex: 23% ↓ BP_{ND}	1.39
				Dorsal anterior cingulate cortex: 22% ↓ BP_{ND}	1.31
				Raphe nuclei: 30% ↓ BP_{ND}	1.18

(continued)

Table 4.4 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Change 5-HT_{1A} binding	Effect size (*d*)
Saijo et al. (2010)	9/9	[^{11}C] WAY-100635	Paroxetine/ fluvoxamine	Prefrontal cortex: 5.8% ↓ BP_{ND} (ns)	0.24
				Medial frontal cortex: 6.2% ↓ BP_{ND} (ns)	0.22
				Temporal cortex: 4.4% ↓ BP_{ND} (ns)	0.19
				Parietal cortex: 2.2% ↓ BP_{ND} (ns)	0.08
				Occipital cortex: 1.9% ↑ BP_{ND} (ns)	0.06
				Anterior cingulate: 7.9% ↓ BP_{ND} (ns)	0.34
				Insula: 7.9% ↓ BP_{ND} (ns)	0.31
				Amygdala: 4.6% ↑ BP_{ND} (ns)	0.21
				Hippocampus: 7.8% ↓ BP_{ND} (ns)	0.37
				Midbrain raphe: 32% ↓ BP_{ND}	1.36
Parsey et al. (2010)	22/9	[^{11}C] WAY-100635	Drug-free (>2 weeks)	Overall: ↑ BP_F (no exact values given)	0.85
Miller et al. (2009a)[a]	28[b] (15 remitted, 13 naive)/51 (healthy)	[^{11}C] WAY-100635	Drug-free (>6 months)	Overall: ↑ BP_F (no exact values given)[c]	[d]
				Overall: 11.4% ↑ BP_{ND} with cerebellar white matter as ref (ns)	
				Overall: 22.6% ↓ BP_{ND} with cerebellar gray matter as ref	
Hirvonen et al. (2008a)[a]	21/15	[^{11}C] WAY-100635	Drug-free (>4 months)	Overall: 19% ↓ BP_P	0.69
Mickey et al. (2008)	14/17		Drug-free (>6 months)	Overall: no effect	[d]

Table 4.4 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Change 5-HT_{1A} binding	Effect size (*d*)
Moses-Kolko et al. (2008)	9 postpartum (4 BD)/7		Drug-free (>3 weeks)	Left lateral orbitofrontal cortex:18% ↓ BP_{ND}	1.35
				Right lateral orbitofrontal cortex: 23% ↓ BP_{ND}	1.96
				Mesiotemporal cortex: 22% ↓ BP_{ND}	2.38
				Subgenual anterior cingulate: 28% ↓ BP_{ND}	2.46
				Pregenual anterior cingulate: 23% ↓ BP_{ND}	2.10
				Postcentral gyrus: 19% ↓ BP_{ND}	1.26
				Occipital cortex: 19% ↓ BP_{ND}	1.42
				Raphe nucleus: 11% ↓ BP_{ND}	0.78
Drevets et al. (2007)	16 (2 BD)/8	[^{11}C] WAY-100635	Drug-free (>3 weeks)	Mesiotemporal cortex: 28% ↓ BP_{ND}	1.19
				Raphe: 42% ↓ BP_{ND}	1.96
Parsey et al. (2006d)[a]	22[b] (13 remitted)/43	[^{11}C] WAY-100635	Drug-free (>2 weeks)	Overall: ↑ BP_F unremitted vs. remitted	[d]
Parsey et al. (2006e)[a]	28[b] (13 naive)/43	[^{11}C] WAY-100635	Drug-free (>2 weeks)	Overall: ↑ BP_F drug-naive	[d]
Bhagwagar et al. (2004)[a]	14 (remitted)/18	[^{11}C] WAY-100635	Drug-free (>6 months)	Several cortical areas: 17% ↓ BP_{ND}	4
				Raphe: 1% ↓ BP_{ND} (ns)	0.22
Meltzer et al. (2004)[a]	17 (late-life)/17	[^{11}C] WAY-100635	Drug-free (>2 weeks)	Raphe: 34% ↓ BP_{ND}	0.98
				Lateral orbitofrontal cortex: 8% ↓ (ns)	0.32
				Pregenual cingulate: 4% ↓ (ns)	0.13
				Subgenual cingulate: 2% ↓ (ns)	0.06
				Hippocampus: 15% ↓ (ns)	0.32
				Mesial temporal cortex: 8% ↓ (ns)	0.20
				Occipital cortex: 1% ↓ (ns)	0.03

(continued)

Table 4.4 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Change 5-HT_{1A} binding	Effect size (*d*)
Rabiner et al. (2004)[a]	7/7	[^{11}C] WAY-100635	Venlafaxine	Raphe: 10% ↓ BP_F (ns)	0.74
				Rest: 17% ↑ BP_F	1.28
Sargent et al. (2000)	15/18	[^{11}C] WAY-100635	Drug-free (>3 months)	Overall: 10.8% ↓ BP_{ND} Medial temporal cortex right: 10.3% ↓ BP_{ND}	0.69
				Temporal pole right : 8.8% ↓ BP_{ND}	0.85
				Temporal pole left: 12.1% ↓ BP_{ND}	1.04
				Orbitofrontal cortex right: 15.8% ↓ BP_{ND}	1.06
				Orbitofrontal cortex left: 12.9% ↓ BP_{ND}	0.79
				Ventral anterior cingulate cortex right: 17% ↓ BP_{ND}	0.88
				Dorsal anterior cingulate cortex right: 15.1% ↓ BP_{ND}	0.79
				Dorsal anterior cingulate cortex left: 14% ↓ BP_{ND}	0.94
				Insula cortex right: 12.9% ↓ BP_{ND}	0.88
				Insula cortex left: 13% ↓ BP_{ND}	0.88
				Dorsolateral prefrontal cortex left: 11.4% ↓ BP_{ND}	0.59
B. Bipolar depression 5-HT_{1A}					
Nugent et al. (2013)	26 (BD)/37	[^{18}F] FCWAY	Unmedicated	Amygdala and hippocampus: 12% ↓ BP_{ND}	[d]
Sargent et al. (2010)[a]	8 (euthymic BD)/8	[^{11}C] WAY-100635	On different drugs	Overall: 2% ↓ BP_{ND} (ns)	0.12
Sullivan et al. (2009)[a]	32 (BD)/47	[^{11}C] WAY-100635	Drug-free (>2 weeks)	Overall: 25.1% ↑ BP_F	[d]
				Male	
				Raphe: 102% ↑ BP_F	

Table 4.4 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Change 5-HT_{1A} binding	Effect size (*d*)
				Forebrain: 29–50% ↑ BP_F	
Drevets et al. (1999)	12 (4 BD)/8	[^{11}C] WAY-100635	Drug-free (>2 weeks)	Mesiotemporal cortex: 27% ↓ BP_{ND} Raphe: 42% ↓ BP_{ND} Hippocampus: 25% ↓ BP_{ND}	1.16 1.27 1.12
C. Unipolar depression 5-HT_{1B}					
Murrough et al. (2011)	10/10	[^{11}C]P943 (5-HT_{1B})	Drug-free (>4 weeks)	Ventral striatum/ pallidum left: 16.1% ↓ BP_{ND}	1.85
				Ventral striatum/ pallidum right: 21.1% ↓ BP_{ND}	1.49

The change in binding ratios is estimated from several brain regions of depressive patients and compared to reported healthy control data

[a]Other statistical test than *t*-test used

[b]Same sample of patients

[c]Values given reflect comparison of patients in remission and healthy controls; comparable results are found for drug-naive MDD patients

[d]No individual data available to calculate the effect size

Only one study used [^{18}F]MPPF as a tracer to compare controls with depressive patients and effects of treatment. As a pilot study, the sample size was small, but a general decrease in BP_{ND} in depressive patients was found. Moreover, 30 days of SSRI treatment increased the reduced BP_{ND} to control levels in the medial orbital cortex (Lothe et al. 2012). Intriguingly, two recent studies have linked 5-HT_{1A} receptor binding to specific cognitive features of MDD (Schneck et al. 2020; Langenecker et al. 2019).

Several studies found an overall increase of BP_F in the brain when healthy controls were compared to MDD patients. The most striking effects were found in patients with BD where an increase in BP_F of 102% was found in the raphe nuclei and 29–50% in the forebrain. Interestingly, this difference was only present in males and not in females (Sullivan et al. 2009).

Other studies also found an increase in BP_F, although heterogeneous results were found in respect to remission and the effects of treatment. Miller and colleagues showed that the increase in 5-HT_{1A} BP_F was similar in patients with symptomatic MDD and patients who had recurrent MDD, but were in remission (Miller et al. 2009a). This is in line with results found by Rabiner et al., who still found an increase in patients who were currently treated with venlafaxine (Rabiner et al. 2004). Contradictorily, Parsey et al. found a significant increase in BP_F in MDD patients that were drug-naive, but as soon as patients had used antidepressants in their lives, the effect was gone (Parsey et al. 2006e). These authors replicated their

findings in a new cohort, where depressive patients who had not recently received antidepressants were compared with healthy controls (Parsey et al. 2010). Additionally, a higher BP_F was observed in non-remitted patients compared to remitted patients after treatment (Parsey et al. 2006d), perhaps an indication that 5-HT_{1A} binding is related to SSRI treatment response. Only two studies did not find any effect on 5-HT_{1A} binding in depressive patients. One study included euthymic patients with BD who used different kinds of medication and did not find differences (Sargent et al. 2010). The second study included non-medicated depressive patients and reported a relation between MAO-A genotype (the enzyme that deaminates serotonin) and 5-HT_{1A} binding in women (Mickey et al. 2008). The difference was apparent in brain regions like the medulla, midbrain, frontal cortex, hippocampus, and amygdala. The different MAO genotypes were not related to disease, which questions whether these genotypes and the related difference in 5-HT_{1A} binding are indeed related to MDD.

Some studies found a relationship to scores of depressive severity as measured by the HDRS (Meltzer et al. 2004; Rabiner et al. 2004). Rabiner et al. discovered that healthy controls showed a higher occupancy of pindolol. This preferential occupancy was negatively correlated to depression severity on HDRS (Rabiner et al. 2004).

Antidepressant treatments appear to decrease 5-HT_{1A} binding. This has been shown for SSRIs in a PET study of 19 MDD patients before and after 5–9-week treatment with either paroxetine, citalopram, or escitalopram, where raphe nuclei [^{11}C]WAY-100635 binding was lower posttreatment irrespective of the magnitude of antidepressant treatment response (Gray et al. 2013). Such an antidepressant-associated downregulation of 5-HT_{1A} autoreceptor binding appears to reverse within 2 weeks of medication discontinuation (Metts et al. 2019). Moreover, a [^{11}C]WAY-100635 PET study in 12 patients with severe MDD undergoing electroconvulsive therapy (ECT) (of whom 10 were responders) showed global decreases in serotonin 5-HT_{1A} binding in the projection areas. No correlation with the magnitude of antidepressant response was detected though (Lanzenberger et al. 2013). On the other hand, in bipolar depression, mood stabilizers (lithium or divalproex) seem to decrease 5-HT_{1A} receptor binding, most prominently in the amygdala and hippocampus (Nugent et al. 2013).

Finally, a few studies have suggested that 5-HT_{1A} receptor binding at baseline can help predict antidepressant treatment response in unipolar depression. Miller et al. (2013b) showed that patients with the highest binding at baseline were most likely to respond successfully to escitalopram treatment. Likewise, in a naturalistic study in bipolar depression (n = 41), higher 5-HT_{1A} receptor binding at baseline predicted remission with treatment with mixed pharmacological approaches (Lan et al. 2013). Also in bipolar depression (n = 27), lithium monotherapy treatment response was related to baseline serotonergic markers including 5-HT_{1A} receptor binding ([^{11}C]-CUMI-101) and 5-HTT binding ([^{11}C]-DASB) such that, in contrast to unipolar depression, the lower the binding, the better response (Ananth et al. 2020). In this study, 5-HT_{1A} binding was able to predict remission with 85% accuracy (87% sensitivity, 80% specificity).

In summary, it appears that 5-HT_{1A} receptors play a role in symptomatology and recovery of depression in some patient groups. Because not all patient groups are similar and almost none of the patients are drug-naive, interpretation of this collection of 5-HT_{1A} studies remains problematic. Although PET imaging shows that there probably is a difference in 5-HT_{1A} receptor binding in depressed patients, the direction of this change appears to be dependent on the kinetic model used.

Several of the studies mentioned above show a trend toward a difference in distribution volume in the cerebellum between healthy controls and depressed patients (Hirvonen et al. 2008a; Meltzer et al. 2004; Miller et al. 2009a). This could severely compromise the results when the cerebellum is used as a reference tissue for kinetic analysis. Indeed, Miller and colleagues compared different outcome parameters to relate to previously performed studies where BP_{ND} was measured instead of BP_F. While they found an increase in BP_F, they found a nonsignificant increase in BP_{ND} when cerebellar white matter was used as a reference tissue, a significant decrease in BP_{ND} when cerebellar gray matter was used as a reference tissue, and no effect when BP_P was used as an outcome measure. These conclusions were also drawn by their colleagues (Parsey et al. 2010). They additionally showed that the BP_{ND} in cerebellar gray matter decreases when the 5-HT_{1A} antagonist pindolol is applied, while this does not account for cerebellar white matter. Therefore, we conclude that the decrease in BP_{ND} found in most studies using the cerebellum as a reference tissue is due to changes in specific binding in the cerebellum. When considering studies that used an arterial input function only, a higher 5-HT_{1A} availability has been observed and replicated (Parsey et al. 2006d, e; Miller et al. 2013b). Therefore, most probably, MDD is associated with an increase in binding to 5-HT_{1A} receptors, which is in line with the observation that both SSRIs and ECT antidepressant treatment of MDD lower 5-HT_{1A} receptor binding as mentioned above and that 5-HT_{1A} binding might be useful to predict treatment outcome (although inconsistent findings exist). It remains difficult to judge whether the observed differences reflect state or trait effect, as some studies do not find an effect of remission or treatment while others do.

Also postmortem studies show contradictory results. Some studies show a reduction in mRNA or radioligand binding (Arango et al. 2001; Lopez et al. 1998), while others show an increase in 5-HT_{1A} receptor binding (Stockmeier et al. 1998).

5-HT_{1B}

The 5-HT_{1B} receptor is another serotonergic autoreceptor, which is present on serotonergic neurons in terminal regions and regulates the release of 5-HT in these regions. Activation of this receptor decreases the amount of 5-HT released in the synapse. Indeed, the amount of 5-HT released in the extracellular space by an SSRI, as measured with microdialysis in rats, is greatly increased by simultaneous 5-HT_{1B} antagonism (Cremers et al. 2000). However, it seems that overexpression of these receptors in the dorsal raphe nuclei actually reduces fear and depressive-like behavior in rats, which is contradictory to the hypothesis that antagonism and the consequential increase in 5-HT would lead to higher efficacy of antidepressants (McDevitt et al. 2011). An experimental study in mice suggested that the antidepressant

properties of the 5-HT_{1B} agonist anpirtoline depend on 5-HT_{1B} heteroreceptors present in the substantia nigra and striatum, but not on the autoreceptors present on 5-HT neurons (Chenu et al. 2008). Interestingly, in the ventral tegmental area and nucleus accumbens, 5-HT_{1B} receptor agonists are known to increase dopamine release, possibly through inhibiting GABA release from interneurons (Yan et al. 2004; Yan and Yan 2001). These preclinical data suggest a role for 5-HT_{1B} receptors in antidepressant effects; at least some of the antidepressant effects may be related to the interaction with the dopaminergic system. In addition, single nucleotide polymorphisms in the 5-HT_{1B} receptor gene seem to be related to antidepressant response in patients with major depression (Villafuerte et al. 2009; Xu et al. 2012). Antidepressant treatment mechanisms may also include reduced 5-HT_{1B} receptor binding in the dorsal brain stem as shown in response to cognitive behavioral therapy of MDD (Tiger et al. 2014).

Only one recent study with a recently developed PET radioligand ([^{11}C]P943) examined the binding of 5-HT_{1B} receptors in MDD patients (Table 4.4C). In this study, a decrease in BP_{ND} was found in the left and right ventral striatum/pallidum, with effect sizes of 1.85 and 1.49, respectively (Murrough et al. 2011). These findings are in accordance with the results of Chenu et al., who found that the antidepressant effect of a 5-HT_{1B} agonist depends on stimulation of heteroreceptors and not on the stimulation of autoreceptors (Chenu et al. 2008).

5-HT_{2A}

The role of the serotonin 2A receptor (5-HT_{2A}) in MDD has been extensively studied in cross-sectional settings, but in BD no studies on 5-HT_{2A} have been done yet. Investigations in MDD have been partly motivated by the fact that serotonergic neurotransmission is critical in the mechanisms of action of antidepressants. Those actions include direct 5-HT_{2A} receptor inhibition and 5-HT_{2A} receptor downregulation, for example, as seen with the SSRIs (Carr and Lucki 2011; Gray and Roth 2001; Meyer et al. 2001a). Also, the 5-HT_{2A} receptor has been one of the few serotonin receptor subtypes in the serotonergic neurotransmitter system where several PET and SPECT tracers have been available for selective mapping and quantification in the living human brain (Paterson et al. 2013). Five radioligands for the 5-HT_{2A} receptor have been used successfully in human studies: the SPECT radioligand [^{123}I]R91150 and the PET radioligands [^{18}F]setoperone, [^{18}F]altanserin, [^{18}F]deuteroaltanserin, and [^{11}C]MDL 100,907. Even though [^{123}I]R91150 displays a lower signal-to-noise ratio and SPECT provides lower resolution compared to the available PET methods, it offers some advantages due to the more widespread availability of SPECT facilities. However, it has not directly been used to study the pathophysiology of MDD or BD. Radiosynthesis of the ^{18}F-labeled R91150 is complicated and therefore has not been feasible in clinical studies. The radioligand [^{18}F]setoperone is less selective than [^{18}F]altanserin and [^{11}C]MDL 100,907 due to a relative high affinity for dopamine D_2 receptors. Nevertheless, due to the differential localization of the 5-HT_{2A} relative to D_2 receptors, [^{18}F]setoperone has been applied successfully in several studies. Of the PET radioligands, [^{18}F]altanserin has continued to be the most widely used, despite its lipophilic radiometabolite. This use is

especially due to its longer-lived ^{18}F-label, which enables the application of a bolus/infusion paradigm that allows for acquisition under steady-state conditions and overcomes the modeling issue with the lipophilic metabolites. [^{18}F]deuteroaltanserin was developed in order to identify a ligand with no lipophilic metabolites crossing the blood–brain barrier; however, with the steady-state modeling of [^{18}F]altanserin, this was no longer needed. [^{11}C]MDL 100,907 is a more selective 5-HT$_{2A}$ ligand than [^{18}F]altanserin in vitro, but is much less widely used as a 5-HT$_{2A}$ radioligand for in vivo studies than [^{18}F]altanserin. The reason for this might be the shorter-lived ^{11}C-label and more demanding modeling requirements for [^{11}C]MDL 100,907 that under ideal circumstances necessitate arterial blood sampling. However, seemingly, reference tissue modeling methods may be feasible for larger group comparisons in populations that tolerate the longer acquisition time of 90–120 min as compared to 40 min for bolus/infusion [^{18}F]altanserin (Talbot et al. 2012). In summary, at the current state of tracer evolution, [^{18}F]altanserin PET and [^{11}C]MDL100,907 PET are the best tools for selective 5-HT$_{2A}$ receptor imaging though with some limitations in subcortical regions where signal-to-noise ratio is low (Paterson et al. 2013). However, these tracers are antagonist ligands and bind to the total pool of both membrane-bound and internalized 5-HT$_{2A}$ receptors. As such, the interpretations of the imaging findings are limited with respect to understanding the role of the biologically active part of the 5-HT$_{2A}$ receptor system which is highly relevant for the pathophysiology of MDD (also see Sect. 4.4.1).

Hereafter, we will outline how postmortem data, data from at-risk individuals, and recent in vivo imaging data, based on highly selective tracers and patients that were not recently medicated, are converging to support that high prefrontal 5-HT$_{2A}$ receptor binding is implicated in MDD. The majority of postmortem studies in suicide victims of major depression report increased 5-HT$_{2A}$ receptor binding in the prefrontal cortex particularly in the Brodmann areas 8 and 9 (Arango et al. 1997; Stockmeier 2003). Table 4.5 summarizes the main findings of in vivo brain imaging studies of 5-HT$_{2A}$ in patients with current or remitted major depression relative to healthy controls.

Initial findings of in vivo receptor imaging studies were contradictory (Attar-Levy et al. 1999; Biver et al. 1997; D'haenen and Bossuyt 1994; Meltzer et al. 1999; Messa et al. 2003; Meyer et al. 1999, 2003; Yatham et al. 2000) with two studies reporting increased, four studies decreased, and three studies similar 5-HT$_{2A}$ availability in MDD patients versus controls. However, two recent studies with selective PET tracers and good control of treatment bias confirmed the postmortem observations in recovered, unmedicated remitted patients with a history of MDD (Bhagwagar et al. 2006) and in unmedicated patients (drug-free >6 months) with severe depression and high levels of dysfunctional attitudes (Meyer et al. 2003), showing increased 5-HT$_{2A}$ availability in MDD patients relative to controls. Furthermore, higher dysfunctional attitudes were correlated with higher 5-HT$_{2A}$ availability. However, one study with the highly selective PET tracer [^{18}F]altanserin by Mintun et al. reported an isolated decrease in hippocampal 5-HT$_{2A}$ receptor binding but no significant differences in cortical regions in depressed patients compared to controls (Mintun et al. 2004). Interestingly, a

Table 4.5 Results of serotonin receptor 2A (5-HT_{2A}) imaging studies (PET/SPECT) in patients with current or remitted MDD as compared to controls

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Outcome	Effect size
Bhagwagar et al. (2006)[a]	20 remitted MDD	[^{11}C]MDL	Medication-free >6 months	Frontal 19%↑	NA
	20 HC			Parietal 25%↑	
				Occipital 19%↑	
				Temporal no difference →	
				Positive correlation with dysfunctional attitudes in recovered patients	
Mintun et al. (2004)	46 MDD 29 HC	[^{18}F] altanserin	Medication-free (4 weeks)	Hippocampus 29% ↓	−0.71
				Pregenual AC 17%↓	−0.36
				Subgenual AC 21% ↓	−0.41
				Gyrus rectus 14% ↓	−0.30
				Dorsolateral prefrontal 16% ↓	−0.36
				Lateral temporal 12% ↓	−0.31
				Superior parietal 17% ↓	−0.38
				Occipital 9% ↓	−0.21
Meyer et al. (2003)	22 MDD	[^{18}F] setoperone	Medication-free (6 months)	No differences between the total groups	NA
	22 HC			Cortex↑ by 21–29% (particularly middle frontal gyrus bilaterally) in severe depression, $N = 11$	NA
				Positive association with dysfunctional attitudes	NA

Table 4.5 (continued)

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Outcome	Effect size
Messa et al. (2003)[b]	19 MDD	[^{18}F] fluoroethyl-spiperone	Antidepressant naive	Frontal 26%↓	−1.03
	20 HC		Benzodiazepines	AC 22%↓	−0.79
				Temporal 22%↓	−1.12
				Occipital 22%↓	−0.92
				Striatum 7%↓	−0.48
	15 MDD on medication		Paroxetine treatment (4th week)	Frontal 5%↓	−0.19
				AC 6%↓	−0.24
	20 HC			Temporal 4%↓	−0.14
				Occipital 4%↑	0.12
				Striatum 1%↓	−0.08
Yatham et al. (2000)	20 MDD	[^{18}F] setoperone	Medication-free (2 weeks)	Left inf. frontal gyrus 23%↓	−0.82
	20 HC			Right AC 27%↓	−0.93
				Left fusiform gyrus 22%↓	−0.88
				Right inf. temporal gyrus 22%↓	−0.83
				Right medial frontal gyrus 24%↓	−0.87
				Right cingulate gyrus 27%↓	−0.91
				Left sup. temporal gyrus 25%↓	−0.85
Attar-Levy et al. (1999)	7 MDD	[^{18}F] setoperone	Antidepressant-free >2 weeks	Frontal 6%↓	−0.26
	7 HC		Benzodiazepines	Temporal 1%↓	−0.05
				Parietal 3%↓	−0.16
				Occipital 16%↑	0.70
	7 MDD treated		Clomipramine 150 mg for 3 weeks	Frontal 25%↓	−1.10
	7 HC			Temporal 20%↓	−1.09
				Parietal 21%↓	−1.15
				Occipital 5%↓	−0.22
Meltzer et al. (1999)[c]	11 MDD	[^{18}F] altanserin	Untreated	No difference in all regions assessed →	NA
	10 HC				

(continued)

Table 4.5 (continued)

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Outcome	Effect size
Meyer et al. (1999)	14 MDD	[^{18}F] setoperone	Medication-free (>6 months)	Prefrontal cortex 11%↓	−0.31
	19 HC			Right/left ratio prefrontal cortex 1%↑	0.025
Biver et al. (1997)	8 MDD	[^{18}F] altanserin	Medication-free (10 days)	Right orbitofrontal-insular cortex 17%↓	−1.08
	22 HC				
D'haenen et al. (1992)	19 MDD	[^{123}I] ketanserin	Medication-free >7 days (10 pts > 3 weeks)	Sup. frontal 14%↑	0.49
				Central sulcus 1%↑	0.03
				Parietal 21% ↑	1.48
	10 HC			Prefrontal 7%↓	−0.32
				Infero-frontal 7%↑	0.36
				Anterior temporal 1%↓	−0.03
				Posterior temporal1% ↑	0.08
				Occipital 4% ↓	−0.16
				Right/left ratio infero-frontal cortex↑	NA

Outcome represents the change in binding potential as estimated from several cortical regions, anterior cingulate, and hippocampus and compared to reported control data. *Arrows* indicate directions of changes calculated as MDD relative to healthy individuals. Effect size is given as Cohen's *d*. NA, not applicable for calculation of Cohen's *d* based on reported measures from the study

Abbreviations: *MDD* Major depressive disorder, *HC* Healthy controls, *Nr* Number, *pts* Patients, *AC* Anterior cingulate

[a]This study included remitted patients with prior, recurrent depression ≥2 episodes

[b]Two groups of patients were compared with the same group of healthy controls; 20 antidepressant naive and 15 patients treated for 4 weeks with paroxetine

[c]Late-life depression

decrease in hippocampal 5-HT$_{2A}$ receptor availability in depressed patients finds some support in the postmortem literature, however, not consistently (Stockmeier 2003). Although Mintun et al. included a large number of patients, a power analysis of [^{18}F]altanserin PET data showed that in order to avoid type II errors, robust detection of differences in the hippocampus would require a sample size twice as large as their study sample (Haugbol et al. 2007). Furthermore, treatment effects may have biased that study since patients were only off medication for 4 weeks. Therefore, we think that the available imaging data is insufficient to conclude on the potential involvement of hippocampal 5-HT$_{2A}$ receptor disbalances in the pathophysiology of major depression.

Treatment effects and scar effects of prior depressive episodes might bias the data provided from cross-sectional studies in patients with a history of depression.

Therefore, studies linking risk factors for developing MDD and PET markers of serotonergic neurotransmission, in the absence of depressive symptoms, may provide important insight to early pathophysiological mechanisms in the development of MDD. Such studies in healthy, never-medicated individuals have pointed toward an association between high frontal 5-HT_{2A} receptor binding and increased risk (represented by higher neuroticism scores (Fanous et al. 2007; Kendler et al. 1993)) (Frokjaer et al. 2008a), or the combination of high neuroticism scores and familial risk for mood disorders (Frokjaer et al. 2010).

In summary, this postmortem data, data from at-risk individuals, and recent in vivo imaging data are converging to support that high prefrontal 5-HT_{2A} receptor binding is implicated in MDD. This may be due to upregulation of 5-HT_{2A} receptors in cortical regions as a compensatory response to disturbances in serotonin homeostasis with low levels of extracellular serotonin. Indeed, sustained low levels of serotonin upregulate 5-HT_{2A} receptor levels in rodents (Cahir et al. 2007; Heal et al. 1985; Reneman et al. 2002). Generalization of these results and this explanation of possible mechanisms remain speculative, because synaptic levels of serotonin cannot be measured in vivo in humans. Rather than being compensatory to low levels of serotonin, a primary high frontal 5-HT_{2A} receptor setting might also, in itself, be adverse in the context of mood disorders. For example, 5-HT_{2A} receptor agonism stimulates cortisol excretion (Van de Kar et al. 2001), and enhanced cortical 5-HT_{2A} receptor signaling is accompanied by a tendency to perceive or judge an environment as risky (Weisstaub et al. 2006).

As indicated above, some data suggest that hippocampal 5-HT_{2A} receptor binding may be low in MDD. This may relate to the consequences of dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis leading to elevated cortisol excretion observed in individuals at familial risk for mood disorders (Mannie et al. 2007; Modell et al. 1998; Vreeburg et al. 2009) and in both recovered and currently depressed patients (Bhagwagar et al. 2003, 2005; Vreeburg et al. 2009). Indeed, animal models support a differential regulation of 5-HT_{2A} receptor levels induced by chronic stress, with upregulation in the frontal cortex and downregulation in the hippocampus, but only in rats prone to develop learned helplessness—a behavioral model of vulnerability to depression (Dwivedi et al. 2005). However, some of these findings may be due to hippocampal volume loss known to be a vulnerability factor in mood disorders (Gilbertson et al. 2002) and a consequence of long-lasting disease processes (MacQueen and Frodl 2011) rather than specific loss of 5-HT_{2A} receptors.

Even though a high prefrontal 5-HT_{2A} receptor binding appears to be associated with risk factors for developing major depression and with the depressed or remitted state, it is not clear if this is predictive of the risk for developing future major depression in healthy at-risk individuals or relapse in remitted patients. Longitudinal studies with clinical follow-up in high-risk populations and non-medicated patients are needed to explore such potential predictive properties of prefrontal 5-HT_{2A} receptor availability.

4.3.2 Dopamine

Depression is also related to the dopaminergic system. Psychomotor speed, motivation, memory, concentration, and the ability to experience pleasure (hedonia) are all regulated, at least in part, by dopaminergic circuits in the brain. These functions are also prominent clinical features of major depression (Dunlop and Nemeroff 2007). Also, in patients suffering from neuropsychiatric diseases which are characterized by loss of dopaminergic neurons, depression is a prominent feature. Indeed, depression may occur in about one out of three patients suffering from Parkinson's disease (PD) where it is often persistent (Aarsland et al. 2012). Finally, although most antidepressants target serotonin and/or norepinephrine transporters, which may indirectly affect the dopaminergic system, new broad-spectrum antidepressants (triple reuptake inhibitors) or second-generation inhibitors targeting primarily the dopamine and norepinephrine transporter (e.g., bupropion) also increase dopamine levels directly (Nutt et al. 2007; Prins et al. 2011). In this regard, it has been suggested that antidepressants that also increase dopamine signaling may be attractive to treat subgroups of depressed patients, e.g., atypical depression, melancholic depression, and/or treatment-resistant depression (Dunlop and Nemeroff 2007; Nutt et al. 2007; Prins et al. 2011). Therefore MDD (or subgroups of depressed patients) may be characterized by a hypodopaminergic neurotransmission (Dunlop and Nemeroff 2007).

Dopamine has also been linked to BD (Gerner et al. 1976). Mania and depression have been considered as a hyperdopaminergic and hypodopaminergic state, respectively (Cousins et al. 2009). Indeed, psychostimulants can increase dopaminergic activity in the brain (Laruelle et al. 1995, 1997b) and induce behavioral effects similar to mania (Jacobs and Silverstone 1986). Also, most second-generation antipsychotics do block dopamine receptors and have demonstrated efficacy in the treatment of mania (El-Mallakh et al. 2010).

Here, we will review the results of PET and SPECT studies in MDD and (depressed) BD that focused on the dopaminergic system. We will also discuss shortly results of molecular imaging studies on the relationship of an altered dopaminergic system and depression in neuropsychiatric disorders other than MDD/BD, as well as the relationship between dopaminergic markers and depressive symptoms in healthy controls. In addition, we will consider some possibilities to use dopaminergic imaging to evaluate the mechanism of action of antidepressants or other treatments.

4.3.2.1 Dopamine Synthesis

Tracers like [^{18}F]DOPA quantify the integrity and dopamine synthesis of presynaptic dopaminergic neurons in vivo in several brain areas (Booij et al. 1999; Booij and Berendse 2011; Kumakura and Cumming 2009). DOPA can be taken up by dopaminergic neurons via the amino acid transporter and is then decarboxylated to fluorodopamine and temporally stored in vesicles (Booij et al. 2014).

DOPA PET studies in MDD patients are scarce. However, striatal DOPA uptake may be similar in depressed patients and healthy controls (Agren et al. 1992). On

the other hand, in a small study, Martinot et al. (2001) showed decreased dopaminergic synthesis in the left caudate nucleus of depressed patients with affective flattening and psychomotor retardation. These findings again highlight that dopaminergic deficits in depression may be restricted to subgroups of patients. Though, as compared to DAT SPECT studies, DOPA PET offers the opportunity to also measure uptake in extrastriatal dopaminergic brain areas. In this regard it is of interest that Agren and co-workers reported on a decreased DOPA uptake in the medial prefrontal cortex in depressed patients, a key region in a circuit involved in the regulation of emotion and reward (Price and Drevets 2012).

Like DOPA PET studies in MDD patients, DOPA PET studies in BP are scarce. Yatham and co-workers found no significant differences in striatal [^{18}F]DOPA uptake rate constants between manic patients and healthy controls. After treatment with divalproex sodium, however, these rate constants were significantly reduced in the patients and were lower in the patients than in the controls (Yatham et al. 2002b).

4.3.2.2 Dopamine Transporter Imaging

MDD Patients Versus Controls

The presynaptic dopaminergic system can be imaged by using tracers for the dopamine transporter (DAT) for PET ([^{11}C]RTI-32, [^{11}C]CFT, [^{18}F]FE-PE2I) and SPECT ([^{123}I]β-CIT, [^{123}I]nor-β-CIT, [^{123}I]FP-CIT, [^{99m}Tc]TRODAT). The DAT is expressed exclusively in terminals of dopaminergic neurons (Miller et al. 1997). Another possibility is to use radiotracers that bind to the vesicular monoamine transporters (i.e., radiotracers derived from tetrabenazine), because in several brain areas (e.g., the striatum), uptake of these tracers reflects primarily binding to dopaminergic neurons (Okamura et al. 2010).

The results of imaging studies of the DAT in MDD are described in Table 4.6A, excluding one study, because mean and SD could not be extracted (Hellwig et al. 2018). Approximately half of these studies did not find statistically significant differences in striatal DAT binding versus age-matched controls. Also, while six studies showed a significant increase of DAT binding in MDD (Amsterdam et al. 2012; Amsterdam and Newberg 2007; Brunswick et al. 2003; Laasonen-Balk et al. 2004; Yang et al. 2008; Hsiao et al. 2013), six studies found the opposite or no effect (Meyer et al. 2001b; Sarchiapone et al. 2006; Wu et al. 2011; Camardese et al. 2014; Helwig et al. 2016; Pizzagalli et al. 2019). It is not likely that this discrepancy is caused by the use of different techniques, because, e.g., the same tracer was used in studies that showed significant increases (Amsterdam and Newberg 2007) or decreases (Wu et al. 2011) of striatal DAT binding. Also, our observations are in line with the results of a recent meta-analysis (Li et al. 2015). Of note, one study did include only anhedonic depressed patients (Sarchiapone et al. 2006). In this regard it is of interest that another study compared depressed patients with and without anhedonia directly and showed lower striatal DAT binding in patients with anhedonia (Camardese et al. 2014).

Most studies did not find a significant correlation between striatal DAT binding and symptomatology (Camardese et al. 2014; Hsiao et al. 2013; Laasonen-Balk

Table 4.6 Results of dopamine transporter imaging studies (PET/SPECT) in patients with unipolar major depression (A) or bipolar disorder (B) as compared to controls

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Change DAT binding	Effect size
A. Unipolar depression					
Pizzagalli et al. (2019)[a]	25 MDD 23 HC	[^{11}C] altropane	Drug-free (>2 weeks)	Put: 8% decrease	-0.66
				VTA: 11% decrease	-0.71
Hsiao et al. (2013)	23 MDD 20 HC	[^{99m}Tc] TRODAT	Drug-free (>6 months)	Put R: 24% increase	1.59
				Put L: 25% increase	1.68
				Caudate R: 24% increase	1.40
				Caudate L: 19% increase	1.26
Camardese et al. (2014)	10 MDD[b] 10 HC	[^{123}I]FP-CIT	Drug-free interval not described	Put R: 16% decrease	0.94
				Put L: 16% decrease	0.87
				Caudate R: 14% decrease	0.82
				Caudate L: 16% decrease	0.99
Amsterdam et al. (2012)	24 MDD	[^{99m}Tc] TRODAT	Drug-free (>6 months)	7% increase (put right)	0.47
	84 HC			12% increase (put left)	1.11
				1% decrease (caudate right) (ns)	−0.16
				2% increase (caudate left) (ns)	0.20
Wu et al. (2011)	13 MDD	[^{99m}Tc] TRODAT	Drug-free (>2 years)	35% decrease (striatum right)	−4.89
	10 HC			35% decrease (striatum left)	−4.65
Lehto et al. (2008b)[c]	11 MDD	[^{123}I] nor-β-CIT	Drug-naive	0.1% decrease (striatum) (ns)	−0.06
	19 HC				
Yang et al. (2008)	10 MDD	[^{99m}Tc] TRODAT	Drug-free (>3 months)	12% increase	1.06
	10 HC				

Table 4.6 (continued)

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Change DAT binding	Effect size
Amsterdam and Newberg 2007	10 MDD	[^{99m}Tc] TRODAT	Drug-free (>1 week)	30% increase (put right ant)	1.59
	46 HC			47% increase (put right post)	1.39
				10% increase (put left ant)	0.46
				27% increase (put left post)	0.89
				12% increase (caudate right)	0.72
				18% increase (caudate left)	1.12
Argyelán et al. (2005)	16 MDD	[^{99m}Tc] TRODAT	9 drug-free (>2 weeks)	7% decrease (ns)	−0.23
	12 HC		7 drug-naive		
Staley et al. (2006)	32 MDD	[^{123}I]β-CIT	14 drug-naive	1% decrease in women (ns)	−0.29
	32 HC		15 drug-free	3% increase in men (ns)	0.59
			3 history unknown		
Sarchiapone et al. (2006)[d]	11 MDD	[^{123}I]FP-CIT	Drug-free (period not described)	20% decrease (put right)	−1.04
	9 HC			23% decrease (left and right)	−1.19
				17% decrease (caudate right)	−0.85
				18% decrease (caudate right)	−1.09
Brunswick et al. (2003)	15 MDD[e] 46 HC	[^{99m}Tc] TRODAT	Drug-free (>1 week)	25% increase (put ant right)	1.26
				9% increase (put ant left)	0.49
				41% increase (put post right)	1.26
				18% increase (put post left)	0.57
				2% increase (caudate right)	0.09
				13% increase (caudate left)	0.86

(continued)

Table 4.6 (continued)

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Change DAT binding	Effect size
Meyer et al. (2001b)	9 MDD	[^{11}C]RTI-32	5 drug-naive	16% decrease (put right)	−0.92
	23 HC		4 drug-free (>3 months)	14% decrease (put left)	−0.86
				14% decrease (caudate right)	−0.90
				12% decrease (caudate left)	−0.75
Dahlstrom et al. (2000)[f]	31 MDD	[^{123}I]β-CIT	Drug-naive	0.4% increase (ns)	0.03
	10 non-MDD				
Laasonen-Balk et al. (1999)	15 MDD	[^{123}I]β-CIT	Drug-naive	24% increase (striatum right)	1.12
Laasonen-Balk et al. (2004)	18 HC			22% increase (striatum left)	1.15
Malison et al. (1998b)	15 MDD	[^{123}I]β-CIT	6 drug-naive	11% decrease (ns)	−0.43
	15 HC				
B. Bipolar depression					
Amsterdam et al. (2012)[g]	15 BD	[^{99m}Tc] TRODAT	Drug-free (>6 months)	3% increase (caudate left)[e]	0.28
				2% decrease (caudate right)	−0.21
	84 HC			13% increase (put left)	1.15
				5% increase (put right)	0.32
Anand et al. (2011)	5 BD euthymic 6 BD depressed (8 BP-I) 13 HC	[^{11}C]CFT	Drug-free (>2 weeks)	20% decrease (caudate left)[f]	−1.38
				21% decrease (caudate right)	−0.78
				14% decrease (put left)	−0.88
				17% decrease (put right) (ns)	−0.57
				7% decrease (ventr str left) (ns)	−0.28
				1% decrease (ventr str right) (ns)	−0.01

Table 4.6 (continued)

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Change DAT binding	Effect size
Chang et al. (2010)	7 BP-I 10 BP-II 17 HC	[^{99m}Tc] TRODAT	Drug-free (>2 months)	16% increase (whole striatum)[g]	1.04
Amsterdam and Newberg 2007	5 BD-II 46 HC	[^{99m}Tc] TRODAT	Drug-free (>1 week)	13% increase (caudate left)	0.91
				5% decrease (caudate right) (ns)	−0.28
				4% increase (ant put left) (ns)	0.25
				16% increase (ant put right) (ns)	0.68
				13% increase (post put left) (ns)	0.45
				34% increase (post put right)	1.23

The change in binding ratios is estimated from whole striatum data (or separately for left and right striatum), or separately for striatal subregions as data are available, and compared to reported control data

ns Not statistically significantly different from control data, *put* Putamen, *VTA* Ventral tegmental area

[a]Means estimated from figure; Cohen d values as published

[b]MDD group without anhedonia

[c]Eight patients with a co-occurrence of major depression and dysthymia ("double depression") were included. As compared to data in controls, the striatal binding ratios were 2% lower (effect size 0.16)

[d]In this study, two patients had a diagnosis of BP-II, and three had a comorbid dysthymic disorder; all were suffering from depression in which anhedonia was a prominent feature

[e]Five of the 15 depressed patients had a diagnosis of BD-II or major depression not otherwise specified

[f]Subjects were children and adolescents. Due to the radiation burden involved, the control group did not consist of healthy controls, but children/adolescents who did not suffer from a depression (but, e.g., a conduct disorder)

[g]BD-II subgroup was not significantly different from the unipolar patient group

et al. 2004; Malison et al. 1998b; Sarchiapone et al. 2006; Staley et al. 2006; Yang et al. 2008), or did not report on it (Amsterdam et al. 2012; Amsterdam and Newberg 2007; Brunswick et al. 2003; Dahlstrom et al. 2000; Meyer et al. 2001b; Wu et al. 2011). On the other hand, Argyelán and co-workers (Argyelán et al. 2005) showed that striatal DAT binding was negatively associated with HDRS scores. Also, Meyer et al. (2001b) showed that age-corrected DAT binding was negatively correlated with scores of the Finger Tapping Test and Stroop Color-Word Test (which are known to be performed more poorly during low dopamine states). In addition, Lehto et al. (2008b) showed that age-adjusted baseline striatal DAT binding correlated inversely with the duration of both dysthymia and MDD in the group with combined MDD and dysthymia (double depression). Also, Wu et al., who showed decreased DAT binding, used a HDRS score of at least 24 plus psychomotor retardation (Wu et al. 2011). Finally, Pizzagalli et al. (2019) showed that the DAT availability in the putamen was negatively correlated with the lifetime number of major depressive episodes and DAT binding in the VTA was associated with scores on the external entrapment scale. All in all, these findings may indicate that dopaminergic deficits are not a feature of MDD per se, but may be specific for subgroups of patients (e.g., with psychomotor retardation, anhedonia, or in severely ill patients, and/or treatment-resistant depression (Camardese et al. 2014; Dunlop and Nemeroff 2007)). In contrast to this hypothesis, baseline striatal DAT binding was similar in responders and nonresponders during long-term treatment for depression (Cavanagh et al. 2006). However, as in many studies on depression, in this study the Hamilton Depression Scale was used (among others) to assess response. Since this scale not necessarily reflects dopaminergic functions, it may be of interest in future studies to include neuropsychological tests that reflect indirectly low dopamine states to unravel the link between dopamine and major depression (Meyer et al. 2001b).

BD Patients Versus Controls

The results of imaging studies of the DAT in BD are shown in Table 4.6B. While at least two studies showed an increase of striatal DAT binding in BD patients in the whole striatum (Chang et al. 2010) or in subdivisions of the striatum (Amsterdam et al. 2012; Amsterdam and Newberg 2007), another study showed a decrease of striatal DAT binding, particularly in the caudate nucleus (Anand et al. 2011). Interestingly, although the numbers of participants in each group are low, no significant differences were found between BD patients suffering from type I versus type II BD (Chang et al. 2010), or between depressed and euthymic BD patients (Anand et al. 2011).

It is remarkable that two studies that showed an increase of striatal DATs in BD patients used a nonselective tracer ([^{99m}Tc]TRODAT-1) and SPECT in most BD-II patients (Amsterdam and Newberg 2007; Chang et al. 2010), while the study that reported decreased DAT binding used a selective DAT tracer ([^{11}C]CFT) and PET (Anand et al. 2011). In two SPECT studies (Amsterdam et al. 2012; Amsterdam and Newberg 2007), the striatal DAT binding was assessed in three striatal subdivisions

(caudate nucleus, anterior and posterior putamen). These SPECT images were not coregistered with individual magnetic resonance imaging (MRI), which makes the accuracy of measurements uncertain. Two studies did not find a significant correlation between striatal DAT binding and symptomatology (Anand et al. 2011), nor duration of the bipolar disorder, nor the number of depressive or manic episodes (Chang et al. 2010), while two did not report on it (Amsterdam et al. 2012; Amsterdam and Newberg 2007).

Zubieta and colleagues assessed the central vesicular monoamine transporter (VMAT-2) with PET in BD. In a first study in euthymic patients diagnosed with bipolar disorder type I, they showed regional increases of VMAT binding in the thalamus and ventral brain stem (but not in the caudate nucleus) as compared to controls (Zubieta et al. 2000). This finding could be replicated in a second study (Zubieta et al. 2001).

DAT Imaging in Healthy Controls and Its Association with Mood

In healthy controls, a possible association between DAT binding and depressed affect was not found. One study showed higher striatal DAT binding in healthy controls with higher profile of mood states (POMS) scores as compared to subjects with low POMS scores and a positive association between DAT and POMS scores (Newberg et al. 2007). However, in a larger study, this could not be replicated (Burke et al. 2011). Finally, Hsieh and co-workers examined healthy controls with first-degree relatives with MDD, but found no change in striatal DAT binding as compared to healthy controls without a family history of MDD (Hsieh et al. 2014).

DAT Imaging in Other Neuropsychiatric Disorders and Its Association with Depression

As mentioned earlier, depression may occur in about one out of three patients suffering from PD (Aarsland et al. 2012). PD is characterized by severe loss of striatal DAT, even in early phases of the disease (Booij et al. 2001; Ponsen et al. 2004). Using [^{11}C]RTI-32 PET as an in vivo marker of dopamine and noradrenalin transporters, Remy et al. (2005) showed lower binding in depressed PD patients in the locus coeruleus and in several regions of the limbic system including the anterior cingulate cortex, the thalamus, the amygdala, and the ventral striatum. In agreement with these findings, Hesse et al. showed lower striatal DAT binding in PD patients with depression than those without depression (using [^{123}I]FP-CIT as a marker for the DAT) (Hesse et al. 2009), although this could not be replicated by other SPECT studies using [^{99m}Tc]TRODAT-1 or [^{123}I]FP-CIT (Felicio et al. 2010; Jaakkola et al. 2019). Also, Chung and co-workers showed no significant change in striatal DAT binding in depressed PD patients versus apathetic PD patients (Chung et al. 2016). Six other studies showed statistically significant correlations between depression scores and striatal DAT binding in PD patients (Eising et al. 1997; Rektorova et al. 2008; Weintraub et al. 2005; Vriend et al. 2014; Yoo et al. 2019; Ceravolo et al. 2013), although this could not be replicated in two other studies in PD (Picillo et al.

2017; Park et al. 2019b), as well as in another neurodegenerative disorder characterized by severe loss of dopaminergic neurons (i.e., (prodromal) Lewy body dementia (Roselli et al. 2009; Kasanuki et al. 2017; Siepel et al. 2016))). Interestingly, also striatal DAT binding was negatively related with depressive symptoms in cervical dystonia (Zoons et al. 2017).

The correlation between DAT binding and depression has not only been studied in neurodegenerative disorders characterized by loss of dopaminergic neurons. Interestingly, in alcoholics a significant relationship between DAT availability and Montgomery-Asberg Depression Rating Scale (MADRS) scores was found, both during withdrawal and after sobriety (Laine et al. 1999). Such a relationship (with HDRS-scores) was also found in alcoholics with comorbid depression (Yen et al. 2016). Also in acutely abstinent cocaine-abusing subjects, an inverse correlation between DAT levels and depression scores was observed (Malison et al. 1998a).

Presynaptic Markers and Treatment

Molecular imaging techniques offer the unique possibility to assess the mechanism of action of antidepressants. For example, Meyer et al. (2002) and Argyelán et al. (2005) studied the occupancy of striatal DAT by the antidepressant bupropion in depressed patients. After 3 weeks of treatment, Meyer et al. found no significant difference in DAT binding after bupropion treatment (300 mg/day) in eight MDD patients in comparison to test–retest data in eight healthy controls. The occupancy after bupropion treatment was 14% (6–22%) (Meyer et al. 2002). Argyelán et al. showed that approximately 20% of DATs were occupied after 4 weeks of treatment with bupropion (300 mg/day), but the occupancy was not correlated with clinical effectiveness (Argyelán et al. 2005).

Interestingly, a recent PET study in monkeys showed that electroconvulsive therapy (ECT) may induce an increase in striatal DAT and vesicular transporters after finalizing a 6-week electroconvulsive therapy course (Landau et al. 2011). A small human study in 11 patients showed that a change of DAT availability in the left caudate nucleus after sleep deprivation was significantly associated with antidepressant ECT response (Hellwig et al. 2018).

In depressed patients who were treated with the SSRIs paroxetine or escitalopram, a significant increase in striatal DAT binding was observed (Kugaya et al. 2003; Rominger et al. 2015). A small [^{99m}Tc]TRODAT SPECT study however could not replicate this finding (Wu et al. 2013). Also, successful psychotherapy for depression may not change presynaptic dopaminergic markers. Indeed, although the severity of depression decreased after 1 year of psychotherapy, striatal DAT binding did not change significantly in a study with ten participants (Lehto et al. 2008a).

Finally, in 14 depressed patients, who did not respond to 8 weeks of SSRI treatment and underwent DOPA PET imaging before and after aripiprazole augmentation, 11 responded to augmentation. Voxel-wise comparisons of pre- and post-aripiprazole scans revealed increased DOPA uptake in the right medial caudate nucleus of augmentation responders (Conway et al. 2014).

4.3.2.3 Postsynaptic Dopamine Receptor Imaging

MDD Patients Versus Controls

The dopamine D_1-like receptor is expressed predominantly on postsynaptic neurons and may be implicated in major depression. Using [^{11}C]NNC-112 PET to assess D1-like receptor binding in vivo, binding to this receptor was found to be reduced in the left caudate nucleus of depressed patients (Cannon et al. 2009). Also, binding correlated negatively with illness duration, and the left-to-right binding ratio correlated inversely with anhedonia ratings. This finding is of interest since the caudate nucleus is the target of afferent neural projections from the orbitofrontal and anterior cingulate cortices where neuropathological changes have been reported in major depression (Cannon et al. 2009). These data also extended a previous finding of decreased D1-like receptor binding in the striatum in patients with major depression with anger attacks (Dougherty et al. 2006). Unfortunately, a recent review demonstrated that no recent DA D_1 receptor PET studies have been performed in major depression (Cervenka 2019).

Many molecular imaging studies in major depression focused on postsynaptic dopamine $D_{2/3}$ receptors (Table 4.7A). Several of these studies did not find a significant difference in dopamine $D_{2/3}$ receptor binding between depressed patients and healthy controls. However, it is remarkable that the studies that did find significant differences between groups found increases in dopamine $D_{2/3}$ receptor binding in depressed patients in the striatum (D'haenen and Bossuyt 1994; Meyer et al. 2006b; Shah et al. 1997; Peciña et al. 2017). Also one PET study reported a significant difference in asymmetry of binding to $D_{2/3}$ receptors in the temporal cortex, with a higher asymmetry in patients than in controls (Lehto et al. 2009). In four of the five studies that showed significant differences between groups, striatal $D_{2/3}$ receptor binding did not correlate with neuropsychological scores or clinical variables (D'haenen and Bossuyt 1994; Meyer et al. 2006b; Shah et al. 1997) or a correlation was not reported (Lehto et al. 2008a, 2009). In one PET study, binding in the left nucleus accumbens/ventral pallidum was negatively associated with anxiety scores (GAD-7 scores), and the average binding in the bilateral nucleus accumbens was negatively associated with anhedonia (EAS) scores (Peciña et al. 2017). Also, Schneier and co-workers showed no association with baseline dopamine $D_{2/3}$ receptor binding and severity of depression (Schneier et al. 2018). Interestingly, psychomotor speed was negatively correlated with dopamine $D_{2/3}$ receptor binding (Meyer et al. 2006b; Shah et al. 1997), as well as with verbal fluency (Shah et al. 1997).

In a recent study, Savitz and co-workers showed that while the Taq1A polymorphism for the dopamine D_2 receptor is negatively associated with striatal dopamine $D_{2/3}$ receptor binding in healthy controls, the opposite might be true for MDD (Savitz et al. 2013), which may suggest that Taq polymorphism should be taken into account when studying dopamine $D_{2/3}$ receptor binding in MDD.

The release of endogenous dopamine by dopaminergic neurons can be assessed by SPECT or PET imaging, using radiotracers for the dopamine $D_{2/3}$ receptor (Breier et al. 1997; Laruelle et al. 1995, 1997b). By using a classic pharmacological

Table 4.7 Results of dopamine $D_{2/3}$ receptor imaging studies (PET/SPECT) in patients with unipolar major depression (A) and bipolar disorder (B) as compared to controls

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Change $D_{2/3}$ binding	Effect size
A. Unipolar depression					
Schneier et al. (2018)	20 MDD 20 HC	[^{11}C]PHNO	Drug-naive	Ventral striatum: 0% difference (ns)	0.0
				Dorsal caudate nucleus: 4% decrease (ns)	0.32
				Posterior caudate: 0% difference (ns)	0.0
				Anterior putamen: 4% decrease (ns)	0.32
				Posterior putamen: 0% difference (ns)	0.0
				Globus pallidus: 4% decrease (ns)	0.28
				Midbrain: 13% decrease (ns)	1.0
				Thalamus: 0% difference (ns)	0.0
Peciña et al. (2017)	12 MDD 16 HC	[^{11}C] raclopride	Drug-free (>6 months)	NA[a]	NA[a]
Savitz et al. (2013)	12 MDD 24 HC	[^{11}C] raclopride	Drug-free (>6 weeks)	NA[a]	NA[a]
Moses-Kolko et al. (2012)	10 MDD 13 HC[b]	[^{11}C] raclopride	8 drug-naive	Anteroventral striatum: 9% decrease (ns)	0.46
			5 drug-free (>3 weeks)	Ventral putamen: 7% decrease (ns)	0.55
				Dorsal caudate: 10% decrease (ns)	0.90
				Dorsal putamen: 6% decrease (ns)	0.49
Saijo et al. (2010)	7 MDD 11 HC	[^{11}C] FLB457	On medication	Right anterior cingulate: 13% increase (ns)	0.40
Yang et al. (2008)	10 MDD 10 HC	[^{123}I]IBZM	Drug-free (>3 months)	Striatum: 2% decrease (ns)	0.23

Table 4.7 (continued)

Lehto et al. (2008a), Lehto et al. (2009)[c]	10 MDD 10 HC	[^{123}I] epidepride	Drug-free (>6 months)	Right temp cortex: 13% decrease (ns)	0.65
				Left temp cortex: 6% decrease (ns)	0.33
				Temporal asymmetry: 7%	1.56
Hirvonen et al. (2008b)	25 MDD 19 HC	[^{11}C] raclopride	Drug-free (>4 months)	Caudate: 2% increase (ns)	0.17
				Putamen: 1% decrease (ns)	0.11
				Thalamus: 3% decrease (ns)	0.24
				Ventral striatum: 4% decrease (ns)	0.46
Montgomery et al. (2007)	7 MDD 7 HC	[^{11}C] FLB457	Drug-free (>3 months)	Amygdala: 1% increase (ns)	0.05
				Hippocampus: 0% change (ns)	0.00
				Frontal cortex: 0% change (ns)	0.00
				Anterior cing cort: 1% increase (ns)	0.06
				Thalamus: 10% increase (ns)	0.45
				Brain stem: 6% increase (ns)	0.21
				Cerebellum: 5%increase (ns)	0.22
Meyer et al. (2006b), Kuroda et al. (2006)	21 MDD 21 HC	[^{11}C] raclopride	12 drug-naive 9 drug-free (>6 months)	Striatum: 6–8% increase	NA[a]
	9 MDD 16 HC	[^{11}C] raclopride	On medication	Right caudate: 1% increase (ns)	0.11
				Left caudate: 0% decrease (ns)	0.03
				Right putamen: 3% increase (ns)	0.22
				Left putamen: 5% increase (ns)	0.41
Parsey et al. (2001)	9 MDD 10 HC	[^{123}I]IBZM	Drug-free (>2 weeks)	Striatum: 6% decrease (ns)	0.55

(continued)

Table 4.7 (continued)

Klimke et al. (1999)	15 MDD 17 HC	[^{123}I]IBZM	Drug-free (>6 months)	Striatum: 1% decrease (ns)	0.06
Shah et al. (1997)	14 MDD	[^{123}I]IBZM	7 drug-free (>3 months)	Striatum right: 6% increase[d]	0.95
	15 HC[e]		8 on medication	Striatum left: 4% increase	0.52
Ebert et al. (1996)	20 MDD	[^{123}I]IBZM	10 drug-free (>6 months); 10 on medication	Striatum right: 8% increase (ns)[f]	0.55
	10 HC			Striatum left: 10% increase (ns)	0.68
D'haenen and Bossuyt (1994)	21 MDD 11 HC	[^{123}I]IBZM	Drug-free (>1 week)	Striatum: 11% increase	0.88
B. *Bipolar depression*					
Moses-Kolko et al. (2012)	7 BD	[^{11}C] raclopride	Drug-free (>3 weeks) or drug-naive	Anteroventral striatum: 5% decrease (ns)	0.34
	13 HC (females)[g]			Ventral putamen: 1% decrease (ns)	0.06
				Dorsal caudate: 3% increase (ns)	0.28
				Dorsal putamen: 5% increase (ns)	0.45
Yatham et al. (2002a)	13 BD (nonpsychot)	[^{11}C] raclopride	AP-naive	Striatum left: 9% decrease (ns)	0.51
				Striatum right: 8% decrease (ns)	0.43
	14 HC			Caudate: 7% decrease (ns)	0.37
				Putamen: 9% decrease (ns)	0.50
Anand et al. (2000)	13 BD 13 HC	[^{123}I]IBZM	AP-free (>6 months)	Striatum: 4% decrease (ns)	0.26
Wong et al. (1997)	7 BD (psychot) 24 HC	[^{11}C]NMSP	AP-naive or AP-free (>6 months)	Striatum: 9% increase (ns)	0.60
	7 BD (non-psychot) 24 HC[h]		AP-naive or AP-free (>6 months)	Striatum: 13% decrease (ns)	0.81
Pearlson et al. (1995)	7 BD (psychot) 12 HC	[^{11}C]NMSP	AP-naive or AP-free (>6 months)	Striatum: 87% increase[g]	1.27
	7 BD (non-psychot) 12 HC		AP-naive or AP-free (>6 months)	Striatum: 11% decrease (ns)[i]	0.22

Table 4.7 (continued)

The change in binding ratios is estimated from whole striatum data (or separately for left and right sides or striatal subregions), or extrastriatal brain areas, and compared to reported control data

ns Not statistically significantly different from control data

[a]In these studies, no data were available to calculate the effect size and/or change in dopamine $D_{2/3}$ receptor binding

[b]In this study only women were studied; also postpartum unipolar and bipolar patients were studied, as well as non-postpartum bipolar patients. In this table, the data of the non-postpartum patients and controls were compared

[c]Same sample of patients

[d]Ratios of binding in striatum versus frontal cortex were used to calculate differences between groups; the data of the 14 patients were compared to the 15 controls (no individual data were available to compare the subgroup of drug-free patients to the controls)

[e]Two patients had a bipolar affective disorder

[f]Ratios of binding in striatum versus cerebellum were used to calculate differences between groups; the 20 patients were compared to the 10 controls (no individual data were available to compare the subgroup of drug-free patients to the controls). Only in the small subgroup of patients with psychomotor retardation, an increased binding was observed

[g]In this study, only females were studied, including postpartum bipolar patients. In this table, the data of the non-postpartum patients and controls were compared

[h]In this study, psychotic patients suffering from bipolar disorder had significantly higher binding than nonpsychotic patients suffering from bipolar disorder

[i]In this study, the B_{max} for dopamine D_2-like receptors was assessed

paradigm, the amphetamine-induced release can be measured by assessing the decrease in dopamine $D_{2/3}$ receptor availability. Using an amphetamine challenge, Parsey et al. (2001) showed that although amphetamine administration induced a transient improvement in symptomatology in depressed patients, the amphetamine-induced dopamine release was not altered in MDD. In line with this finding, also a more recent PET study showed no significant difference in striatal dopamine release induced by amphetamine in MDD versus healthy controls (Schneier et al. 2018). However, contrary to this observation, female fibromyalgia patients with comorbid MDD may show a larger striatal DA release induced by monetary rewards assessed with ^{11}C-raclopride PET, compared to FMS patients without MDD (Ledermann et al. 2017).

BD Patients Versus Controls

Using [^{11}C]SCH23390 PET to assess D_1-like receptor binding, Suhara et al. showed that the binding of this tracer in the frontal cortex was significantly lower in bipolar patients than in healthy controls, whereas binding in the striatum was not significantly different (Suhara et al. 1992).

Five molecular imaging studies focused on the assessment of postsynaptic dopamine $D_{2/3}$ receptors in bipolar disorder (Table 4.7B). Four of these studies did not find a statistically significant difference compared to data obtained in healthy controls (Anand et al. 2000; Moses-Kolko et al. 2012; Wong et al. 1997; Yatham et al. 2002a). It is remarkable that in one study in which the B_{max} for striatal $D_{2/3}$ receptors was calculated, psychotic BD patients showed an increased B_{max} for these receptors

as compared to data obtained in healthy controls (Pearlson et al. 1995). This is of interest since a meta-analysis of imaging studies showed a significant but mild increase of striatal $D_{2/3}$ receptors in schizophrenia (Laruelle 1998), although a more recent meta-analysis suggested that this may not be evident in drug-naive patients (Howes et al. 2012).

The release of endogenous dopamine by dopaminergic neurons was assessed by Anand et al. in euthymic BD patients. These authors showed that, although amphetamine administration induced a significantly greater behavioral response in BD patients than in age-matched controls, the amphetamine-induced dopamine release was not increased (Zubieta et al. 2000).

Dopamine Receptor Imaging in Other Neuropsychiatric Disorders and Its Association with Depression

Apathy and depression occur frequently after deep brain stimulation for PD. In a prospective study, Thobois et al. showed that 17 out of the 63 included PD patients developed transient depression after subthalamic nucleus stimulation (Thobois et al. 2010). Except one, these patients also scored higher on apathy. Interestingly, presurgery [^{11}C]raclopride dopamine $D_{2/3}$ receptor binding was greater in bilateral OFC, DLPFC, posterior ACC, temporal cortices, left striatum, and right amygdala in apathetic versus non-apathic patients. This finding also underlines a link between dopaminergic deficits and depression.

Zoons and co-workers showed that striatal dopamine $D_{2/3}$ receptor binding was significantly lower in depressed patients with cervical dystonia compared to those without depression; however, the severity of depression was not correlated with dopamine $D_{2/3}$ receptor binding (Zoons et al. 2017).

In addition, Jolly and co-workers demonstrated lower dopamine $D_{2/3}$ receptor binding in the caudate nucleus in traumatic brain injury (TBI) patients with comorbid depression compared to controls, but this binding was not lower compared to TBI patients without depression (Jolly et al. 2019).

Dopamine Receptor Markers and Treatment

After treatment of MDD with an SSRI, Klimke et al. showed that the change in striatal dopamine $D_{2/3}$ receptors was positively correlated with the percentage improvement (measured by HDRS scores) (Klimke et al. 1999). In addition, baseline dopamine $D_{2/3}$ receptor binding was lower in responders ($n = 9$) than in nonresponders ($n = 6$). In contrast, Ebert et al. showed that 3-week treatment with amitriptyline (150 mg/daily) led to a decrease in $D_{2/3}$ receptor binding in the five patients who improved clinically (Ebert et al. 1996). Dopamine $D_{2/3}$ receptor binding remained unchanged in nonresponders. In a larger study, Hirvonen et al. showed in a randomized trial that 4-month treatment with fluoxetine (20–40 mg daily) or psychotherapy did not significantly change striatal $D_{2/3}$ receptor binding in the fluoxetine group ($n = 19$) nor in the psychotherapy group ($n = 21$), although treatment was successful in both groups (Hirvonen et al. 2011). In this study, fluoxetine

but not psychotherapy increased $D_{2/3}$ receptor binding in the lateral thalamus, but this increase was not correlated with clinical improvement. In line with this finding, a recent PET study in nonhuman primates showed that electroconvulsive therapy did not significantly influence dopamine $D_{2/3}$ receptors early after finalizing a 6-week electroconvulsive therapy treatment (Landau et al. 2011). However, by using [^{11}C]FLB 457 in humans, Saijo et al. showed a significant reduction of $D_{2/3}$ receptor binding in the right rostral anterior cingulate cortex following electroconvulsive therapy (Saijo et al. 2010). Interestingly, de Kwaasteniet et al. (2014) showed that in vivo striatal dopamine $D_{2/3}$ receptor binding was not significantly different between patients with treatment-resistant depression and controls.

As mentioned earlier, using an amphetamine challenge, Parsey and co-workers (Parsey et al. 2001) showed that although amphetamine administration induced a transient improvement in symptomatology in depressed patients, the amphetamine-induced dopamine release was not altered in MDD. In contrast, prefrontal repetitive transcranial magnetic stimulation in patients suffering from major depression may induce dopamine release (as measured by [^{123}I]IBZM SPECT) in the striatum (Pogarell et al. 2006). Although this small study lacked a placebo condition and a healthy control group, the included patients had a longer disease history than the ones included in the study by Parsey et al. (2001). Also this finding could not be replicated in a larger [^{11}C]raclopride PET study (Kuroda et al. 2006).

Using a high-affinity tracer for the dopamine $D_{2/3}$ receptors ([^{11}C] FLB457) and PET, Saijo et al. showed that electroconvulsive therapy induced a detectable dopamine release in the ACC (Saijo et al. 2010).

General Remarks Related to Dopaminergic Receptor Imaging in Unipolar and Bipolar Depression

The increased dopamine $D_{2/3}$ receptor binding, which was observed in some studies in depressed patients (and in one on bipolar disorder), may be caused by a reduced extracellular dopamine concentration in the synaptic cleft (D'haenen and Bossuyt 1994; Meyer et al. 2006b). Indeed, dopamine depletion can increase striatal $D_{2/3}$ receptor binding (Boot et al. 2008; Laruelle et al. 1997a). Also, dopamine D_1-like receptors measured by [^{11}C]NNC-112 may be sensitive to changes in endogenous dopamine (Guo et al. 2003). Therefore, and taking into account the findings on dopamine $D_{2/3}$ receptors, one may expect that a decrease of endogenous dopamine may cause an increased binding of [^{11}C]NNC-112. Nevertheless, the reported decreased D1-like receptor binding in MDD may not reflect changes in receptor binding associated with changes in dopamine concentrations, but rather a reduction in afferent neuronal terminals from the cortex and thus in the number of D_1-like receptors expressed postsynaptically (Cannon et al. 2009).

4.3.3 Monoamine Oxidase Imaging

The monoamine oxidase (MAO) enzyme catabolizes the major monoamines dopamine, noradrenalin, and serotonin (Shih et al. 1999; Youdim and Bakhle 2006). The

MAO-A enzyme especially catabolizes serotonin and noradrenalin, while the MAO-B enzyme catabolizes particularly dopamine. Classic irreversible MAO inhibitors (e.g., tranylcypromine and phenelzine) irreversibly damage both MAO-A and MAO-B; the reversible MAO-A inhibitor moclobemide does not affect MAO-B (Stahl and Felker 2008). Two selective, reversible PET ligands for MAO-A exist: [^{11}C]clorgyline (Fowler et al. 1987) and [^{11}C]harmine (Bergstrom et al. 1997b, c; Ginovart et al. 2006); the latter showed high brain uptake. In healthy controls, [^{11}C]harmine MAO-A density in the PFC was negatively correlated with the "angry/hostility" personality style (measured with the NEO-PI-R) (Soliman et al. 2011), which was reported before (with a different tracer and different personality scale) (Alia-Klein et al. 2008). However, the "deliberateness" personality style correlated positively with MAO-A density, which might indicate an evolutional advantage of this trait, when MAO-A density is moderately increased in healthy persons (Soliman et al. 2011). In 19 non-smoking healthy controls, MAO-A density as measured with [^{11}C]harmine appeared to be dynamic and adapted within 2.5–4 h to decreases of serotonin by tryptophan depletion (decrease of MAO-A in the PFC) and increases in dopamine by administration of carbidopa–levodopa (increase of MAO-A in the striatum) (Sacher et al. 2012a). This suggests rapid adaptation of the brain to externally induced changes in monoamine levels. Furthermore, increased MAO-A levels were found in the prefrontal and anterior cingulate cortices during acute cigarette withdrawal, which was associated with depressed mood (Bacher et al. 2011). In addition, Sacher et al. (2010) found elevated MAO-A in the PFC, ACC, thalamus, dorsal putamen, hippocampus, and midbrain in early puerperal mothers who were in the middle of their postpartum blues.

In medication-free patients with MDD, Meyer et al. (2006a) showed that MAO-A levels (more precisely: an index of MAO-A density) measured with [^{11}C]harmine PET were increased in every brain region assessed (from 27% in the midbrain to 39% in the thalamus; average magnitude 34%) (Meyer et al. 2006a). In later studies, this finding was replicated in early-onset MDD patients (Chiuccariello et al. 2014) and women with postpartum depression (Sacher et al. 2015), but not in seasonal affective disorder patients (Spies et al. 2018), nor in patients with treatment-resistant depression (TRD) (Baldinger-Melich et al. 2019). Moreover, Meyer et al. showed that MAO-A density remained elevated during 6 weeks of SSRI treatment (Meyer et al. 2009). Furthermore, after recovery, MAO-A levels were still significantly elevated in each brain region. Patients who had a recurrence in the following 6 months (despite a 1-year period of recovery and no drug treatment at baseline) had significantly higher MAO-A densities in the prefrontal and anterior cingulate cortex (and most regions assessed) than those who did not experience a recurrence (Meyer et al. 2009) (Table 4.8A).

MAO-B density in MDD was quantified with the highly selective tracer [^{11}C]SL25.1188 in one study, showing densities of MAO-B to be elevated by 13–26% in MDD patients relative to controls (Moriguchi et al. 2019). This finding is intriguing as increased MAO-B is associated with increased oxidative stress and mitochondrial dysfunction, possibly pointing at a metabolically deranged subtype of MDD (Table 4.8B).

Treatment of MDD patients with the reversible inhibitor of MAO-A (RIMA) moclobemide (600 mg) decreased MAO-A density on average by 74%, while in a hypothesized herbal treatment for MDD (St. John's wort 600 mg) and retesting of controls, no significant change of MAO-A binding was observed (Sacher et al. 2011). This reduction in MAO-A was replicated in a study using moclobemide (300–1200 mg/day) and the irreversible MAO inhibitor phenelzine (45–60 mg/day); these studies reported reductions between 63 and 85% and 80 and 86%, respectively (Chiuccariello et al. 2015). Electroconvulsive therapy, applied to patients with TRD, did not change MAO-A levels (Baldinger-Melich et al. 2019). [^{11}C]clorgyline was used in a dose-finding study with a new RIMA: CX157 (Fowler et al. 2010) (Table 4.8C).

These studies propose a revised monoamine deficiency theory for the pathogenesis of MDD and combine this with findings of increased SERT availability in patients with more severe negative dysfunctional attitudes (Meyer 2012). If patients suffer from increased levels of MAO-A enzymes, this will reduce intrasynaptic monoamines, e.g., serotonin. If there are few SERTs, the reduction in serotonin might be (partially) compensated, while subjects with high SERT availability (or during winter) will have more severe depressive symptoms (as expressed by more severe dysfunctional attitudes). Treatment with serotonin reuptake inhibitors (e.g., SSRIs/SNRIs and some TCAs) will block SERT and compensate the loss of serotonin. However, since increased MAO-A levels are only compensated but not changed by treatment, the persistently increased levels of MAO-A enzyme require prolongation of treatment after response/remission and may also explain recurrence. This is corroborated by MAO-A enzyme levels in patients with recurrence of their MDD in the forthcoming 6 months. This, in combination with the finding that MAO-A levels are not (or nonsignificantly) increased in a small group of TRD patients, suggests that further studies should aim to clarify whether [^{11}C]harmine scanning could be used to identify patients prone for recurrence and/or treatment with MAO inhibitors. Moreover, this hypothesis should be combined with the suggestion of decreased dopaminergic neurotransmission in a subgroup of depressed patients with treatment-resistant depression (Dunlop and Nemeroff 2007). Due to the limited evidence in small patient groups, more exploration is required before this theory is clinically applicable.

4.3.4 Monoamine Depletion Imaging

Tryptophan and tyrosine are essential amino acids in the formation of serotonin and noradrenalin/dopamine, respectively. Depletion of monoamines can be achieved by drinking amino acid mixtures without these essential amino acids. An alternative is blocking the enzyme that is crucial for the formation of the monoamine. Because of toxicity, this is not possible for serotonin, but for noradrenalin/dopamine the blockade of formation of noradrenalin/dopamine can be achieved with alpha-methylparatyrosine (AMPT) (Ruhe et al. 2007). Some depletion studies in

Table 4.8 Results of monoamine oxidase A (MAO-A) enzyme imaging studies (PET) in patients with major depression as compared to controls

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size
A. MAO-A availability					
Baldinger-Melich et al. (2019)	16 MDD (≥2 antidepressant treatments; TRD) 16 HC	[^{11}C] harmine	Various antidepressants (MAO-A affecting drugs ≥6 months)	No significant, only numerical differences between groups, indicating slightly lower mean MAO-A VT in healthy controls compared to TRD	–
				Post hoc, increased MAO-A availability in TRD women compared to healthy controls	–
Spies et al. (2018)	24 SAD 27 HC	[^{11}C] harmine	>6 months	No sign. differences in MAO-A availability between SAD patients and HC	–
				Sign. decrease in MAO-A availability after bright light therapy in SAD patients: -7.6% ($p < .001$) In spring/summer MAO-A availability decreased in HC (−8.2%), but not in SAD ($p = .03$)	–

Table 4.8 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size
Sacher et al. (2015)	15 MDD (postpartum) 12 HC (postpartum crying) 15 HC (recently pregnant) 15 HC (female)	[^{11}C] harmine	>3 months Non-smokers >1 year	Contrast MDD-postpartum vs. HC (female)	
				PFC: 18%↑ (p = .003) in MDD	1.3
				ACC: 16%↑ (p = .003) in MDD	1.0
				Ventral striatum: 18%↑ (p = .006) in MDD[b]	–
				Dorsal putamen: 14%↑ (p = .006) in MDD[b]	–
				Thal: 16%↑ (p = .006) in MDD[b]	–
				Midbr: 11%↑ (p = .006) in MDD[b]	–
				Hippoc: 13%↑ (p = .006) in MDD[b]	–

(continued)

Table 4.8 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size
Chiuccariello et al. (2014) Kolla et al. (2016)	42 early-onset MDD (15 patients from Meyer et al. 2009) 37 HC	[^{11}C] harmine	Drug-free >2 weeks (n = 37 SSRI users drug-free >1 m)	PFC: 17%↑ ($p < .001$) in MDD[b]	–
				ACC: 16%↑ ($p < .001$) in MDD[b]	–
				Ventral striatum: 13%↑ ($p = .004$) in MDD[b]	–
				Dorsal putamen: 11%↑ ($p = .004$) in MDD[b]	–
				Thal: 15%↑ ($p = .004$) in MDD[b]	–
				Midbr: 17%↑ ($p = .004$) in MDD[b]	–
				Hippoc: 14%↑ ($p = .004$) in MDD[b]	–
				More severe MDD had higher MAO V_T in PFC and ACC ($p = .008$) MAO V_T was also higher in MDD patients with reverse neuro-vegetative symptoms in all regions ($p < .03$)	

Table 4.8 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size
Meyer et al. (2009)	16 MDD	[^{11}C] harmine	>7 months (MDD; 9 drug-naive)	PFC: 27/22%↑ ($p < .001$) in MDD/rMDD[b]	1.6/1.4[b]
	18 rMDD (remitted) 28 HC		>1 year (rMDD)	ACC: 20/13%↑ ($p < .001$) in MDD/rMDD	1.3/0.8
				ATL: 23/15%↑ ($p < .001$) in MDD/rMDD	1.3/0.9
				Putamen: 30/23%↑ ($p < .001$) in MDD/rMDD	1.8/1.4
				Ventr. Striat: 25/21%↑ ($p < .001$) in MDD/rMDD	1.5/1.3
				Thal: 31/29%↑ ($p < .001$) in MDD/rMDD	1.7/1.6
				Midbr: 21/14%↑ ($p < .05$) in MDD/rMDD	0.9/0.7
				Hippoc: 28/28%↑ ($p < .001$) in MDD/rMDD	1.3/1.4
				$DV_T \approx$ (−1.6 to −9.2%; $p > .08$) after treatment with CIT (20–40 mg) or SER (50–100 mg)	
				rMDD with recurrence in 6 months ($n = 6$) had higher DVT in PFC, ACC ($p = .02$)	

(continued)

Table 4.8 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size
Meyer et al. (2006a)	17 MDD	[^{11}C] harmine	>5 months (11 drug-naive)	PFC: 34%↑ ($p < .001$) in MDD[b,c]	2.0[b]
	17 HC			ATL: 35%↑ ($p < .001$) in MDD	2.4
				ACC: 35%↑ ($p < .001$) in MDD	1.9
				PCC: 35%↑ ($p < .001$) in MDD	2.2
				Thal: 39%↑ ($p < .001$) in MDD	2.0
				Caudate: 42%↑ ($p < .001$) in MDD	1.7
				Putamen: 30%↑ ($p < .001$) in MDD	1.3
				Hippoc: 30%↑ ($p < .001$) in MDD	1.9
				Midbr: 27%↑ ($p < .001$) in MDD	1.5
				No correlations with severity, duration of illness/ episode, AD use ($p > .1$)	

Table 4.8 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size
B. MAO-B availability					
Moriguchi et al. (2019)	20 MDD 20 HC	[^{11}C] SL25.1188	≥1 month drug-free (11 drug-naive)	PFC: 26%↑ ($p < .001$) in MDD VLPFC: 26%↑ ($p < .001$) in MDD DLPFC: 16%↑ ($p < .01$) in MDD OFC: 13%↑ ($p < .04$) in MDD Thal: 17%↑ ($p < .005$) in MDD Inf. parietal: 16%↑ ($p < .005$) in MDD MAO-B availabilities in VLPFC, DLPFC, OFC, ACC, Thal., and Inf. parietal, temporal, and occipital cortex were associated with longer duration of illness ($p < .001$)	1.4 1.1 0.9 0.7 1.0 1.0

(continued)

Table 4.8 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size
C. MAO-A occupancy/inhibition					
Baldinger-Melich et al. (2019)	16 MDD (≥2 antidepressant treatments; TRD) 16 HC	[^{11}C] harmine	Various antidepressants (MAO-A affecting drugs ≥6 months); treatment with right unilateral ECT	No significant change by ECT on MAO-A levels; the effect of ECT on MAO-A availability was −3.8%; comparable with a test–retest difference of −3.1% before ECT ($p > .24$)	−0.29
Chiuccariello et al. (2015)	22 MDD	[^{11}C] harmine	>2 week (No drug-naive not reported) 18 MDD treated with moclobemide (300, 600, 900, 1200 mg) 4 MDD treated with phenelzine (45, 60 mg)	Moclobemide Occ (300–1200 mg; $n = 20$)[b]	Phenelzine Occ (45–60 mg; $n = 4$)[b]
				PFC: −64 to −80%	−86%
				ACC: −67 to −84%	−86%
				Ventr Striat: −68 to 81%	−80%
				Dors. Putamen: −64 to −77%	−83%
				Thal: −63 to −78%	−84%
				Midbr: −64 to −76%	−83%
				Hippoc: −69 to −85%	−83%
				Occupancy in PFC and ACC (and all other regions) was predictive of remission ($p < .02$)	

Table 4.8 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size
Sacher et al. (2011)	13 MDD	[^{11}C] harmine	>5 weeks (5 drug-naive) 6 MDD treated with moclobemide (600 mg) 7 MDD treated with St John's wort (1200 mg)	Moclobemide Occ (n = 6)[b,d]:	
	10 HC			PFC: −64%	
				ACC: −67%	
				ATL: −68%	
				Putamen: −64%	
				Thal: −67%	
				Hippoc: −66%	
				Midbr: −64%	
				St. John's wort Occ (n = 7): −11–4%	
				Test–retest: −9.4 to −3.2%	
Fowler et al. (2010)	15 HC	[^{11}C] clorgyline	CX157 20–80 mg administered once or 40 mg twice daily for 1 week	CX157 Occ (n = 15)	
				Administered once: 47–72% (>20 mg)	
				1 week: 48.3%	

ATL Anterior temporal cortex, *BDL* Borderline personality disorder patients, *ECT* Electroconvulsive therapy, *TRD* Treatment-resistant depression, *Ventr. Striat* Ventral striatum, *SAD* Seasonal affective disorder

[a]MAO-A binding expressed as DV_T, unless specified otherwise

[b]No exact data; estimated from figures

[c]DV_S as outcome measure

[d]Study reports an average occupancy of 74%

(recovered) MDD patient samples combined one of these approaches with molecular imaging, which will be shortly reviewed hereafter (Table 4.9).

4.3.4.1 Acute Tryptophan Depletion (ATD)

Three studies in recovered unipolar patients investigated the changes in cerebral metabolism or blood flow after depletion of tryptophan (Bremner et al. 1997; Neumeister et al. 2006; Nugent et al. 2008; Smith et al. 1999). Two [^{18}F]FDG studies reported a significant decrease in metabolism in cortical structures (in the middle frontal gyrus, DLPFC, OFC, thalamus), while significant increases were reported in the sgACC, pgACC, OFC, amygdala, (para)hippocampus, VMPFC, midbrain, and striatum (Bremner et al. 1997; Neumeister et al. 2006; Nugent et al. 2008). To some extent opposed to these changes, a $H_2{}^{15}O$ PET study showed decreased blood flow in the OFC, sgACC, caudate, and superior parietal cortex in association with increased depressive symptoms (Smith et al. 1999). Significant interactions of depletion and relapse (recurrence of depressive symptoms) were reported,

Table 4.9 Results of acute tryptophan depletion (ATD; A) and alpha-methylparatyrosine (AMPT; B) imaging studies (PET/SPECT) in patients with major depression and/or controls

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Outcome	Effect size
A. ATD					
Sacher et al. (2012a)	7 HC 6 controls	[^{11}C] harmine	None	ATD: MAO-A density ↓ (−14% ± 9%) in prefrontal cortex ($p < .031$)	
Yatham et al. (2012)	17 remitted MDD	[^{18}F]–setoperone	SSRI	5-HT2 binding was significantly decreased in the depletion session versus control session in the nondepressed group (ACC $p = .005$; medial OFC $p = .02$) but not in the group who experienced a relapse	
Neumeister et al. (2006), Nugent et al. (2008)	27 rMDD (recov)	^{18}FDG	None	ATD (rMDD > HC): ↑ rCMRGlu in OFC ($p = .01$), sgACC ($p = .03$), pgACC ($p = .05$). Amygd, Hippoc, striatum (n.s.)	
	26 controls			Interaction with 5-HTTLPR polymorphism: Hippoc ($p = .03$), sgACC ($p = .048$), Amygd ($p = .08$; esp. left): ↑ rCMRGlu in L/L vs. ↓ in S carriers	
Praschak-Rieder et al. (2005)	25 HC (14 ATD; 11 test–retest)	[^{11}C]DASB	None	ATD vs. sham depletion difference: DLPFC −2.6%, mPFC 8.1%, ACC 1.4, caudate −2.0%, putamen −4.0%, Thal 1.4%, midbrain −5.6%	
				Test–retest differences: DLPFC 4.4%, mPFC −5.1%, ACC −3.7, caudate 1.6%, putamen 2.6%, Thal 2.5%, midbrain 0.3%	

Table 4.9 (continued)

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Outcome	Effect size
Smith et al. (2000), Smith et al. (1999)	8 rMDD (recov)	$H_2{}^{15}O$	3 SSRI, 1 AMI, 1 MAOI, 1 AMI + MAOI, 2 Li addition, 2 drug-free	Increasing HDRS scores associated with:	
				↓ activity OFC, sgACC, caudate, Sup. parietal Ctx	
				↓ activity dACC during fluency task	
Bremner et al. (1997)	21 MDD (recov)	^{18}FDG	SSRIs (1–355 weeks)	Pts with (n = 7) vs. without (n = 14) relapse after ATD:	
				↓ rCMRGlu in middle frontal gyrus/DLPFC, OFC, thalamus	
				↑ rCMRGlu in amygdala, parahippocampus, VMPFC, midbrain	
B. *AMPT*					
Hasler et al. (2008)	15 MDD (recov)	^{18}FDG	None >3 months	AMPT vs. plac: MDD > HC: ↑ metabolism in VMPFC, rThal, l Ventr. Striat, sgACC, l Sup. Temp. gyrus, l Inf. Parietal, l precentral gyrus, medACC	
	13 controls				
Bremner et al. (2003)	18 MDD patients (recov)	^{18}FDG	Desipramine 75–300 mg or nortriptyline 150 mg (for 5–46 weeks)	Metabolism AMPT < plac: DLPFC, OFC, thalamus	
				Metabolism AMPT > plac: OFC, middle frontal gyrus, (para)hippocampus, amygdala, temporal/ parietal cortex	
				Abnormalities were esp. seen in patients with relapse	

Abbreviations: *MAO-A* Monoamine oxidase A, *rMDD* Recurrent MDD, *SSRI* Selective serotonin reuptake inhibitor

indicating that these changes are only occurring in remitted patients who experienced a relapse. Of note, the same cortical and limbic regions were also identified in resting state PET and SPECT studies in MDD patients and after sad mood induction, as described in Sect. 4.2. Neumeister et al. also investigated the interaction of genetic polymorphisms of the 5-HTTLPR SERT promoter region with the effects of tryptophan depletion (Neumeister et al. 2006). Relative to controls, patients with an L_A allele had a recurrence of symptoms. Relative to sham depletion, recovered MDD patients who carried the L_A/L_A genotype showed increased metabolism during depletion in the left amygdala, the hippocampus, and the sgACC. Patients with the S/S genotype showed decreased metabolism during tryptophan depletion in the hippocampus. The authors explain these differences in the context of an interplay with 5-HT_{1A} receptors and propose that recovered MDD patients with the L_A/L_A genotype have lower postsynaptic 5-HT_{1A} receptors but increased presynaptic 5-HT_{1A} receptors, resulting in a decreased threshold that makes firing less likely. After depletion, this inhibition is released, which might explain the increase in metabolism.

Two of these studies included patients who recovered but still used the antidepressant drugs that improved their symptoms (mainly SSRIs) (Bremner et al. 1997; Smith et al. 1999). These patients are most prone to recurrences induced by tryptophan depletion (Ruhe et al. 2007), which—from a critical point of view—might not represent a full recurrence of the depressive episode, but rather reflect the direct effects of sharp decreases of serotonin induced by depletion. This phenomenon is also seen when patients forget to take their antidepressants, including sudden deteriorations of mood, and is recognized as the antidepressant discontinuation syndrome (Henry et al. 2003; Rosenbaum et al. 1998). One study investigated whether depletion of tryptophan influenced [^{11}C]DASB binding, but the observed change did not exceed test–retest differences (Praschak-Rieder et al. 2005). However, after studying dynamic, rapid changes in MAO-A levels in healthy controls, Sacher et al. (2012a) suggested that given the rapid decrease in MAO-A density following ATD (proposed as a compensatory adaptation to maintain serotonin levels), compensatory MAO-A fluctuations in healthy subjects (with normal MAO-A levels and adaptation) explain why these subjects do not show mood effects after ATD, while vulnerable subjects (with proposed increased levels of MAO-A activity (Meyer et al. 2009)) do show decreased mood after ATD (Ruhe et al. 2007). In addition, Yatham et al. (2012) measured reductions in 5-HT_2 receptors after ATD and showed that the reduction in 5-HT_2, believed to compensate for lower 5-HT levels due to ATD, did not occur in patients who experienced a relapse after ATD, while those remaining without relapse indeed showed decreased 5-HT_2 receptors after ATD. Both findings may suggest specific pharmacological interventions (MAO inhibitors and atypical antipsychotics, respectively) for pre-identifiable patients vulnerable for recurrence, which should be investigated further.

4.3.4.2 AMPT

Two [^{18}F]FDG PET studies investigated changes in metabolism after AMPT-induced noradrenalin/dopamine depletion in recovered unipolar MDD patients. One studied

drug-free patients in contrast with controls (Hasler et al. 2008); another studied relapse-related changes in metabolism in patients who used noradrenergic antidepressants (Bremner et al. 2003). Versus controls, noradrenalin/dopamine depletion resulted in increased metabolism in ventral/limbic/subcortical regions (VMPFC, right thalamus, left ventral striatum, sgACC) and some dorsal/cortical regions (medial ACC, temporal and parietal cortex) (Hasler et al. 2008). In patients who experienced a relapse after AMPT, metabolism was decreased in dorsal regions (DLPFC, OFC, and thalamus), while metabolism was increased in dorsal and limbic regions (middle frontal gyrus, (para)hippocampus, amygdala, temporal/parietal cortex). Again, these are regions that were also identified in resting state PET and SPECT studies in depressed patients (Sect. 4.2).

4.3.4.3 Depletion and Depressive Episodes

The interpretation of these ATD and AMPT findings could be that the depressed state resembles a situation in which serotonin and/or noradrenalin/dopamine is (acutely) depleted (in line with the monoamine hypothesis). However, an alternative hypothesis could be that after acute depletion the brain tries to compensate for withdrawal symptoms and impaired emotion regulation by activations that resemble the brain activity of a depressed state, but differ in the sense that they can easily be restored after the depletion experiment. In order to really understand this state versus adaptation hypothesis, the changes in mood and metabolism should be studied at several time points during prolonged depletion. Such studies are probably hard to do for ethical reasons.

4.4 New Perspectives

This chapter has provided an extensive overview of PET and SPECT imaging data drawn from studies investigating the molecular basis for the pathophysiology and treatment of MDD and BD. The majority of these studies focus on monoamine neurotransmitter systems and tracers related to their pharmacological targets. Although several monoamine tracers are approved for use in human subjects, novel tracers to image relatively less characterized monoamine targets are being evaluated on an ongoing basis. At the same time, recent pathophysiological research in mood disorders has identified several potential novel non-monoamine pharmacological targets. This has led to an upsurge in CNS drug discovery and the identification of new molecular entities that serve as ligands for such novel targets over the past decade. In vivo PET and SPECT imaging can be applied to track the pharmacokinetic and pharmacodynamic characteristics of novel compounds and, as a consequence, contribute to rational drug development by allowing optimal dose selection based on RO in clinical trials.

This section focuses on both novel monoaminergic and non-aminergic tracers that are currently under development or are already being applied in innovative pathophysiological research and CNS drug development in mood disorders.

4.4.1 Ongoing Radioligand Development for Imaging Serotonergic Neurotransmission

The 5-HT receptors are among the most diverse group of neurotransmitter receptors. At least 14 different receptor subtypes have been described so far. In addition, the SERT and 5-HT synthetic and degrading enzymes contribute to the system's function and regulation. At present, only few of these targets can be reliably imaged in vivo by PET or SPECT techniques, and even fewer are the subject of clinical imaging studies (Paterson et al. 2013). Therefore, there are many targets for future radioligand development. Recent advances for in vivo imaging in humans include PET imaging of the 5-HT_4 receptor with [^{11}C]SB207145 (Madsen et al. 2011; Marner et al. 2009; Marner et al. 2010) and a series of compounds for 5-HT_7 imaging that at present have been tested in cats and may prove useful for imaging of 5-HT_7 in humans (particularly [^{18}F]2FP3) (Andries et al. 2011; Lemoine et al. 2011).

PET imaging of the 5-HT_4 receptor with [^{11}C]SB207145 holds promise to index the serotonergic tone apart from mapping 5-HT_4 receptor per se (Haahr et al. 2014). Therefore larger studies with the tracer in both healthy individuals and patients with MDD have been initiated. Data on 5-HT_4 receptor density in healthy individuals at high risk for depression is starting to emerge (Madsen et al. 2014), and links between 5-HT_4 receptor binding and stress hormone regulation have been established (Jakobsen et al. 2016). However, no full article versions of data in clinical populations of MDD or BD have been published. Yet, recent data indicate that MDD patients display lower 5-HT_4 binding relative to controls, possibly reflecting compensatory mechanisms in terms of heightened serotonergic tone and low capacity for 5-HT_4 agonism to be implicated in the pathophysiology (Koehler-Forsberg et al. 2019).

At the current state of radioligand evolution, most 5-HT receptor imaging is acquired by the use of antagonist radioligands (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, and 5-HT_4 receptors and SERT) (Paterson et al. 2013). However, antagonist ligands bind to receptors in their high-affinity as well as low-affinity state, and the high-affinity state represents the active form of the receptor that is coupled to G proteins. So, serotonin occupies more receptors in their high-affinity than in their low-affinity state. Therefore, one may expect that an agonist radiotracer will show an increased sensitivity to detect serotonin release compared to an antagonist radiotracer. Interestingly, agonist PET tracers for evaluation of the serotonergic system are under development (Paterson et al. 2010). Currently, [^{11}C]Cimbi-36 is the most promising agonist candidate for imaging of 5-HT_{2A} receptor binding and has been evaluated in pigs (Ettrup et al. 2011) and humans (Ettrup et al. 2014; da Cunha-Bang et al. 2019). Such tools may allow us to explore the interplay between the serotonergic neurotransmission and experimental challenges (either physiological or psychological stimuli or pharmacological interventions), such as amphetamine challenge which holds promise to measure serotonin release capacity (Erritzoe et al. 2020). For the dopamine system, methods are available to measure endogenous dopamine release using, e.g., antagonists [^{11}C]raclopride and [^{123}I]IBZM (Breier et al. 1997; Ginovart 2005; Laruelle et al. 1995, 1997b) or the DA agonist PHNO, and these methods have contributed valuable insights in dopaminergic mechanisms

in, e.g., schizophrenia and addiction. Importantly, agonist radiotracers for the dopamine D_2 receptor have been developed successfully, and indeed they may be more sensitive to detect DA release than D_2 receptor antagonist radiotracers.

Other tracers that are promising candidates to detect endogenous 5-HT release are the partial 5-HT_{1A} agonist [^{11}C]CUMI-101 (Selvaraj et al. 2012) and two 5-HT_{1B} antagonists [^{11}C]AZ10419369 (Finnema et al. 2010, 2012) and [^{11}C]p943 (Cosgrove et al. 2011; Ridler et al. 2011). A recent study in humans by Selvaraj et al. reported that SSRI infusion (citalopram 10 mg) increased [^{11}C]CUMI-101 binding with approximately 7% in cortical projection areas relative to placebo, but not in the raphe nuclei where the serotonergic neuronal cell bodies are located (Selvaraj et al. 2012). SSRI exposure may initially generate an inhibitory 5-HT_{1A} autoreceptor effect at the raphe level, which first reduces serotonergic activity (and synaptic 5-HT in projection areas), represented by increased [^{11}C]CUMI-101 binding. On the contrary, another study with a comparable setup could not confirm that [^{11}C]CUMI-101 was sensitive to citalopram infusion (Pinborg et al. 2012).

Two 5-HT_{1B} antagonist radioligands ([^{11}C]AZ10419369 and [^{11}C]p943) are reported to show dose-dependent displacement in response to a potent 5-HT-releasing challenge (fenfluramine infusion) in nonhuman primates. [^{11}C]p943 is also displaceable with an SSRI (Ridler et al. 2011). Nevertheless, even though these radioligands are now available for human studies, their sensitivity to human endogenous 5-HT release has not yet been established.

Recent and potential future advances in radioligand development for imaging the serotonergic neurotransmission thus include the identification of selective radioligands for remaining targets, potential development, and use of agonist tracers that image the biologically active pool of membrane-bound receptors and methods to measure synaptic levels of 5-HT. In the light of these advances, further exploration of the serotonergic system in vivo is in reach and, hopefully, will advance the pathophysiological insight in, e.g., MDD and BD in order to support development of better 5-HT-related treatments.

4.4.2 Imaging of the Norepinephrine System

Recent advances in ligand development provided suitable PET radioligands for NET, although improvements can still be achieved. The possibility to quantify NET occupancy is important for the development and evaluation of pharmacological agents targeting the NET, which are used for treatment of MDD, anxiety disorders, and attentional deficit hyperactivity disorder (ADHD). Especially (S,S)-2-(α-(2-[^{18}F]fluoro[$^{2}H_2$]methoxyphenoxy)-benzyl)-morpholine ((S,S)-[^{18}F]FMeNER-D_2) proved to have adequate affinity, specificity, selectivity, and binding kinetics to provide valid measurements also in regions with low density of NET (e.g., cerebellum, striatum, and insula) (Rami-Mark et al. 2013), while [^{11}C]-(S,S)-methylreboxetine ([^{11}C]MRB) had higher nonspecific binding in low-NET-containing regions (e.g., the basal ganglia/caudate nucleus) and therefore performed worse on signal to noise/sensitivity (Severance et al. 2007), making (S,S)-[^{18}F]FMeNER-D_2 the best

ligand for NET to date. However, given the long half-life of [^{18}F] tracers and the possibility of in vivo defluorination of (S,S)-[^{18}F]FMeNER-D_2 (Gallezot et al. 2011), [^{11}C]MRB may be preferred when repeated scans over days are requested.

Both ligands were tested in nonhuman primates using a variety of NET-occupying drugs (atomoxetine, clomipramine, milnacipran, venlafaxine) (Seneca et al. 2006; Takano et al. 2009; Gallezot et al. 2011; Takano et al. 2011a, b; Takano et al. 2013; Ding et al. 2014), showing dose-dependent occupancies of NET in different regions of the brain (locus coeruleus, (anterior) cingulate gyrus, mesencephalon, and thalamus).

In humans, (S,S)-[^{18}F]FMeNER-D_2 was first used in six healthy males, scanned twice before and after a single dose of nortriptyline (10–75 mg) (Sekine et al. 2010). NET occupancies in the thalamus varied between 16.4% (10 mg) and 41.1% (75 mg), while locus coeruleus occupancies varied between 41.6 and 90.3%, although not dose-dependently. In another study on 11 (male and female) healthy subjects, a single dose of methylphenidate (2.5–40 mg or placebo) was administered followed by 2 h of dynamic [^{11}C]MRB PET scanning (Hannestad et al. 2010). NET occupancies in the thalamus exceeded 80% in the locus coeruleus, raphe nuclei, and hypothalamus at 40 mg dose, while for this dose, occupancies in the thalamus varied between 50 and 60%. In nine healthy males treated for 6–8 days with variable dose of quetiapine XR (150–300 mg), repeated (S,S)-[^{18}F]FMeNER-D_2 PET scanning showed a mean NET occupancy in the thalamus of 19% at 150 mg and 35% at 300 mg, which is presumably caused by the norquetiapine metabolite (Nyberg et al. 2013).

In MDD patients, two studies have been published. First, six male patients using the dual-action antidepressant milnacipran at variable dose (25–200 mg) were investigated with a single (S,S)-[^{18}F]FMeNER-D_2 PET scan and compared to an age-matched healthy control to calculate NET occupancy in the thalamus (Nogami et al. 2013). NET occupancy varied between 25.3% at 25 mg and 49.9% at 200 mg. In the same study SERT occupancy in the thalamus was determined likewise by [^{11}C]DASB PET scans in six different patients treated with milnacipran (50–200 mg), showing SERT occupancies between 33.0% and 61.5%. Finally, in a study investigating ten MDD patients responding to treatment with variable doses of nortriptyline (75–200 mg) scanned once with (S,S)-[^{18}F]FMeNER-D_2 PET and compared to the mean NET availability of age-matched controls, NET occupancy varied between 50 and 70% with no association between residual symptoms and NET occupancy (Takano et al. 2014).

The above results indicate that future studies to investigate NET occupancy by antidepressants and other pharmacological agents targeting this transporter are possible, although the quality of the ligands is not yet comparable to those for SERT imaging. Studies in clinical samples are scarce, and prospective studies using repeated PET scanning to properly assess occupancies induced by norepinephrinergic drug treatment within patients are lacking.

4.4.3 Radioligands for Glutamate Targets

Glutamate is the main stimulatory amino acid in the human CNS and an endogenous ligand for ionotropic and metabotropic glutamate receptors. Ionotropic glutamatergic receptors (iGluRs) predominantly occur postsynaptically and include N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and kainate (KA) receptors. AMPARs and KARs are responsible for excitatory neurotransmission, while NMDARs play a crucial role in processes mediated by synaptic plasticity such as long-term potentiation and excitotoxicity. Metabotropic glutamate receptors (mGluRs) are G-protein-coupled receptors (GPCRs) that are expressed both pre- and postsynaptically. As a result, mGluRs bind glutamate to activate diverse secondary messenger systems, which enables more complex modulatory downstream effects compared to iGluRs. Thus far eight distinct mGluRs have been identified and, based among others on sequence homology and agonist selectivity, are divided into three main groups (I, II, and III). Groups I, II, and III comprise mGluR1 and mGluR5; mGluR2 and mGluR3; and mGluR4, mGluR6, mGluR7, and mGluR8, respectively.

The widespread expression of glutamate receptors might facilitate their in vivo quantification using PET. However, tracer development for glutamate targets is often hampered by inferior in vivo results such as limited blood–brain barrier penetration, rapid clearance, and nonspecific receptor binding (Kassenbrock et al. 2016).

Despite the complexity associated with developing radioligands for iGluRs, several radiotracers have been developed to quantify the in vivo concentrations of iGluRs, as well as to investigate the distribution and pharmacology of these receptors in health and disease. Thus far PET tracers for NMDARs have been most numerous, followed by tracers for AMPARs, while only one has been reported for KARs (Fu et al. 2019). Among the iGluR imaging agents, a number of candidate ligands were successfully radiolabeled and showed promising in vitro properties such as high affinity and good receptor selectivity. However, in vivo results have been generally disappointing for reasons such as poor brain penetration, extensive metabolism, and high nonspecific binding in humans (Majo et al. 2013). Similarly, the recent PET ligand for the NMDAR ion channel site 3-(2-chloro-5-(methylthio) phenyl)-1-(3-([^{18}F]fluoromethoxy)phenyl)-1 methylguanidine ([^{18}F]PK-209) did not demonstrate sufficiently reproducible binding, effectively eliminating itself as candidate tracer (van der Aart et al. 2018). Only one SPECT ligand exists, N-(1-napthyl)-N′-(3-[(^{123})I]-iodophenyl)-N-methylguanidine ([^{123}I]CNS-1261), but has had limited success in clinical NMDAR studies due to activation by the NMDAR coactivator D-serine and high nonspecific binding, which hamper detection of small changes in receptor availability (Knol et al. 2009; Stone et al. 2008; Owens et al. 2000). No radioligands for either the glycine site or the NR2B binding site showed sufficient promise to warrant clinical studies. A recent paper reported the evaluation of N-((5-(4-fluoro-2-[^{11}C]methoxyphenyl)pyridin-3-yl)methyl)cyclopentanamin ([^{11}C]HACH242) in nonhuman primates with administration of the NR2B negative allosteric modulator radiprodil. Although [^{11}C]HACH242 demonstrated a suitable kinetic profile and low accumulation of lipophilic radiometabolites, radiprodil did

not consistently change [^{11}C]HACH242 brain uptake (van der Aart et al. 2019). Although limited progress has been achieved in the development of radiotracers for AMPARs and KARs, a PET tracer for AMPA receptors ([^{11}C]K-2) has recently been developed and studied in healthy human volunteers and patients with epilepsy, showing specific binding to AMPA receptors (Miyazaki et al. 2020). Increased understanding of AMPAR and KAR protein structures in the closed, active, and desensitized states has improved understanding of receptor–ligand interactions at the molecular level, which may lead to opportunities for future PET tracer development for iGluRs.

Tracer development for iGluRs is relevant given the observation that the non-competitive NMDA antagonist ketamine acts as a rapid antidepressant in treatment-resistant depression (TRD) (Aan het Rot et al. 2012; Park et al. 2019a). This provided an important impetus to the hypothesis that glutamate may play a crucial role in the pathophysiology of (persistent) unipolar mood disorders. Although such evidence is still mounting, the (S)-enantiomer of ketamine has recently been approved by regulatory authorities for the treatment of TRD. However, due to undesirable (psychomimetic) side-effects associated with ketamine, efforts are underway to develop compounds that modulate the NMDAR via alternative sites, such as the channel blocker site (lanicemine/AZD 6765), the glycine site (rapastinel/GLYX-13), and the NR2B subunit of the NMDAR (traxoprodil/CP-101,606 and CERC-301/MK-0657) (Ionescu and Papakostas 2017; Kadriu et al. 2019). Apart from mechanisms of action involving iGluRs, several metabotropic receptor modulators such as the mGluR5 antagonist basimglurant (RG7090 or RO4917523) and the mGluR2/3 antagonist decoglurant (RG1578 or RO4995819) have been developed (Kadriu et al. 2019).

In contrast to the scenario with NMDARs, several PET ligands for group I mGluRs have been developed and have demonstrated promising results in clinical studies. Among the mGluR5 imaging agents, 3-(6-methyl-pyridin-2-ylethynyl)-cyclohex-2-enone-O-^{11}C-methyl-oxime ([^{11}C]ABP-688), ^{18}F-3-fluoro-5-(pyridin-2-ylethynyl)benzonitrile ([^{18}F]FPEB), and 3-fluoro-5-(2-(2-[^{18}F](fluoromethyl)-thiazol-4-yl)ethynyl) ([^{18}F]-SP203) benzonitrile have been the most successful PET radioligands and are currently being investigated in clinical trials, including the evaluation of mGluR5 availability in disease states (Fuchigami et al. 2015; Esterlis et al. 2018). Recently, the mGluR2 PET ligand [^{11}C]JNJ-42491293 was evaluated in vivo, and although it initially appeared promising, its development seems to have been abandoned due to off-target binding (Leurquin-Sterk et al. 2017). Based on results from preliminary animal PET studies, [^{18}F]MK-1312 holds promise as suitable imaging agent for mGluR1 (Fuchigami et al. 2015). PET radioligands for mGluR1, such as 4-[^{18}F]fluoro-*N*-[4-[6-(isopropylamino)pyrimidin-4-yl]-1,3-thiazol-2-yl]-*N*-methylbenzamide ([^{18}F]FITM), *N*-(4-(6-(isopropylamino)pyrimidin-4-yl)-1,3-thiazol-2-yl)-4-[^{11}C]methoxy-*N*-methylbenzamide ([^{11}C]ITMM), N-(4-(6-(isopropylamino)pyrimidin-4-yl)-1,3-thiazol-2-yl)-*N*-methyl-4-[^{11}C]methylbenzamide ([^{11}C]ITDM), and 4-(^{18}F)fluoranyl-*N*-methyl-*N*-[4-[6-(methylamino)pyrimidin-4-yl]-1,3-thiazol-2-yl]benzamide ([^{18}F]FIMX), have proven useful in clinical PET studies (Fuchigami et al. 2015; Zanotti-Fregonara et al. 2016). One of

the limiting factors for developing PET tracers for group III mGluRs has been the lack of availability of subtype-selective high-affinity ligands, necessitating the future development of high-affinity and selective ligands for these receptors.

4.4.4 Imaging of the Central Opioid System

The endogenous opioid neuropeptides β-endorphin, enkephalins, and dynorphins act preferentially at the μ (MOR), δ (DOR), and κ (KOR) opioid receptors, respectively (Lutz and Kieffer 2013). The nociception opioid peptide receptor (NOR), also known as the nociceptin/orphanin FQ (N/OFQ) receptor or kappa-type 3 opioid receptor, is a fourth related opioid receptor that binds nociceptin (Meunier et al. 1995). The σ receptor was previously considered an opioid receptor, but since it rather binds drugs that are unrelated to opioids and it is not blocked by opioid receptor antagonists, its functional significance remains poorly understood (Corbett et al. 2006). Together these receptors represent a subfamily of GPCRs that are ubiquitously expressed in the CNS and peripheral nervous system. Physiologically, the opioid system is increasingly recognized as an important modulator of processes such as mood regulation, reward and aversion, pain, responsivity to stressful stimuli, and adverse environmental experiences. In fact, a multidimensional model for opioid receptor involvement in depression is currently emerging: although MOR and DOR agonism can improve mood, KOR antagonists may be capable of reversing depressed mood since endogenous KOR activation is associated with dysphoria. Taken together, the endogenous opioid system is a potentially promising avenue to pursue in search of novel antidepressants (Jacobson et al. 2020).

Morphine-like opioids preferentially bind to MORs, which are concentrated in regions associated with descending analgesic pathways, such as the periaqueductal gray, rostroventral medulla, medial thalamus, and dorsal horn of the spinal cord. Importantly, these regions significantly overlap with neurocircuits that have been implicated in emotion regulation, and MORs occur in reward-related regions including the ventral tegmental area (VTA) of the midbrain and the nucleus accumbens. MORs are therefore believed to mediate the hedonic effects of natural rewards and, as a consequence, the addictive effects of opiates. In addition, MORs are expressed in the dorsal striatum and in the locus coeruleus (LC), where they mediate aspects of physical opioid dependence and withdrawal (Peciña et al. 2019). The selective MOR PET ligand [^{11}C]carfentanil has been applied to investigate the relationship between opioid neurotransmission and emotion regulation. In 2003, Zubieta et al. studied 14 healthy women with a mood induction and [^{11}C]carfentanil PET scans. During the sad mood, a significant increase of mu-opioid binding (representing deactivation of neurotransmission) occurred in the rostral ACC, ventral pallidum, amygdala, and inferior temporal cortex, which correlated with the ratings of affect (Zubieta et al. 2003). However, in 2013, Hsu et al. also applied in vivo measures of MORs during a sadness induction paradigm and demonstrated reduced endogenous opioid neurotransmission in a diffuse network of regions implicated in emotion

regulation (Hsu et al. 2013). In addition, several studies have identified baseline measures of MOR availability as a predictor for monoaminergic antidepressant response (Peciña et al. 2019). Finally, human neuroimaging studies suggest that the endogenous opioid system, in particular MORs, plays a key role in the processing of social cues, which seems to be particularly altered in patients with MDD (Hsu et al. 2013).

KORs in particular have been associated with maintenance of hedonic tone (Lutz and Kieffer 2013). PET has therefore been applied to identify changes in KOR binding potential in patients with MDD and in drug development programs involving KOR antagonists as potential ADs and/or anxiolytics (Carroll and Carlezon Jr. 2013). Several selective KOR radioligands are available for clinical use and have been applied in studies with both mood and stress-related disorders. Agonist ligands include ^{11}C-methyl 4-[(3,4-dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate ([^{11}C]-GR89696) and (-)-4-[^{11}C]methoxycarbonyl-2-[(1-pyrrolidinylmethyl]-1-[(3,4-dichlorophenyl)acetyl]-piperidine ([^{11}C]-GR103545), while antagonist ligands comprise (3R)-7-hydroxy-N-((1S)-1-[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-2-methylpropyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide ([^{11}C]-MeJDTic), carbonyl-^{11}C] (*S*)-3-chloro-4-(4-((2-(pyridine-3-yl)pyrrolidin-1-yl)methyl)phenoxy)benzamide ([^{11}C]-LY2795050), and [^{11}C]-LY2459989 (Richards et al. 2016). Using [^{11}C]LY2795050, low KOR expression in the amygdala–anterior cingulate cortex (ACC)–ventral striatal circuit was related to severity of loss-related symptoms in trauma-exposed individuals (Pietrzak et al. 2014). However, decreased KOR availability within the insula, caudate, thalamus, and hypothalamus was negatively related to severity of loss-related symptoms (Van't Veer and Carlezon Jr 2013). However, in a separate study with the selective KOR agonist radiotracer [^{11}C]GR103535, no effects of MDD on KOR binding within the amygdala, hippocampus, raphe nucleus, or ventral striatum were detected (Miller et al. 2018).

Several different KOR antagonists exist, including irreversible, long-acting, and short-acting compounds (Carroll and Carlezon Jr. 2013; Carlezon and Krystal 2016; Urbano et al. 2014). The prototypical selective KOR antagonists include 5-acetamidinoethylnaltrindole (ANTI), 5-guanidinonaltrindole (GNTI), (3R,4R)-dimethyl-4-(3-hydroxyphenyl) piperidine-based JDTic, and norbinaltorphimine (nor-BNI). Preclinically, these compounds have demonstrated low brain penetration and a slow onset of antagonist activity (peak at approximately 24 h), a long duration of action in vivo (up to 3–4 weeks following a single systemic exposure), and undesirable side effects. In addition, GNTI has poor oral bioavailability (Mague et al. 2003), and DIPPA binds KOR irreversibly (Carroll and Carlezon Jr. 2013). Their long duration of action and irreversibility make these compounds less suitable for clinical use. Novel KOR antagonists with a shorter duration of action and faster absorption would be more applicable to clinical trials. These include JNJ-67953964, LY2444296, zyklophin, PF-04455242, and AZ-MTAB. However, AZ-MTAB has poor brain penetration and high hERG activity which is associated with QT-interval prolongation (Urbano et al. 2014), and PF-04455242 was terminated after phase I studies due to toxicity. In addition, several mixed opioid antagonists also have

substantial affinity for KORs, including buprenorphine, the buprenorphine derivative BU10119, ALKS-5461, naltrexone, and m-trifluoromethyl-diphenyl diselenide [(m-CF3-PhSe)2]. Currently, CERC-501(LY-2456302) and ALKS 5461 survived and entered into phases II and III, respectively (Li et al). The development of KOR antagonists suitable for clinical use in the treatment of MDD is obviously still in its infancy, but steady progress is being made.

The localization of DORs in the amygdala, cortex, and hippocampus may be consistent with modulation of mood regulation, fear, and anxiety (Torregrossa et al. 2004). The selective DOR antagonist [^{11}C]-methyl-naltrindole is available for human use, but has not yet been applied to mood disorders (Madar et al. 1996). Although still in early development, DOR agonists including UFP-512 (Vergura et al. 2008) and AZD2327 (NCT00759395) (Richards et al. 2016) show potential since both preclinical and clinical studies have found positive antidepressant-like effects. However, the mechanisms through which DOR are involved in mood disorders in humans are unclear.

In summary, despite the availability of several compounds which modulate the endogenous opioid system, the limited availability of acceptable radiotracers hampers grasping the relevance of these systems to MDD and their potential as future therapeutic targets.

4.4.5 Imaging Inflammation and Depression

Given the heterogeneity of symptoms of MDD, the complexity of the affected neurotransmitter systems as described above, and the failure to successfully treat MDD based on these systems, alternative metabolic theories of depression should be considered (Gardner and Boles 2011). One of the emerging hypotheses on MDD relies on inflammatory mechanisms.

Treating nondepressed patients with pro-inflammatory cytokines, such as interferon alpha, can induce depression. In these cases, a peripheral induction of inflammation has central nervous system effects and induces depression (Dantzer et al. 2008). Furthermore, central nervous system inflammatory diseases such as multiple sclerosis (MS) have also profound effects on mood and may cause depression by direct release of pro-inflammatory cytokines in the CNS. In hepatitis C patients, depression occurs frequently and is sometimes aggravated or caused by interferon treatments (although a direct effect of the virus on the brain cannot be ruled out).

Activation of microglia, the immune-competent cells in the brain, is a well-described feature of severe diseases that are accompanied by depressive symptoms. Microglia activation can be visualized with tracers binding to the translocator protein (TSPO, previously known as peripheral benzodiazepine receptor (PBR)) (Doorduin et al. 2008), since TSPO expression is associated with a pro-inflammatory state. Current tracers used to visualize microglia activation are [^{11}C]PK11195, [^{11}C]-PBR28, and [^{18}F]-FEPPA. The affinity of [^{11}C]-PBR28 and [^{18}F]-FEPPA depends on a single polymorphism (SNP, rs6971) in the TSPO gene, which is not the case for [^{11}C]PK11195 (Owen et al. 2012). In practice, use of ligands with

dependence on this SNP requires methodological or statistical adjustments, but these ligands tend to be more sensitive than [^{11}C]PK11195.

Earlier, with [^{11}C]PK11195, patients with chronic hepatitis C virus infections were shown to have inflammatory lesions (Grover et al. 2012). In MS, inflammatory lesions in the white matter are well defined and accompanied by microglia activation. In Alzheimer's disease, microglia activation is a core feature and is associated with large emotional and cognitive changes (Versijpt et al. 2003). In psychotic disorders, an increase in microglia activation was demonstrated after a first psychotic episode (van Berckel et al. 2008). During a psychotic episode, this inflammation was found to predominate in the hippocampus (Doorduin et al. 2009). Finally, microglia express all neurotransmitter receptors (Pocock and Kettenmann 2007) and are also important in the reuptake of these neurotransmitters, especially the potentially toxic glutamate. Glutamate is an important mediator in MDD and is involved in aberrant prefrontal functioning in emotion regulation (Muller and Schwarz 2007; Walter et al. 2009).

In the first published TSPO study concerning MDD, [^{11}C]-PBR28 did not demonstrate an increase in binding in ten MDD patients compared to ten healthy controls (Hannestad et al. 2013), but not all MDD patients were currently depressed. In an earlier conference paper, van Otterloo et al. (2005) also did not find increased density of activated microglia in the white matter of the orbitofrontal region in ten MDD subjects. A larger, subsequent study including 20 MDD patients and 20 healthy controls using [^{18}F]-FEPPA demonstrated increased binding in the prefrontal cortex, anterior cingulate cortex, and insula of patients (Setiawan et al. 2015). In a third study, using [^{11}C]PK11195, binding was increased in the subgenual anterior cingulate cortex of 5 elderly patients with MDD, compared to 13 healthy controls, showing that microglia activation is also present in elderly patients (Su et al. 2016). A fourth study, also using [^{11}C]PK11195, again demonstrated increased binding in the anterior cingulate cortex of 14 medication-free patients with MDD, compared to 13 healthy controls. In a post hoc analysis, TSPO binding was found to be specifically increased in patients having suicidal thoughts, compared to patients that did not have such thoughts (Holmes et al. 2018). Cognitive functioning was found to be related to [^{18}F]-FEPPA binding in 50 medication-free MDD patients (Li et al. 2018a).

In a relatively large-scale PET study, including 51 patients, [^{18}F]-FEPPA binding was found to be greater in patients with chronologically advanced major depressive disorder and long periods of no antidepressant treatment than in patients with major depressive disorder and short periods of no antidepressant treatment (Setiawan et al. 2018). A yearly increase in microglial activation was not evident when antidepressant treatment was given. A similar relationship of [^{11}C]-PBR28 binding with duration of illness was found in another study in 28 MDD patients but not in medicated patients (Richards et al. 2018). Cognitive behavioral therapy, but not supportive psychotherapy, was found to reduce [^{18}F]-FEPPA binding in 20 patients with MDD (Li et al. 2018b).

Thus far, in BD increased [^{11}C]PK11195 binding has been demonstrated in the hippocampus of 14 euthymic type I patients, compared to 11 healthy controls (Haarman et al. 2014).

In summary, microglia activation has been demonstrated quite robustly in MDD patients with varying duration of illness and age. Both treatment with antidepressants and cognitive behavioral therapy seem to have an ameliorating effect on this activation.

Recently, Meyer (2017) proposed that microglia activation in MDD is associated with reduced astroglia availability (Rajkowska and Stockmeier 2013) and increased activity of MAO-A (see above), which could be resulting in increased extracellular glutamate levels. These abnormalities might be contributing to a pathological reorganization of the nervous system ("neuroprogression") along the course of MDD. For further clarification, additional studies are needed, which may also investigate the possibility to use these different markers for treatment stratification (Meyer 2017).

Patients with recurrent and/or persistent unipolar mood disorders have demonstrated alterations in the innate immune system and inflammatory responses, including increased concentrations of circulating cytokines such as IL-1β. The P2X7 receptor (P2X7R) is one of seven subtypes of adenosine triphosphate (ATP)-gated P2X ion channels present on various human cells. Peripherally, P2X7R is expressed mainly by monocytes, while in the central nervous system (CNS), the receptor is mostly expressed by microglia (Romagnoli et al. 2008). P2X7R activation by ATP may arise from diverse stimuli such as oxidative stress, hypoglycemia, ischemia, inflammation, cellular injury, or chronic stress. During such conditions, ATP activates the P2X7R which leads to inflammatory-like activation and subsequent production of pro-inflammatory cytokines including interleukin (IL)-1β in both the CNS and the periphery. Because of the well-recognized role of the P2X7R in IL-1β release, it is hypothesized that antagonists might have beneficial effects in the treatment of mood disorders. A number of CNS-penetrant high-affinity and selective P2X7R antagonists such as JNJ-54175446 and JNJ-55308942 are currently in development (Bhattacharya 2018; Timmers et al. 2018). A PET tracer ([^{18}F]-JNJ-64413739) has been developed for the P2X7R and has been evaluated preclinically in rhesus monkeys, demonstrating reproducible and dose-dependent receptor occupancy of P2X7R antagonists, making it suitable for P2X7R imaging studies in humans (Kolb et al. 2019).

Substance P acts both as a neurotransmitter and neuromodulator and has pro-inflammatory properties by binding neurokinin-1 receptors (NK1Rs). Previous failure of the NK1R antagonist aprepitant to separate from placebo in severe MDD trials was ascribed to inadequate central NK1R occupancy. This has led to renewed interest in the NK1R antagonists casopitant and orvepitant (GW823296) for the treatment of MDD, for which several PET tracers such as 2-[^{18}F]fluoromethoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]([2*S*,3*S*]2-phenyl-piperidin-3-yl)-amine ([^{18}F]SPA-RQ), (2*S*,3*S*)-*N*-[[2-[^{11}C]methoxy-5-[5-(trifluoromethyl) tetrazol-1-yl]phenyl]methyl]-2-phenyl-piperidin-3-amine ([^{11}C]GR205171), and N1-(2,6-dimethylphenyl)-2-(4-(2R,4S)-2-benzyl-1-[3,5-di(trifluoromethyl) [carbonyl-^{11}C]benzoyl]hexahydro-4-pyridinyl(piperazino)acetamide ([^{11}C]R116301) are available to quantify NK1R occupancy in humans (Masdeu 2011; Majkowska-Pilip et al. 2019).

4.4.6 Imaging of Other Neurotransmitter Systems and Neuropeptides

Although the majority of research in MDD has addressed monoamine systems, glutamate, inflammatory pathways, other neurotransmitter systems that are potentially less well-known and/or less implicated in mood disorders, and neuropeptides are currently subject of investigation.

Cannon et al. reported a reduction of muscarinic receptor binding of [^{18}F]FP-TZTP in the ACC in bipolar, but not unipolar, depression. Until now, it remains unknown whether this finding represents a reduction in M_2 receptor density or affinity or an elevation in endogenous acetylcholine levels (Cannon et al. 2006a). Nevertheless, this system merits further research as muscarinic receptor agonists, genetic polymorphisms of the M_2 receptor, or acetylcholinesterase inhibitors are associated with depressive symptoms (Comings et al. 2002; Dilsaver 1986).

Scopolamine is a selective muscarinic-1 receptor (M_1R) antagonist that has been shown to reduce symptoms of depression and anxiety following intravenous administration in MDD patients (Furey and Drevets 2006; Drevets and Furey 2010). 8-((1S,2S)-2-Hydroxycyclohexyl)-5-((6-(methyl-t3)pyridin-3-yl)methyl)-8,9-dihydro-7H-pyrrolo[3,4-h]quinolin-7-one ([^{3}H]PT-1284) is currently under development as radioligand to investigate the effect of positive allosteric modulators (PAMs) that target M_1R (Smith et al. 2016). CP-601-927 is a α4β2 nicotinic acetylcholine (nACh) receptor partial agonist which demonstrated no efficacy as an augmentation agent in TRD (Fava et al. 2015). [^{18}F]Flubatine displayed favorably kinetics and imaging properties, suggesting it to be a suitable and clinically applicable PET tracer for in vivo imaging of α4β2 nAChRs (Sabri et al. 2015). Current nAChR radiotracer development focuses on improving specificity for the α7 subtype while maintaining or improving brain uptake over known tracers (Kassenbrock et al. 2016).

The orexins/hypocretins have been shown to regulate the sleep–wake cycle and vigilance in numerous preclinical and clinical studies (Yamanaka 2013). Orexin nuclei are primarily located in the lateral and posterior hypothalamus, from where efferent axons project to the cerebral cortex and structures involving the limbic system such as the nucleus accumbens (NA), mesocorticolimbic VTA, and the histaminergic tuberomammillary nucleus (TMN). In addition, neuronal projections to brain stem nuclei such as the locus coeruleus and raphe nuclei are involved in modulating noradrenergic and serotonergic neurotransmission, which are implicated in the regulation of arousal (Inutsuka and Yamanaka 2013). Interestingly, the absence of orexin-producing cells in the lateral hypothalamus results in narcolepsy with cataplexy (narcolepsy type I) in humans. Overactivity of the orexin system has therefore been related to MDD symptoms related to hyperarousal such as insomnia, anxiety, and/or anhedonia. Orexinergic effects are mediated by the excitatory neuropeptides orexin A (OX-A) and orexin B (OX-B) that function as endogenous ligands for the G-protein-coupled orexin-1 receptor (OX1R) and orexin-2 receptor (OX2R). The affinity of OX-A for OX1R is roughly 100 times higher compared to OX-B, whereas for OX2R, the affinity is similar for both endogenous ligands.

Suvorexant is a nonselective dual OX1R/OX2R antagonist (DORA) which is currently registered in Japan, the USA, and Australia for the treatment of insomnia. However, selective OX2R antagonists such as seltorexant (JNJ-54717793/MIN-202) may have broader applications since they promote a more balanced sleep in preclinical models and display a lower narcoleptic/cataplectic potential compared to DORAs. Pharmacological manipulation of OX2R is of particular interest to treat insomnia as they are primarily expressed in histaminergic neurons in the TMN. Studies with the selective OX2R antagonist seltorexant (JNJ-54717793/MIN-202) have indeed shown beneficial effects on sleep (de Boer et al. 2018; Brooks et al. 2019). Also, antidepressant effects, albeit limited, were demonstrated in a proof-of-concept study in MDD although mood improvement could have been secondary to improved sleep (Recourt et al. 2019). The ligand [^{11}C]CW4 has been synthesized and investigated in rats and nonhuman primates using PET-MR imaging and displayed rapid kinetics and high nonspecific binding, indicating excellent brain penetrance and possible future application as a lead compound for developing new CNS-penetrant PET imaging probes of orexin receptors (Wang et al. 2013). In addition, [N-methyl-(11)C](S)-N-([1,1′-biphenyl]-2-yl)-1-(2-((1-methyl-1H-benzo[d]imidazol-2-yl)thio) acetyl)pyrrolidine-2-carboxamide ([^{11}C]BBAC) and [N-methyl-(11)C](S)-N-([1,1′-biphenyl]-2-yl)-1-(3-(1-methyl-1H-benzo[d]imidazol-2-yl)propanoyl)pyrrolidine-2-carboxamide ([^{11}C]BBPC) have been synthesized successfully, but limited brain uptake has thwarted their continued development (Liu et al. 2012).

4.4.7 Imaging the Blood–Brain Barrier

It has been proposed that dysfunction of the blood–brain barrier (BBB) contributes to the pathophysiology of MDD. Influx of proteins or other molecules across the barrier is tightly regulated; however, small, lipophilic, and uncharged molecules can pass the BBB and are expelled by the P-glycoprotein pump (P-gp). It has been hypothesized that hyperactivity of the P-gp, which also expels lipophilic drugs like antidepressants, contributes to MDD and/or treatment-resistant depression (TRD). One study investigated P-gp activity in 13 MDD patients (of whom 7 had TRD) with [^{11}C]verapamil (de Klerk et al. 2009). Relative to controls, MDD patients showed decreased [^{11}C]verapamil uptake in the DLPFC, temporal lobe, ACC, and amygdala. This is indeed indicative of increased P-gp activity in MDD patients, which might preclude appropriate levels of antidepressants in the brain. Since all patients used antidepressants, it cannot be ruled out that these drugs influenced the study outcomes by P-gp induction or by affecting the pharmacokinetics of the tracer. This is of relevance as it was shown that P-gp expression may affect the binding of different radioligands (e.g., [^{18}F]MPPF and [^{11}C]flumazenil (Ishiwata et al. 2007)). In the future, this involvement of the P-gp in MDD or BD merits further investigation, especially in the context of TRD (Smith and Jakobsen, 2013).

4.4.8 Imaging Synaptic Density

Synaptic dysfunction appears to be involved in the pathophysiology of depression, which is supported by reduction of dendritic spine number and function of neurons in the prefrontal cortex (PFC) in animal models of depression (Liu and Aghajanian 2008). Symptoms of MDD include cognitive impairment and loss of memory (Rock et al. 2014; Ahern and Semkovska 2017; De Winter et al. 2017) even when patients are in remission (Smith et al. 2018), and the severity of cognitive deficits appears to increase with each depressive episode and may be a risk factor for AD (Gorwood et al. 2014). Until recently, it has not been possible to image synaptic density in vivo. Now, novel radioligands have been established for clinical PET studies. The ^{11}C-UCB-J PET radioligand for the synaptic vesicle glycoprotein 2A (SV2A) can be used to assess the number of nerve terminals, representing an indirect estimate of synaptic density (Mendoza-Torreblanca et al. 2013; Koole et al. 2019). In MDD, only one study (n = 26 mixed MDD or PTSD patients vs. 21 controls) has been published. Here, MDD severity was inversely correlated to synaptic density, and severely affected MDD patients had lower SV2A binding than healthy controls (Holmes et al. 2019).

4.4.9 Multimodal (Molecular) Imaging

From the abovementioned studies, it is clear that the brain is a complex system in which many neurotransmitters and brain functions interact. With the enormous amount of single modality studies that have emerged since the 1990s, much information about separate systems has been gathered. However, this information often led to slightly different or even conflicting results, which can often be understood in the perspective of system interactions (e.g., 5-HT$_{1A}$ receptor and SERT). Indeed these systems have been started to be investigated in conjunction (Frey et al. 2008; Takano et al. 2011a, b). We expect that in the (near) future different techniques will be combined in larger groups of MDD patients to study the interactions of these systems. This could be either dual isotope tracer studies (Frey et al. 2008; Hsieh et al. 2010; Takano et al. 2011a, b; Yang et al. 2008), preferably with short half-life isotopes like [^{11}C] to avoid changes over time, or the combination of MRI and molecular imaging (Paillere Martinot et al. 2010) or magnetic resonance spectroscopy combined with fMRI (Horn et al. 2010; Walter et al. 2009).

4.5 Discussion and Conclusions

This chapter summarizes findings of a large number of molecular imaging studies in the field of unipolar and bipolar depression. Brain function/metabolism in depressed unipolar and bipolar patients is generally hypoactive in the bilateral middle frontal gyri, pgACC, posterior ACC, left superior temporal gyrus, insula, and cerebellum, while a hyperactivity exists in subcortical (caudate, thalamus), limbic

(amygdala, anterior hippocampus), and medial and inferior frontal regions. A review based on fMRI studies has reached similar conclusions (Phillips et al. 2003a, b, 2008). In addition, monoamine depletion studies showed that after depletion of serotonin or noradrenalin/dopamine in vulnerable (recovered) MDD patients, a similar response pattern in metabolism occurs, especially when subjects show a recurrence of depressive symptoms.

Findings on the pre- and postsynaptic dopaminergic system are not yet conclusive, although there are indications that at least in subgroups of retarded MDD patients, presynaptic dopaminergic markers may be decreased, while postsynaptic markers may be increased. The observed abnormalities may be interpreted as a result of reduced extracellular dopamine concentrations in the synaptic cleft. Although not new in the perspective of the monoamine hypothesis, recent reviews resulted in increased attention for dopaminergic dysfunction in MDD and especially in TRD (Dunlop and Nemeroff 2007).

Despite contradictory results, the findings regarding 5-HT synthesis, pre- and postsynaptic imaging, can be synthesized to a loss of 5-HT in MDD, while this remains unclear in BD. A reduction of 5-HT (and dopamine) was proposed in a revised version of the monoamine hypothesis (Meyer 2012), which focused more on the abnormalities found at the level of the MAO enzyme. As shown, MAO-A density may be increased dramatically in several brain areas, and enzyme levels remain elevated after treatment and even during remission. Increased density and activity of MAO-A result in increased breakdown of 5-HT. This decrease in 5-HT might become problematic and lead to a depressive episode when subjects have increased SERT availability and/or fail to downregulate their SERT. Increased SERT will then remove the remaining 5-HT from the synaptic cleft, reducing serotonergic neurotransmission. As a result of this low 5-HT state, compensatory increases in postsynaptic 5-HT_{2A} receptors occur, while it has been suggested that a decrease of 5-HT_2 might be a better compensatory response, at least in ATD studies (Yatham et al. 2012). For the dopaminergic system, less research has been done and only in patients with retardation of movement, but comparable effects could occur after increased breakdown of dopamine (unaltered DAT, but increased D_2 receptors). This might suggest that in these patients the MAO-B enzyme might be involved, which has partly been corroborated by one study (Moriguchi et al. 2019).

Future research should clarify whether changes in MAO-A density are a trait marker of disease in euthymic or at-risk (yet healthy) states. It may further be hypothesized that MAO-A abnormalities might only exist in subgroups of patients, and if such subgroups exist, it would be of interest to evaluate whether these patients should be treated differently (more quickly) with, for example, MAO inhibitors.

Finally, reduced or unchanged SERT and postsynaptic serotonergic receptors (as reviewed in this chapter) and vulnerability findings especially for the low-SERT-expressing S/S polymorphism (Caspi et al. 2003; Willeit and Praschak-Rieder 2010) do not corroborate or at least challenge this revised monoamine hypothesis. Also, the dopaminergic system must be investigated more in depth in MDD and TRD, and it may become possible to study norepinephrine, glutamate, opioid, and inflammatory pathways in relation to MDD.

Finally, because of a lack of longitudinal molecular imaging studies at different clinical mood states in the same subjects, it remains unclear whether the changes of SERT and DAT, or the increases in 5-HT_{2A} or D_2 receptors, are compensatory responses to reduced levels of serotonin or dopamine or reflect different, potentially causal mechanisms. Also, as outlined in this chapter, measurements in this field are still hindered by suboptimal methodology, tracers, and reference standards, thus needing further standardization (Innis et al. 2007). We expect that these challenges will be solved in the future.

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SPECT and PET in Late-Life Depression

5

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Abstract

Late-onset late-life depression (LLD, depression with an age of onset above 60 years) appears to differ from depression with early onset in its association with cerebral small vessel disease, beta-amyloid and tau deposition, and neurodegenerative processes. Multimodality imaging (SPECT, PET, MRI) supports this concept and the notion that late-life depression relies on dysfunctioning of the frontal lobe, but also highlights that mechanisms underlying late-onset depression are heterogeneous and diverse. The future of PET and SPECT imaging in depression research relies on progress in data analysis, the development of novel molecular probes for specific cerebral targets, and combination of different imaging modalities (e.g., PET and MRI). Relatively unexplored areas for future research are gender differences, longitudinal changes of brain function associated with subclinical and clinical depression, and analysis of the default network activity.

5.1 The Concept of Late-Life Depression

5.1.1 Prevalence and Burden of LLD

Depressive disorder is a syndromal diagnosis most often classified according to the criteria of DSM-V or ICD-10. Depressive disorder is diagnosed when at least five out of nine symptoms have been present including at least one of the two core symptoms, i.e., (1) a persistently depressed mood or (2) loss of pleasure in normal daily activities, also called anhedonia. Additional symptoms include cognitive-affective symptoms—i.e., (3) diminished ability to think or concentrate or indecisiveness; (4) feelings of worthlessness or excessive, inappropriate guilt; (5) recurrent thoughts of death, suicidal ideation, or suicide attempt—as well as somatic-affective symptoms, i.e., (6) significant weight loss when not dieting or weight gain, (7) psychomotor agitation or retardation, (8) fatigue or loss of energy, and (9) altered sleep-wake cycle. Furthermore, these symptoms should occur in combination, during the same 2-week period and should cause clinically significant distress or impairment in daily functioning.

Although it is generally assumed that the prevalence of depressive disorder increases with age, epidemiological data show the opposite. A hallmark publication showed that the pooled prevalence rate for major depressive disorder (MDD) among

community-dwelling elderly aged 55 years or older was 1.8% (Beekman et al. 1999), being one-third of prevalence rates generally found in younger aged populations (Ferrari et al. 2013). A meta-analysis challenged these findings identifying a pooled prevalence rate of 7.2% (95% CI, 4.4–10.6%) for MDD in persons aged 75 years and over living in the community and/or residential care facilities (Luppa et al. 2012). In addition to a real difference, partially explained by taking nursing home residents into account, the higher prevalence rates of the latter meta-analyses might be inflated by overdiagnosing depression due to motivational problems in the oldest age group (Prince et al. 1999).

Interestingly, minor depression (depressed mood or anhedonia accompanied by one to three additional symptoms) has been found to be more prevalent in older adults than full-threshold MDD. The previously reported meta-analyses identified a pooled prevalence of 9.8 % for minor depression (Beekman et al. 1999), and values of 13.5% and 17.1 % were found for clinically relevant depressive symptoms based on cutoff score on a depression severity measure (Beekman et al. 1999; Luppa et al. 2012). These "subthreshold" disorders are associated with impairments similar to those of MDD, including decreased levels of physical function, poorer self-rated health, and increased days lost due to disability (Beekman et al. 1995). Thus, one may ask whether current classification systems are valid for older people.

LLD is a devastating condition for both individual patients and society. Patients suffering from LLD experience greater functional disability and cognitive decline than those without (Dombrovski et al. 2007; Lenze et al. 2005). Moreover, LLD has been linked prospectively to an increased risk of several age-related somatic diseases and mortality (Ganguli et al. 2002). Meta-analyses of prospective studies show a 60% increased risk on incident cardiovascular disease (Van der Kooy et al. 2007), increased mortality risk, and recurrent cardiovascular events in cardiac patients (Meijer et al. 2011), diabetes (Mezuk et al. 2008), stroke (Dong et al. 2012), dementia—both Alzheimer's disease and vascular dementia (Gao et al. 2013)—and even cancer (Gross et al. 2010). This increased risk is assumed to be caused by both maladaptive health risk behaviors and physiological abnormalities intrinsically related to LLD. Moreover, the association between chronic somatic diseases and LLD is bidirectional, which means that depression not only magnifies the negative consequences of chronic somatic condition but somatic diseases also negatively affect the course of depression (Katon et al. 2009; Kennedy et al. 1991). These lines of research have culminated in an overarching theory proposing depression as a disease of accelerated aging (Wolkowitz et al. 2011).

LLD has a chronic course and higher relapse rates compared to depression in younger adults (Licht-Strunk et al. 2007; Mitchell and Subramaniam 2005; Mueller et al. 2004). In a community-based sample, 44% of the persons with LLD showed a fluctuating course, and 32% had a severe chronic course during 6 years of follow-up (Beekman et al. 2002). This poor prognosis has been related to the abovementioned comorbidity with somatic diseases, especially cerebrovascular disease and cognitive decline (Comijs et al. 2001), besides the presence of anxiety disorders which leads to longer time to remission as well as higher recurrence rates (Andreescu et al. 2007).

Although age-specific diagnostic criteria for depression are lacking, numerous studies point to distinctive clinical and neuroimaging features in LLD compared to depression in younger people (Alexopoulos 2005; Brodaty et al. 2001; Herrmann et al. 2007; Hickie and Scott 1998; Hickie et al. 2009; Thomas et al. 2009). The etiology of depression becomes more heterogeneous with aging, consisting of both long-term illness-specific effects of early-onset depression and underlying cerebrovascular damage and prodromal neurodegenerative disease which give rise to late-onset depression.

5.1.2 Late-Onset Depressive Disorder

To date, no consensus exists on the age cutoff that defines late-onset depression. The age cutoff varies from 50 to 65 years, with 60 years most commonly applied. Although empirical results point to important differences between early and late-onset depression, well-designed longitudinal studies are lacking. Therefore, many studies simply compared symptom profiles between LLD and early-life depression. Compared to younger depressed adults, older depressed persons were found to show more psychomotor dysregulation, cognitive impairment, and somatic disturbances such as fatigue and sleep disturbance (Brodaty et al. 1991, 1997) and to have much more apathy without the more traditional symptoms of sadness (Adams 2001; Gallo et al. 1997; Newmann et al. 1991). A meta-analysis of studies comparing younger and older depressed persons on the Hamilton Depression Rating Scale revealed more agitation, hypochondriasis, and general as well as gastrointestinal somatic symptoms, but less guilt and loss of sexual interest (Hegeman et al. 2012). Negative findings have also been published, but it should be taken into account that most studies selected younger and older patients on the same criteria for diagnosing depression, thereby limiting the variability between samples.

The identified differences in symptom profiles might be hypothesized to result from differences in the underlying causative factors between early-life depression and LLD. Several studies, although mainly cross-sectional, suggest that personality characteristics, a family history of affective disorders, and work and family relationship dysfunctions may play a larger role in the onset of depression at early age, whereas LLD has been hypothesized to be more strongly associated with (cerebro) vascular disease, frailty-associated processes, and neurodegenerative biological abnormalities (Brodaty et al. 2001; Baldwin and Tomenson 1995; Hickie et al. 1995a). Interestingly, the relevance of genetic risk to vascular risk factors increases with a later age of onset, whereas genetic risk factors associated with early-onset depression decline in later life (Kendler et al. 2008, 2009). Presumed differences are highly relevant for daily practice where approximately half of the patients presenting with a major depression do have a late onset.

The typical presentation of late-onset depression is supposed to rely on dysfunctioning of the frontal lobe due to ischemic disease as well as neurodegenerative processes. Compared with early-onset depression, neurobiological models of late-onset depression intrinsically place less emphasis on functioning of the limbic

system. Instead, they highlight the critical nature of vascular and other intercurrent medical risk factors that result in structural disruptions of fronto-subcortical circuits. Structural damage to fronto-subcortical circuits is also hypothesized to underlie the negative longitudinal course (Schweitzer et al. 2002; Sheline et al. 2010), as both vascular disease burden and executive dysfunctioning have been associated with a delayed treatment response and higher risk of relapse. These concepts are mainly based on an increased burden of white matter lesions (WMLs), seen as "hyperintense" on T2-weighted images. Such lesions have been specifically linked to LLD with a late onset (e.g., (Alexopoulos et al. 1997a; Hickie et al. 1995b; Krishnan et al. 1997; O'Brien et al. 1996)).

Cognitive impairment in depressed older people has been well described and predominantly includes impairments in processing speed, executive functions (i.e., "frontal" or higher-order functions), and to a minor degree learning and memory (Herrmann et al. 2007; Kohler et al. 2010a; Naismith et al. 2006; Sheline et al. 2006). While it was previously thought that such deficits would abate with adequate treatment, it appears that at least some degree of cognitive dysfunction may persist with symptom resolution (Devanand et al. 2003; Kohler et al. 2010b). Executive dysfunctioning in LLD and specifically in late-onset depression includes deficits in planning, organization, sequencing, response inhibition, problem-solving, and set shifting (Herrmann et al. 2007; Naismith et al. 2003; Pisljar et al. 2008; Salloway et al. 1996). The presence of executive deficits is associated with symptom persistence, recurrence, and poor treatment responsiveness (Sheline et al. 2010; Baldwin et al. 2004; Sneed et al. 2007), which has led to the introduction of the "depression-executive dysfunction syndrome" aimed to describe a subtype of LLD with prominent executive and psychomotor change, apathy, disproportionate disability, and less guilt and insight (Alexopoulos et al. 2002). Although executive dysfunctioning is generally considered as the most important underlying cognitive deficit, a meta-analysis has shown that psychomotor speed may be impaired to the same degree as executive function in subjects with late-onset depression (Herrmann et al. 2007). Such central deficits have been suggested to underlie impairments in other domains of functioning (Sheline et al. 2006).

5.2 Neuroimaging Findings

Neuroimaging has evolved tremendously in the past decades. Increasing availability of magnetic resonance imaging (MRI) since the 1990s has stimulated many research projects on the volumetric analyses of key structures including prefrontal, striatal, and limbic regions (Soares and Mann 1997; Steffens and Krishnan 1998). Simultaneously, greater resolution of the white matter offered by MRI compared to computed tomography has led to an increased awareness of WMLs associated not only with age and vascular risk factors but also with a vulnerability for depression and cognitive impairment. Further sophistication of neuroimaging acquisition and analysis techniques has enabled more detailed examination of disrupted white matter tracts using diffusion tensor imaging. In this chapter, PET and SPECT findings concerning cerebral blood

flow and metabolism in LLD will be reviewed. Imaging data concerning alterations of dopaminergic and serotonergic neurotransmission in depression are extensively reviewed in another chapter of this volume (Ruhé et al. 2020).

5.2.1 Imaging of Cerebral Blood Flow

The regional distribution of cerebral blood flow is related to neuronal activity (Ingvar 1979). For this reason, cerebral perfusion PET and SPECT imaging have been widely used for evaluation of functional abnormalities in patients with neuropsychiatric disorders, including subjects with LLD. Such studies employed the tracers ^{99m}Tc-hexamethylpropyleneamine oxide (also known as exametazime, or HMPAO), ^{99m}Tc-ethyl cysteinate dimer (ECD), *N*-isopropyl-*p*-^{123}I-iodoamphetamine (IMP), ^{133}Xe, ^{15}O-water, and $C^{15}O_2$ (see Table 5.1).

Cerebral blood flow is usually expressed in relative units by comparing tracer uptake in a studied region to uptake in a well-perfused reference region (e.g., cerebellum). Absolute quantification of flow is more difficult as it requires simultaneous registration of the time course of radioactivity in cerebral tissue and arterial blood. Flow can be examined in the resting condition but also after the subjects have been asked to perform a well-defined task. By using such "activation paradigms," flow changes related to execution of the task can be assessed, both in patients and in healthy volunteers, and abnormal brain activation identified.

Results of SPECT and PET studies concerning cerebral perfusion are summarized in Table 5.1. Some general conclusions may be drawn:

1. Alterations of regional blood flow in depressed individuals have been consistently observed. Most studies suggest that flow in the frontal lobe (particularly the prefrontal area (Bench et al. 1992; Dolan et al. 1994; Cho et al. 2002; Akiyama et al. 2008; Levy-Cooperman et al. 2008; Nagafusa et al. 2012; Hayashi et al. 2016)) is reduced, but the involvement of other areas remains controversial. Discrepancies between investigations may be due not only to differences in scan methodology (tracer, imaging modality, and data analysis) but also to patient selection and heterogeneity of the mechanisms underlying MDD. Treatment-resistant depression may be associated with perfusion reductions in a greater number of areas than treatment-responsive depression (Nagafusa et al. 2012). Since the prefrontal cortex has been linked to selective attention, short-term memory, emotion, and volition, reductions of flow in this area may be related to losses of attention, mood changes, and psychomotor inhibition in subjects with depression. Most imaging findings are in agreement with the hypothesis that LLD relies on dysfunctioning of the frontal lobe. Frontal dysfunction has been reported not only in primary depression but also in depression associated with neurodegenerative diseases such as Parkinson's (Jagust et al. 1992; Ring et al. 1994; Palhagen et al. 2009; Kim et al. 2016a), Huntington, and Alzheimer's disease (Vercelletto et al. 2002; Liao et al. 2003; Hanada et al. 2006; Akiyama et al. 2008; Levy-Cooperman et al. 2008; Staffen et al. 2009; Kataoka et al. 2010; Honda et al. 2014).

Table 5.1 SPECT and PET studies of regional cerebral blood flow in LLD

Study groups and subject numbers	Age (years)	Tracer	Findings (depression-related)	Reference
MDD (41) Matched normal controls (40)	60 ± 12	^{133}Xe	rCBF reduced in several cortical regions (frontal, central, superior temporal, anterior parietal). Extent of reduction related to age and depression severity	Sackeim et al. (1990)
MDD (18) Alzheimer's disease (14) Healthy controls (12)	54–91	^{99m}Tc-HMPAO	rCBF in cortical areas of MDD patients intermediate between controls and demented subjects, i.e., modestly but nonsignificantly reduced	Upadhyaya et al. (1990)
Elderly with suspected dementia (160)	64 ± 8	^{99m}Tc-HMPAO	Nondemented patients with depression or anxiety show frequently (16/21) abnormal pattern of rCBF resembling that in multi-infarct dementia	Launes et al. (1991)
Primary depression without (23) and with (10) cognitive impairment Age-matched controls (23)	57 ± 13	^{15}O-Water	Depression is associated with reduced rCBF in left prefrontal and left anterior cingulate cortex, depression-related cognitive impairment with additional changes	Bench et al. (1992)
Parkinson patients (20) Demented Alzheimer's patients (21) Healthy controls (24)	68 ± 6	^{123}I-IMP	Depression in PD appears to be associated with decreased perfusion in the dorsolateral frontal lobe	Jagust et al. (1992)
MDD (20) Alzheimer's dementia (20) Age-matched controls (30)	60–81	^{99m}Tc-HMPAO	Depression-related flow deficits in anterior cingulate and frontal cortex found in men only	Curran et al. (1993)
MDD (10) Healthy controls (9)	77 ± 8	^{99m}Tc-HMPAO	Flow reduced in parietal, left temporal, and left occipital cortex, not correlated with severity of depression but rather with psychotic symptoms. Flow reductions in frontal cortex related to anxiety	Philpot et al. (1993)
MDD (29)	58 ± 13	$C^{15}O_2$	Neuropsychological (intellectual) deficits in depression are related to reduced flow in medial prefrontal cortex	Dolan et al. (1994)
Depressed patients (39) Healthy controls (20)	>50	^{133}Xe ^{99m}Tc-HMPAO	Flow reduced bilaterally in orbitofrontal and temporal areas particularly in male patients	Lesser et al. (1994)

(continued)

Table 5.1 (continued)

Study groups and subject numbers	Age (years)	Tracer	Findings (depression-related)	Reference
Depressed patients (10)	64 ± 10	$C^{15}O_2$	Depression in PD related to bilateral reductions of flow in medial prefrontal and cingulate cortex. Similar reductions seen in patients with primary depression	Ring et al. (1994)
Parkinson patients with (10) and without (10) depression				
Healthy controls (10)				
Geriatric depression (17)	66 ± 11	^{99m}Tc-HMPAO	rCBF in cortical areas of depressed patients intermediate between controls and demented subjects, greater perfusion deficits in left parieto-occipital cortex in dementia	Stoppe et al. (1995)
Alzheimer's dementia (23)				
Age-matched controls (12)				
MDD (20)	59 ± 10	^{99m}Tc-HMPAO	Flow deficits related to depression severity. Flow increased in responders, unchanged in nonresponders after ECT	Bonne et al. (1996)
Alzheimer's disease (39)	70 ± 10	^{99m}Tc-HMPAO	Lower CBF in both hemispheres is correlated with higher geriatric depression scores	Sabbagh et al. (1997)
MDD (18)	66 ± 7	^{99m}Tc-HMPAO	Flow reductions in many brain areas, not related to severity of depression. Further decline in second scan, particularly in anterior cingulate and prefrontal cortex, is related to refractoriness or chronification of depression	Awata et al. (1998)
Age-matched controls (13)				
Elderly depressed patients (39)	74 ± 5	^{99m}Tc-HMPAO	Demented patients show more perfusion abnormalities than late-onset depressives and these more than early-onset depressives	Ebmeier et al. (1998)
Alzheimer's dementia (15)				
Healthy volunteers (11)				
Elderly depressed patients (175)	65–91	^{99m}Tc-HMPAO	Perfusion in cingulate increased in patients who improved after treatment. But no reliable predictor of clinical outcome identified	Halloran et al. (1999)
39 subjects scanned and followed up after 2 years, 10 scanned twice				
Alzheimer's with depression (17)	64–99	^{99m}Tc-HMPAO	AD patients with depression show less flow in the left temporal area than AD patients without depression	Ritchie et al. (1999)
Alzheimer's without depression (11)				
Age-matched volunteers (57)				

Table 5.1 (continued)

Study groups and subject numbers	Age (years)	Tracer	Findings (depression-related)	Reference
Alzheimer's dementia (25)	74 ± 8	^{99m}Tc-HMPAO	Reductions of flow in frontal cortex associated with negative symptom severity but not with depressive symptoms or cognitive impairment	Galynker et al. (2000)
Elderly depressed (6)	59–82	^{15}O-Water	Patients have bilateral activation deficits during paced word generation in anterior cingulate gyrus and hippocampus	de Asis et al. (2001)
Healthy controls (5)				
MDD (30)	72 ± 8	^{99m}Tc-HMPAO	Flow reduced in anterior frontal regions, particularly left	Navarro et al. (2001)
Healthy controls (20)			No correlation with symptom severity	
MDD (9)	63 ± 4	^{99m}Tc-HMPAO	Flow reduced in anterior cingulate and caudal orbitofrontal cortex (bilaterally), insular cortex, and posterior middle frontal gyrus (right). Increased after ECT. Persistent reductions of flow in anterior paralimbic regions may indicate risk of relapse, medication failure, and chronic illness	Awata et al. (2002)
Age-matched healthy subjects (9)				
Depressed nondemented (7)	67 ± 8	^{99m}Tc-HMPAO	Left frontal flow in depressed subjects significantly reduced	Cho et al. (2002)
Depressive pseudodementia (7)			Depressive pseudodementia group showed right temporal and bilateral parietal flow reductions similar to AD group	
Alzheimer's dementia (7)			AD group has additional right frontal perfusion deficit	
Healthy controls (7)				
Alzheimer's disease (32)	77 ± 6	^{99m}Tc-ECD	Frontal hypoperfusion appears correlated with negative symptoms but correlation is at limit of significance	Vercelletto et al. (2002)
Healthy controls (19)				
MDD (35), scanned during acute depression and in remission, after 12 months	73 ± 8	^{99m}Tc-HMPAO	Flow significantly reduced in left anterior frontal region	Navarro et al. (2002)
Age-matched healthy controls (20)			This deficit disappears during successful treatment	
			No correlation between flow reduction and clinical symptoms	

(continued)

Table 5.1 (continued)

Study groups and subject numbers	Age (years)	Tracer	Findings (depression-related)	Reference
Nonvascular depression (11)	67 ± 11	^{123}I-IMP	Patients with vascular depression have lower left anterior frontal flow than patients with nonvascular depression	Kimura et al. (2003)
Vascular depression (9)			Perfusion improves in both groups during remission, particularly in left anterior temporal region	
Scanned before/after remission				
Alzheimer's with depression (8)	73 ± 5	^{99m}Tc-HMPAO	Depression in AD associated with hypoperfusion in cingulate gyri and precuneus, same regions affected in primary depression. Flow inversely correlated with depression scores	Liao et al. (2003)
Alzheimer's without depression (35)				
MDD, in remission after ECT (14) and after drug treatment (22)	74 ± 11	^{99m}Tc-HMPAO	After 12 months in remission, no perfusion deficits were observed anymore in both patient groups	Navarro et al. (2004a)
Age-matched healthy controls (25)				
MDD, before and after 12-week antidepressant treatment (34 remitters, 13 non-remitters)	74 ± 7	^{99m}Tc-HMPAO	Perfusion ratio (left anterior frontal cortex to cerebellum) at baseline is predictive of treatment outcome, particularly if age of onset and duration of index episode are taken into account as co-variables	Navarro et al. (2004b)
MDD (10)	57 ± 5	^{123}I-IMP	Depressed group had lower flow in lateral and medial frontal areas and left thalamus than AD group. Flow patterns in AD and MDD can be distinguished	Hanada et al. (2006)
Early Alzheimer's disease (10)				
Depression (32)	56 ± 12	^{99m}Tc-HMPAO	Smaller increases of blood flow in the patients after proceeding to the more complex task are associated with longer choice reaction times (psychomotor slowing)	Hickie et al. (2007)
Age-matched healthy controls (17)				
Scanned performing a simple and a more complex reaction time task				
Alzheimer's disease with (26) and without (18) depression	74 ± 6	^{99m}Tc-ECD	Depression in AD is associated with hypoperfusion in left prefrontal area	Akiyama et al. (2008)
Depressed patients (25) before and after drug treatment (avg 13.7 weeks)	70 ± 8	^{99m}Tc-ECD	Patients show decreased rCBF in anterior medial prefrontal cortex. Therapy results in increased flow in part of this area (left dorsolateral prefrontal cortex) but not in the other parts	Ishizaki et al. (2008)

Table 5.1 (continued)

Study groups and subject numbers	Age (years)	Tracer	Findings (depression-related)	Reference
Alzheimer's disease with (27) and without (29) depression	78 ± 7	^{99m}Tc-ECD	Depression in AD is associated with relative hypoperfusion in prefrontal cortex—Partially due to atrophy	Levy-Cooperman et al. (2008)
Nondemented elderly subjects (61)	69 ± 7 (at scan 1)	^{15}O-water	Higher scores for depression associated with longitudinal decreases of flow in frontal (♂, ♀) and temporal (♂) regions	Dotson et al. (2009)
Scanned twice with interval of 9 years			Similar flow patterns in subclinical and clinical depression	
Screened annually for depression				
M. Parkinson with depression (11)	64 ± 10	^{99m}Tc-HMPAO	Major depression in PD appears associated with "spotted" hypoperfusion in lower part of right frontal lobe	Palhagen et al. (2009)
Idem without depression (14)			Perfusion deficits become smaller after treatment	
Depression only (12)			But none of these effects were statistically significant	
Depressed scanned before/after citalopram treatment (12 weeks)				
Depression + cogn impairment (127)	63 ± 11	^{99m}Tc-HMPAO	Depressed, cognitively impaired subjects have reduced flow in medial temporal cortex, thalamus, lentiform nucleus	Staffen et al. (2009)
Mild cognitive impairment (149)			Frontal perfusion deficits seen only in AD, associated with conversion from MCI to AD. Depression early symptom of neurodegeneration?	
Alzheimer's dementia (131)				
Cognitively normal controls (123)				
Alzheimer's dementia with (17) and without (18) depression	73 ± 7	^{99m}Tc-ECD	Depressive symptoms in AD are associated with reduced perfusion in left frontal cortex	Kataoka et al. (2010)
MDD (37)	55 ± 16	^{99m}Tc-HMPAO	Depressed, cognitively impaired subjects with white matter hyperintensities (WMH) in basal ganglia have greater perfusion deficits than less depressed subjects with WMH in other regions (or absent) but respond equally well to antidepressants	Vardi et al. (2011)
Healthy controls (27)				
Alzheimer's disease (81), of these 9 with depression and 9 with apathy, 18 age-matched without either depression or apathy	75 ± 6	^{99m}Tc-HMPAO	Depression subscores inversely correlated with flow in left inferior frontal and right middle frontal gyri, apathy with other regional deficits. Apathy and depression in AD may involve distinct functional circuits	Kang et al. (2012)

(continued)

Table 5.1 (continued)

Study groups and subject numbers	Age (years)	Tracer	Findings (depression-related)	Reference
MDD (61) Healthy controls (107)	30–79	^{99m}Tc-ECD	Depressed subjects have reduced flow in prefrontal area (predominantly left), no age-specific pattern detected	Nagafusa et al. (2012)
MDD after 8 weeks of SSRI treatment, 12 responders, 33 nonresponders Healthy controls (30)	69 ± 7	^{99m}Tc-ECD	Nonresponders had greater hypoperfusion in middle frontal cortex than responders. This difference may already have been present before treatment (but no baseline scan was made)	Hanada et al. (2013)
Men with borderline or mild depression (31) Control group (89)	82	^{99m}Tc-HMPAO	Similar CBF in the case and control groups. In the case group, a negative correlation between depressive symptoms and CBF in subcortical areas, left and right thalamus, and basal nuclei. No such correlation in the control group. In the case group, worse peripheral circulation in the legs, and higher systolic blood pressure determined decreased CBF in frontal lobes and especially in parietal areas.	Siennicki-Lantz et al. (2013)
AD (76), 46 with low depression score and 30 with high depression score	77 ± 7	^{99m}Tc-ECD	Patients with high scores showed significant hypoperfusion in the left inferior frontal region.	Honda et al. (2014)
AD (116)	77 ± 8	^{99m}Tc-ECD	Significant correlation between positive affect scores and rCBF in the left precentral and superior frontal gyri	Hayashi et al. (2016)
Parkinson's disease (78), 35 patients depressed and 43 patients nondepressed	69 ± 9	^{99m}Tc-HMPAO	Perfusion in the left cuneus was increased, while that in the right superior temporal gyrus and right medial orbitofrontal cortex was reduced in the depressed as compared with nondepressed patients. rCBF decreased also in the amygdala, anterior cingulate cortex, hippocampus, and parahippocampal gyrus in the depressed group. Positive correlation between depression scores and rCBF in the left cuneus cluster in depressed patients	Kim et al. (2016a)

Table 5.1 (continued)

Study groups and subject numbers	Age (years)	Tracer	Findings (depression-related)	Reference
Dementia (847) Depression (3269) Dementia and depression (425)	68 59 65	^{99m}Tc-HMPAO	In general, persons with cognitive disorders have decreased perfusion compared to those with depression in multiple regions including the hippocampus, amygdala, frontal, and temporal regions among others. Persons with cognitive disorders and depression generally showed a higher magnitude of additive hypoperfusion in these regions compared to those with either diagnosis	Amen et al. (2017)

2. Several investigators have examined whether the magnitude or regional extent of flow changes is correlated with the severity of depressive symptoms. In many published articles, flow values and scores on depression scales were significantly and inversely correlated (Sackeim et al. 1990; Bonne et al. 1996; Sabbagh et al. 1997; Liao et al. 2003; Kang et al. 2012; Siennicki-Lantz et al. 2013; Honda et al. 2014; Hayashi et al. 2016; Kim et al. 2016a). However, in other studies no significant correlation between flow and depression severity was observed (Philpot et al. 1993; Dolan et al. 1994; Awata et al. 1998; Galynker et al. 2000; Navarro et al. 2001, 2002; Vercelletto et al. 2002), although flow was sometimes correlated with other phenomena, such as psychosis, anxiety, negative symptoms, or intellectual deficits. Combination of the data of an initial scan with data of a second scan made after an interval of at least 1 year may provide meaningful information. Longitudinal decreases of flow can indicate refractoriness and chronification of depression (Awata et al. 1998) or be related to higher depression scores (Dotson et al. 2009).
3. Many studies have focused on persistence or reversibility of flow deficits during treatment, which comprised either electroconvulsive therapy (ECT) or administration of antidepressant drugs. Increases of regional cerebral blood flow were noticed in responders but were absent or nonsignificant in nonresponders to the applied therapy (Bonne et al. 1996; Halloran et al. 1999; Awata et al. 2002; Navarro et al. 2002, 2004a; Kimura et al. 2003; Ishizaki et al. 2008; Palhagen et al. 2009). The ratio of perfusion in the left anterior frontal cortex and cerebellum at baseline may be predictive of treatment outcome, low values being associated with a greater risk of therapy resistance, particularly if age of onset and duration of index episode are included as co-variables (Navarro et al. 2004b; Hanada et al. 2013). Complete reversal of the initial perfusion abnormalities was observed in some studies during successful therapy (Navarro et al. 2002, 2004a), but other researchers found both reversible and persistent perfusion deficits (Awata et al. 2002; Ishizaki et al. 2008), suggesting that flow reductions in cer-

tain brain regions are disease state-related, whereas deficits in other areas may reflect traits underlying vulnerability to depression.

4. Some studies reported gender differences in flow patterns associated with LLD. Curran et al. detected perfusion deficits in anterior cingulate and frontal cortex only in male patients (Curran et al. 1993). Lesser et al. observed reduced flow in orbitofrontal and temporal areas of depressed individuals which were more striking in men than in women (Lesser et al. 1994). Dotson et al. found more widespread decreases of flow in elderly depressed males than in females (Dotson et al. 2009). These findings may be related to the fact that clinical depression is associated with greater decreases in frontal volumes in men than in women (Lavretsky et al. 2004) and depressive symptoms are associated with an increased risk for dementia in men but not in women (Dal Forno et al. 2005; Fuhrer et al. 2003). Most published imaging studies involved subject groups consisting of individuals from both sexes. It would be interesting to examine longitudinal blood flow changes associated with subclinical and clinical depression in a sex-specific manner.
5. It is a pity that deficiencies of cerebral blood flow have only rarely been linked to structural findings obtained with MRI. Particularly in neurodegenerative disease, two different mechanisms may contribute to relative hypoperfusion: (1) an actual loss of tissue in the target region and (2) a reduced function of existing tissue. The regional distribution and number of white matter hyperintensities in T2-weighted MRI images may reflect cerebral small vessel disease and can be compared to the regional pattern of hypoperfusion in the brain of patients with LLD (Lesser et al. 1994; Ebmeier et al. 1998, 1997; Kimura et al. 2003; Vardi et al. 2011). The term "vascular depression" has been coined to describe a subtype of depression which occurs in the context of cerebrovascular disease (Alexopoulos et al. 1997a, b; Krishnan et al. 1997). The response of regional blood flow to successful therapy in depressed individuals may depend on the underlying pathophysiology. Whereas perfusion deficits in nonvascular depression can disappear completely during remission (Navarro et al. 2002, 2004a), rCBF in the frontal lobe of subjects with vascular depression may remain subnormal both in the depressed and remitted states (Kimura et al. 2003).
6. Only a few reports have examined flow differences between individuals with early-onset and late-onset depression. Initial studies found no significant effect of age at onset upon rCBF (Curran et al. 1993; Philpot et al. 1993), although patients with late-onset depression tended to have lower relative flow in affected brain areas (Lesser et al. 1994). Later reports have suggested that late-onset depression is associated with more perfusion abnormalities, particularly in the left temporal lobe, than early-onset depression and also with more periventricular white matter changes in MRI (Ebmeier et al. 1998, 1997). Thus, late-onset depression may be associated more frequently with cerebral small vessel disease.
7. Flow studies have supported the concept of a continuum of severity of depressive syndromes. Subthreshold depressive symptoms are associated with relatively small alterations in regions implicated in clinical depression (Dotson et al. 2009).

SPECT with automated, semiquantitative techniques of data analysis can discriminate Alzheimer's dementia from depression with cognitive impairment (Staffen et al. 2009; Amen et al. 2017), but may not be accurate enough to differentiate Alzheimer's dementia from mild cognitive impairment, or mild cognitive impairment from depression with cognitive impairment. Early diagnosis of degenerative dementias may require the combination of SPECT with other molecular imaging techniques.

8. The symptoms of mild depression in the elderly may be multifaceted and be based on various underlying mechanisms. Both vascular and degenerative processes may play a significant role (Siennicki-Lantz et al. 2013).

5.2.2 Imaging of Cerebral Glucose Metabolism

Regional blood flow and metabolism are tightly coupled in the normal brain (Baron et al. 1982; Fox et al. 1988; Wong et al. 2006). It is thus not surprising that measurements of cerebral glucose metabolism using the PET tracer ^{18}F-FDG have produced findings which are quite similar to those acquired with flow tracers (see Table 5.2). FDG-PET studies also support the concept that LLD relies on dysfunctioning (i.e., reduced metabolism) of the frontal lobe (Kuhl et al. 1985; Mayberg et al. 1990; Kumar et al. 1993; Hirono et al. 1998; Mentis et al. 2002; Holthoff et al. 2005; Herting et al. 2007; Fujimoto et al. 2008; Lee et al. 2010; Sakurai et al. 2017; Nicholas et al. 2017; Youn et al. 2018), whereas the involvement of other brain regions has also been reported (Krell-Roesch et al. 2016), but seems more variable and controversial. In one study, successful antidepressant treatment was found to be associated with increases of glucose metabolism (Marano et al. 2013). Another study noted that hypometabolism in various regions of the cortex is significantly related to some symptoms of depression (apathy and anhedonia), but is not related to other symptoms (anxiety and dysphoria) (Donovan et al. 2015). However, in a few studies, a surprising elevation of rCMRglu was observed in subjects with geriatric depression (Smith et al. 2009; Auning et al. 2015). Such findings have been interpreted as a compensatory response to atrophy.

A recent study (involving PET imaging with [^{18}F]FDG and [^{18}F]florbetaben) has suggested that cerebral glucose metabolism in depressed and mild cognitively impaired elderly subjects may be a surrogate marker that reflects cerebral amyloidopathy. Subjects with an amyloid-positive brain scan showed rCMRglu values comparable to AD, whereas subjects with an amyloid-negative scan displayed more heterogeneous patterns of FDG uptake, Thus, FDG-PET could contribute to early identification of subjects at risk of progressing to AD (Youn et al. 2018). However, in another study the regional pattern of glucose hypometabolism in depressed and cognitively impaired subjects was observed to be extremely variable, and the conclusion was reached that subjects with LLD cannot be accurately distinguished from AD, or subjects with LLD progressing to AD from subjects with LLD with another prognosis, based on FDG data alone (Liguori et al. 2018).

Table 5.2 PET studies of regional cerebral glucose metabolism in LLD

Study groups and subject numbers	Age (years)	Tracer	Findings (depression-related)	Reference
LLD (7) Multiple-infarct dementia (6) Alzheimer's disease (6) Healthy controls (6)		[^{18}F]FDG	Depressed patients have reduced rCMRglu in posterior-inferior frontal cortex, otherwise normal pattern of glucose metabolism	Kuhl et al. (1985)
M. Parkinson with (**) and without (**) depression Age-matched controls (**)		[^{18}F]FDG	rCMRglu in orbital-inferior area of the frontal lobe is inversely correlated with depression scores. Depression in PD associated with hypometabolism in that frontal lobe area and in caudate	Mayberg et al. (1990)
LLD (8) Alzheimer's disease (8) Age-matched controls (8)	71 ± 6	[^{18}F]FDG	Depression associated with reduced rCMRglu in frontal, temporal, and parietal cortex, anterior cingulate and orbitofrontal cortex, and caudate	Kumar et al. (1993)
Alzheimer's disease (53), of these 19 subjects with depression	69 ± 8	[^{18}F]FDG	Depression scores correlated with rCMRglu in bilateral superior frontal gyri and left anterior cingulate cortex	Hirono et al. (1998)
M. Parkinson, nondemented (15)	59 ± 9	[^{18}F]FDG	Dysphoria in PD correlated with decreased rCMRglu in lateral frontal and anterior limbic cortex	Mentis et al. (2002)
Alzheimer's disease (53)	69 ± 8	[^{18}F]FDG	Depression in AD associated with hypometabolism in dorsolateral prefrontal regions	Holthoff et al. (2005)
Multiple system atrophy (11) Progressive supranuclear palsy (9) Age-matched controls (25)	64 ± 7	[^{18}F]FDG	Depression (both in MSA and PSP) associated with dorsolateral prefrontal glucose hypometabolism.	Herting et al. (2007)
MDD (10), nonresponders to antidepressants	51 ± 4	[^{18}F]FDG	rCMRglu decreased not only in prefrontal but also in cingulate and parietal regions (bilaterally) and right temporal area	Fujimoto et al. (2008)

Table 5.2 (continued)

Study groups and subject numbers	Age (years)	Tracer	Findings (depression-related)	Reference
Geriatric depression (16) Age-matched controls (13)	65 ± 9	[^{18}F]FDG (+MRI)	Surprising elevation of rCMRglu in superior frontal gyrus, precuneus, inferior parietal lobule. May be a compensatory response to atrophy	Smith et al. (2009)
Mild cognitive impairment with (18) and without (18) depression Healthy controls (16)	69 ± 10	[^{18}F]FDG	Depression in MCI is associated with reduced rCMRglu in the right superior frontal gyrus	Lee et al. (2010)
LLD (9) Control subjects (7) Scanned at baseline, after 8 weeks of citalopram (patients only) and after 2 years of follow-up	68 ± 8	[^{18}F]FDG	Patients show greater increases of rCMRglu in anterior cingulate and insula than controls. Seven out of nine patients remitted	Marano et al. (2013)
LLD (16) Elderly controls (12) Young controls (20)	65 ± 9 67 ± 8 28 ± 8	[^{18}F]FDG	Increased fasting serum glucose correlated with decreased cerebral glucose metabolism in heteromodal association cortices involved in mood symptoms and cognitive deficits (bilateral middle frontal gyrus, left putamen, right insula, and left fusiform gyrus), in LLD patients to a greater extent than in elderly controls. In young controls, negative correlations were observed in sensory and motor regions	Marano et al. (2014)
Subjective cognitive impairment (22) Mild cognitive impairment (38)	59 ± 7 61 ± 7	[^{18}F]FDG (+MRI)	Significantly higher glucose metabolism in orbital cortex of depressed patients compared to those without depressive symptoms. Similar finding when SCI and MCI were assessed separately	Auning et al. (2015)

(continued)

Table 5.2 (continued)

Study groups and subject numbers	Age (years)	Tracer	Findings (depression-related)	Reference
Cognitively normal individuals with subthreshold symptoms of depression (SSD) (248)	66 ± 6	[^{18}F]FDG PiB (+MRI)	Higher depression score was marginally related ($p = 0.06$) to FDG hypometabolism. Higher apathy-anhedonia was significantly related to FDG hypometabolism in bilateral temporal, parietal, and posterior cingulate cortices, but other sub-domains (anxiety-concentration or dysphoria) of depressive symptoms were not. SSD were not related to the amyloid burden	Donovan et al. (2015)
Cognitively normal participants (668)	70 or older	[^{18}F]FDG	Two hundred and five participants had an abnormal FDG-PET in AD-related regions. Abnormal FDG-PET was associated with depression, even further in ApoE ε4 carriers. Significant association between abnormal FDG-PET and depressive and anxiety symptoms when treated as continuous measures	Krell-Roesch et al. (2016)
Community-dwelling participants without major depression (158)	65–85	[^{18}F]FDG	Higher depression scores were associated with lower normalized rCMRglc in the ventrolateral prefrontal and orbitofrontal cortices. Adjusting for frequency of going outdoors, the association between depression score and normalized rCMRglc in the orbitofrontal cortex was attenuated, whereas the relationship between depression score and the ventrolateral prefrontal cortex remained significant	Sakurai et al. (2017)

Table 5.2 (continued)

Study groups and subject numbers	Age (years)	Tracer	Findings (depression-related)	Reference
Participants cognitively normal and absent of a major psychiatric diagnosis (133)	63 ± 6 (age at PET)	[^{18}F]FDG	Greater positive affect was associated with higher cerebral glucose metabolism in the bilateral posterior cingulate gyrus/precuneus, left angular/supramarginal gyrus, left middle/inferior temporal gyrus, and left middle/frontal gyrus	Nicholas et al. (2017)
Depression + MCI (31): With amyloid-β (16) Without amyloid-β (15) Normal cognition group (21)	76 ± 8 75 ± 6 69 ± 5	[^{18}F]FDG (all participants) + [^{18}F] Florbetaben (depression + MCI)	Reduced regional glucose metabolism in the right precuneus, left inferior temporal, right middle temporal, and right angular regions in the group with amyloid-β compared to the cognitively normal group Glucose metabolism in the left inferior orbitofrontal and the right anterior cingulate was lower in the amyloid negative than the amyloid-positive group	Youn et al. (2018)
Depressed and demented patients (256): AD group (201) and LLD group (55) Age- and sex-matched controls	≥65	[^{18}F]FDG	AD patients showed a significant reduction of uptake in temporoparietal regions compared to both controls and LLD. LLD and control groups did not differ at PET analysis, although LLD patients showed heterogeneous patterns of glucose hypometabolism involving cortical and subcortical brain areas: Putaminal and thalamic nuclei, insula, right parietal and temporal cortex, left limbic cortex, left frontal cortex, left rectal gyrus, medial frontal gyrus, and anterior cingulate cortex	Liguori et al. (2018)

5.2.3 Imaging of Cerebral Neurotransmitter Systems and of Cerebral Protein Deposition

The monoamine hypothesis assumes that the biological or neuroanatomical basis for depression is a deficiency of central noradrenergic and/or serotonergic systems. Unfortunately, suitable PET or SPECT tracers for central beta-adrenergic receptors are not available (Van Waarde et al. 2004) in contrast to the noradrenaline transporter for which ligands such as (*S*,*S*)-[^{11}C]methylreboxetine exist (Ding et al. 2005). Many PET and SPECT tracers have been developed for visualization and quantification of elements of the serotonergic system. These include the 5-HT$_{2A}$ receptor ligands [^{11}C]MDL100,907 and [^{18}F]altanserin, the 5-HT$_{1A}$ receptor ligands [^{11}C]WAY100635 and [^{18}F]MPPF, the serotonin transporter ligands [^{11}C]DASB and [^{123}I]ß-CIT, and the serotonin precursor [^{11}C]5-hydroxytryptophan. Such tracers have been applied to study alterations of the serotonergic system in depression. The resulting imaging findings are extensively reviewed in another chapter of this volume (Ruhé et al. 2020).

PET and SPECT tracers for imaging elements of the dopaminergic system are also available, such as the dopamine DA$_1$ receptor ligands [^{11}C]NNC-112 and [^{11}C]SCH23390, the dopamine DA$_2$ receptor ligands [^{11}C]raclopride and [^{11}C]FLB 457, the monoamine oxidase inhibitor [^{11}C]clorgyline, the dopamine transporter ligands [^{11}C]CFT and [^{99m}Tc]TRODAT, and the dopamine storage tracer [^{18}F]fluorodopa. Findings acquired with these ligands are also discussed in (Ruhé et al. 2020).

Since LLD is considered as both a risk factor and a premonitory symptom of dementia (Gao et al. 2013; Schweitzer et al. 2002; Kohler et al. 2010a; Dal Forno et al. 2005; Marano et al. 2013; Lieberman 2006), studies with cholinergic tracers and probes for ß-amyloid or tau deposition are of particular interest (see Table 5.3). Two reports have suggested that depression is associated with cholinergic hypofunction in elderly subjects with Parkinson's disease. Cortical acetylcholinesterase activity, measured with the PET tracer [^{11}C]methyl-4-piperidinyl propionate, is inversely correlated with depression scores in this patient group, and losses of enzyme activity tend to be more prominent when dementia is present (Bohnen et al. 2007). Binding potential of the $\alpha_4ß_2$ nicotinic acetylcholine receptor ligand 2-[^{18}F]FA85380 in various brain regions (anterior cingulate cortex, occipital cortex, putamen, and midbrain) is also inversely correlated with depressive symptoms in Parkinson's disease (Meyer et al. 2009). More extensive investigation of cholinergic mechanisms in geriatric depression, including patients with mild cognitive impairment, dementia, and parkinsonian syndromes, is definitely required.

Amyloid senile plaques and tau neurofibrillary tangles are neuropathologic hallmarks of Alzheimer's disease and may be present in the aging brain long before the diagnosis of dementia, possibly in association with mild cognitive impairment or symptoms of depression. Such protein deposits can be visualized with various PET tracers, e.g., [^{11}C]-labeled Pittsburgh Compound B (PiB) and [^{18}F]FDDNP. An early study with [^{11}C]PiB in a small group of subjects suggested that tracer retention in the brain of depressed elderly without cognitive impairment is not significantly elevated. However, in subjects with major depression and associated cognitive impairment, tracer retention is increased. The amount of retention is variable and

Table 5.3 PET studies with cholinergic and ß-amyloid tracers in LLD

Study groups and subject numbers	Age (years)	Tracer	Findings (depression-related)	Reference
Parkinson's disease with (6) and without (12) dementia	73 ± 9	[^{11}C] Methyl-4-piperidinyl-propionate	Cortical acetylcholinesterase activity is inversely correlated with scores on Cornell scale for depression in dementia	Bohnen et al. (2007)
Normal controls (10)				
Parkinson's disease (22)	63 ± 9	2-[^{18}F] FA85380	$\alpha_4ß_2$ nicotinic acetylcholine receptor binding in anterior cingulate cortex, putamen, midbrain, and occipital cortex is inversely correlated with depressive symptoms (and reduced vs. controls)	Meyer et al. (2009)
Healthy controls (9)				
Remitted major depression with (7) and without (2) cognitive impairment	72 ± 6	[^{11}C]PiB	Normal tracer retention in LLD without MCI	Butters et al. (2008)
Healthy elderly (7)			Increased retention in LLD with MCI, ranging to levels observed in AD	
Mild cognitive impairment (23)	66 ± 12	[^{18}F]FDDNP	Depression in MCI is correlated with lateral temporal tracer retention. Depression in control group is correlated with medial temporal tracer retention	Lavretsky et al. (2009)
Cognitively normal (20)				
MDD (20)	67 ± 8	[^{18}F]FDDNP	Depressed subjects have increased tracer retention in lateral temporal regions and cingulate	Kumar et al. (2011)
Age-matched healthy controls (19)				
Remitted from depression (28)	50–76	[^{11}C]PiB (+ MRI)	Previous depressive episodes *not* associated with increased tracer retention in the brain	Madsen et al. (2012)
Healthy control subjects (18)			But associated with vascular damage as depressed group had more white matter lesions	
Subcortical vascular cognitive impairment (127)	74 ± 7	[^{11}C]PiB (+ MRI)	Cortical-to-cerebellum ratios of tracer uptake are not correlated with depressive symptoms but with delusions and irritability	Kim et al. (2013)
Mild cognitive impairment (35)	40–85	[^{18}F]FDDNP	Less tracer retention in posterior cingulate cortex is associated with higher scores on the POMS vigor-activity subscale	Chen et al. (2014)
Normal cognition (35)				

(continued)

Table 5.3 (continued)

Study groups and subject numbers	Age (years)	Tracer	Findings (depression-related)	Reference
Depressed patients (25) Nondepressed comparison subjects (11)	68 ± 5	[^{18}F]AV-45	Significantly higher SUVR in parietal and precuneus cortex of depressed than comparison subjects. SPM indicated a wider distribution of tracer uptake over frontal, parietal, temporal, and occipital areas in depressed than in comparison subjects. The greatest differences were observed in bilateral precuneus and right middle temporal cortex. Global and regional SUVR did not show a significant correlation with age at onset of depression, number of major depressive episodes, time since onset of depression, or late-onset major depression	Wu et al. (2014)
MCI (371): Aβ+ nondepressed (141) Aβ+ depressed (65) Aβ− nondepressed (124) Aβ− depressed (41)	72	[^{18}F]AV-45 [^{18}F]FDG (+MRI)	Aβ+ depressed subjects showed large clusters with a higher amyloid load in the frontotemporal and insular cortices with coincident hypermetabolism in the frontal cortices than nondepressed subjects. Faster progression to AD was observed in subjects with depressive symptoms and in Aβ+ subjects. Coincident depressive symptoms additionally shortened the conversion time in all Aβ+ subjects and to a greater extent in those with a high amyloid load	Brendel et al. (2015)
Remitted LLD with MCI (36) Remitted LLD with normal cognitive function (44)	≥65	[^{11}C]PiB (+MRI)	No differences in gray matter volume or brain Aβ Deposition between groups	Diniz et al. (2015)
MCI with history of major depressive episodes (33)	77 ± 4	[^{18}F]AV-45 (+MRI)	The rate of Aβ positivity and the SUVR were higher in late-onset than in early-onset depression	Tateno et al. (2015)
Healthy control group (22)	72 ± 5			

Table 5.3 (continued)

Study groups and subject numbers	Age (years)	Tracer	Findings (depression-related)	Reference
Cognitively normal participants (118) at baseline and 66 at follow-up after 1 yr	73 ± 5	[^{11}C]PiB	Changes in mood from baseline to 1-year follow-up were associated with CSF and PET biomarkers, greater mood disturbances (anxiety, depression, confusion) being related to biomarker values in the absence of cognitive decline	Babulal et al. (2016)
Patients with history of MDD and with subjective memory complaint (13)	72 ± 4	[^{18}F] Florbetaben	Ten subjects were judged as Aβ− and 3 subjects as Aβ+. Depressive symptom severity did not differ between the Aβ−and Aβ+ groups	Kim et al. (2016b)
Cognitively normal participants without MDD history (29)	> 55	[^{11}C]PiB	Positive correlation between depressive symptoms and binding potential in the precuneus/posterior cingulate.	Yasuno et al. (2016)
Current LLD (48) age- and gender-matched Healthy comparison subjects (53)	74 ± 8	[^{18}F] Flutemetamol (+MRI)	Mean normalized total hippocampal volume was significantly lower in patients relative to comparison subjects, but there was no group difference in the distribution or median amyloid load. There was no significant association between amyloid levels and onset of depression	De Winter et al. (2017)
MDD (16)	73 ± 7	[^{18}F]FDDNP	[^{18}F]FDDNP binding in the anterior cingulate cortex was negatively associated with the apathy score (where lower apathy score corresponds to higher apathy severity), but regional levels of tracer binding were not significantly associated with depression severity	Eyre et al. (2017)
Cognitively normal subjects without history of moderate to severe MDD (111)	76 ± 7	[^{18}F]AV-1451 [^{11}C]PiB	Higher depression score was significantly associated with greater inferior temporal tau and marginally associated with greater entorhinal cortex tau. No significant association of depression score with amyloid.	Gatchel et al. (2017)

(continued)

Table 5.3 (continued)

Study groups and subject numbers	Age (years)	Tracer	Findings (depression-related)	Reference
Nondemented community-dwelling subjects (27)	78 ± 6	[^{18}F] Flutemetamol	No association between [^{18}F] flutemetamol binding and depression levels	Hammers et al. (2017)
Cognitively normal subjects without depression:		[^{11}C]PiB or [^{18}F]AV-45 or [^{18}F] flutemetamol, at baseline	No difference in probable depression between groups at baseline; incidence of clinically significant depressive symptoms was 4.5 times greater within the high Aβ group than the low Aβ group at the assessment after 54 months	Harrington et al. (2017)
High Aβ (81) Low Aβ (n = 278)	74 ± 7 69 ± 6			
Cognitively affected subjects: MCI (225) AD (31) Cognitively unaffected subjects (153) From the cognitively affected, subjects with subsyndromal depression (73) subdivided to:		[^{18}F]AV-45 (+MRI) at baseline and 2-year follow-up	Cognitive performance in SSRI(+) subjects with depressive symptoms showed less deterioration at 2-year follow-up compared to SSRI(−) subjects with such symptoms, independent of amyloid load at baseline. SSRI treatment reduced the progression of gray matter atrophy, notably in frontotemporal cortex. A slight trend toward lower rate of amyloid deposition was observed in SSRI(+) versus SSRI(−) subjects with depressive symptoms, most notably in the frontal cortex	Brendel et al. (2018)
Those receiving SSRI medication (24) Those without SSRI (49)	72 ± 9 72 ± 8			
Cognitively normal community-dwelling subjects (270) scored below cutoff for mild depression	74 ± 6	[^{11}C]PiB at baseline	Higher [^{11}C]PiB binding predicted accelerated rates of increase in depression score over time, adjusting for depression history	Donovan et al. (2018)

Table 5.3 (continued)

Study groups and subject numbers	Age (years)	Tracer	Findings (depression-related)	Reference
Cognitively normal subjects without depression:		[^{11}C]PiB or [^{18}F]AV-45 or [^{18}F] flutemetamol, at baseline	Incident cases of screen-positive depression were not increased in high Aβ cognitively normal subjects, although small increases in overall depressive symptoms severity and apathy-anxiety symptoms were No associations between cognitively normal individuals whose clinical disease stage progressed to either MCI or AD and incidence of screen-positive depression or increase in depressive symptoms were observed	Perin et al. (2018)
High Aβ (136) Low Aβ (449)	75 ± 7 71 ± 6			
MDD (63):		[^{18}F]AV-45 (+MRI)	A greater proportion of the MDD/MCI group (12.5%) exhibited both amyloid positivity and hippocampal atrophy as compared to 4.5% in the control and 5.1% in the MDD/non-MCI group A considerable proportion of the MDD/MCI group (29.2%) showed only hippocampal atrophy and no amyloid deposition, as compared to 0% in the control and 5.1% in the MDD/non-MCI group	Wu et al. (2018)
– MCI (24) – Non-MCI (39) Control group (22)	67 ± 6 65 ± 7 67 ± 7			
Nondemented LLD subjects (34) treated twice weekly with electroconvulsive therapy until remission	73 ± 8	[^{18}F] Flutemetamol (+MRI), at baseline	No correlation between amyloid load at baseline and baseline depression severity. Hippocampal volume, WMH, and amyloid load at baseline did not predict response or remission at 1 and 4 weeks post ECT, nor relapse at week 4 nor depression free interval after 6 months of follow-up	Bouckaert et al. (2019)

can in some cases be as high as that observed in patients with Alzheimer's disease (Butters et al. 2008). This preliminary result, and data from some subsequent studies (Wu et al. 2014; Brendel et al. 2015; Harrington et al. 2017), is consistent with the hypothesis that depression is a premonitory symptom of dementia because of a shared underlying neurobiological mechanism. However, other authors have hypothesized that the increased risk of AD in subjects with LLD is not directly related to abnormal metabolism of Aß, but rather to a reduced brain reserve in depressed elderly individuals that makes their brains more vulnerable to downstream toxic effects of Aß deposition (Diniz et al. 2015). An early PET study observed significant correlations between depression scores in elderly subjects and retention of the tracer [^{18}F]FDDNP in temporal areas, suggesting that relatively mild mood symptoms may be associated with measurable increases of ß-amyloid and tau deposition in the human brain (Lavretsky et al. 2009). Significantly increased retention of [^{18}F]FDDNP was later indeed observed in lateral temporal and cingulate brain regions of elderly patients with MDD (Kumar et al. 2011), and several subsequent studies have suggested that accumulation of ß-amyloid (and/or tau) in specific brain regions may be related to depression (Lavretsky et al. 2009; Kumar et al. 2011; Wu et al. 2014; Brendel et al. 2015; Babulal et al. 2016; Yasuno et al. 2016; Gatchel et al. 2017; Harrington et al. 2017; Donovan et al. 2018). One study has indicated a particularly strong link between Aß positivity and late-onset LLD (Tateno et al. 2015). Another PET study reported that psychological well-being in subjects with mild cognitive impairment is associated with lower retention of [^{18}F]FDDNP in the posterior cingulate cortex (Chen et al. 2014).

In contrast to these positive findings, many other PET studies (Donovan et al. 2015; Madsen et al. 2012; Kim et al. 2013, 2016b; De Winter et al. 2017; Eyre et al. 2017; Hammers et al. 2017; Perin et al. 2018; Bouckaert et al. 2019) did not observe any relationship between the cerebral retention of Aß tracers and previous or present depressive symptoms, although in one study (Kim et al. 2013), tracer uptake was positively correlated with the frequency of delusions and irritability, whereas in other studies (Eyre et al. 2017; Perin et al. 2018), it corresponded to the severity of apathy. Various findings have indicated that the relationship between increased levels of Aß and symptoms of depression or the presence of a depressive disorder is not causal or direct: (i) SSRI medication improved the declining cognitive performance and attenuated gray matter atrophy in cognitively affected elderly patients with depressive symptoms, although binding of the Aß tracer [^{18}F]AV-45 was not reduced (Brendel et al. 2018), and (ii) cognitive normal elderly subjects can show high levels of Aß in their brains and not have any symptoms of depression (Perin et al. 2018).

In summary, many PET studies support the hypothesis that deposition of amyloid plaques and tau tangles in the aging brain can result in both cognitive and non-cognitive behavioral symptoms, although depressive symptoms are probably not a direct consequence of Aß accumulation. The neurobiological processes in elderly patients with MDD appear to be quite heterogeneous. Some patients with MDD and MCI showed evidence of neurodegeneration and were in the prodromal stage of AD, whereas others were amyloid negative but showed abnormal atrophy of the hippocampus. The latter subjects could be in the prodromal stage of other (non-AD) types of dementia (Wu et al. 2018).

Table 5.4 PET studies of metabotropic glutamate receptors and of neuroinflammation in LLD

Study groups and subject numbers	Age (years)	Tracer	Findings (depression-related)	Reference
MDD (20) Age-matched healthy volunteers (22)	63 ± 6	[^{11}C] ABP688	No significant difference in [^{11}C] ABP688 binding between subjects with MDD and healthy volunteers. [^{11}C] ABP688 binding was also similar between subgroups with early- or late-onset depression	DeLorenzo et al. (2015)
LLD (5) Controls (13)	65–78	[^{11}C] PK11195	Participants with depression had significantly higher [^{11}C]PK11195 binding compared with controls in left subgenual anterior cingulate cortex and right parahippocampus	Su et al. (2016)

5.2.4 Imaging of Metabotropic Glutamate Receptors and of Neuroinflammation

Other processes, such as the availability of metabotropic glutamate receptors in the brain and neuroinflammation, have been implicated in the underlying pathology of depression. An overview of PET studies about these subjects is provided in Table 5.4.

The metabotropic glutamate receptors bind glutamate within a large extracellular domain and transmit signals through the receptor protein to intracellular signaling partners, and its widespread expression makes these receptors particularly attractive targets for drugs. One study analyzed brain metabotropic glutamate receptor subtype 5 binding by performing [^{11}C]ABP688 PET in elderly patients suffering from MDD, and in contrast to previously published research in younger individuals, no significant difference in binding was observed between elderly subjects with MDD and healthy volunteers. [^{11}C]ABP688 binding was also similar between subgroups with early-onset depression and late-onset depression, suggesting that there are differences in the pathophysiology of elderly depression and depression earlier in life (DeLorenzo et al. 2015).

The radioligand [^{11}C]PK11195 selectively binds to the translocator protein (TSPO), a receptor expressed on activated microglia, and is used to evaluate neuroinflammation in vivo by PET. Interestingly, [^{11}C]PK11195 binding has been found to be raised in brain regions associated with depression in patients with LLD compared with controls.

5.3 Conclusion

Imaging studies, particularly the results of multimodality imaging, support the concept that late-onset depression differs from depression with early onset in its association with cerebral small vessel disease, beta-amyloid and tau deposition, and neurodegenerative processes. Although imaging data also support the hypothesis that late-onset depression relies on dysfunctioning of the frontal lobe, many

studies highlight the fact that the mechanisms underlying late-onset depression are heterogeneous and diverse. Divergent findings in imaging studies are not only due to heterogeneity of disease mechanisms but also to progress in scanner technology and data analysis techniques. Simple ratio methods of data analysis have been replaced by more advanced analytical tools such as statistical parametric mapping (SPM), principal (or independent) component analysis, and other data-driven research methods. The future of PET and SPECT imaging in depression research seems to rely on progress in data analysis, the development of novel molecular probes for specific targets in the aging human brain, and combination of different imaging modalities. Interesting (and relatively unexplored) areas for future research are gender differences, longitudinal changes of brain function associated with subclinical and clinical depression, and analysis of the default network activity.

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Neuroimaging in Seasons and Winter Depression

6

Irena Dajić, Nicole Praschak-Rieder, Rupert Lanzenberger, Christoph Spindelegger, Siegfried Kasper, and Matthäus Willeit

Contents

Abstract

Seasonal fluctuations in mood, behaviour, energy level and appetite are common in humans living in temperate and polar zones. These changes are not necessarily associated with clinical symptoms; however, some people regularly experience severe changes in mood and drive during the dark season. Seasonal affective disorder (SAD) is regarded as an extreme reaction to changes in environmental light. The underlying mechanism of these seasonal changes and the pathobiology of *SAD* still remain unclear. However, several lines of evidence suggest a key role

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of monoamines in modulating seasonal fluctuations in animals and humans. Here, we review the literature on neuroimaging including MRI, SPECT and PET in SAD. Furthermore, the effects of season on the monoamine neurotransmitter systems serotonin and dopamine are discussed.

6.1 Introduction

Seasonal fluctuations in metabolism and behaviour are common in organisms living in temperate and polar zones. These fluctuations are evolutionary coping strategies, necessary for adapting to dramatic changes in temperature, light and food availability (Levitan et al. 2006, 2010; Praschak-Rieder and Willeit 2012). The degree of this adaptation in humans is known as 'seasonality'. Seasonal changes in mood, behaviour, energy level and appetite are not necessarily associated with psychopathological symptoms, as they are normally distributed in the general population (Hardin et al. 1991; Kasper et al. 1989; Praschak-Rieder and Willeit 2012; Winkler et al. 2002). Extreme seasonal variations in mood and drive were first described in a psychiatric context by Rosenthal et al. (1984). 'Seasonal affective disorder' (SAD) is considered a clinical subtype of major depression. A milder form of SAD, termed 'winter blues' or 'subsyndromal SAD (s-SAD)', was described by Kasper et al. (1988). Altogether, prevalence rates of SAD and s-SAD have been reported between 1.5 and 17.8% in the Northern Hemisphere (Kasper 1994). Based on the hypothesis that SAD is triggered by photoperiod variations and the fact that these variations are larger in higher latitudes closer to the poles, increased prevalence rates of SAD have been assumed in these regions (Mersch et al. 1999). Although some studies found a significant positive correlation between latitude and prevalence of SAD (Potkin et al. 1986; Rosen et al. 1990), climate, social as well as cultural factors seem to have a more considerable impact on its prevalence (Mersch et al. 1999). Gender disparity is substantially greater in SAD than in other forms of depression with a female-to-male sex ratio of up to 9:1 according to some studies (Boyce and Parker 1988; Thompson and Isaacs 1988; Winkler et al. 2002; Wirz-Justice et al. 1986).

The 'winter seasonal pattern' constitutes the most common form of SAD. According to DSM-IV, this form of the disorder is characterised by a recurrent pattern of major depressive episodes during fall and winter (in the absence of seasonal psychosocial stressors) and remission of depressive symptoms during spring and summer (Rosenthal et al. 1984; Lam and Levitan 2000). In contrast to the winter form of SAD, Wehr described a less prevalent form of SAD with depressive symptoms during summer and hypomania during winter (Wehr et al. 1987). On a symptom level, winter SAD is frequently characterised by atypical depressive symptoms such as increased sleep duration, hyperphagia and subsequent weight gain (Praschak-Rieder and Willeit 2003; Rosenthal et al. 1984). In parallel to nonseasonal depression, the neurotransmitters serotonin, norepinephrine and dopamine have been suggested to play a crucial role in the aetiology and pathophysiology of SAD (Levitan 2007). A transient decline in brain serotonin due to depletion of tryptophan, the amino acid precursor of serotonin, has been reported to result in lower mood and

increased irritability or aggressive responding in several studies (for review, see Young and Leyton 2002). Tryptophan depletion caused a relapse of depressive symptoms in remitted SAD patients (Neumeister et al. 1998a) and reversed the therapeutic effect of bright light treatment (Lam et al. 1996; Neumeister et al. 1998b). Alterations in norepinephrine and dopamine neurotransmission were hypothesised to be essential for the occurrence of fatigue and reduced levels of subjective arousal in SAD patients (for review, see Levitan 2007). In addition, dopamine has been reported to act as a chemical messenger for light adaptation (Witkovsky 2004). Patients with SAD show reduced light sensitivity (Hebert et al. 2004), supporting the hypothesis of the involvement of dopamine in the pathogenesis of SAD.

Based on evidence derived from several randomised, placebo-controlled studies using dim light or deactivated ion generators as comparator, light therapy is recognised as effective and is recommended as first-line treatment for SAD (Lewy et al. 1998; Terman 2006; Terman et al. 1989). The pathophysiology of SAD is still not sufficiently understood (Magnusson and Partonen 2005), though theories on its pathogenesis are intimately tied to the biological mechanisms of light therapy (Lam and Levitan 2000).

Although SAD and its subsyndromal form show a high prevalence, imaging studies investigating patients with SAD and the effects of seasonality on the brain are scarce. The following synopsis will give an overview of neuroimaging in SAD and seasonal effects on brain monoamine pathways.

6.2 Structural and Functional Magnetic Resonance Imaging

6.2.1 Structural MRI Studies

Despite a large body of research addressing structural brain abnormalities associated with nonseasonal depression, to date only two volumetric MRI studies were conducted in patients with SAD.

In line with evidence for the hyperactivity of the hypothalamic-pituitary adrenal (HPA) axis in depression, there is some indication of larger pituitary volumes in patients with major depression and bipolar disorder (for a review see Delveccio et al. 2017). In contrast, a study in 19 patients with SAD did not show any significant pituitary volume changes (Schwartz et al. 1997). Since the participants of this study underwent MRI scans of the pituitary gland both in summer and winter, this study was further able to demonstrate that pituitary volumes did not change between seasons, supporting the notion that the aetiology of SAD is associated with factors other than HPA dysregulation. The findings of Schwartz et al. have been replicated in a Brazilian investigation (Miranda-Scippa et al. 2008). Miranda-Scippa and her colleagues compared pituitary gland volumes of 12 patients suffering from SAD and 12 healthy controls matched for age, gender and menstrual cycle. No significant differences in pituitary gland volume between patients and controls were found. Light therapy was shown to significantly reduce depressive symptoms, but it did not alter pituitary gland volumes. However, pituitary volumes in winter correlated positively with the severity of depression in patients.

While some studies have suggested adrenal gland enlargement in nonseasonal depression (Kessing et al. 2011), to our knowledge, there are no investigations focusing on adrenal gland volumes in SAD.

In summary, the available data on structural changes in SAD provide no clear evidence of structural brain alteration during depressive episodes or remission.

6.2.2 Functional MRI (fMRI) Studies

Electroretinographical studies have shown a reduced retinal light sensitivity in SAD patients (Hebert et al. 2004) with seasonal variations in rod and cone function. Furthermore, a normalisation of rod and cone function was found after 4 weeks of bright light therapy (Lavoie et al. 2009). Based on these findings, Vandewalle et al. (2011) conducted an fMRI study investigating the impact of light on emotional processing in untreated depressed SAD patients ($n = 14$). Patients showed an increased response to auditory emotional stimuli in the posterior hypothalamus under blue light (480 nm) exposure, whereas green light (550 nm) decreased hypothalamic response. Furthermore, increased responsiveness to vocal stimuli was found in thalamus and brainstem areas in patients. The authors suggested that altered emotional processing during coloured light exposure, as shown by the abnormal light responsiveness of the hypothalamus, may constitute a neurobiological substrate of SAD.

Emotional processing in SAD was further examined in a more recent study by Borgsted et al. (2018). Seventeen patients with the disorder and 15 age-matched healthy controls completed an implicit emotional faces fMRI paradigm twice, in winter and in summer. Informed by findings of increased amygdala activation to aversive stimuli in MDD (Stuhrmann et al. 2011), the study primarily assessed the amygdala response to angry versus neutral faces. Although no effect of group or season was found, the results showed decreased amygdala activation in the patient group, across all face types and scan times.

Out of two resting-state (rs)-fMRI studies conducted in SAD patients, one found increased functional connectivity in 11 out of 47 resting state networks identified by independent component analysis (Abou Elseoud et al. 2014). The networks displaying altered functional connectivity in non-medicated patients ($n = 45$) relative to HC ($n = 45$) involved visual, sensorimotor and attentional areas of the cortex. In addition, the amplitude of low-frequency fluctuations, an index of spontaneous synchronous neural activity at the voxel level, was higher in the visual and sensorimotor cortices.

The other study employed rs-fMRI and graph theory to investigate functional brain network properties in 12 patients with SAD and a matching number of healthy subjects (Borchardt et al. 2015). The main finding of the study was a hyperfunctional primary visual cortex, as indicated by hyperefficiency in the left and hyperconnectedness in the right hemisphere, in the patient group. Additionally, globally decreased network efficiency was reported in patients.

6.3 Single-Photon Emission Computed Tomography (SPECT) Studies

The monoamine neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) has been implicated in various physiological functions, including regulation of circadian rhythms as well as in the pathophysiology of numerous neuropsychiatric disorders.

Based on several findings of a seasonal rhythm in brain and peripheral serotonin (5-HT) activity in humans, serotonin was suggested to play a major role in the pathomechanisms of SAD (Kasper et al. 1996; Lam and Levitan 2000; Willeit et al. 2000, 2008) and the mechanisms of action of bright light therapy (Praschak-Rieder et al. 2008). In a human post-mortem study, Carlsson and colleagues were able to show a seasonal variation in hypothalamic 5-HT concentrations with lowest levels of 5-HT occurring in winter (Carlsson et al. 1980). Confirming these findings in vivo, an Australian study by Lambert et al. reported reduced serotonin turnover in the Australian winter months between June and August (Lambert et al. 2002).

One of the key molecules in serotonergic neurotransmission is the serotonin transporter (SERT or 5-HTT). After release of 5-HT into the synaptic cleft, SERT mediates reuptake into the presynaptic neuron. Thereby, SERT activity is able to control spatial and temporal spread of the serotonergic signal. Selective serotonin reuptake inhibitors (SSRIs) exert their antidepressive effect by blocking SERT and show comparable efficacy to light therapy in the treatment of SAD (Lam et al. 2006; Praschak-Rieder and Willeit 2003).

The availability of brain SERT binding sites in serotonin-rich regions like the midbrain can be assessed in vivo via the nonspecific monoamine transporter ligand [^{123}I]-2-beta-carbomethoxy-3-beta-(4-iodophenyl)-tropane ([^{123}I]ß-CIT) and single-photon emission computed tomography (SPECT; Brucke et al. 1993). In addition to its use as a SERT ligand, [^{123}I]ß-CIT can be employed to assess dopamine transporter (DAT) availability, as its binding in the striatum—where equilibrium binding is achieved later than in the midbrain—is mainly to DAT (Laruelle et al. 1993; Staley et al. 1994).

Preliminary evidence for higher SERT and DAT binding during summer was found in a small sample of healthy females (n = 11) using [^{123}I]ß-CIT SPECT (Neumeister et al. 2000). A more recent study of SERT availability in a larger sample of nonseasonally depressed patients (n = 49) demonstrated opposite findings, with significantly higher [^{123}I]ß-CIT binding in winter (Ruhe et al. 2009). However, male-depressed patients showed a significant reduction in SERT availability compared to healthy controls.

A SPECT study from Taiwan investigated striatal dopamine $D_{2/3}$ availability in 68 healthy subjects with respect to their exposure to sunshine 30 days prior to their individual SPECT scan (Tsai et al. 2011). Since there is little seasonal variation in day length and daily sunlight in Taiwan, only 35 subjects in the lowest (n = 18) and highest (n = 17) quartile of average sunshine duration were analysed. Higher [^{123}I]iodobenzamide ([^{123}I]IBZM) binding was revealed in subjects exposed to higher amounts of sunshine than in those with lower sunshine exposure prior to SPECT scans. Results have to be interpreted with caution: [^{123}I]IBZM is sensitive towards changes in extracellular dopamine levels (Laruelle 2000), and the findings of higher [^{123}I]IBZM binding could either be due to a higher amount of dopamine $D_{2/3}$ receptors or reduced levels in extracellular dopamine. Moreover, rates of tobacco use differed significantly between groups.

Only a small number of SPECT studies have been conducted in patients with SAD. In a study by Willeit et al. (2000), drug-free patients with SAD (n = 11)

showed decreased [^{123}I]ß-CIT binding in the midbrain thalamus-hypothalamus area compared to controls matched for age, gender, menstrual cycle and time of scanning. A study on SERT binding in platelets of patients with SAD and healthy controls failed to show differences in SERT B_{max} values between fall/winter and spring/summer (Willeit et al. 2008). However, this study showed increased efficiency in SERT-mediated 5-HT uptake during winter depressive episodes, suggesting a hyperactive state of the 5-HTT, and less extracellular serotonin, in patients with SAD. After successful light therapy and during natural remission in summer, SERT function returned to control levels.

The dopaminergic system was implicated in the pathophysiology of SAD by a [^{123}I]ß-CIT study of Neumeister et al. (2001), who found reduced striatal availability of DAT in a small cohort (n = 11) of untreated SAD patients during winter.

Apart from transporter and receptor studies, an investigation of regional cerebral blood flow (rCBF) in a small sample of untreated patients with SAD and healthy controls using [^{99m}Tc]hexamethylpropyleneamine oxime ([^{99m}Tc]HMPAO) and SPECT suggested decreased left frontal rCBF in patients with SAD (Praschak-Rieder et al. 1998). Following successful bright light therapy, normalisation in left frontal rCBF was found.

Some of the mentioned SPECT studies revealed reduced availabilities of SERT and DAT as well as alterations in regional cerebral blood flow in depressed patients with SAD. Moreover, possible seasonal effects on $D_{2/3}$ receptors have been demonstrated in healthy subjects. Findings of these preliminary studies were partly strengthened by results obtained in studies using more selective radioligands and positron emission tomography (PET—see Sect. 6.4). However, independent replications and further studies are needed before firm conclusions on SERT and DAT binding in patients with SAD can be drawn.

6.4 Positron Emission Tomography (PET) Studies

First PET studies specifically investigating patients used [^{11}F]deoxy-glucose ([^{11}F]FDG) to determine whether patients with SAD showed abnormalities in cerebral metabolic rates. Cohen et al. (1992) compared brain metabolic rates between a small sample (n = 7) of patients with winter SAD and healthy controls. All patients were drug-free for at least 3 months and were investigated in an untreated condition (*off-lights*). Furthermore, six patients were also scanned after at least 10 days of light treatment (*on-lights*), consisting of 2.5 h long exposure to 2500-lux full-spectrum light twice a day. Patients with SAD showed lower superior medial frontal and global metabolic rates under *on-* and *off-lights* condition. As suggested by the authors, the insufficient length of light therapy might have contributed towards the failure to detect differences between *on-* and *off-light* conditions in patients. However, light therapy proved sufficient to reverse depressive symptoms.

The second PET study on cerebral glucose metabolism was conducted in patients suffering from summer SAD (Goyer et al. 1992). The nine patients investigated showed significantly different regional glucose metabolic rates in orbital frontal cortex and in left inferior parietal lobule compared to healthy controls.

In view of the findings provided by other methodologies, more recent PET studies on seasonality and SAD largely focused on the serotonergic system. In parallel to SPECT imaging, seasonal effect on SERT binding was demonstrated by several cross-sectional studies conducted in healthy volunteers (Table 6.1).

Table 6.1 Neuroimaging in patients with SAD

Method	Author	Subjects	Main outcome
Structural MRI	Schwartz et al. (1997)	19 SAD/19 HC	No change of pituitary volume due to winter depression or season
	Miranda-Scippa et al. (2008)	12 SAD/12 HC	No differences in pituitary volume between SAD and HC
Functional MRI	Vandewalle et al. (2011)	14 SAD/16 HC	Increased response to auditory emotional stimuli in the posterior hypothalamus due to exposure to blue light in SAD
	Abou Elseoud et al. (2014)	45 SAD/45 HC	Increased functional connectivity in 11/47 resting state networks and higher ALFF in the visual and right sensorimotor cortex in SAD
	Borchardt et al. (2015)	12 SAD/12 HC	Hyperconnectedness and hyperefficiency in the inferior occipital cortex and lower global routing efficiency in SAD
	Borgsted et al. (2018)	17 SAD/15 HC	Decreased amygdala response to aversive and neutral faces
SPECT			
[^{123}I]ß-CIT	Willeit et al. (2000)	11 SAD/11 HC	Decreased [^{123}I]ß-CIT binding in thalamus-hypothalamus in SAD
[^{123}I]ß-CIT	Neumeister et al. (2001)	11 SAD/11 HC	Reduced availability of striatal DAT in patients with SAD
[^{99m}Tc] HMPAO	Praschak-Rieder et al. (1998)	24 SAD	Hemispheric asymmetry in frontal rCBF. Normalisation of rCBF after successful light therapy
PET			
[^{18}F]FDG	Cohen et al. (1992)	7 SAD/38 HC	Lower metabolic rates with or without light treatment in SAD
[^{18}F]FDG	Goyer et al. (1992)	9 summer SAD/45 HC	Altered glucose metabolism in orbital frontal cortex and left inferior parietal lobule in SAD
[^{11}C]DASB	Tyrer et al. (2016)	20 SAD/20 HC	Greater seasonal variation in [^{11}C]DASB binding in patients
[^{11}C]DASB	McMahon et al. (2016)	17 SAD/23 HC	Higher global wintertime [^{11}C]DASB binding in SAD. Correlation between seasonal change in binding and change in SIGH-SAD scores
[^{11}C]DASB	Nørgaard et al. (2017)	6 SAD/13 HC	Different patterns of seasonal fluctuations in [^{11}C]DASB binding in patients compared to HC
[^{11}C] harmine	Spies et al. (2018)	24 SAD/27 HC	Seasonal dynamics in MAO-A levels in HC, but not SAD. Decrease in MAO-A levels following BLT

MRI Magnetic resonance imaging, *SPECT* Single-photon emission computed tomography, *PET* Positron emission tomography, *SAD* Seasonal affective disorder, *HC* Healthy controls, *DAT* Dopamine transporter, *rCBF* Regional cerebral blood flow

A PET study by Praschak-Rieder et al. conducted in a large group of healthy drug-naïve subjects (n = 88) (Praschak-Rieder et al. 2008) was able to demonstrate a considerable effect of season on SERT by using the specific SERT radioligand [^{11}C]3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)benzonitrile ([^{11}C]DASB) and PET. The study revealed a uniform decrease in [^{11}C]DASB binding potential (BP_{ND}) values from autumn and winter to spring and summer in six different predefined regions of interest (ROI), with differences as large as 40% between peaks and troughs (Fig. 6.1). Furthermore, [^{11}C]DASB BP_{ND} values showed a negative correlation with the duration of daily sunshine and day length. Concordant results were offered by Kalbitzer et al. (2010), who reported a negative correlation of [^{11}C]DASB BP_{ND} values and daylight minutes. In the latter study, 54 healthy subjects were investigated using [^{11}C]DASB PET and genotyped for a polymorphism in the promoter region of the SERT gene (5-HTTLPR). Only carriers of 5-HTTLPR s-allele showed significant effects of season on [^{11}C]DASB binding. In contrast, 5-HTTLPR l-allele homozygous subjects did not exhibit seasonal variation of SERT availability. A [^{11}C]DASB PET study by Murthy et al. in 63 healthy subjects failed to find an influence of the 5-HTTLPR polymorphism on SERT binding; however, the authors did not control for season of scanning (Murthy et al. 2010).

In a more recent study, Matheson et al. (2015) aimed at examining diurnal and seasonal changes in 5-HT_{1A} and SERT binding in 56 healthy subjects using the HT_{1A} radioligand [^{11}C]WAY-100635 and the SERT ligand [^{11}C]MADAM, respectively.

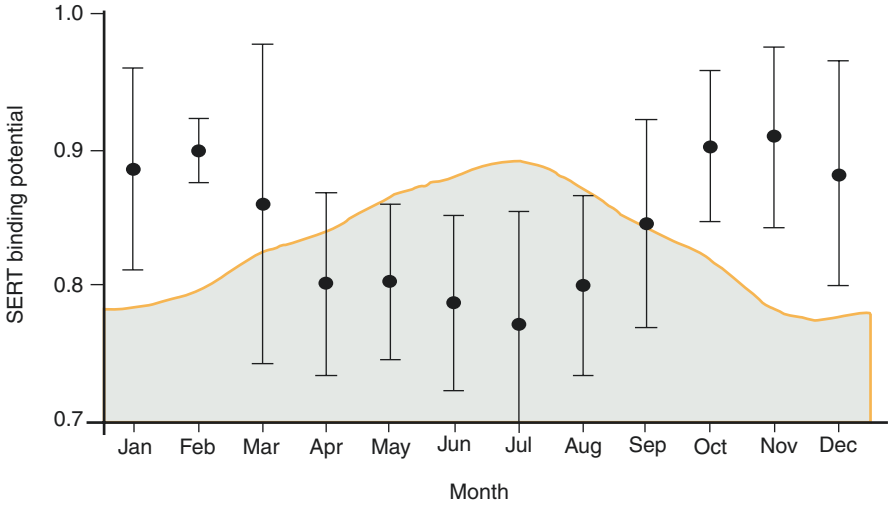

Fig. 6.1 Reciprocal peaks and troughs of serotonin transporter (*SERT*) binding and duration of sunshine in 88 healthy subjects. *Shaded area*: duration of sunshine in Toronto, Ontario (range between 2.4 and 9.2 h a day). SERT BP_{ND} measured by the selective SERT radioligand [^{11}C]DASB and positron emission tomography. *Circles* represent bimonthly moving averages of mean binding potential values in six predefined regions of interest (prefrontal cortex, anterior cingulate, caudate, putamen, thalamus and midbrain). *X*-axis: calendar months (modified according to Praschak-Rieder and Willeit 2012)

While a decrease in midbrain SERT binding was observed across the day, no seasonal changes in SERT binding were found.

Additionally, effects of season on SERT binding were demonstrated by Buchert et al. (2006) using PET and the radioligand trans-1,2,3,5,6,10b-hexahydro-6-[4-(methylthio)-phenyl]pyrrolo-[2,1-a]-isoquinoline ([^{11}C]-(+)McN5652). This study investigated age-related effects on SERT binding in 29 healthy subjects. In line with the results obtained by [^{11}C]DASB PET, SERT binding measured with [^{11}C]-(+) McN5652 PET was higher in winter, while age did not show any effect on SERT availability in this sample.

While cross-sectional studies in healthy subjects provided evidence of increased SERT availability during winter months, longitudinal studies in patients with SAD and healthy controls yielded more ambiguous results.

In a study comparing seasonal fluctuations in [^{11}C]DASB binding between 20 patients with SAD and a corresponding number of healthy controls (Tyrer et al. 2016), a greater change in [^{11}C]DASB BP_{ND} from winter to summer was observed in the prefrontal cortex, anterior cingulate cortex and midbrain of patients. The difference was more pronounced between healthy controls and the patient group with severe SAD symptoms, extending to striatal regions and the hippocampus. Furthermore, in SAD subjects, symptom severity was positively correlated with the magnitude of seasonal change in SERT binding in the prefrontal cortex, thalamus and striatum. No group effect on BP_{ND} was detected in either season.

In contrast, McMahon et al. (2016) found higher wintertime [^{11}C]DASB BP_{ND} in 17 patients with SAD relative to a HC cohort ($n = 23$) consisting of only 5-HTTLPR s-allele carriers. In addition, seasonal variation in [^{11}C]DASB BP_{ND} differed between patients and HC, as healthy subjects exhibited a larger decrease in SERT availability during winter. Both sex and genotype had a significant effect on seasonal change in global $BP_{ND.}$ Notably, whereas healthy females tended to downregulate SERT during winter, the seasonal change in female patients with SAD followed the opposite pattern.

A subsequent examination of healthy subjects' data (McMahon et al. 2018) confirmed lower [^{11}C]DASB binding in winter, with a more pronounced decrease from summer to winter in female participants. Given that a small subset of participants ($n = 7$) scanned with PET and [^{11}C]SB207145, a selective 5-HT4 receptor ligand, showed no seasonal change in BP_{ND} values, the authors suggested that the winter downregulation of SERT observed in healthy subjects with the short 5-HTTLPR genotype serves to maintain stable levels of 5-HT over the year. The original study (McMahon et al. 2016) primarily assessed global [^{11}C]DASB BP_{ND}, but post hoc analyses indicated similar results across all sampled ROIs (raphe nuclei, hippocampus, anterior cingulate cortex, thalamus). However, a direct comparison of only female s-allele carriers revealed a differential pattern of seasonal SERT fluctuations between patients ($n = 6$) and healthy controls ($n = 13$) (Nørgaard et al. 2017). Partial least-squares analysis of PET data showed higher winter binding in the globus pallidus, left hippocampus, brain stem and right superior frontal gyrus in HC, while patients had higher wintertime binding in the ventral striatum, amygdala, right orbitofrontal cortex, middle frontal gyrus and left somatosensory cortex.

In addition to the investigations into SERT availability, further evidence of the effect of season on serotonergic neurotransmission was provided by two studies exploring light-dependent alterations of brain serotonin 1A (5-HT_{1A}) receptor binding. The inhibitory 5-HT_{1A} autoreceptors constitute the decisive factor in a negative auto-regulatory loop of serotonin release (Bundgaard et al. 2006), and alterations in 5-HT_{1A} receptor binding have been reported in several neuropsychiatric disorders such as anxiety (Akimova et al. 2009) and depression (Drevets et al. 2007).

Spindelegger et al. investigated 36 healthy drug-naïve subjects by quantifying 5-HT_{1A} BP_{ND} using PET and the highly specific ^{11}C-labelled tracer [*N*-(2-(1-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl))-*N*-(2-pyridyl)-cyclohexane-carboxamide] (*carbonyl*-[^{11}C]WAY-100635). Individual exposure to external factors such as global radiation (defined as total of direct solar radiation and diffuse sky radiation received by a unit horizontal surface) correlated with regional 5-HT_{1A} BP_{ND}, demonstrating a positive correlation between the accumulated (5 days prior to PET scan) amount of global radiation and 5-HT_{1A} receptor binding. Moreover, this investigation showed a significant difference between the groups of subjects exposed to low versus high amounts of global radiation (see Fig. 6.2). Up to 30% differences in regional 5-HT_{1A} BP_{ND} were found between the different exposure groups.

The results of Spindelegger et al. were subsequently corroborated by Matheson et al. (2015), who reported seasonal changes in 5-HT_{1A} binding in 56 healthy male subjects, with higher 5-HT_{1A} availability in summer in serotonin projection regions, as well as an increase in cortical 5-HT_{1A} receptor binding over the course of the day.

In summary, seasonal fluctuations in serotonergic neurotransmission were revealed by a number of studies investigating either SERT or 5-HT_{1A} receptor binding in healthy volunteers. Based on limited findings from the clinical population, there is some evidence that this seasonal dynamic is disrupted in SAD, to a degree that could possibly be related to symptom severity. The apparent discrepancies between findings from different cohorts can largely be accounted for by sample selection and individual factors shown to influence the serotonin system, such as sex and 5-HTTLPR genotype. Future research that takes these factors into account is needed to clarify the exact nature of serotonergic alterations associated with SAD.

Dopamine neurotransmission has been suggested to be regulated in part by photoperiodic and light-dependent rhythms. Dopamine is strongly involved in physiological functions such as motor control, cognition, reward, emotion and memory processes (Dalley and Everitt 2009). Limited evidence for seasonal effects on dopamine neurotransmission is provided by SPECT studies mentioned before (Neumeister et al. 2001; Tsai et al. 2011) and a PET study by Eisenberg et al. (2010) reporting higher striatal fluorine-18-L-dihydroxyphenylalanine ([^{18}F]DOPA) uptake in autumn and winter as compared to spring and summer. Eisenberg and colleagues investigated a large sample of healthy subjects (n = 86) showing higher striatal K_i values in subjects scanned during the winter season. The increased K_i values in the posterior putamen were interpreted as greater presynaptic dopamine synthesis and storage capacity in this region. Based on the resulting higher levels of dopamine in times of less light, these results would be in line with recent findings of lower striatal [^{123}I]IBZM binding in times of less light exposure (Tsai et al. 2011) due to greater

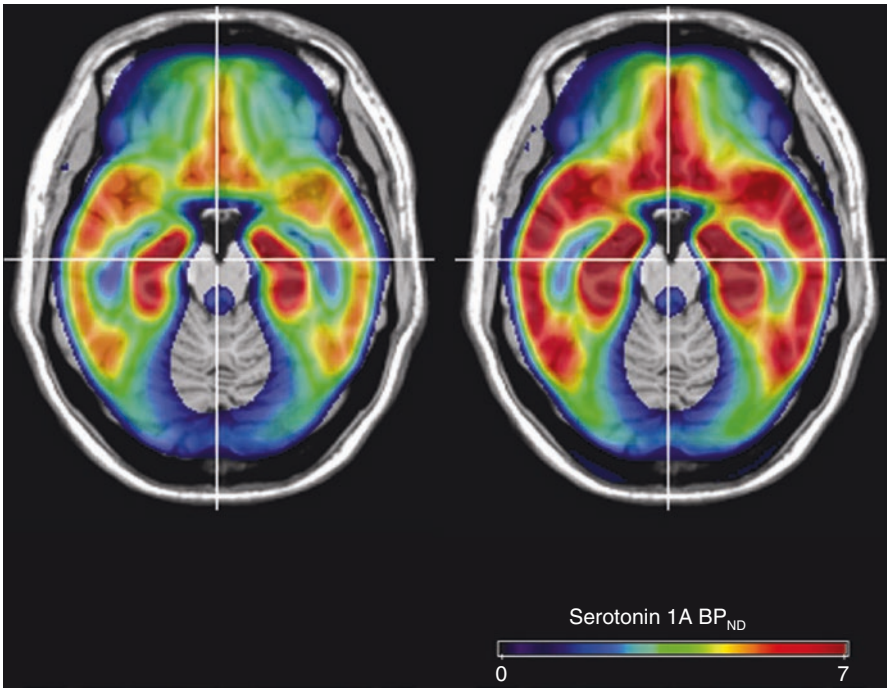

Fig. 6.2 Mean serotonin-1A receptor binding potential (5-HT$_{1A}$ BP$_{ND}$) in subjects exposed to low amounts of global radiation (*left*) versus subjects exposed to high amounts of global radiation (*right*) showing 5-HT$_{1A}$ BP$_{ND}$ values in the group exposed to a low amount of global radiation, especially in limbic brain regions. Subjects exposed to low amounts of global radiation (n = 22), 5-day accumulation of global radiation was lower than 8946 J/cm^2; subjects exposed to high amounts of global radiation (n = 14), 5-day accumulation of global radiation was higher than 8946 J/cm^2 (modified according to Spindelegger et al. (2012))

competition at postsynaptic D$_{2/3}$ receptors. Since there is only limited evidence supporting this hypothesis, further investigations are needed to clarify the underlying mechanisms.

Finally, a recent study by Spies et al. (2018) investigated seasonal variations in the activity of cerebral monoamine oxidase A (MAO-A), a mitochondrial enzyme responsible for the degradation of monoamine neurotransmitters. Spies and colleagues used 7-[^{11}C]methoxy-1-methyl-9*H*-[3,4-*b*]indole ([^{11}C]harmine) PET to assess MAO-A distribution volumes in 24 SAD patients and 27 HC. All participants underwent three PET scans: two in fall/winter (before and after 3 weeks of bright light therapy or placebo) and one in spring/summer. Although no group difference in MAO-A distribution volume was detected, healthy subjects showed a decrease in MAO-A levels from fall/winter to spring/summer, whereas no change was seen in the patient group. Since MAO-A primarily degrades serotonin, these results provide further support for altered seasonal dynamics in 5-HT neurotransmission in SAD, although a contribution of other substrates of the enzyme cannot be dismissed at this

point. Consistent with the posited influence of light on the monoamine systems, bright light therapy resulted in a decrease of MAO-A levels in all participants, while placebo failed to produce a similar effect. This finding aligns with that of Harrison et al. (2015), who observed decreased SERT binding in healthy volunteers following a 2-week exposure to bright light therapy.

6.5 Summary

Seasonal affective disorder and its subsyndromal form constitutes a prevalent neuropsychiatric disorder characterised by severe seasonal changes in mood and behaviour. Atypical or reverse vegetative symptoms such as increased sleep duration, hyperphagia and subsequent weight gain are frequent in SAD, and severity of symptoms tends to correlate positively with latitude. During the last two decades, only a limited number of neuroimaging studies specifically investigating SAD have been conducted. Apart from brain metabolic changes and altered functional brain connectivity, the most substantial findings concern the serotonergic system. Whereas healthy subjects living in zones with substantial seasonal changes in the environment show a seasonal variation in serotonin transporter binding (Praschak-Rieder et al. 2008; Kalbitzer et al. 2010), the seasonal dynamic of the serotonergic neurotransmission seems to be disturbed in SAD, as shown by several neuroimaging studies (Tyrer et al. 2016; McMahon et al. 2016; Spies et al. 2018). Other intriguing findings, such as seasonal changes in dopamine neurotransmission (Eisenberg et al. 2010; Tsai et al. 2011), are still awaiting replication. Given the scarcity of neuroimaging studies in SAD, further research is needed to characterise the molecular background of SAD and seasonal changes in the human brain.

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Bipolar Disorders

7

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Abstract

Bipolar disorder is characterized by (hypo)manic episodes and depressive episodes which alternate with euthymic periods. It causes serious disability with poor outcome, increased suicidality risk, and significant societal costs. This chapter describes the findings of the PET/SPECT research efforts and the current ideas on the pathophysiology of bipolar disorder.

First, the cerebral blood flow and cerebral metabolism findings in the prefrontal cortex, limbic system, subcortical structures, and other brain regions are discussed, followed by an overview of the corticolimbic theory of mood disorders that explains these observations.

Second, the neurotransmitter studies are discussed. The serotonin transporter alterations are described, and the variation in study results is explained, followed by an overview of the results of the various dopamine receptor and transporter molecules studies, taking into account also the relation to psychosis.

Third, a concise overview is given of dominant bipolar disorder pathophysiological models, proposing starting points for future molecular imaging studies.

Finally, the most important conclusions are summarized, followed by remarks about the observed molecular imaging study designs specific for bipolar disorder.

Abbreviations

ACC	Anterior cingulate cortex
BA	Brodmann areas
BD	Bipolar disorder
BD-I	Bipolar I disorder
BD-II	Bipolar II disorder
CBF	Cerebral blood flow
CFT	[O-methyl-^{11}C]-carbomethoxy-3β-(4-fluorophenyl)tropane
CMR	Cerebral metabolic rate
DASB	3-^{11}C-amino-4-(2-dimethylaminomethylphenylsulfanyl)benzonitrile
DAT	Dopamine transporter
DTBZ	(+)-α-^{11}C-dihydrotetrabenazine
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
FDG	^{18}F-labeled fluorodeoxyglucose
fMRI	Functional magnetic resonance imaging
HMPAO	Hexamethylpropylene amine oxime
IDO	Indoleamine 2,3 dioxygenase
IMP	Iodoamphetamine
LCSPT	Limbic-cortical-striatal-pallidal-thalamic
McNeil 5652	Trans-1,2,3,5,6,10-hexahydro-6-[4-(methylthio)phenyl] pyrrolo-[2,1-a] isoquinoline
MD	Mean diffusivity
MDD	Major depressive disorder

MRS	Magnetic resonance spectroscopy
NAA	N-acetylaspartate
PBR	Peripheral benzodiazepine receptor
PET	Positron-emission tomography
PFC	Prefrontal cortex
SPECT	Single-photon emission computed tomography
TZTP	3-(3-(3-[^{18}F]Flouropropyl)thio)-1,2, 5-thiadiazol-4-yl)-1,2,5,6-tetrahydro-1-methylpyridine
VMAT2	Vesicular monoamine transporter 2

7.1 Introduction

Bipolar disorder (BD) (American Psychiatric Association 2013) is a mood disorder characterized by episodic pathologic disturbances in mood: (hypo)manic episodes and depressive episodes which alternate with euthymic periods, i.e., with normal mood. BD has to be distinguished from (unipolar) major depressive disorder (MDD), which is characterized by only depressive episodes. The main criterion of a (hypo) manic episode is the occurrence of pathologic elated (euphoria), expansive, or irritable mood. DSM-5 added increased energy or activity to this list. In addition there are other symptoms such as inflated self-esteem or grandiosity, decreased need for sleep, being more talkative than usual, flight of ideas, distractibility, increase in goal-directed activity or psychomotor agitation, and excessive involvement in pleasurable activities that have a high potential for painful consequences. A depressive episode consists of at least one of the core symptoms depressed mood and loss of interest or pleasure, completed with symptoms such as sleep problems, psychomotor changes, fatigue or loss of energy, feelings of worthlessness or excessive feelings of guilt, difficulty concentrating, or making decisions and recurrent thoughts of death (American Psychiatric Association 2013). Two types of BD are recognized: bipolar I disorder (BD-I) and bipolar II disorder (BD-II), characterized by the occurrence of manic episode(s) or by only hypomanic episode(s), respectively. The difference between manic and hypomanic episodes (and thus between BD-I and BD-II) is that manic episodes are associated with marked impairment in occupational, relational, or social functioning, which can lead to hospitalization, while hypomanic episodes do not have this marked impairment and do not lead to hospitalization. When manic and depressive symptoms co-occur (or alternate very quickly) in the same episode, in DSM-IV it is labeled as a mixed episode and in DSM-5 as a bipolar disorder, manic or depressive episode with mixed features. Manic, depressive, and mixed episodes can be complicated by the presence of concurrent psychotic symptoms. Besides the mood symptoms, many patients with BD also show cognitive dysfunctions which may persist during euthymic periods, and which involve disturbances in various domains such as attention, verbal memory, and executive functioning (Arts et al. 2008; Bora et al. 2009).

The lifetime prevalence of BD-Is about 2% across different countries, women being affected as frequently as men (Pini et al. 2005; Merikangas et al. 2011). Across the world, the disorder is sixth among all health conditions in terms of causing disability (World Health Organization 2001) with poor clinical and functional

outcome (Goodwin 2007), increased risk for suicidality (Baldessarini and Tondo 2003), and significant societal costs (Begley et al. 2001).

Although the clinical picture seems clear at first glance, making the diagnosis is more complicated in practice. On average, there is a lag time of about 6 years between the first episode and the making of the right diagnosis and another 6 years before the start of adequate treatment. This is in most cases in part impeded by the precedence of depressive episodes without obvious (hypo)manic symptoms in the beginning of the disease (Suppes et al. 2001). Because antidepressants appear less effective in the treatment of bipolar depressive episodes (Sachs et al. 2007), delayed diagnosis often leads to prolonged illness and dysfunction.

It is generally accepted that the cause of BD-Is multifactorial, with multiple genes making someone vulnerable, and with psychological and social factors causing the genes to be expressed. Moreover, somatic factors are supposed to play a role. To unravel the complex interplay between genotype and phenotype researchers are trying to find intermediary processes, so called endophenotypes. These are more related to the underlying genotype than the ultimate phenotype. Endophenotypes should be consistently associated with the illness and represent persistent "trait" rather than episodic or "state" features. By definition, they also should be found in high-risk individuals such as non-affected first-degree family members at a higher rate than in the general population (Gottesman and Gould 2003). Over the last three decades, many molecular neuroimaging studies have been performed in BD. Alterations of function assessed by molecular neuroimaging may be regarded as important endophenotypes.

Probably the best approach in neuroimaging of bipolar disorder is to study patients during their depressive and manic episodes as well as during the euthymic phase with different (functional) neuroimaging techniques. However, these are very complicated patients, both technically and practically (e.g., one can never be sure that the same patient will develop both manic and depressive episodes within a certain time frame).

In this chapter, we will describe the findings of various PET/SPECT studies, sometimes performed in combination with other imaging techniques, as well as current ideas on the BD pathophysiology.

7.2 PET/SPECT

7.2.1 General Information

Positron-emission tomography (PET) and single-photon emission computed tomography (SPECT) are imaging techniques that use radiolabeled, biological active compounds (PET or SPECT tracers) to gain information on specific functions of the brain, by measuring brain metabolism or blood flow, or functions of individual cells, such as transporter mechanisms or receptors.

The tracers involved are administered in such small doses that pharmacological activity or chemical toxicity is practically absent and due to the usual short half-life of the radionuclides total radiation remains within generally accepted safety levels.

Where PET uses positron-emitting radionuclides, that give rise to two oppositely directed 511 kV gamma rays after annihilation of positrons with electrons, the radionuclides in SPECT directly emit gamma rays. Because the gamma rays are emitted in 180° opposite directions, PET does not need a collimator for position information and is able to achieve higher spatial resolutions (about 4 mm) than SPECT (7–12 mm). SPECT is more widely accessible due to the lower maintenance costs and generally easier tracer handling.

7.2.2 Cerebral Blood Flow and Cerebral Metabolism

Accumulating scientific evidence supports the theory of metabolic alterations in specific parts of the brain in patients with mood disorders: the prefrontal cortex, the limbic system, and subcortical regions (Fig. 7.1). With molecular imaging techniques, the metabolic activity in the brain (cerebral metabolic rate (CMR)) as well as the blood flow in specific regions (cerebral blood flow (CBF)) can be measured (Table 7.1). It is generally accepted that CMR and CBF are physiologically coupled,

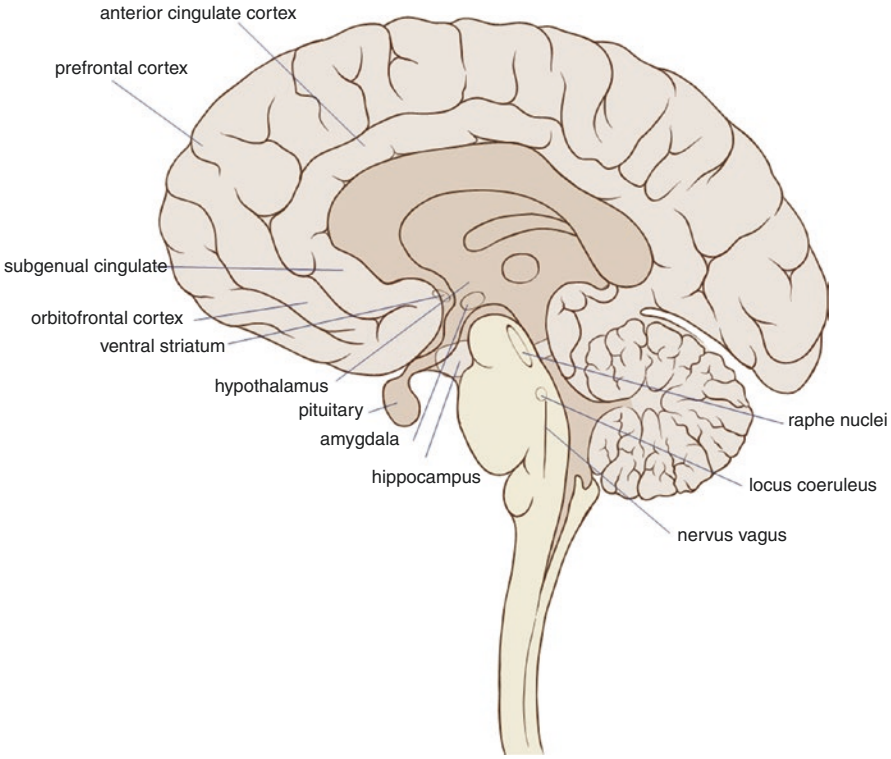

Fig. 7.1 Neuroanatomic regions important in mood disorders. Adapted from Patrick J. Lynch, medical illustrator, and C. Carl Jaffe, MD, cardiologist, under the Creative Commons Attribution 2.5 Generic license (CC BY 2.5))

Table 7.1 Overview of PET/SPECT studies on cerebral blood flow and cerebral metabolism in BD patients

Study (author (year))	Subjects	Medication	Method	Main findings
al-Mousawi et al. (1996)	15 BD-I (15 M) 14 SZ 10 MDD 10 HC	+	^{18}FDG PET Resting state	Decreased left dorsolateral prefrontal cortex and left amygdala in the manic BD patients compared to HC
Altamura et al. (2013)	26 BD 26 SCZ	+	^{18}FDG PET Resting state	White matter metabolic rates significantly differed between schizophrenia and bipolar disorder, whereas no differences were shown for cortical activity
Altamura et al. (2017)	27 BD (10 +SUD) 16 SIP 54 HC	+	^{18}FDG PET Resting state	A unique pattern of GM volumes reduction, with concomitant increased of striatal metabolism, was observed in SIP patients compared to BD and HC
Bauer et al. (2005)	9 BD-I (9 D) 1 BD-II (1 D)	+	^{18}FDG PET Treatment with levothyroxine CPT	Before levothyroxine treatment, BD patients exhibited significantly higher activity in the right subgenual cingulate cortex, left thalamus, medial temporal lobe (right amygdala, right hippocampus), right ventral striatum, and cerebellar vermis and had lower relative activity in the middle frontal gyri bilaterally. Levothyroxine decreased relative activity in the right subgenual cingulate cortex, left thalamus, right amygdala, right hippocampus, right dorsal and ventral striatum, and cerebellar vermis
Bauer et al. (2010)	10 BD (10 D)	+	^{18}FDG PET Treatment with levothyroxine	New analysis on Bauer et al. (2005). After treatment anxiety was improved significantly. Change in trait anxiety covaried positively with changes in relative activity in right amygdala and hippocampus. Change in state anxiety covaried positively with changes in relative activity in the hippocampus bilaterally and left thalamus and negatively with changes in left middle frontal gyrus and right dorsal anterior cingulate

Table 7.1 (continued)

Study (author (year))	Subjects	Medication	Method	Main findings
Bauer et al. (2016)	25 BD (25 E)	+	^{18}FDG PET RCT treatment with levothyroxine	A significant decrease in regional activity was demonstrated in the left thalamus, right amygdala, right hippocampus, left ventral striatum, and the right dorsal striatum. Decreases in the left thalamus, left dorsal striatum, and the subgenual cingulate were correlated with a reduction in depression scores
Baxter et al. (1985)	5 BD (5 M, 2 Mi, 5 D) 11 MDD HC	+	^{18}FDG PET Resting state	The whole-brain CMR for patients with bipolar depression increased going from depression or a mixed episode to a euthymic state or manic episode
Baxter et al. (1989)	15 BD (10 D, 5 M) 10 MDD 10 OCD w/o D 14 OCD w/ D 12 HC	+	^{18}FDG PET Resting state	The results in CMR of the dorsal anterolateral PFC for MDD and BD D were the same, but lower than in controls
Benabarre et al. (2005)	43 BD (12 D, 3 E, 8 HM, 7 M) 6 HC	+/–	^{99m}Tc-HMPAO SPECT Resting state	Several corrected correlations between neuropsychological function and CBF were identified
Blumberg et al. (1999)	11 BD-I (6 E, 5 M) 5 HC	+	$H_2{}^{15}O$ PET Word generation, letter repetition, resting state	Decreased right rostral and orbital prefrontal cortex activation during word generation and decreased orbitofrontal activity during rest were associated with mania
Blumberg et al. (2000)	11 BD-I (6 E, 5 M) 5 HC	+	$H_2{}^{15}O$ PET Resting state	The principal findings were an increased activity in left dorsal anterior cingulate and left head of caudate during manic episodes
Bøen et al. (2019)	22 BD-II 22 BPD 21 HC	+	^{18}FDG PET Resting state	Reduced metabolism in the insula regions was shown in both disorders
Bonne et al. (1996)	9 BD (9 D) 11 MDD 21 HC	+	^{99m}Tc-HMPAO SPECT Resting state	Examining individual regions of interest significantly lower perfusion in the left superior temporal, right parietal, and bilateral occipital regions in the patient group was found

(continued)

Table 7.1 (continued)

Study (author (year))	Subjects	Medication	Method	Main findings
Brooks et al. (2006)	8 BD (8 D) 27 HC	–	^{18}FDG PET CPT	No statistically significant differences in performance in CMR between the two groups was found
Brooks et al. (2010)	10 BD-I 6 BD-II 11 HC	+	^{18}FDG PET Resting state	Relative to HC, in BD commission errors were more strongly related to inferior frontal gyrus hypometabolism and paralimbic hypermetabolism. Relative to HC, in BD omission errors were more strongly related to dorsolateral prefrontal hypometabolism and greater paralimbic, insula, and cingulate hypermetabolism
Buchsbaum et al. (1986)	16 BD (16 D) 4 MDD 24 HC	–	^{18}FDG PET Electrical stimulation to the forearm	Global cerebral metabolism was found to be significantly higher in subjects with affective ness (both unipolar and bipolar depressed) compared to normal controls
Caletti et al. (2017)	36 BD-I 27 PD	+	^{18}FDG PET Resting state	Patients with low insight, compared to those with high insight, showed decreased metabolism in the right fusiform gyrus, left precuneus, superior temporal gyrus, and insula bilaterally, as well as increased metabolism in the left orbitofrontal gyrus
Culha et al. (2008)	16 BD (16 E) 10 HC	+	^{99m}Tc-HMPAO SPECT Resting state	The mean regional cerebral blood flow values of the euthymic BD patients were significantly lower than those of the controls in the bilateral medial-basal temporal, occipital; medial frontal; parietal regions and in the cingulate gyrus
Drevets et al. (1997)	21 BD (9 D, 8 E, 4 M) 17 MDD 51 HC	+	^{18}FDG and $H_2{}^{15}O$ PET Resting state	An area of abnormally increased activity in the prefrontal cortex ventral to the genu of the corpus callosum in both familial bipolar depressives and familial unipolar depressives has been found after correction for grey matter volume
Drevets et al. (2002)	15 BD (7 D, 9 E) 21 MDD 12 HC	–	^{18}FDG PET Resting state	Amygdala activity, which was correlated with stress plasma cortisol levels, was increased in depressed BD patients. Mood stabilizers normalize the amygdala activity in remitted BD

Table 7.1 (continued)

Study (author (year))	Subjects	Medication	Method	Main findings
Dunn et al. (2002)	27 BD (27 D) 31 MDD	–	^{18}FDG PET Auditory CPT	In both MDD and BD, the psychomotor-anhedonia symptom cluster correlated with lower absolute metabolism in right insula, claustrum, anteroventral caudate/putamen, and temporal cortex, and with higher normalized CMR in anterior cingulate
Forlenza et al. (2014)	19 BD (12 Li, 7 non-Li)	+	^{18}FDG PET Resting state	Chronic lithium treatment was not associated with any significant increase in brain glucose metabolism in the studied areas. A significant reduction in glucose uptake in several clusters of the cerebellum and in both hippocampi was demonstrated
Goodwin et al. (1997)	14 BD (14 E)	+	^{99m}Tc-EMZ SPECT Lithium withdrawal	Lithium withdrawal was associated with an important redistribution of brain perfusion, with increases in inferior posterior regions and decreases in limbic areas, particularly ACC
Gyulai et al. (1997)	13 BD (7 HM, 2 M)	+	^{123}I-IMP SPECT Resting state	The CBF distribution in the anterior part of the temporal lobes was asymmetric in both depressive and manic but not in euthymic state. Images taken sequentially on the same patient showed temporal lobe asymmetry in the pathological mood states that diminished or disappeared in the euthymic state
Ito et al. (1996)	6 BD (6 D) 11 MDD 9 HC	+	^{99m}Tc-HMPAO SPECT Resting state	Significant decreases in CBF in the prefrontal cortices, limbic systems, and paralimbic areas were observed in both depression groups compared with the healthy control group
Ketter et al. (2001)	14 BD-I (11 D, 4 E) 29 BD-II (22 D, 7 E) 43 HC	–	^{18}FDG PET CPT	In bipolar depression a pattern of prefrontal hypometabolism was observed additionally a cerebello-posterior cortical normalized hypermetabolism was seen in all bipolar subgroups

(continued)

Table 7.1 (continued)

Study (author (year))	Subjects	Medication	Method	Main findings
Krüger et al. (2006)	9 BD-I (9 E) 9 HS	+	$H_2{}^{15}O$ PET Transient sadness induction	Common to all three groups with induced sadness were CBF increases in the dorsal/rostral anterior cingulate and anterior insula and decreases in the orbitofrontal and inferior temporal cortices. Distinguishing the groups were decreases in the medial frontal cortex in the patients but an increase in this region in the siblings
Li et al. (2012)	17 BD-I (17 E) 17 BD-II (17 E) 17 HC	+	^{18}FDG PET Resting state	No difference in attention and memory tests was found among these three groups. Brain PET analysis showed that BD-I patients (compared to BD-II patients) had significantly lower glucose uptake in the bilateral anterior cingulum, insula, striatum, and part of the prefrontal cortex, and higher glucose uptake in the left parahippocampus
Li et al. (2015)	20 BD (20 E) 20 HS 20 HC	+	^{18}FDG PET Resting state	A dysfunctional connection with intact glucose uptake was demonstrated in the dlPFC-amygdala circuit of the HS, which highlights a vulnerability in families with BD
Mah et al. (2007)	13 BD-II (13 D) 18 HC	+	^{18}FDG PET Resting state	CMR was increased in the bilateral amygdala, accumbens area, and anteroventral putamen, left orbitofrontal cortex, and right pregenual ACC in depressive patients versus healthy control subjects. Post hoc exploratory analysis additionally revealed increased metabolism in left parahippocampal, posterior cingulate, and right anterior insular cortices in depressive patients versus healthy control subjects
Nugent (2014)	21 BD (21 D)	+	^{18}FDG PET Ketamine or placebo	Subjects had significantly lower glucose metabolism in the left hippocampus following the ketamine infusion than following the placebo infusion

Table 7.1 (continued)

Study (author (year))	Subjects	Medication	Method	Main findings
Rubin et al. (1995)	11 BD-I (11 M) 11 MDD 11 HC	+	^{133}Xe SPECT Resting state	The three groups were equivalent in global CBF. Both patient groups showed significant reductions of CBF in anterior cortical areas and reduction of the normal anteroposterior gradient
Rubinsztein et al. (2001)	6 BD (6 M) 6 MDD 10 HC	+	$H_2{}^{15}O$ PET Probability-based decision-making task	Task-related activation was increased in the manic patients compared with the control patients in the left dorsal ACC but decreased in the right frontal polar region
Rush et al. (1982)	12 BD 16 HC		^{133}Xe SPECT Resting state	During manic episode global CBF was increased compared to HC
Silfverskiöld and Risberg (1989)	40 BD (10 D, 30 M) 22 MDD 61 HC	+/–	^{133}Xe SPECT Resting state	Both patient groups showed a normal cerebral blood flow level and regional distribution compared with age- and sex-matched normal controls
Tutus et al. (1998)	7 BD (7 D) 10 MDD 9 HC	+/–	^{133}Xe SPECT Between groups and before/after medication Resting state	No significant differences in CBF emerged between the BD patients and the healthy control subjects
Zhang et al. (2011)	20 BD-I 20 BD-II 20 HC	+	^{18}FDG PET	PBMC p11 mRNA expression is associated with CMR in the mPFC, aCC, left insula, bilateral orbitofrontal cortex (OFC), and left middle, inferior, and superior temporal gyri of BD patients

HS Healthy sibling, *D* Depressive episode, *E* Euthymic episode, *M* Manic episode, *HM* Hypomanic episode, *Mi* Mixed episode, *CPT* Continuous performance test, *ADT* Auditory discrimination task, *SUD* Substance use disorder, *SIP* Substance-induced psychosis, *PD* Psychotic disorder

and both are indeed closely correlated in healthy controls (Drevets 2000). This appeared also to be the case in BD. Dunn et al. (Dunn et al. 2005) demonstrated that CMR and CBF were coupled globally and in most regions in BD, except the left pregenual anterior cingulate cortex.

CMR can be investigated with an ^{18}F-labeled fluorodeoxyglucose (FDG) PET scan. CBF is measured in PET by ^{15}O-labeled water. The most common SPECT tracers to measure CBF are ^{133}Xe, ^{123}I-labeled iodoamphetamine (IMP) and ^{99m}Tc-labeled hexamethylpropylene amine oxime (HMPAO). CMR and CBF can be measured in resting state or during various tasks.

Across the whole-brain level, it remains unclear whether there is an overall global CMR and CBF change in BD when compared to healthy controls. When investigated across mood states, some studies found reduced global CMR (Baxter et al. 1985, 1989; Ketter et al. 2001), while in other studies, no alterations were found in CMR (Bauer et al. 2005; Brooks et al. 2006).

In depressed patients CMR was found to be reduced when compared to controls and manic patients in some studies (Baxter et al. 1985, 1989) but increased in another study (Buchsbaum et al. 1986). One study investigating CBF found an increased perfusion in manic patients compared to controls (Rush et al. 1982), but others did not find any difference between the different mood states (Silfverskiöld and Risberg 1989; Tutus et al. 1998).

7.2.2.1 Prefrontal Cortex

The prefrontal cortex (PFC) is the area of the frontal lobes of the cerebral cortex that is located before the motor and premotor areas. It plays an important role in executive functioning such as planning complex behavior, personality expression, decision-making, and moderating social behavior (Miller et al. 2002). Regions of the brain are defined as Brodmann areas (BA) based on their cytoarchitectonic structure.

In general, BD patients in a depressive or manic episode have a decreased prefrontal cortex CMR and CBF, compared to euthymic patients or healthy controls. Blumberg et al. found a reduced CBF in the right orbital PFC (BA 11) and medial frontal gyrus (BA 10) in manic patients when compared to euthymic patients (Blumberg et al. 1999). Euthymic patients demonstrated orbitofrontal CBF decrease (Culha et al. 2008). The healthy siblings of BD patients demonstrated a comparable CBF decrease in the orbitofrontal PFC during induced sadness (Krüger et al. 2006).

In manic patients, a decrease in dorsolateral PFC (BA 8, 9, 46) CBF has been demonstrated (Rubin et al. 1995; al-Mousawi et al. 1996). Manic patients also showed a decrease of CMR during a decision-making task in the ventrolateral PFC (BA 47) when compared to controls (Rubinsztein et al. 2001). Furthermore, euthymic older BD patients (50–65 years) had a lower CMR in this region than controls of the same age (Brooks et al. 2006).

7.2.2.2 Limbic System and Subcortical Structures

The limbic system is a combination of in origin different brain structures that are involved in visceral behavioral patterns (related to survival: eating, drinking, sexual activity), emotions, and memory. Some structures, such as the hippocampus, amygdala, and anterior thalamic nuclei, are phylogenetically rather old structures (hence the other name paleomammalian brain), while the septum, fornix and limbic cortex are more recently developed structures.

The limbic cortex consists of the parahippocampal gyrus (BA 34–36), the cingulate gyrus (BA 23–26; 29–33), the insula (BA 13), and the dentate gyrus, which are parts of the frontal, parietal. and temporal cortical lobes on the medial surfaces of both hemispheres, surrounding the corpus callosum. The anterior part of the cingulate gyrus, the anterior cingulate cortex (ACC, BA 24, 25, 32, 33), plays a role in

autonomic functions (regulating blood pressure, heart rate), rational cognitive functions (reward anticipation, decision-making, empathy), pain perception, and emotion (Luu and Posner 2003).

In BD patients with depressive or manic episodes, an increased CMR and CBF were demonstrated in various parts of the limbic system. In depressed BD patients, Drevets et al. found an increased CMR in the subgenual portion of the ACC (BA 25) when compared to controls, after correction for grey matter volume (Drevets et al. 1997). This finding was repeated both in treated (Bauer et al. 2005) and in untreated depressed patients (Dunn et al. 2002). Dunn reported an association between this CMR increase and the presence of psychomotor and anhedonia symptoms. A similar increase in CMR was demonstrated in the pregenual and ventral area (BA 33, 24) of the ACC (Mah et al. 2007), whereas a decreased CMR was demonstrated in the insula (Bøen et al. 2019). Decreased CMR in the right fusiform gyrus, the left precuneus, superior temporal gyrus, and the insula bilaterally was associated with low insight (Caletti et al. 2017).

In manic patients, an increase in CBF, in the subgenual portion of the ACC (BA 25), was described compared to controls (Drevets et al. 1997). This increase was also found in the left dorsal ACC (BA 32) when compared to euthymic patients (Blumberg et al. 2000). In the manic patients, CMR during a decision-making task was increased in the left dorsal ACC, when compared with controls (Rubinsztein et al. 2001). In untreated manic patients, a SPECT study showed that increased cingulate cortex CBF is associated with poor executive functioning (Benabarre et al. 2005).

Goodwin et al. (Goodwin et al. 1997) examined 14 euthymic patients on lithium with SPECT before and after acute double-blind withdrawal of lithium. As often seen clinically, rapid withdrawal was associated with an increase of manic symptoms. The increase of manic symptoms correlated with a CBF decrease in the limbic areas, particularly the ACC.

Euthymic patients also demonstrated ACC CBF aberrations (Culha et al. 2008). The healthy siblings of BD patients demonstrated an comparable CBF increase in the ACC during induced sadness (Krüger et al. 2006). In another study in euthymic BD patients, p11 expression in peripheral blood mononuclear cells associated with CMR in the mPFC, aCC, left insula, bilateral orbitofrontal cortex (OFC), and left middle, inferior, and superior temporal gyri (Zhang et al. 2011). p11, also known as S100A10, is protein that belongs to a family of proteins that regulate a number of cellular processes such as cell cycle progression and differentiation. It is linked with the transport of neurotransmitters and found in the brain of humans and other mammals; it has been implicated in the regulation of mood (Hedhli et al. 2012).

The amygdala, part of the limbic system, is one of the subcortical areas that is known to be involved in BD. Others are the nucleus accumbens, globus pallidus, and striatum (including nucleus caudatus), all part of the basal ganglia of the brain that play a role in higher-order motor control. Individually they are involved in different functions, the nucleus accumbens in the reward circuitry, nucleus caudatus in learning and memory, particularly regarding feedback processing, and the globus pallidus in visceral regulation such as fever induction and emotion-induced tachycardia (Packard and Knowlton 2002).

Initially, studies of depressed BD patients versus controls described a reduced CMR in the amygdala (al-Mousawi et al. 1996) as well as the striatum (Baxter et al. 1985; Bonne et al. 1996; Ito et al. 1996). However, thereafter, various PET studies in depressed patients showed increased activity in the striatum, together with increased activity in limbic structures including the amygdala, hippocampus, and parahippocampal regions (Ketter et al. 2001; Drevets et al. 2002; Bauer et al. 2005; Mah et al. 2007; Brooks et al. 2009; Altamura et al. 2017). Additionally, amygdala and ventral striatal CMR correlated positively with depression severity and with cortisol levels (Ketter et al. 2001; Drevets et al. 2002). The difference between these initial and later studies is most probably explained by a higher signal quality and more careful patient selection in the later studies (Gonul et al. 2009).

Bipolar depression-related anxiety was found to respond to levothyroxine (Bauer et al. 2010, 2016). Change in anxiety covaried positively with changes in relative CMR in right amygdala and hippocampus. Change in state anxiety covaried positively with changes in relative CMR in the hippocampus bilaterally and left thalamus and negatively with changes in left middle frontal gyrus and right dorsal anterior cingulate (Bauer et al. 2010).

High CMR or CBF was also observed in the nucleus caudatus in manic patients (Blumberg et al. 2000) and nucleus accumbens in depressed patients (Benabarre et al. 2005).

7.2.2.3 Other Cortical Regions

An asymmetric CBF was found in the anterior temporal cortex in manic and depressed patients but not when the patients were euthymic (Gyulai et al. 1997). In a more recent study, it was demonstrated that euthymic older BD patients (50–65 years) have a higher CMR in this region than controls of the same age (Brooks et al. 2009). Furthermore, CBF in the temporal cortex of BD patients was positively associated with executive functions but negatively with attention and memory (Benabarre et al. 2005).

7.2.2.4 Corticolimbic Theory of Mood Disorders

Partly based on the above mentioned molecular imaging results, complemented with functional MRI (fMRI) research, a meta-analysis displays an overall hyperactivation of limbic brain regions in BD patients relative to controls, along with an overall hypoactivation of frontal regions (Kupferschmidt and Zakzanis 2011). This corresponds to findings in other mood disorders, especially MDD, which is known as the corticolimbic theory of depression (Mayberg 1997). Hypo- and hyperactivity in frontal and limbic regions, respectively, was most pronounced in manic patients, although also present in depressed and euthymic ones. Depressed patients exhibit more pronounced hypoactivation of frontal regions than euthymic patients, whereas euthymic patients display, surprisingly, more hyperactivity in limbic regions than their depressed counterparts.

CMR activation related to a decision-making task was decreased in manic patients in the PFC (Rubinsztein et al. 2001). Corticolimbic metabolic disbalance

was found to be negatively associated with cognitive functioning, including executive functioning and attention in two other studies (Brooks et al. 2010; Li et al. 2012).

The corticolimbic theory has some overlap with several neurological networks that have been described and are thought to lay at the basis of physiological emotional processing. These networks can be divided into circuits that lay within the cerebral cortex and those that exceed to other parts of the brain (Price and Drevets 2010).

The limbic-cortical-striatal-pallidal-thalamic (LCSPT) circuit connects the PFC to the limbic and subcortical areas of the brain (al-Mousawi et al. 1996). This LCSPT circuit is thought to be particularly important to mediate emotional expression, because of its relation to visceral control structures (Drevets et al. 2008).

The mood-related cortico-cortical networks interact with and extend to the LCSPT (Ongür et al. 2003) via top-down inhibitory control (Savitz and Drevets 2009). The orbital prefrontal network consists of the central and caudal part of the orbital cortex and the ventrolateral PFC, and it includes sensory association areas such as the visual-associated areas in the inferior temporal cortex and somatic sensory-associated areas in the insula and frontal operculum, as well as olfactory and taste cortex. In addition to sensory integration, this system codes for affective characteristics of stimuli such as reward, aversion, and relative value (salience) (Drevets et al. 2008).

The medial prefrontal network of cortical areas includes the ventromedial PFC, the dorsolateral PFC, the anterior and posterior cingulate cortex, anterior temporal cortex, and the entorhinal and posterior parahippocampal cortex. This system does not have substantial sensory connections, but is a visceromotor system that is particularly involved in introspective functions such as mood and emotion and visceral reactions to emotional stimuli (Price and Drevets 2010). It is widely known as the "default system," because it appeared activated as a network of areas that become inactive in most tasks that involve external attention in fMRI imaging (Gusnard et al. 2001). It has been proposed that the "ventral" orbital prefrontal network and the "dorsal" medial prefrontal network are reciprocally connected and that the orbital PFC may mediate connections between higher-order dorsolateral prefrontal regions and subcortical limbic regions such as the amygdala during emotion regulation (Phillips et al. 2008).

Corticolimbic functional disconnection has been demonstrated in both patients with BD and their healthy siblings. But only in patients, not in healthy siblings, was this associated with CMR aberrations (Li et al. 2015).

7.2.3 Neurotransmitter Studies

Departing from the neurotransmitter theory of affective disorders (Schildkraut 1965). PET/SPECT radioligand studies have focused on the serotonergic, dopaminergic, and cholinergic systems (Table 7.2).

Table 7.2 Overview of PET/SPECT studies on neurotransmitter systems in BD patients

Neurotransmitter	Study (author (year))	Subjects	Medication	Target	Method	Main findings
Serotonin	Yatham et al. (2005b)	7 BD (7 M)	+	5-HT_2	^{18}F-setoperone PET Valproate treatment	Treatment with valproate had no significant effect on brain 5-HT_{2A} receptor binding in manic patients
	Yatham et al. (2010)	10 BD (10 M) 10 HC	+	5-HT_2	^{18}F-setoperone PET	Brain 5-HT2 receptors are decreased in patients with acute mania
	Lan et al. (2013)	41 BD (41 D)	–	5-HT_{1A}	[^{11}C]WAY-100635 PET	Higher pretreatment brain 5-HT_{1A} receptor binding was associated with remission after 3 months of pharmacological treatment in bipolar depression
	Sargent et al. (2010)	8 BD (8 E) 8 HC	+	5-HT_{1A}	[^{11}C]WAY-100635 PET	No difference in 5-HT_{1A} receptor binding between medicated euthymic bipolar patients and healthy controls
	Nugent et al. (2013a)	10 BD (10 D)	+	5-HT_{1A}	[^{18}F]FCWAY PET valproate treatment, lithium treatment	Mean 5-HT_{1A} binding potential increased following mood stabilizer treatment, most prominently in the hippocampus and amygdala
	Nugent et al. (2013b)	26 BD 37 HC	–	5-HT_{1A}	[^{18}F]FCWAY PET	5-HT_{1A} receptor binding potential was lower in BD subjects compared to HC in cortical regions where 5-HT_{1A} receptors are expressed postsynaptically, most prominently in the mesiotemporal cortex. Across subjects the BPP in the mesiotemporal cortex was inversely correlated with plasma cortisol levels
	Ichimiya et al. (2002)	6 BD (1 D, 5 E) 7 MDD 21 HC	–	SERT	^{11}C(+)-McNeil 5652 PET	Binding potential in the thalamus was significantly increased in patients with mood disorders as compared to control subjects, whereas binding potential in the midbrain did not differ between the groups
	Oquendo et al. (2007)	18 BD (18 D) 41 HC	–	SERT	^{11}C(+)-McNeil 5652 PET	BD patients had 16–26% lower SERT density in the midbrain, amygdala, hippocampus, thalamus, putamen, and ACC

	Chou et al. (2010)	10 BD-I 14 BD-II 28 HC	–	SERT	^{123}I-ADAM SPECT	A lower SERT density was found in de midbrain of euthymic BD-I patients when compared to euthymic BD-II patients and healthy controls
	Chou et al. (2012)	23 BD-I (23 E) 23 HC	–	SERT	^{123}I-ADAM SPECT	A lower SERT density was found in de midbrain of euthymic BD-I patients when compared healthy controls. No correlation with BDNF was found
	Chou et al. (2015)	28 BD 28 HC	–	SERT	^{123}I-ADAM SPECT	Cortisol was associated with SERT availability in the midbrain in the HCs, but not in BD
	Hsu et al. (2014)	20 BD (20 E) 20 HC	–	SERT	^{123}I-ADAM SPECT	SERT availability was significantly lower in the midbrain and caudate of patients with BD compared with HC, but not in the thalamus and putamen. There was a significant association of SERT availability and IL-10 in the thalamus, but not in the midbrain, caudate, or putamen
	Cannon et al. (2006b)	18 BD (18 D) 37 HC	–	SERT	^{11}C-DASB PET	In BD, the mean SERT BP was increased in thalamus, dorsal cingulate cortex (DCC), medial prefrontal cortex, and insula and decreased in the brain stem at the level of the pontine raphe nuclei when compared to controls
	Cannon et al. (2007)	18 BD (18 D) 18 MDD 34 HC	–	SERT	^{11}C-DASB PET	Relative to the healthy group both MDD and BD groups showed significantly increased 5-HTT BP in the thalamus (24%, 14%, respectively), insula (15%), and striatum (12%). The bipolar depressives had reduced 5-HTT BP relative to both HC and MDD groups in the vicinity of the pontine raphe nuclei
	Miller et al. (2016)	17 BD (17 D) 31 HC	–	SERT	^{11}C-DASB PET	No abnormal SERT binding in bipolar depression using V_T/f_P
Dopamine	Pearlson et al. (1995)	14 BD (3 D, 11 M) 10 SZ 12 HC	–	D_2	^{11}C-3-N-methylspiperone PET	No statistical difference in D_2-binding was found between nonpsychotic BD patients and controls. Post hoc tests showed higher binding for psychotic patients with BD and SZ compared with controls and for SZ and psychotic BD patients compared to nonpsychotic BD patients

(continued)

Table 7.2 (continued)

Neurotransmitter	Study (author (year))	Subjects	Medication	Target	Method	Main findings
	Anand et al. (2000)	13 BD (13 E) 13 HC	+	D_2	^{123}I-IZBM SPECT Baseline, after amphetamine induction	BD patients and healthy subjects did not differ in terms of mood state or striatal D_2-receptor binding at baseline. Amphetamine challenge led to a significantly greater behavioral response in BD patients than in healthy subjects. However, there was no significant difference between the two groups in the amphetamine-induced decrease in striatal binding
	Jauhar et al. (2017)	22 BD 16 SZ 22 HC	+	DOPA uptake	^{18}F-DOPA PET	Dopamine synthesis capacity in the striatum was elevated in the psychotic BD and the SCZ group, compared with HC
	Yatham et al. (2002b)	13 BD-I (13 M) 14 HC	–	DOPA uptake	^{18}F-DOPA PET Baseline, after valproate treatment	No significant differences in ^{18}F-DOPA uptake rate constants in the striatum were found between the manic patients and the comparison subjects. After treatment with valproate, ^{18}F-DOPA rate constants were significantly reduced in the patients and were lower in the patients than in the comparison subjects
	Suhara et al. (1992)	10 BD (3 D, 6 E, 1 M) 21 HC	+	D_1	^{11}C-SCH23390	The binding potentials for the frontal cortex for the patients were significantly lower than those for normal controls, whereas those for striatum were not significantly different
	Yatham et al. (2002a)	13 BD-I (13 M) 14 HC	–	D_2	^{11}C-raclopide PET Baseline, after valproate treatment	The D_2 binding potential was not significantly different in manic patients than in the comparison subjects in the striatum. Treatment with valproate had no significant effect on the D2 binding potential in manic patients
	Amsterdam and Newberg (2007)	5 BD-II (5 D) 10 MD 46 HC	–	DAT	^{99m}Tc-TRODAT-1 SPECT	BD patients had greater binding compared to controls in the right posterior putamen and in the left caudate region. BD patients had modestly lower binding in all brain regions examined and a significantly lower binding in the right caudate region compared to MDD patients

	Chang et al. (2010)	17 BD (17 E) 17 HC	–	DAT	^{99m}Tc-TRODAT-1 SPECT	Compared to the controls, the euthymic BD patients had significantly higher availability of striatal DAT
	Anand et al. (2011)	11 BD-I (6 D; 5 E) 13 HC	–	DAT	^{11}C-CFT PET	BPD subjects had significantly lower DAT availability relative to controls in bilateral dorsal caudate
	Zubieta et al. (2001)	15 BD-I (15 E) 12 SZ 15 HC	+	VMAT	^{11}C-DTBZ PET	Binding of VMAT2 in the thalamus was higher in BD patients than in control subjects and SZ patients. Conversely, ventral brain stem binding was nearly identical between BD and SZ patients and was higher than in the control group
Norepinephrine	Yatham et al. (2018)	5 BD (5D) 5 MDD (5D) 9 HC	+	NET	(S,S)-[^{11}C]O-methyl reboxetine PET	NET density was significantly lower in locus ceruleus in MDD and BD patients compared with HC
Choline	Cannon et al. (2006a)	16 BD (16 D) 17 MDD 23 HC	–	mAChR M_2	^{18}F-FP-TZTP PET	Receptor binding was found to be decreased in the ACC of BD patients when compared to MDD patients and controls
	Cannon et al. (2011)	16 BD (16 D) 24 MDD 25 HC	–	mAChR M_2	^{18}F-FP-TZTP PET	Decreased receptor binding in BD-Is associated with genetic variation within CHRM2
	Hannestad et al. (2013)	25 BD (15 D, 10 E) 25 HC	+	nAChR β2	[^{123}I]5IA-85,380 PET	Lower receptor availability in subjects with bipolar depression compared with euthymic and control subjects across frontal, parietal, temporal, and anterior cingulate cortex, hippocampus, amygdala, thalamus, and striatum

HS Healthy sibling, *D* Depressive episode, *E* Euthymic episode, *M* Manic episode, *HM* Hypomanic episode, *Mi* Mixed episode, *CPT* Continuous performance test, *ADT* Auditory discrimination task

7.2.3.1 Serotonin

Serotonin (5-hydroxytryptamine) is a monoamine neurotransmitter that is formed out of the amino acid tryptophan. It is mainly found in the gastrointestinal tract, where its secreting cells regulate intestinal movement, in platelets, where it is released during aggregation, and in the central nervous system. Serotonin has a regulatory effect with regard to mood, sleep, sexual activity, and appetite.

The neurons located in the raphe nuclei, a cluster of nuclei in the brain stem, are the main source of serotonin in the brain. The axons from the raphe nuclei neurons project to nearly every part of the central nervous system. After serotonin is released in the synaptic cleft, it can bind to one of the various receptors, or it can be removed for reuse by the presynaptic neuron via the serotonin transporter.

As the primary site of serotonergic antidepressant activity, the serotonin transporter (SERT) is the part of the serotonin neurotransmitter system that has received the most attention in molecular imaging. Among the various ligands that are available, the PET ligands *trans*-1,2,3,5,6,10- -hexahydro-6-[4-(methylthio) phenyl] pyrrolo-[2,1-a] isoquinoline (^{11}C(+)-McNeil 5652), 3-^{11}C-amino-4-(2-dimethylam inomethylphenylsulfanyl)benzonitrile (^{11}C-DASB), and the SPECT ligand 2-([2-([dimethylamino]methyl)phenyl]thio)-5-^{123}I-iodophenylamine (^{123}I-ADAM) are used in BD research. An increase of SERT density was found in the thalamus using ^{11}C(+)-McNeil 5652 in a combined group of euthymic or mildly depressed patients (Ichimiya et al. 2002) and a reduction in the midbrain, hippocampus, thalamus, putamen, and ACC in a group of untreated depressed patients (Oquendo et al. 2007). With the use of ^{123}I-ADAM SPECT, a lower SERT density was found in de midbrain of euthymic BD-I patients when compared to euthymic BD-II patients and healthy controls (Chou et al. 2010, 2012, 2016; Hsu et al. 2014). This lower SERT density was not associated with changes of brain-derived neurotrophic factor (BDNF) (Chou et al. 2012). Using the more stable and selective ^{11}C-DASB ligand, an increased SERT density was found in the thalamus, dorsal cingulate cortex, medial prefrontal cortex, and insula of depressed untreated BD patients in some studies (Cannon et al. 2006b, 2007), but not all (Miller et al. 2016).

Although the results are inconsistent, it can be concluded that serotonin transporter alterations occur in BD, especially in parts of the limbic system. Taking the regulatory function and the observed metabolic changes into account, the SERT density alterations may be interpreted as an exponent of a dysfunctional frontolimbic network. It furthermore suggests that there might be (yet to be identified) modulators of gene expression or that other effects, such as serotonin transporter internalization, occur during different mood states.

At the level of the postsynaptic receptors a study using ^{18}F-setoperone demonstrated 5-HT$_2$ receptors to be decreased in patients with acute mania (Yatham et al. 2010). In another study investigating the treatment effect of valproate on the 5-HT$_2$-receptor binding, no difference before or after treatment in manic patients was found (Yatham et al. 2005b). 5-HT$_{1A}$ receptor binding potential was lower in BD subjects compared to healthy controls in mesiotemporal cortical regions (Nugent et al. 2013a, b). This binding potential correlated inversely with plasma cortisol levels (Nugent et al. 2013a) and increased with mood stabilizer treatment (Nugent

et al. 2013b). Also higher pretreatment 5-HT_{1A} receptor binding was associated with remission after 3 months of pharmacological treatment in bipolar depression (Lan et al. 2013). However, in another study no difference in 5-HT_{1A} receptor binding between medicated euthymic bipolar patients and healthy controls could be found (Sargent et al. 2010).

7.2.3.2 Dopamine

Dopamine is a catecholamine neurotransmitter that is formed out of L-DOPA, which in turn is made out of the amino acid tyrosine, while dopamine itself is the precursor of norepinephrine and epinephrine. A dopaminergic imbalance plays an important role in Parkinson's disease and psychotic symptomatology (psychotic symptoms during mood episodes and schizophrenia (SZ) (Beaulieu and Gainetdinov 2011). Additionally it is thought to be of importance in mania because of the antimanic effect of dopamine receptor blockers (antipsychotics) and the mania producing effect of dopamine-inducing substances, such as amphetamines (Cousins et al. 2009).

Five subtypes of dopamine receptors are known. The D_1-like family consists of D_1 and D_5 receptors, which lead to the stimulation of intracellular adenylate cyclase upon activation, causing cAMP to rise. The D_2-like family consists of D_2, D_3, and D_4 receptors, which lead to the inhibition of intracellular adenylate cyclase upon activation, causing cAMP to decrease. Overall, the D_1-receptor and D_2-receptor are the most abundant dopamine receptor subtypes in the brain, with particularly high expression in the striatum and nucleus accumbens and lower levels in the olfactory tubercle. The D_2-receptor is the prominent receptor in the substantia nigra, a region where the D_1-receptor is absent (Hartman and Civelli 1996).

After release into the synaptic cleft and having its neurotransmitting effect via the receptors, dopamine is pumped back into the cytosol of the presynaptic neuron by the dopamine transporter (DAT) from where it can be broken down by enzymes or be reused in synaptic vessels via the vesicular monoamine transporter 2(VMAT2) (Little et al. 2003).

Parts of the dopaminergic neurotransmission than can be examined with molecular imaging are the various dopamine receptors, dopamine release, and the dopamine transporter. These in turn can be investigated during resting state or after an amphetamine challenge (stimulating dopamine release).

The D_2-receptor is an obvious research target because of the known effectiveness of D_2-receptor blocking antipsychotic medication on manic and psychotic symptoms (Yildiz et al. 2011). Radioligands targeting this receptor are benzamides, such as raclopride and iodobenzamide, and butyrophenones, such as methylspiperone. The binding potential of the benzamides is known to fluctuate with changing endogenous dopamine concentrations, e.g., after amphetamine challenge. It is proposed that benzamides and butyrophenones do not bind to the same configuration of theD_2-receptor. Butyrophenones may bind primarily to the monomer form, whereas benzamides may bind to both the monomer and dimer forms of the receptor (Ginovart 2005).

In untreated nonpsychotic manic patients studies with the butyrophenone methylspiperone (Wong et al. 1985; Pearlson et al. 1995) and the benzamides

iodobenzamide and raclopride (Anand et al. 2000; Yatham et al. 2002) did not find striatal D_2-density difference compared to controls. Pearlson et al. however, did find a higher D_2-recepter density in the caudate nucleus of BD patients with psychotic features during their depressive or manic episodes when compared to BD patients during episodes without psychotic features (Pearlson et al. 1995). Within the group with psychotic features, the severity of the psychotic symptoms correlated with the receptor density, which was not the case with severity of mood symptoms. This suggests that the D_2-receptor density is specifically related to psychosis but not to mood symptoms. This theory is further supported by the finding that D_2-receptor density in the striatum was elevated in both psychotic BD and SZ patients, compared to HC (Jauhar et al. 2017), and the observation that the mood stabilizing anti-epileptic valproate sodium did not alter the D_2-receptor density in nonpsychotic manic patients (Yatham et al. 2002).

Concerning the D_1-recepter, Suhara et al. (Suhara et al. 1992) found the binding potential of SCH23390 to be decreased in the frontal cortex of BD patients with various mood states when compared to controls. In the striatum, results were comparable among patients and controls.

Dopamine synthesis can be investigated by measuring the striatal uptake of ^{18}F-labeled 6-fluoro-L-DOPA, which is a precursor to dopamine, as described above. Dopamine synthesis was found to be comparable among untreated nonpsychotic manic patients and controls. In view of the finding that valproate did not change D_2-receptor density, it is interesting that valproate was able to reduce dopamine synthesis in effectively treated manic patients (Yatham et al. 2002a, b). Perhaps the valproate-induced reduction of dopamine synthesis might be explained by an improved function of the PFC and fronto-limbic network resulting in an enhanced regulation of dopamine in the striatum.

Endogenous dopamine release can be measured with an amphetamine challenge, in which dopamine release is stimulated by blocking sequestering via DAT and VMAT2 and inhibiting the breakdown enzyme monoamine oxidase (MOA). In BD amphetamine challenge elicited a greater behavioral response, as measured with the Brief Psychiatric Rating Scale (BPRS) and the Young Mania Rating Scale (YMRS) in BD patients compared to controls. However, a difference between D_2-receptor binding potential of ^{123}I-iodobenzamide between these groups was not found (Anand et al. 2000). Because it is known that benzamide binding can fluctuate during amphetamine-induced endogenous dopamine binding, it cannot be ruled out that BD patients may have a more sensitive dopamine system to challenges with stimulants and treatment with mood stabilizers (Gonul et al. 2009).

In recent years the DAT gained scientific attention because it is hypothesized that some of the efficacy of mood stabilizing medication may be due to their action on DAT (Yatham et al. 2005a). In SPECT studies using ^{99m}Tc TRODAT-1 DAT density was increased in the right posterior putamen and in the left caudate in depressive BD-II patients (Amsterdam and Newberg 2007) and in the striatum of euthymic BD-I and BD-II patients (Chang et al. 2010). However, in untreated BD-I patients, a study using [O-methyl-^{11}C]β-CFT (^{11}C-CFT) PET showed decreased DAT density in the bilateral dorsal caudate. These contradictive results may be explained by

differences in patient groups (BD-I versus BD-II) and the difference in spatial resolution between SPECT and PET (Anand et al. 2011).

Using the (+)-α-^{11}C-dihydrotetrabenazine (^{11}C-DTBZ) ligand, an elevated VMAT2 density was found in the thalamus and ventral striatum in euthymic BD patients with a history of psychotic symptoms, which was comparable to SZ patients, but differed from controls (Zubieta et al. 2001), This would suggest a relation with psychotic symptoms in BD; however, in the absence of research describing the VMAT2 density in BD patients without psychosis, a relation with affective symptoms cannot be ruled out.

Overall, it can be assumed that altered dopamine neurotransmission plays a disease modifying role, especially in BD patients that experience psychotic symptoms in addition to affective symptomatology. However, dopamine neurotransmission as a pathophysiological mechanism in nonpsychotic BD patients needs further research.

7.2.3.3 Norepinephrine

Norepinephrine, also called noradrenaline or noradrenalin, is an organic chemical in the catecholamine family that is formed out of dopamine and functions in the brain and body as a hormone and neurotransmitter. Norepinephrine is the main neurotransmitter used by the sympathetic nervous system, which consists of about two dozen sympathetic chain ganglia located next to the spinal cord, plus a set of prevertebral ganglia located in the chest and abdomen. It is a neuromodulator of the peripheral sympathetic nervous system but is also present in the blood, mostly through "spillover" from the synapses of the sympathetic system. The noradrenergic neurons in the brain form a neurotransmitter system, that, when activated, exerts effects on large areas of the brain. The effects are manifested in alertness, arousal, and readiness for action.

In BD, quetiapine is effective in treating depressive symptoms, and although the underlying mechanisms are not yet completely understood, norquetiapine has high affinity for the norepinephrine transporter. Using (S,S)-[^{11}C]O-methylreboxetine, the norepinephrine transporter occupancy was found to be decreased in BD and MDD patients, compared to healthy controls, providing support for the hypothesis that norepinephrine transporter occupancy by norquetiapine may play a role in the antidepressant effect of quetiapine (Yatham et al. 2018).

7.2.3.4 Choline

Acetylcholine is a neurotransmitter in both the peripheral nervous system and central nervous system. In the central nervous system, it has a variety of effects as a neuromodulator upon plasticity (specifically in learning and memory), salience of sensory stimuli, arousal, and reward.

Interestingly, cholinesterase inhibitors were found to increase depressive symptoms in BD and MDD patients (Dilsaver 1986).

Muscarinic type 2 receptor binding was decreased in the ACC of depressed BD patients when compared to MDD patients and controls, using 3-(3-(3-[^{18}F]flouropropyl)thio)-1,2, 5-thiadiazol-4-yl)-1,2,5,6-tetrahydro-1-methylpyridine (^{18}F-FP-TZTP)

(Cannon et al. 2006a). This decrease in muscarinic type 2 receptor binding in BD patients was associated with a genetic variation in cholinergic muscarinic-2 receptor gene (Cannon et al. 2011). Furthermore, the depression and anxiety severity in BD patients were negatively correlated with the binding potentials, emphasizing a contribution of the cholinergic neurotransmitter system in BD pathophysiology.

Lower nicotinic β2 receptor availability was demonstrated using [^{123}I]5IA-85380 PET in subjects with bipolar depression compared to euthymic and control subjects across frontal, parietal, temporal, and anterior cingulate cortex, hippocampus, amygdala, thalamus, and striatum (Hannestad et al. 2013).

7.3 Other Pathophysiological Models

Besides the abovementioned corticolimbic theory and the neurotransmitter theory, several other pathophysiological theories have been proposed for BD. Of these, we will address the neuroinflammation theory, the white matter tract integrity disruption theory, and the mitochondrial dysfunction theory to illustrate the even broader neuroimaging field in this type of BD research. These theories provide starting points for future molecular imaging research.

7.3.1 Neuroinflammation

The "macrophage theory of depression" postulates an aberrant pro-inflammatory state of monocytes/macrophages in patients with mood disorder and considers this aberrant state of the cells as a driving force behind the illness (Smith 1991). The theory is based on a higher frequency of autoimmune diseases in mood disorders, aberrant pro-inflammatory cytokines, and elevated pro-inflammatory gene expression in monocytes.

Autoimmune thyroiditis is considered to be an endophenotype of BD (Vonk et al. 2007). Patients with BD and MDD have a raised prevalence of autoimmune thyroiditis (Carta et al. 2004; Bunevicius et al. 2007). Not only BD patients but also their offspring (affected as well as non-affected) and their monozygotic (affected and non-affected) and dizygotic (affected, but not as much unaffected) co-twins have a raised prevalence of autoimmune thyroiditis (Hillegers et al. 2005; Vonk et al. 2007). It was hypothesized that an activated inflammatory response system in monocytes constitutes the shared genetic susceptibility factor for both BD and thyroid autoimmunity, leading to the extensive investigations of neopterin, IL-1β, IL-6, and TNF-α in mood disorders. With regard to the serum concentration of these compounds, increased levels were also described in BD when compared to controls, and concentrations of individual compounds were found to be associated with mood state (Rowland et al. 2018). To investigate the pro-inflammatory state of monocytes in a more precise and robust manner, a Q-PCR analyses of CD14+ purified monocytes were performed in which 22 mRNAs for inflammatory, chemokinesis/motility, cell survival/apoptosis, and MAP kinases pathway molecules were found to

have an increased expression in BD patients compared to controls (Padmos et al. 2008).

Interactions between the immune system and the HPA-axis, as well as interactions between the immune system and the neuronal system via indoleamine 2,3 dioxygenase (IDO) pathways, have been suggested to result in mood disorder symptomatology. The HPA-axis is a complex set of direct influences and feedback interactions among the hypothalamus, the pituitary gland, and the adrenal glands that controls reactions to stress and regulates many body processes. The adrenal glands produce cortisol, which is a major stress hormone and has effects on many tissues in the body, including the brain where it binds to glucocorticoid receptors in the PFC, the amygdala, and the hippocampus (Spijker and van Rossum 2012). Moreover, glucocorticoid insensitivity has been associated with a higher risk on developing an depressive episode (Spijker and van Rossum 2012). In various in vivo and ex vivo studies, a strong association between the activation of the inflammatory response system and glucocorticoid insensitivity has been demonstrated, linking at least in part the overproduction of pro-inflammatory cytokines to the HPA-axis disturbances in major mood disorders (Almawi et al. 1991; Pariante et al. 1999; Ito et al. 2006).

Molecular imaging techniques are of added importance in investigating the neuroinflammation theory. Microglia are the central cells involved in immune regulation in the brain. These cells present the peripheral benzodiazepine receptor (PBR) on their mitochondrial membrane, when activated (Doorduin et al. 2008). Using translocator protein (TSPO) targeting PET ligands, such as ^{11}C-PK11195 and ^{11}C-PRB28, areas of microglia activation in the brain can be visualized. Using [^{11}C]-(R)- PK11195, in BD we demonstrated a statistically significant increased binding potential in the right hippocampus and a, similar but trend level, increased binding potential in the left hippocampus of BD-I patients as compared to healthy controls. This is indicative of microglial activation (Haarman et al. 2014). In the subsequent explorative analyses, we identified a positive association between microglial activation and the NAA + NAAG concentration in the left hippocampus, indicating a positive relation between microglial activation and neuronal integrity in vivo (Haarman et al. 2015). In another study, using ^{123}I-ADAM SPECT, a significant association of SERT availability and peripheral blood IL-10, an anti-inflammatory cytokine, was demonstrated in the thalamus (Hsu et al. 2014).

7.3.2 White Matter Tract Integrity Disruption

Interest in the white matter tracts in BD started with the observation of diffuse cortical and callosal white matter pathology in structural MRI studies in BD patients (Kempton et al. 2008; Vita et al. 2009). With the development of diffusion tensor imaging (DTI), a MRI technique allowing for the investigation of the preferred direction and rate of water diffusion, the integrity of the white matter tracts can be investigated in more detail, because in the physiological situation water diffusion is restricted by the axonal structures (Le Bihan 1996). The main parameters derived

from DTI are the fractional anisotropy (FA) and mean diffusivity (MD). MD measures the magnitude of water molecule diffusion and FA is an index of the degree of directionality of water diffusivity. FA is reduced in diseased states known to be associated with axonal loss and destruction of myelin sheaths in several diseases, e.g., multiple sclerosis, leukoencephalopathies and Alzheimer's disease (Le Bihan 2003).

In BD most studies reported reduced FA and/or elevated MD compared to controls involving the prefrontal lobe frontal lobe, corpus callosum, internal capsule, uncinate fasciculus, and superior and inferior longitudinal fasciculi and suggesting a role for white matter integrity disruption in BD pathophysiology (Heng et al. 2010).

The studies focusing on the specific mood states of BD patients revealed FA to be altered in the different mood states (Zanetti et al. 2009). In the euthymic state, FA was usually found to be increased in the genu of corpus callosum, internal capsule, anterior thalamic radiation, and uncinate fasciculus compared to controls, whereas during depressive episodes, a lower FA has been shown in the genu of the corpus callosum and in corona radiate compared to controls. In mixed samples higher and lower FA values were found in different brain regions (Bellani and Brambilla 2011).

The place of white matter integrity disruption with regard to other disease mechanisms in the pathophysiology is a matter of ongoing investigation. It has been suggested that FA changes, in analogy to multiple sclerosis (Zanetti et al. 2009), could be related to inflammation-related processes in BD or metabolic dysregulation (Altamura et al. 2013).

7.3.3 Mitochondrial Dysfunction

Using various different techniques, scientific evidence for a cellular energy metabolism disturbance has been presented. When observed in cell biological research, abnormal mitochondrial morphology is often linked to altered energy metabolism. In BD patients mitochondria were smaller and concentrated proportionately more within the perinuclear region than in distal processes of the cells, when compared to controls (Cataldo et al. 2010). Conversely, patients with mitochondrial diseases have a higher lifetime prevalence of MDD (54%) or BD (17%) than the average population (Fattal et al. 2007).

Magnetic resonance spectroscopy (MRS) is a neuroimaging technique that allows the investigation of the metabolism on a cellular level. It is a MRI technique that provides additional biochemical information of a selected voxel compared to a regular T1 or T2 image. The cellular metabolites are presumed to represent different cell functions: N-acetyl-aspartate (NAA) relates to cell viability, choline to cell membrane phospholipids integrity and creatine is a measure of cellular metabolism (Gillard et al. 2004). Creatine plays an important role as a cell energy buffer, especially in high-energy consuming cells such as muscular and brain cells. Using the creatine energy buffer reaction (Fig. 7.2), cells with an abundance of ATP can store

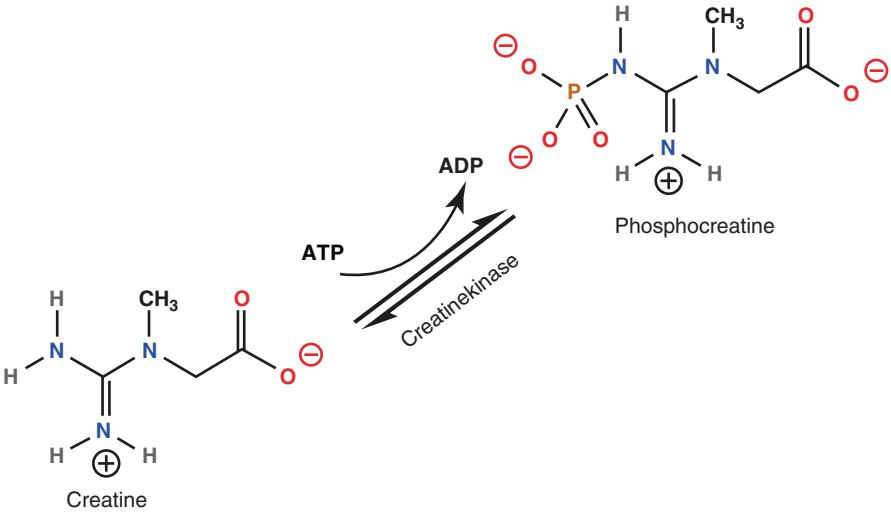

Fig. 7.2 Creatine energy buffer reaction

the energy by converting creatine to phosphocreatine. When in energy demanding circumstances, the ATP stock becomes depleted, ATP can temporarily be supplied by reconverting phosphocreatine to creatine until the phosphocreatine stock is also depleted or energy is resupplied via other routes such as the oxidative phosphorylation.

With ^{31}P-MRS creatine and phosphocreatine concentrations can be measured separately as well as the total concentration of both metabolites. The total concentration can also be measured with ^{1}H-MRS, the separate concentrations to a lesser degree when advanced quantification tools are being used. In BD patients a decreased phosphocreatine (Kato et al. 1993) and reduced total creatine (Frey et al. 2007; Port et al. 2008) was described, when compared to controls, supporting the mitochondrial dysfunction theory. Findings in other MRS metabolites such as a reduced pH and increased lactate, exponents of cell metabolism exhaustion, add indirectly to this theory (Kato et al. 1993; Dager et al. 2004).

A study concerning the nature of the metabolic dysfunction revealed a paradoxical downregulation of mitochondria-related genes to glucose deprivation in fresh lymphocytes derived from BD patients, whereas cells from control subjects showed an upregulation. This finding would suggest that patients with BD might have impairment in molecular adaptation to energy stress (Naydenov et al. 2007). However there is still debate whether this dysregulation is based on mitochondrial DNA disturbances or mitochondria-related nuclear DNA disturbances or due to other mechanisms (Kato 2008). Furthermore, it is not known if this dysregulation occurs in all brain regions and whether there is an association with neuroinflammation or neurotransmitter disturbances. Combined PET-MRI study efforts may help to answer this question.

7.4 Conclusion

Since the beginning of the earliest PET and SPECT studies in patients with BD in the 1980s, this field of research gave rise to many new insights in the pathophysiology of BD. The first, mainly metabolism and blood flow-oriented studies aided to the study of various aspects of the metabolism based disease model in which PFC hypoactivity is accompanied by limbic hyperactivity. This model in its comprehensive form is however probably not precise enough to account for most of the specific mood and cognitive disease features, and efforts are being made to provide more detail. The role of molecular imaging as the main imaging technique in metabolism studies has been taken over by fMRI, but molecular imaging is still used to answer specific questions in which fMRI falls short. Molecular imaging demonstrated the importance of serotonin transporter alterations in parts of the limbic system in BD and underscored the role of dopamine and cholinergic neurotransmission.

Apart from serotonergic/dopaminergic dysfunction, and the corticolimbic theory of mood disorders, the neuroinflammation theory is of particular interest because it endeavors to incorporate the complex interactions between the neurologic, immunologic, and endocrine systems into one model. In addition, the white matter tract integrity disruption and mitochondrial dysfunction models provide other invigorating viewpoints to the BD disease mechanism.

Most molecular imaging studies in BD have unique designs, extending the knowledge on the pathophysiological mechanisms but also complicating comparisons between studies. The earlier studies with selection of heterogeneous patient groups, including both BD-I and BD-II patients and being in different mood states (manic, depressed, and euthymic) led to results that were difficult to interpret. Moreover, use of medication can affect study outcomes, while studies with only medication-naïve patients, studies with washout periods and naturalistic studies, all have their specific advantages but also disadvantages. Naturalistic study designs have the advantage that they are generally easier to perform and less burdensome for patients with this serious psychiatric disorder, but the effect of medication use can never be evaluated in a valid way. The obvious advantage of studies in medication-naïve subjects is the exclusion of these medication effects. The question arises however in how far the uniqueness of these patients in that they are able to function without medication, interferes with the investigated mechanism (i.e., the internal validity), and limits the generalizability (i.e., the external validity). In washout studies one could argue that drug withdrawal interferes with the investigated mechanism.

Another complicating factor is that the molecular imaging studies are limited in patient number because of careful ethical considerations due to the ionizing nature of the technique, which complicates comparisons between subgroups. Finally, some ligands are generally expected to measure the same biological property but are later on found to differ in some specific aspects of the measurement complicating comparison between studies. Nevertheless, because of its unique selectivity emanating from a large and continuously extending range of ligands, molecular imaging remains an important tool in BD research.

The important challenge for the next years will be to position and interconnect the individual models and observations into a more comprehensive model, explaining not only the specific mood characteristics of the disorder but also other aspects like, e.g., vulnerability for relapses, the variability in cognitive disturbances associated with BD, although not in all patients. Furthermore, genetic, epigenetic, and developmental vulnerabilities need to be more incorporated into these models. Finally, BD and its pathophysiology do not stand on its own, but there is overlap with other psychiatric disorders, which also makes it important to study proposed mechanisms not only in BD but also in the other disorders, in order to further understand the similarities as well as the difference between the various disorders.

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PET and SPECT in Psychiatric Complications of Parkinson's Disease

8

Valtteri Kaasinen

Contents

Abstract

The psychiatric complications of Parkinson's disease (PD) are a source of additional disability and greatly reduce the quality of life of both the patients and the caregivers. Depression, psychosis, impulse control disorders, and other comorbid psychiatric disorders in PD may result from both intrinsic disease-related and iatrogenic treatment-related factors. Functional neuroimaging with PET and SPECT, with tracers for monoamine transmitters, glucose metabolism, and cerebral blood flow, has been used to reveal neuropathophysiological processes underlying specific psychiatric complications of PD. This chapter covers the current knowledge concerning brain PET and SPECT imaging in the psychiatric complications of PD, with a particular focus on the dopaminergic system.

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Abbreviations

BDI	Beck depression inventory
CNS	Central nervous system
DAT	Dopamine transporter
ECD	[^{99m}Tc]ethyl-cysteinate-dimer-bicisate
FDOPA	6-[^{18}F]fluoro-L-DOPA
MADRS	Montgomery-Åsberg Depression Rating Scale
PD	Parkinson's disease
PET	Positron-emission tomography
rCBF	Regional cerebral blood flow
ROI	Region of interest
SERT	Serotonin transporter
SPECT	Single-photon emission computed tomography
SPM	Statistical parametric mapping

8.1 Introduction

James Parkinson described "shaking palsy" as a condition where "the senses and intellects" remain intact. In many early patients with Parkinson's disease (PD), this indeed is the case. In advanced medicated patients; however, PD is often associated with various cognitive and psychiatric complications. The nonmotor aspects of PD have drawn increased scientific attention during the last years, and the psychiatric aspects of the disease are currently a mainstream research target together with the pathophysiology and treatment of PD motor dysfunction. The psychiatric complications of PD have certain unique phenomenological factors compared to general psychiatry. PD psychiatric complications, particularly impulse control disorders and visual hallucinations, can be iatrogenic and induced by dopaminergic medications. Persistent visual hallucinations in PD can also be nonpsychotic without the necessity of accompanying psychiatric symptoms, and the depression in PD may be unique to PD with clinical differences compared to major depression in non-PD populations.

PET and SPECT studies have mostly focused on depression and psychosis/hallucinations in PD, the most prominent psychiatric complications of PD. A relatively new line of research focuses on impulse control disorders and other repetitive behaviors in PD. Irrespective of the individual psychiatric complication, many studies have attempted to characterize dopamine function in relation to psychiatric disorders in PD. This is due to the key role of dopamine in the pathogenesis and treatment of PD, although there are also highly relevant and interesting studies on other neurotransmitter systems, metabolism, and regional cerebral blood flow. These studies may prove to be important when targeted treatments for these complications are developed in the future.

8.2 Depression in Parkinson's Disease

Depression is arguably the most common neuropsychiatric complication of Parkinson's disease (PD), although the prevalence of depressive symptoms in PD is not well established, with large variation in prevalence estimates. The majority of studies report that 10–45% of PD patients are affected by clinically significant major depressive disorder (Galts et al. 2019). The presence of depression in PD is associated with excess disability, worse quality of life, increased caregiver distress, and more rapid progression of motor impairment and disability (Weintraub and Stern 2005). Depressive symptoms can precede those of motor dysfunction (Taylor et al. 1986), and the natural history of depression does not parallel the progression of physical symptoms of PD, suggesting that it may be an independent process. Experts' opinion and epidemiological, pathophysiological, and therapeutic data favor the hypothesis that depression in PD is a specific entity (Even and Weintraub 2012). In an individual patient, certain factors such as right-sided onset of PD, poor treatment response to SSRIs, and no recent personal history of depression point toward a higher likelihood of a depression specifically linked to PD (Even and Weintraub 2012). Presence and severity of depression in PD strongly correlates with the health-related quality of life of the patients (Schrag 2006).

8.2.1 Dopamine and Depression in Parkinson's Disease

The question of what role dopamine hypofunction plays in the pathophysiology of depression remains an open one, although there is evidence supporting its role in major depression (Dunlop and Nemeroff 2007). Research on the role of dopamine in depression has been largely overshadowed by research on noradrenaline and serotonin circuits. Motivation, psychomotor speed, concentration, and the ability to experience pleasure are all regulated in part by dopamine neurons, and impairment of these functions is a prominent feature of depression (Dunlop and Nemeroff 2007).

Dopamine transporter (DAT) imaging with SPECT or PET is a common diagnostic procedure in movement disorders, and the methodology has been used in an attempt to differentiate PD patients with and without depression. Rektorova and colleagues used [^{123}I]FP-CIT SPECT to study DAT binding in a group of 20 PD patients without major depression (Rektorova et al. 2008). Within this group of patients, they correlated Montgomery and Åsberg Depression Rating Scale (MADRS) scores and DAT binding, and the results indicated a negative correlation between MADRS and DAT in the left striatum and the putamen, i.e., the more pronounced the depressive symptoms, the lower the dopamine transporter binding. Also another DAT SPECT ligand, [^{99m}Tc]TRODAT-1, has been used to similarly show that increasing severity of anxiety and depression is correlated with decreased DAT binding in the left putamen in patients with PD (n = 76) (Weintraub et al. 2005). A small PET study with [^{11}C]RTI-32, a marker of both DAT and noradrenaline transporter, has further shown lateralized results to the left hemisphere (8

depressed patients vs. 12 nondepressed patients). The uptake in the depressed patients was lower in the left ventral striatum in addition to other, mostly noradrenergic regions (Remy et al. 2005). Finally, in a retrospective analysis of 140 PD patients, those with depression ($n = 30$) had lower striatal [^{123}I]FP-CIT binding compared to patients without depression ($n = 110$) (Hesse et al. 2009).

The preliminary results have thus indicated that there may be a presynaptic dopaminergic defect in PD depression, which exceeds the defect induced by PD alone. It would also appear that early dysfunction in the caudate nucleus DAT function may be associated with increased risk of developing depression (Pasquini et al. 2019a). Some studies indicate that the link between depression and DAT may be lateralized to the left hemisphere. However, Felicio et al. again used [^{99m}Tc]TRODAT-1 SPECT ($n = 20$) and reported that DAT binding, in fact, was higher in depressive PD patients compared to nondepressive patients (the difference significant in the left caudate and the right putamen) (Felicio et al. 2010). As the authors discuss, the results also in non-PD depression patients are somewhat conflicting, showing increased, decreased, or no alterations in DAT density when depressed patients have been compared to healthy control subjects.

The regional accumulation of 6-[^{18}F]fluoro-L-DOPA (FDOPA) in PET reflects aromatic amino acid decarboxylase activity in the CNS. Within the striatum, the uptake of the tracer is considered to reflect dopamine synthesis capacity. Broussolle and colleagues reported no correlations between FDOPA uptake and affective symptoms and striatal uptake in patients without diagnosed depression (Broussolle et al. 1999). They studied a relatively heterogeneous group of 27 PD patients (de novo, moderate and advanced disease) and used the Beck Depression Inventory (BDI) for depression measurements together with cognitive measurements and motor symptom evaluation. Using the same ligand, Koerts et al., on the other hand, reported that depressive symptoms (MADRS score) were negatively correlated with FDOPA uptake in the putamen (combined left and right side) in 23 patients with advanced Parkinson's disease without a diagnosis of major depression (Koerts et al. 2007). Also a study by Joutsa and colleagues suggested a relevant link between FDOPA uptake and depression (as measured with BDI), but only in 15 de novo unmedicated PD patients, not in 20 medicated advanced patients (Joutsa et al. 2013). Therefore, the current evidence concerning the relationship between DAT/FDOPA and depression in PD indicates lower binding in depressed patients (Hesse et al. 2009; Joutsa et al. 2013; Koerts et al. 2007; Rektorova et al. 2008; Remy et al. 2005; Weintraub et al. 2005), although there are also indications for an opposite effect (Felicio et al. 2010) and negative results (Broussolle et al. 1999). Recent PET results in non-PD patients with major depressive disorder support a relevant reduction of striatal presynaptic dopaminergic function in the pathogenesis of depression (Pizzagalli et al. 2019).

Dopamine receptor binding in the course of PD is affected together with the presynaptic dopaminergic function. The decrease in receptor binding is widespread involving D2-like receptors in the striatum and extrastriatal regions, although there is compensatory receptor upregulation in early disease (Antonini et al. 1997; Kaasinen et al. 2000, 2003; Ko et al. 2013; Niccolini and Politis 2014; Rinne et al. 1990). PET studies with [^{11}C]Scheme 23390 and [^{11}C]NNC 112 have, however, indicated that D1-like receptors are unaltered in PD (Cropley et al. 2008; Niccolini

and Politis 2014; Ouchi et al. 1999; Shinotoh et al. 1993). Although dopamine receptor binding characteristics have been studied relatively well in PD, there are very few studies concerning mood disorders and dopamine receptor binding in PD. Boileau et al. used a D3 dopamine receptor-preferring ligand [^{11}C]-(+)-PHNO and a D2/D3 ligand [^{11}C]raclopride for ten PD patients and nine controls and reported that the decreased [^{11}C]-(+)-PHNO/[^{11}C]raclopride ratio was associated with motor deficits and lowered mood (Boileau et al. 2009). Although the number of subjects is small, the preliminary results therefore suggest that depression in PD may be related more to the relative changes in D2-like receptor subtypes, rather than to a general up-or downregulation of receptors.

Apathy is also common in PD, and it is characterized by a lack of motivation, manifested by diminished goal-directed cognition and behavior, with decreased emotional involvement. Several studies have implied that apathy and depression are distinct syndromes, although the separation of apathy from the motor symptoms of PD and depression can be problematic. Thobois et al. compared 12 PD patients with apathy with 13 patients without apathy and scanned them with [^{11}C]raclopride before and after methylphenidate challenge. The results indicated that, at baseline, binding potentials were greater in apathetic patients bilaterally in the orbitofrontal cortex, dorsolateral prefrontal cortex, posterior cingulate cortex and temporal cortices, left striatum, and right amygdala. The non-apathetic patients seemed to release more dopamine in several extrastriatal regions due to methylphenidate compared to apathetic patients. The authors concluded that the occurrence of apathy, anxiety, and depression could be explained by a lower density of presynaptic dopaminergic terminals, especially in the mesocorticolimbic system (Thobois et al. 2010). However, a major weakness of the study is the low signal-to-noise ratio of [^{11}C]raclopride in the extrastriatal regions. Test-retest studies have indicated that reliable cortical measurements are not possible with [^{11}C]raclopride PET (Hirvonen et al. 2003). It would also appear that striatal DAT function does not contribute to the degree of apathy in PD (Chung et al. 2016).

8.2.2 Serotonin and Depression in Parkinson's Disease

A role of the serotonergic system in PD depression has been indicated by decreased levels of the serotonin metabolite 5-hydroxyindoacetic acid in the CSF, sonographically determined abnormalities of raphe echogenicity, and the influence of allelic variation in the serotonin transporter (SERT) gene promoter (reviewed in (Hesse et al. (2009)). There are also data to suggest that, although intrastriatal transplantation of dopamine-rich fetal mesencephalic tissue is able to improve motor performance and restore basal ganglia dopamine function, nonmotor symptoms such as depression and hallucinations persist, together with ongoing degeneration of serotonergic projections as measured with [^{11}C]DASB PET (Politis et al. 2012).

Although [^{123}I]FP-CIT and [^{99m}Tc]TRODAT-1 binding reflect DAT in the striatum, the tracers also show specific binding from the thalamus downward to the brainstem, and the extrastriatal binding may reflect binding to SERT. Simultaneous DAT and SERT measurements have been attempted during one scanning session

with [^{123}I]FP-CIT. Hesse et al. retrospectively studied [^{123}I]FP-CIT scans from 140 PD patients and 18 healthy controls and showed that PD patients with depression (n = 30) had lower tracer binding in the thalamus and the midbrain compared to healthy controls, whereas PD patients without depression (n = 110) did not differ from controls (Hesse et al. 2009). The results therefore indicated a SERT binding loss in extrastriatal regions in PD depression. However, since [^{123}I]CIT binds also to noradrenaline transporters, the loss of noradrenaline transporters in depression could also contribute to the decreased tracer binding. Moreover, although [^{123}I]FP-CIT SPECT is able to detect longitudinal reductions in raphe nuclei serotonergic function, there appears to be no correlations with depression scores in early PD (Pasquini et al. 2019b; Qamhawi et al. 2015).

On the other hand, [^{11}C]DASB PET studies of SERT in PD depression have provided opposite or negative results. Boileau et al. reported in a small PET study with seven PD patients with depression and seven healthy controls that the extrastriatal binding was increased in depressive patients and that the depressive symptom severity correlated positively with the binding in the orbitofrontal cortex (Boileau et al. 2008). In a further study, Politis et al. used [^{11}C]DASB PET for a larger group of antidepressant-naive patients (10 PD depressed, 24 PD nondepressed, and 10 healthy controls) and also reported increased binding in PD depression compared to PD nondepression in the amygdala, the hypothalamus, caudal raphe nuclei, and posterior cingulate cortex (Politis et al. 2010b). Finally, Strecker et al. used [^{11}C]DASB in nine early nondepressed PD patients and nine healthy controls. They found that the binding was preserved in these early patients and that depression scores did not seem to correlate with binding parameters (Strecker et al. 2011). However, it must be noted that all PD patients were below the cutoff of clinical depression and the number of patients was small for correlation analyses. Postsynaptically, Ballanger and colleagues have reported decreased 5-HT_{1A} receptor availabilities in limbic regions of PD patients with depression, as measured with [^{18}F]MPPF PET (Ballanger et al. 2012).

The results concerning SERT are thus limited and mixed with indications of lower binding in PD depression (Hesse et al. 2009), increased binding in PD depression (Boileau et al. 2008; Politis et al. 2010b), and no relationship between depression scores and SERT (Strecker et al. 2011). It is also important to note that the studies have used different cohorts of PD patients at different stages of the disease, and the mixed results may partly be related to a nonlinear progression of serotonergic dysfunction in PD (Politis et al. 2010a).

8.2.3 Glucose Metabolism and Cerebral Blood Flow in Parkinson's Disease Depression

SPECT studies measuring regional cerebral blood flow (rCBF) in patients with major depression without PD have generally shown regional hypoperfusion and normalization after treatment. Global rCBF in major depression has been reported to be either reduced or comparable/equal to controls. SPECT studies in PD without

depression have demonstrated either no differences in rCBF compared to controls or hypoperfusions in parietal, frontal, or temporal regions (reviewed in (Pålhagen et al. 2009)).

Many rCBF studies in PD depression are in line with the studies performed in non-PD depression (hypoperfusion at baseline and increased perfusion after treatment). First, an early study by Ring et al. indicated that rCBF in depressed PD patients is decreased in the medial prefrontal cortex and cingulate cortex (Ring et al. 1994). Second, Matsui et al. used [^{123}I]IMP for 22 PD patients with depression and 18 patients without depression and reported left lateral frontal hypoperfusion in patients with depression (Matsui et al. 2006c). Third, Fregni et al. reported lower rCBF in the left prefrontal cortex, posterior cingulate, left insula, and parietal cortex in PD depression compared to healthy controls and an increase in rCBF in the posterior cingulate gyrus after antidepressant treatment (Fregni et al. 2006). Fourth, Imamura et al. reported global rCBF reductions in PD depression compared to nondepressed PD patients. Also patients with minor depression showed blood flow reductions in several regions (Imamura et al. 2011). The investigators repeated [^{123}I]IMP SPECT studies 12 months after baseline, and the results indicated that the patients who had received selegiline 5 mg/day had less depression and higher rCBF compared to the patients who had not received selegiline.

In contrast to these studies, Pålhagen et al. reported increased rCBF in depressed PD patients. They studied 11 depressed PD patients, 14 nondepressed PD patients, and 12 depression patients without PD with [^{99m}Tc]HMPAO SPECT. The SPECT scans were taken before and after a 12-week treatment with citalopram (for depressive patients). At baseline, depressed PD patients showed increased rCBF in the frontal regions compared to PD patients without depression. Treatment with citalopram reduced this hyperperfusion in the left frontal dorsolateral regions (Pålhagen et al. 2009). In the most recent study with [^{99m}Tc]HMPAO SPECT and 78 PD patients (35 with depression), Kim and colleagues identified a specific regional pattern of brain perfusion that distinguished depressed PD patients from nondepressed patients. This pattern included occipital hyperperfusion in combination with frontotemporo-limbic hypoperfusion (Kim et al. 2016).

Using 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG), Mayberg et al. studied depressed PD patients, nondepressed PD patients, and healthy controls and showed results which indicated that depressed PD patients had lower metabolic activity in the caudate and orbital-inferior regions compared to the other two groups. There was also a significant inverse correlation between glucose metabolism in the orbital-inferior regions of the frontal lobe and depression scores (Mayberg et al. 1990). Le Jeune et al. later used FDG for 12 PD patients before and after (3 months between scans) the implementation of subthalamic deep brain stimulation (STN-DBS). Their preliminary results indicated that apathy scores increased after STN-DBS and this variation was positively correlated with the glucose metabolism in the right frontal middle gyrus (Brodmann area 10) and right inferior frontal gyrus (Brodmann areas 46 and 47). However, negative correlations between the two were observed in the right posterior cingulate gyrus (Brodmann area 31) and left medial frontal lobe (Brodmann area 9) (Le Jeune et al. 2009).

The imaging studies concerning metabolism/rCBF and depression in PD have therefore mostly indicated hypoperfusion/hypometabolism in depressed patients and normalization after antidepressive treatment (Fregni et al. 2006; Imamura et al. 2011; Matsui et al. 2006c; Ring et al. 1994), although there are also directly opposite (Pålhagen et al. 2009) and mixed results (Kim et al. 2016; Le Jeune et al. 2009). Again, the interpretation of the results is difficult due to the low number of investigated patients in some studies.

8.3 Psychosis in Parkinson's Disease

Psychosis occurs in fewer than 10% of untreated PD patients, but hallucinations or illusions have been estimated to occur in 15–40% of patients treated with antiparkinsonian medications. Persistent psychotic symptoms are associated with greater functional impairment, reduced quality of life, development of dementia, caregiver burden, and nursing home placement (Fénelon and Alves 2010; Weintraub and Stern 2005).

Visual hallucinations are particularly common in PD patients and are associated with more advanced disease and cognitive impairment (reviewed in (Nagano-Saito et al. 2004)). There are only a few reported rCBF studies of visual hallucinations in PD with mixed results (hypo- and hyperperfusion reported). Using SPECT with [^{99m}Tc]HMPAO, Okada et al. reported lower rCBF in the left temporal regions in 12 PD patients with hallucinations compared to 21 patients without hallucinations (Okada et al. 1999). Oishi et al., on the other hand, used [^{123}I]IMP SPECT to study rCBF in 24 PD patients with nonpsychotic visual hallucinations and 41 patients who had never experienced visual hallucinations. The results indicated that visual hallucinations in PD may be associated with both hypoperfusion in the right fusiform gyrus and hyperperfusion in the right superior and temporal gyri. Since the temporal regions are involved in visual object recognition, the authors suggested that the rCBF changes in these regions may responsible for nonpsychotic visual hallucinations in PD (Oishi et al. 2005).

Verbal and visual hallucinations in PD have been studied by Matsui and colleagues in three rCBF studies. First, they studied ([^{123}I]IMP for rCBF) 11 patients with both verbal and visual hallucinations and compared them to 17 patients with only visual hallucinations. Patients with verbal hallucinations were reported to have hypoperfusion in the bilateral prefrontal cortex (mainly Brodmann area 10) and right superior temporal gyrus (mainly Brodmann area 21) (Matsui et al. 2006a). In their second study, the same tracer was used to study visual hallucinations in PD. They included 31 patients with visual hallucinations and 39 patients without visual or other hallucinations. Hallucinatory patients demonstrated significant perfusion reductions in the bilateral inferior parietal lobule, inferior temporal gyrus, precuneus gyrus, and occipital cortex compared to nonhallucinatory patients (Matsui et al. 2006b). In their third rCBF study (labeled as a pilot study by the authors) with the same tracer, they investigated 83 PD patients of whom 6 had

verbal hallucinations. The patients with verbal hallucinations showed increased right thalamic perfusion (Matsui et al. 2007). In the most recent rCBF study, Usui et al. investigated eight PD patients with medication-related psychotic symptoms. They scanned the patients before and after electroconvulsive therapy with [^{99m}Tc]ethyl-cysteinate-dimer-bicisate (ECD, uptake proportional to rCBF at the time of injection). The treatment not only decreased psychotic symptoms and improved PD motor symptoms but also increased rCBF in the right middle frontal gyrus (Usui et al. 2011). The presence of REM sleep behavior disorder in PD is associated with an increase of psychotic disorders. However, Yoritaka et al. studied 81 PD patients with REM sleep behavior disorder and compared them to 69 PD patients without REM sleep behavior disorder using ECD SPECT. No group differences were seen in the pons, substantia nigra, red nucleus, occipital lobe, or total cerebral blood flow (Yoritaka et al. 2009).

There are thus some studies which have shown hypoperfusion in selected regions in psychotic PD patients and in visual and auditory hallucinations in PD (Matsui et al. 2006b; Okada et al. 1999; Usui et al. 2011), although there are also studies showing hyperperfusion (Matsui et al. 2007), both hypo- and hyperperfusion in different brain regions (Oishi et al. 2005), and the results in patients with REM sleep behavior disorder have been negative (Yoritaka et al. 2009). There are also some FDG studies reported of hallucinations in PD. Nagano-Saito et al. used FDG with statistical parametric mapping (SPM) for 8 PD patients with visual hallucinations and 11 patients without hallucinations and reported hypermetabolism in the left superior frontal gyrus in patients with hallucinations. The difference was nonsignificant with the conventional region-of-interest analysis (Nagano-Saito et al. 2004). Nishio and colleagues reported a larger FDG study with 20 PD patients with visual hallucinations and showed results which suggested temporoparietal hypometabolism in hallucinating patients (Nishio et al. 2018).

There is a lack of monoaminergic imaging studies in PD hallucinations. In a small pilot study using [^{18}F]setoperone, serotonin 2A receptor binding was studied in seven PD patients with visual hallucinations and seven PD patients without visual hallucinations. The patients with visual hallucination showed increased binding in the ventral visual pathway, bilateral dorsolateral prefrontal cortex, medial orbitofrontal cortex, and insula with SPM (ROI-results not performed/reported) (Ballanger et al. 2010). However, later results from the same group suggested decreased [^{18}F]setoperone binding in several brain regions in patients with visual hallucinations (Cho et al. 2017). In dementia with Lewy bodies, Roselli et al. have reported that decreased striatal DAT levels, as measured with [^{123}I]FP-CIT, are associated with more severe visual hallucinations (n = 18) (Roselli et al. 2009). Interestingly, the inverse association of DAT levels with positive symptoms has also been reported in schizophrenic patients (Schmitt et al. 2006). In PD, low striatal DAT function particularly in the ventral part of the striatum may predispose PD patients to visual hallucinations (Jaakkola et al. 2017), whereas in patients currently experiencing visual hallucinations, the DAT defect may be particularly clear in caudate nuclei (Kiferle et al. 2014). Landis and Burkhard have described two PD patients who

reported positive olfactory symptoms preceding motor manifestations of PD. [^{123}I]FP-CIT SPECT for these two patients showed striatal reductions in binding, and the disappearance of the phantosmias in both patients coincided with the development of typical PD. However, although phantosmias or odor distortions can be considered hallucinations in some patients, the phantosmias in these two cases are not necessarily representations of psychiatric complication of PD but rather premotor manifestations of the disease (Landis and Burkhard 2008). Othello syndrome is an organic delusional syndrome, characterized by pathological jealousy, which is presumed to be associated with dopamine agonist treatment (Georgiev et al. 2010). To date, there have been no reported imaging studies concerning Othello syndrome in PD.

8.4 Impulse Control Disorders in Parkinson's Disease

Impulse control disorders (ICDs) are a group of psychiatric disorders, which are characterized by repetitive behaviors due to lost control over psychological impulses. Pathological gambling, the most extensively studied ICD, is currently considered as behavioral addictions, a novel category in the spectrum of psychiatric disorders that debuted in the fifth version of the *Diagnostic and Statistical Manual of the American Psychiatric Association* (DSM-V) (Holden 2010).

The prevalence of ICDs in PD (problem gambling, hypersexuality, compulsive shopping, and compulsive eating) is estimated to be approximately 14% (Weintraub et al. 2010), and up to one third of patients, report these behaviors (Joutsa et al. 2012c) although, in many patients, the behavioral changes can be mild and subclinical. There is a substantial amount of evidence linking PD ICDs to dopamine replacement therapy (Gallagher et al. 2007; Grosset et al. 2006; Singh et al. 2007; Weintraub et al. 2010), but also other factors such as male sex, younger age, younger age at PD onset, earlier or family history of gambling, and substance abuse have been associated with ICDs in PD (Ambermoon et al. 2011; Ceravolo et al. 2009). These abnormal behavioral patterns reduce the quality of life of patients and their families (Vilas et al. 2012).

8.4.1 Dopaminergic Tracers

PET studies using [^{11}C]raclopride for dopamine D2-like receptors have indicated an enhanced dopaminergic ventral striatal response to winning gambling in PD patients with pathological gambling and also to reward-related cues in PD patients with ICDs (O'Sullivan et al. 2011; Steeves et al. 2009). Many studies have used a displacement paradigm with [^{11}C]raclopride with the assumption that endogenous dopamine induces competitive inhibition of radioligand binding, and reductions of binding following a challenge (or a task) are thus considered an indirect measure of dopamine release. One study investigated seven PD patients with pathological

gambling and seven patients without history of gambling with [^{11}C]raclopride. Each participant was scanned twice, during simulated gambling (certain winning) and control task (gambling with no winning or losing). SPM-based analysis was performed, and the results suggested that dopamine release was greater during gambling in PD patients with pathological gambling (Steeves et al. 2009). O'Sullivan et al. studied 11 PD patients with ICDs and 7 patients without ICDs with [^{11}C]raclopride and used reward-related pictures as cues (such as pictures of foods, gambling, and money). PD patients with ICDs were reported to have a greater reduction of ventral striatal tracer binding (dopamine release) following reward-related visual cues (O'Sullivan et al. 2011). Further, PD patients with dopamine dysregulation syndrome (DDS), another repetitive behavior, have been reported to similarly release more ventral striatal dopamine in response to a dose of levodopa than patients without DDS (n = 8 DDS patients vs. 8 non-DDS patients), and the amount of dopamine release correlated with subjective rating of wanting the drug (Evans et al. 2006). It would therefore appear that PD ICD behavior and other repetitive behaviors, such as punding and DDS, may be associated with enhanced or supersensitized striatal dopamine responses in the presence of relevant cues. These findings are against the hypothesized dopamine reward deficiency theory but are in line with PET results in non-PD ICDs (enhanced dopaminergic responses to relevant stimuli) (Joutsa et al. 2012a).

Although one study has also reported that the baseline D2-like receptor binding may be lower in patients with pathological gambling (n = 7) compared to patients without pathological gambling (n = 7) (Steeves et al. 2009), there are currently mainly negative findings concerning baseline differences in [^{11}C]raclopride binding in PD ICDs (Evans et al. 2006; O'Sullivan et al. 2011) and in non-PD pathological gamblers (Joutsa et al. 2012a; Linnet et al. 2011), with some indications of extrastriatal changes as measured with [^{11}C]FLB457 (Ray et al. 2012). A recent meta-analysis of all published PET and SPECT studies in PD ICDs has suggested that there are no differences in baseline dopamine receptor availability between ICD-positive and ICD-negative patients, although dorsal striatal DAT binding is decreased in patients with ICDs (Martini et al. 2018).

Lower right ventral striatal DAT binding in PD patients with pathological gambling (n = 8) compared to control PD patients (n = 21) has been reported using [^{123}I]FP-CIT (Cilia et al. 2010). However, FDOPA-PET has not shown differences in striatal FDOPA uptake between PD patients with ICDs (n = 10) and patients without ICDs (n = 10), although higher FDOPA uptake was seen in the medial orbitofrontal cortex in patients with ICDs and particularly in patients with pathological gambling (Fig. 8.1) (Joutsa et al. 2012b).

Dopaminergic PET and SPECT studies therefore indicate that dorsal striatum DAT binding may be decreased and ventral striatal dopamine release may be increased in PD patients with repetitive behavioral disorders compared to control PD patients, reflecting supersensitized dopaminergic mesolimbic system to reward and reward-related cues.

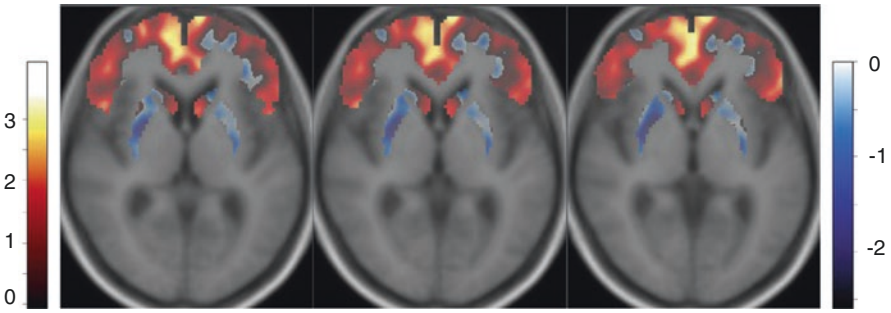

Fig. 8.1 Differences in brain FDOPA uptake between Parkinson's disease patients with impulse control disorders compared to Parkinson's disease patients without behavioral or mood disorders. Statistical pseudo-T map of the voxel-wise group comparison is shown. *Red-yellow* color shows regions with higher binding in patients with impulse control disorders (Courtesy of Dr. J. Joutsa)

8.4.2 Other Tracers

Brain perfusion studies in PD ICDs have provided partially conflicting results. A SPECT study using ECD for rCBF measurement has shown increased resting perfusion in the right hemisphere including the orbitofrontal cortex, the hippocampus, the amygdala, the insula, and the ventral pallidum in PD patients with pathological gambling (11 PD gamblers vs. 40 PD controls vs. 29 healthy controls) (Cilia et al. 2008). Cilia et al. further studied 15 PD patients with pathological gambling, 15 PD controls, and 15 healthy controls. Gambling severity (SOGS score) correlated negatively with rCBF in several brain regions such as the right ventrolateral prefrontal cortex, right anterior cingulate cortex, right posterior cingulate cortex, bilateral insula, and the left striatum (more severe symptoms associated with lower perfusion). The region with the highest level of significance was the right ventrolateral prefrontal cortex. The authors suggested that this region may have a role in risk-taking behaviors (Cilia et al. 2011). However, the authors also reported positive correlations between SOGS scores and resting state rCBF in the left fusiform gyrus and the cerebellum.

The same group also studied seven PD patients with pathological gambling and seven control patients with [^{15}O]H_2O using the same stimulus as in their [^{11}C]raclopride study (simulated card game, mostly the same patients as in the previous study) (Steeves et al. 2009; van Eimeren et al. 2010). The patients were scanned before and after subcutaneous administration of apomorphine. Interestingly, the variant of the task (financial/neutral) did not influence rCBF. The main finding was the effect of apomorphine: in gamblers, the drug decreased rCBF in regions such as the orbitofrontal cortex and the rostral cingulate zone, whereas in controls, the effect was the opposite. As the authors point out, the sample size is relatively small and limits the generalizability of these results.

8.5 Personality Changes in Parkinson's Disease

It has been claimed that PD could be associated with a specific, possibly premorbid personality type. The "parkinsonian personality" has been described as introverted, quiet, morally rigid, serious, stoic, industrious, inflexible, and punctual. PD patients have been claimed to have less novelty seeking behavior, which is considered a personality trait primarily modulated by dopamine, but a systematic review of the literature has shown that existing studies are mostly insufficient and prospective personality data is needed (Ishihara and Brayne 2006). A later large follow-up study of more than 7000 individuals, followed over four decades, indicated that novelty seeking and introversion do not predict the long-term risk of Parkinson's disease (Arabia et al. 2010).

Although the first PET study with nine PD patients using FDOPA indicated that the striatal dopaminergic function may be associated with novelty seeking (Menza et al. 1995), a later study with 47 patients failed to show significant correlations between striatal FDOPA uptake and novelty seeking (Kaasinen et al. 2001). Similar results have been reported with [^{11}C]CFT, a DAT PET tracer, which has not shown correlations with personality measured in PD patients or healthy controls (Ishii et al. 2016). However, studies in both healthy controls (Suhara et al. 2001) and PD patients (Kaasinen et al. 2004) indicate that dopamine D2 receptor binding potential in the insular cortex (as measured with [^{11}C]FLB 457) may be negatively associated with novelty seeking scores. The combined results suggest that the novelty seeking trait may relate to specific insular dopaminergic function, not to the level of the dopaminergic activity per se.

Although novelty seeking does not seem to correlate well with striatal dopamine function in PD, caudate FDOPA uptake seems to be related to harm avoidance, a personality trait arguably associated more with serotonin function and anxiety-related behavioral responses (Kaasinen et al. 2001).

Also other personality characteristics, apart from novelty seeking, have been studied in PD with neuroimaging. FDG-PET study about "honesty" in patients with PD has been performed (resting state glucose metabolism in 32 patients with PD and 20 healthy controls). Patients with PD had difficulties in telling lies as compared to controls, and this difficulty of making deceptive responses was correlated to prefrontal hypometabolism (Abe et al. 2009).

8.6 Conclusions

The great majority of studies concerning neuroimaging and PD psychiatric complications have been published during the last 10 years. The research area is new, and the results are mostly preliminary. There is still considerable variation in published results and studies with apparently comparable methodology may show contradictory findings. The variation in the results could reflect the interindividual variation

and complexity of the psychiatric phenomenon. In addition, the scales that are used to measure psychiatric symptoms differ from study to study, such as in the case of depression. The disease severity and the stage of the overall disease (early unmedicated de novo vs. moderate medicated non-fluctuating vs. advanced with motor fluctuations and cognitive defect) is another factor, which greatly affects the results. It is also possible that the apparently contradictory results reflect different stages in the development of psychiatric complications in PD and are a demonstration of a continuum from a compensatory upregulation to end-stage downregulation of neurotransmission. Finally, the statistical power in some pilot studies can be questioned.

Even with the limitations, and the limited number of studies, the combined results demonstrate the feasibility of functional neuroimaging in PD psychiatry. The studies show that both baseline neurotransmission and treatment response can be investigated. As larger confirmatory studies are performed, the method may prove to be a useful tool to monitor neurotransmission in clinical drug trials for psychiatric complications in PD.

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Psychiatric Disorders in Dementia

9

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Abstract

Alzheimer's disease (AD) is the most common form of dementia, a neurodegenerative disorder which is characterized not only by cognitive deterioration but also by a diversity of *behavioral and psychological signs and symptoms of dementia* (BPSD). BPSD in AD or other dementia subtypes such as frontotemporal dementia (FTD) or dementia with Lewy bodies (DLB) consist of delusions, hallucinations, activity disturbances, aggression/agitation, diurnal rhythm disturbances, mood disorders, apathy, and anxieties/phobias. Neuroimaging modalities such as *positron emission tomography* (PET) and *single-photon emission computed tomography* (SPECT) are very essential and useful imaging tools to differentially diagnose between AD and non-AD or healthy control subjects or between different dementia subtypes, such as AD and DLB or FTD. Besides their diagnostic utility, PET and SPECT are useful tools to investigate the cerebral pathophysiology of BPSD in dementia.

Below, PET and SPECT neuroimaging research in dementia spanning the last three decades has been systematically reviewed. The most commonly used PET and SPECT radioligands, as well as new developments in the field, all targeting different and unique aspects of neurodegeneration, are described. Furthermore, PET and SPECT research in BPSD with a main focus on depression, apathy, and psychosis in AD, DLB, and FTD are discussed in detail. On the whole, both PET and SPECT have demonstrated that depending on the behavioral phenomenon and dementia subtype, BPSD are the fundamental expression of very regional cerebral pathological events rather than a diffuse brain illness.

Abbreviations

^{11}C-DASB	^{11}C-3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile
^{11}C-PMP	^{11}C-methylpiperidin-4-yl propionate
^{11}C-RAC	^{11}C-raclopride
^{123}I-β-CIT	^{123}I-2beta-carbomethoxy-3beta-(4-iodophenyl)tropane
^{123}I-IBVM	^{123}I-iodobenzovesamicol
^{123}I-IDEX	^{123}I-iododexetimide
^{123}I-FP	^{123}I-fluoropropyl
^{123}I-IMP	N-isopropyl-p-^{123}I-iodoamphetamine
^{18}F-FDG	^{18}F-fluorodeoxyglucose
^{99m}Tc-ECD	^{99m}Technetium-ethyl-cysteinate dimer
^{99m}Tc-HMPAO	^{99m}Technetium-hexamethylpropyleneamine oxime
3DSRT	3-D stereotactic region of interest template
5-HT	Serotonin (5-hydroxytryptamine)
Aβ	Beta-amyloid
ABS-score	Abe's BPSD score
AD	Alzheimer's disease
ADAS-(non)cog	Alzheimer's Disease Assessment Scale, (non)cognitive portion
AD+CVD	Alzheimer's disease with cerebrovascular disease
ADRDA	Alzheimer's Disease and Related Disorders (see NINCDS)
ALS	Amyotrophic lateral sclerosis
ANCOG	Antwerp cognition
APOE	Apolipoprotein E
APP	Amyloid precursor protein
BA	Brodmann area
BADL	Basic activities of daily living
Behave-AD	Behavioral pathology in Alzheimer's disease rating scale
BPSD	Behavioral and psychological signs and symptoms of dementia
BPSD-DS	Behavioral and psychological signs and symptoms of dementia in Down syndrome
bvFTD	Behavioral variant frontotemporal dementia
CBD	Corticobasal degeneration
CC	Cingulate cortex
CIS	Cingulate island score
COX	Cyclooxygenase
CMAI	Cohen-Mansfield agitation inventory
CSDD	Cornell Scale for Depression in Dementia
CSF	Cerebrospinal fluid
CVD	Cerebrovascular disease
DA	Dopamine
DAT	Dopamine transporter
DLB	Dementia with Lewy bodies
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

EPS	Extrapyramidal symptoms
ERDA	Epidemiology research on dementia in Antwerp
eZIS	Easy Z-score imaging system
FDDNP	^{18}F-2-(1-(2-(N-(2-fluoroethyl)-N-methylamino)naphthalene-6-yl) ethylidene)malononitrile
FDG	Fluorodeoxyglucose
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
GDS	Geriatric depression scale
HDS	Hamilton Depression Rating Scale
IAD	Instrumental activities of daily living
IDO	Indoleamine 2,3-dioxygenase
IMPY	6-Iodo-2-(4′-dimethylamino-)phenyl-imidazo[1,2]pyridine
LC	locus coeruleus
LOAD	Late-onset Alzheimer's disease
MAPT	Microtubule-associated protein tau
MCI	Mild cognitive impairment
MFS	Middelheim Frontality Score
MMSE	Mini-Mental State Examination
MRB	Methylreboxetine
MXD	Mixed dementia
NE	Norepinephrine
NET	Norepinephrine transporter
NFT	Neurofibrillary tangles
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke (see ADRDA)
NPI	Neuropsychiatric Inventory
NPI-C	Neuropsychiatric Inventory-Clinician
NPI-NH	Neuropsychiatric Inventory-Nursing Home version
NPI-Q	Neuropsychiatric Inventory Questionnaire
NPS	Neuropsychiatric symptoms
NSAID	Nonsteroidal anti-inflammatory drugs
PBR-TSPO	Peripheral benzodiazepine receptor-translocator protein
PD	Parkinson's disease
PD-1	Programmed death-1
PDD	Parkinson's disease dementia
PET	Positron emission tomography
PGRN	Progranulin
PiB	Pittsburgh compound-B
PSEN	Presenilin
PSP	Progressive supranuclear palsy
Py	Person years
RBD	REM sleep behavioral disorder
rCBF	Regional cerebral blood flow
ROI	Regions of interest

SB-13	4-N-methylamino-4'-hydroxystilbene
SD	Semantic dementia
SNCA	α-Synuclein
SPECT	Single-photon emission computed tomography
SPM	Statistical parametric mapping
TDP-43	TAR DNA-binding protein 43
U	Ubiquitin
VAD	Vascular dementia

9.1 Dementia: Definition and Epidemiology

9.1.1 Definition

According to the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5*, dementia is referred to as a "major or mild neurocognitive disorder (NCD)." Major or mild NCD include NCD due to Alzheimer's disease (AD), vascular NCD, NCD with Lewy bodies, NCD due to Parkinson's disease (PD), frontotemporal NCD, and NCD due to Huntington's disease. It is noted, however, that the term "dementia" is not precluded from use in etiological subtypes in which this term is standard and can be used in settings where physicians and patients are accustomed with this term. Overall, dementia is a clinical syndrome characterized by a gradual loss of function in multiple cognitive domains leading to a significant impairment in social and occupational functioning (American Psychiatric Association 2013). The diagnostic criteria for major NCD are summarized in Table 9.1.

Besides cognitive aspects, dementia is also characterized by numerous behavioral symptoms entitled *behavioral and psychological signs and symptoms of dementia* (BPSD) (Reisberg et al. 1987)—also referred to as *neuropsychiatric symptoms* (NPS) (Lyketsos et al. 2011). BPSD/NPS consist of delusional ideation, hallucinations, activity disturbances, agitation/aggression, circadian rhythm disturbances, affective disturbances, and anxiety disorders and is considered a major component of the dementia syndrome. Lastly, basic and instrumental activities of daily living (BADL and IADL, respectively) complete the definition of dementia. BADL refer to daily self-care activities such as personal hygiene, getting dressed, eating, and general mobility, whereas IADL require more complex abilities such as driving a car, utilizing a phone, taking medication, doing groceries, and managing finances (Lawton and Brody 1969). During the course of dementia, IADL are affected first, followed by BADL (Gauthier et al. 1997). Several studies also showed a direct association between cognitive decline and worsening of BADL and IADL in dementia patients and non-demented elderly (Mitnitski et al. 1999).

The difference between a major and mild NCD primarily lies in the fact that in mild NCD, the cognitive decline is rather modest and there is no interference with BADL or IADL.

Table 9.1 Diagnostic criteria for major NCD according to DSM-5

A.	Evidence of *significant cognitive decline from a previous level of performance in one or more cognitive domains* (complex attention, executive function, learning and memory (amnesia), language (aphasia), perceptual motor (apraxia), or social cognition (agnosia)) based on: 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function 2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment
B.	The cognitive deficits *interfere with independence in everyday activities* (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living (IADL) such as paying bills or managing medications)
C.	The cognitive deficits *do not occur exclusively in the context of a delirium*
D.	The cognitive deficits *are not better explained* by another mental disorder (e.g., major depressive disorder, schizophrenia)
Specification of	1. The etiological subtype (e.g., due to AD, frontotemporal lobar degeneration, or Huntington's disease) 2. Presence/absence of behavioral disturbance 3. Current severity (mild, moderate, severe)

Abbreviations: *AD* Alzheimer's disease; *DSM-5* Diagnostic and Statistical Manual of Mental Disorders, 5th edition, *NCD* Neurocognitive disorder. Based upon the American Psychiatric Association (2013)

The definition above emphasizes that the term "dementia/major NCD" is a syndrome (i.e., association of several clinically recognizable features, signs, and symptoms) rather than only a cognitive disorder and is completed by important behavioral and functional shortcomings (Fig. 9.1).

As a matter of convenience, the term "BPSD" rather than "NPS" will be used throughout this chapter.

9.1.2 Prevalence and Incidence

Although dementia strikes irrespective of age, the prevalence of dementia generally rises with it. Women seem to be more frequently affected by dementia than men (Breteler et al. 1992) although this observation might be attributed to a slower progression rate of the disease in women combined with a proportionally longer life expectancy (Bachman et al. 1993). Prevalence estimates of dementia in the aged population show distinct variation due to differences in population selection, case ascertainment procedures, and diagnostic criteria, which often results in overestimation or underestimation of dementia occurrence (De Deyn et al. 2011). In general, however, the prevalence of moderate-to-severe dementia approximately doubles every 5 years starting at a rate of 2% between the age of 65 and 69, augmenting to 4% in people aged between 70 and 74 up to 16% in octogenarians (Henderson 1990; Morris 1994). These numbers correspond to a prevalence of 5 up

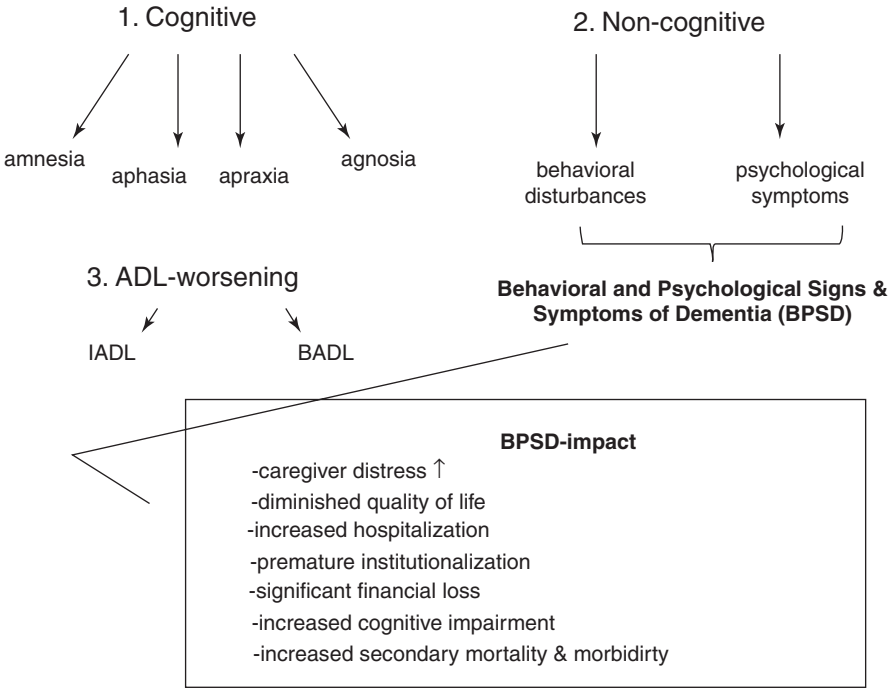


Fig. 9.1 Dementia symptomatology. The dementia syndrome consists of cognitive and noncognitive symptomatology. Worsening of BADL and IADL completes the definition. BPSD examples are delusional ideation and hallucinations, activity disturbances, aggression and agitation, sleep disturbances, mood disorders, and anxiety. Abbreviations: basic activities of daily living (BADL); behavioral and psychological signs and symptoms of dementia (BPSD); instrumental activities of daily living (IADL)

to 10% in the elderly aged 65 and older. In Europe, the prevalence of dementia varies between 1% at the age of 60 and 64 rising up to 34.7% in elderly aged 95 and 99 (Hofman et al. 1991). A recent study by Niu and colleagues (2017) confirms these figures for the European continent, with an overall prevalence rate for AD of 5.05%. Interestingly, the prevalence in women is twice as high as in men (7.13% versus 3.31%).

In the Netherlands, prevalence of dementia in people aged 75–79 was estimated to be 5.2% in 1992 (in a rural area near Zwolle) (Boersma et al. 1998) and 6.1% in 1993 (in the Rotterdam suburb of Ommoord) (Ott et al. 1995; Breteler et al. 1998), while in Belgium, it was estimated to be 7.6% in 1993 (in the semirural area of Heist-op-den-Berg) (Roelands et al. 1994). More recent figures of Belgian dementia prevalence estimates came from the *Antwerp Cognition* (ANCOG) study. This longitudinal cohort study of 825 community-dwelling elderly aged between 75 and 80, living in six different districts of Antwerp, with a 3-year follow-up period ($n = 363$) resulted in an overall prevalence rate of 8.7% (De Deyn et al. 2011).

To give exact numbers, Wimo et al. (2003) assessed the worldwide occurrence of dementia from 1950 until 2000 and also estimated its progression until 2050. The worldwide number of persons with dementia in 2000 was estimated at about 25 million persons. Almost half of the demented individuals lived in Asia (46%), 30% in Europe, and 12% in North America. Fifty-two percent lived in developing regions. About 6.1% of the population aged 65 years and older suffered from dementia (about 0.5% of the worldwide population), and 59% were female. The number of new cases of dementia in 2000 was calculated to be approximately 4.6 million. The forecast indicated a considerable increase in the number of demented elderly from 25 million in the year 2000 to 63 million in 2030 (41 million in less developed regions) and to 114 million in 2050 (84 million in developing regions). In the meantime, the 2015 World Alzheimer Report has updated these numbers, with an expected count of 131 million people worldwide suffering from dementia by 2050 (67 million in Asia, 19 million in Europe, 30 million in the Americas, and 16 million in Africa) (Alzheimer's Disease International 2015).

It thus becomes clear that due to progressive aging of the general population, a further increase of dementia prevalence during the next decades is expected, with an astonishing proportionate worldwide increase of 181% for the period 2015–2050. Moreover, the majority of demented elderly will live in low- and middle-income countries, with an approximate 68% in 2050 (Alzheimer's Disease International 2015).

Less data is available regarding dementia incidence estimates (i.e., a measure of the risk to develop dementia within a specific period of time). Versporten et al. (2005) reported an overall incidence rate of dementia of 41 per 1000 person years (Py) for men and 33 per 1000 Py for women (i.e., 41 or 33 persons out of 1000 that were observed for 1 year). This *Epidemiology Research on Dementia in Antwerp* (ERDA) study started in 1990 and consisted of 937 non-demented elderly aged 65 and older. Moreover, individuals with less than 7 years of education in this study population were—independent of gender—at higher risk of developing dementia compared with those receiving higher education (Versporten et al. 2005). In agreement with the ERDA study, the ANCOG study resulted in a cumulative incidence rate of 36.60 per 1000 Py with annual incidence rates ranging from 34.39 over 35.16 to 49.09 per 1000 Py. In America, the average incidence rate varies between 3 per 1000 Py in people aged 65 up to 69 years old and a maximum of 56 per 1000 Py in 90 year olds (Kukull et al. 2002). These age-dependent figures are consistent with a previously executed large-scale European study (Launer et al. 1999). More recently, Niu et al. (2017) conducted a meta-analysis and concluded that incidence rates of AD in Europe were 3.43, 13.78, and 35.74 cases per 1000 Py for patients aged 65–74 years, 75–84 years, and 85 and older, respectively.

9.1.3 Alzheimer's Disease (AD) and Specific Dementia Syndromes

Dementia syndromes are commonly subdivided according to their reversible or irreversible nature (Katzman et al. 1988).

Primary dementia syndromes are irreversible neurodegenerative disorders such as Alzheimer's disease (AD), frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD), Huntington's disease, and Creutzfeldt-Jakob disease.

On the contrary, secondary dementia syndromes are "potentially" reversible and originate from a specific acquired central nervous system disorder which led to "dementia-like deficits" (i.e., cognitive dysfunction, behavioral phenomenology). Some examples are brain tumors, cerebrovascular accidents (vascular dementia (VAD)), infections (meningitis, AIDS dementia complex), head traumas (subdural hematoma), alcohol abuse (Korsakoff syndrome), or normal pressure hydrocephalus.

Lastly, pseudodementias are "completely" reversible dementia subtypes that very much resemble primary dementia syndromes although the aspect of abundant neurodegeneration itself is absent. Examples are psychiatric disturbances (depression, schizophrenia), endocrine/metabolic disorders (hypothyroidism), malnutrition/vitamin deficiency (vitamin B12 or folic acid deficiency), or toxicological/pharmacological/substance-related conditions (certain sleep medication, anxiolytica, or sedatives) (Katzman et al. 1988).

For this chapter, we will be exclusively focusing on primary dementias such as AD, FTD, and DLB. Secondary and pseudodementias will not be considered in the further discussion of this chapter.

9.1.3.1 Alzheimer's Disease (AD)

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and is named after Dr. Alois Alzheimer, who first described this syndrome in 1906 in a 51-year-old female patient, named Auguste Deter, who suffered from a progressive cognitive impairment associated with significant behavioral changes. A probable major NCD due to AD (code 331.0 (G30.9)) applies with the DSM-5 criteria for the dementia syndrome described above (Table 9.1) (American Psychiatric Association 2013) and is manifested by (1) evidence of a causative genetic mutation from either family history or genetic testing and (2) all three of the following: (a) multiple cognitive deficits such as memory impairment but also aphasia, apraxia, agnosia, and/or executive dysfunctioning; (b) steadily progressive, gradual decline in cognition, without extended plateaus; and (c) no evidence of mixed etiology (e.g., cerebrovascular disease (CVD)). If not all of the preceding criteria are met, possible NCD due to AD should be diagnosed. Additionally, a major NCD due to AD is encoded based on the presence (294.11 (F02.81)) or absence (294.10 (F02.80)) of an associated clinically significant behavioral disturbance. The same categorization can be applied for a probable or possible mild NCD due to AD (American Psychiatric Association 2013).

Diagnosis

The *National Institute on Aging-Alzheimer's Association* (NIA-AA) workgroups (McKhann et al. 2011) updated the *National Institute of Neurological and Communicative Disorders and Stroke* (NINCDS) and the *Alzheimer's Disease and*

Related Disorders (ADRDA) criteria of 1984 (McKhann et al. 1984), which ought to be used by both general healthcare providers without access to neuropsychological testing, advanced imaging, and cerebrospinal fluid (CSF) measures and specialized investigators involved in research or in clinical trial studies who would have these tools available. The NIA-AA criteria have subdivided AD into probable, possible, and definite. Probable AD is characterized by cognitive deficits in at least two cognitive domains with an insidious onset and a progressive worsening over time, a clear-cut history of cognitive worsening by report or observation, and the most prominent cognitive deficits are evident on history or clinical examination in an amnestic (e.g., impairment in learning recall and at least one other cognitive domain) or nonamnestic (aphasia/apraxia/agnosia/executive dysfunctioning) manner (core criteria) (McKhann et al. 2011). Supportive criteria are among others a family history of AD, associated BPSD, disturbed ADL, and a CT scan not displaying central nervous system pathology, which may underlie the dementia syndrome. A new subcategory of probable AD compared to the 1984 criteria is the *probable AD with evidence of the AD pathophysiological process* category. In this category, biomarker evidence of CSF amyloid-beta (Aβ), total- (T-tau) and phosphorylated tau (P-tau$_{181P}$) levels, positive PET amyloid imaging, or a decreased ^{18}fluorodeoxyglucose (FDG) uptake on PET in temporoparietal cortex may increase the certainty of an active AD pathophysiological process in persons who meet the core clinical criteria for probable AD. Possible AD differs from probable AD as it is manifested by a somewhat atypical course and heterogeneity of symptoms with an either sudden onset of cognitive impairment or etiologically mixed presentation, such as concomitant CVD. The core criteria of AD, however, remain present (McKhann et al. 2011).

Finally, definite AD (McKhann et al. 1984) or *pathophysiologically proved AD dementia* (McKhann et al. 2011) is applicable if the core criteria for probable AD were met and in addition a (postmortem) neuropathological examination demonstrated the presence of AD pathology.

In order to better define the various clinical phenotypes and integrate biomarkers into the diagnostic process, covering the full staging of the disease, the International Workgroup (IWG-2) proposed research diagnostic criteria for AD in 2014 (Dubois et al. 2014). Particularly the inclusion and combination of volumetric MRI, amyloid PET, and biomarker panel of CSF A$\beta_{1–42}$, T-tau, and P-tau$_{181P}$ levels have redefined the clinical states of AD into presymptomatic, asymptomatic, typical, atypical, and mixed (with CVD or DLB) (Dubois et al. 2014). Finally, in 2016, the A/T/N classification scheme was introduced by Jack Jr and colleagues (2016) to further highlight the importance of AD biomarkers. The A/T/N system includes the new modality tau PET. Following this classification system, seven major AD biomarkers are divided into three binary categories based on the nature of the pathophysiology that each measures. “A” refers to the value of an Aβ biomarker (amyloid PET or CSF A$\beta_{1–42}$), “T” the value of a tau biomarker (CSF P-tau$_{181P}$ or tau PET), and “N” biomarkers of neurodegeneration or neuronal injury (FDG-PET, structural MRI, or CSF T-tau). Each biomarker category is rated as positive or negative. An individual score might appear as A+/T+/N−, A+/T-/N−, etc.

With reference to the A/T/N classification system, Jack et al. introduced the NIA-AA research framework in 2018 (Jack Jr et al. 2018). Its intended use is for observational and interventional research only, not routine clinical care. Unlike the 2011 NIA-AA guidelines, AD is defined as a continuous process in both cognitive and biomarker domains rather than as three separate clinical entities (i.e., cognitively unimpaired, mild cognitive impairment (MCI), dementia). The use of biomarkers is also harmonized across the disease continuum in this research framework, which was not the case in 2011. Furthermore, the research framework outlines two different systems for staging of severity of cognitive symptoms, i.e., a *syndromal categorical scheme*, which defines different A/T/N biomarker combinations over the three previously mentioned cognitive stages in function of the Alzheimer's continuum profile, and, a *numerical clinical staging scheme* (stages 1–6), which describes the gradual disease progression for individuals of the Alzheimer's continuum, mainly based on clinical, neuropsychological, and neurobehavioral observations and tests.

Pathophysiological Mechanisms

AD and other dementia subtypes are all proteinopathies. The histopathological hallmarks of the AD brain are extracellular deposits of Aβ plaques and intracellular neurofibrillary tangles (NFT), which lead to a widespread synaptic loss and neurodegeneration with a consequent neurotransmission failure, especially of the cholinergic neurotransmitter system (Van Dam and De Deyn 2006). Familial AD is an autosomal dominant disorder with onset before the age of 65 (Blennow et al. 2006). Mutations in the amyloid precursor protein (APP) gene on chromosome 21 or in the presenilin 1 (PSEN1) or presenilin 2 (PSEN2) genes account for familial early-onset cases, which cause fully penetrant monogenic forms of AD. However, these rare familial forms, often explained by rare variants with a strong effect, only have a prevalence of approximately 1% (Harvey et al. 2003). In most sporadic AD cases (>95%) with an age of onset above 65, the etiology is not entirely known. These late-onset AD (LOAD) cases are influenced by multiple common variants with low effect sizes. In January 2019, a new genome-wide association study of more than 600,000 individuals identified nine novel AD risk genes, raising the total count of independent risk loci to 29 (Bertram and Tanzi 2019; Jansen et al. 2019). The apolipoprotein E (APOE) is the strongest genetic risk locus for LOAD. The APOE ε4 allele may increase the risk of the disease by 3 times in heterozygotes and 15 times in homozygotes (Jansen et al. 2019; Farrer et al. 1997). Other examples are PICALM, TREM2, ADAMTS4, ALPK2, ABCA7, HESX1, CLNK, and, KAT8 (Jansen et al. 2019).

The *amyloid cascade hypothesis* is the most dominant etiological AD hypothesis and states that Aβ accumulation results from an imbalance between Aβ production and clearance (Blennow et al. 2006). Physiologically, APP is a cell membrane expressed protein not only in neurons but also in many other tissues and is likely to be involved in maintenance and modulation of neuronal networks (Loo et al. 1993). Posttranslational cleavage of APP by consecutive α- and ɣ-secretases releases a p3-fragment (non-amyloidogenic pathway), whereas the combined effect of β- and

ɣ-secretases releases non-soluble Aβ peptides of various lengths, i.e., $Aβ_{1–40}$ or $Aβ_{1–42}$ (amyloidogenic pathway). In normal situations, the non-amyloidogenic pathway is mostly active. In familial AD, however, a mutation in PSEN1/PSEN2 (which form the catalytic subunits of the secretases) or around the cleavage site of APP causes an overproduction of the hydrophobic $Aβ_{1–42}$ and consequently leads to a shifted $Aβ_{1–40}/Aβ_{1–42}$ balance. This is mainly due to a destabilization of the ɣ-secretase/$Aβ_n$ complexes, which further enhances amyloidogenic $Aβ_{1–42}$ production (Szaruga et al. 2017). As a result, enormous amounts of $Aβ_{1–42}$ fragments aggregate and form extracellular "senile plaques" (Hardy and Selkoe 2002). Whereas in familial AD there is an overproduction of $Aβ_{1–42}$ due to certain mutations, sporadic AD cases seem to fail sufficient Aβ clearance which leads to gradually increasing and accumulating Aβ levels in the brain. As mentioned above, genetic risk factors such as APOE ε4 but also aging and certain environmental risk factors were proven to be strongly associated with sporadic AD (Blennow et al. 2006).

The second hallmark of AD pathology is the presence of intracellular NFT, which results from the hyperphosphorylation and aggregation of the axonal tau proteins, a group of microtubule-associated proteins that contribute to the assembly and stabilization of microtubules in neurons among others (Grundke-Iqbal et al. 1986). Tau phosphorylation is regulated by the balance between multiple kinases (e.g., GSK-3β and CDK5) and phosphatases (e.g., PP-1 and PP-2A) (Iqbal et al. 2005). An imbalance between the protein kinases and phosphatases causes tau to be hyperphosphorylated into insoluble fibrils, also called "paired helical filaments." Tau hyperphosphorylation starts intracellularly and leads to sequestration of normal tau and other microtubule-associated proteins, which causes disassembly of microtubules and thus impaired axonal transport, compromising neuronal and synaptic function (Iqbal et al. 2005). Tau pathology starts early in the disease process in neurons of the transentorhinal region, from where it further spreads to the hippocampus and amygdala and finally to other cortical and neocortical association areas (Braak et al. 1999; Smith 2002).

Figure 9.2 depicts the pathological spread of Aβ and tau in AD brain. Interestingly, tau aggregates have been theorized to spread in a bottom-to-top-like fashion, starting from the locus coeruleus (LC) in the brainstem and moving upward toward the entorhinal cortex and neocortex.

Besides Aβ deposits and NFT, oxidative stress and inflammation are two key factors in the etiological hypotheses of AD as well.

Oxidative damage to different classes of biological molecules such as sugars, lipids, proteins, and DNA is a common aspect of both normal aging and most neurodegenerative disorders (Moreira et al. 2005). In early AD, oxidative stress might have an important pathogenic role as neurons themselves use different antioxidant defense systems in case of increased oxidative stress. Evidence demonstrates that Aβ depositions and hyperphosphorylation of tau form two primary defense lines against oxidative stress. With disease progression, both Aβ and tau transform into prooxidants due to a profound redox imbalance (Smith et al. 2002).

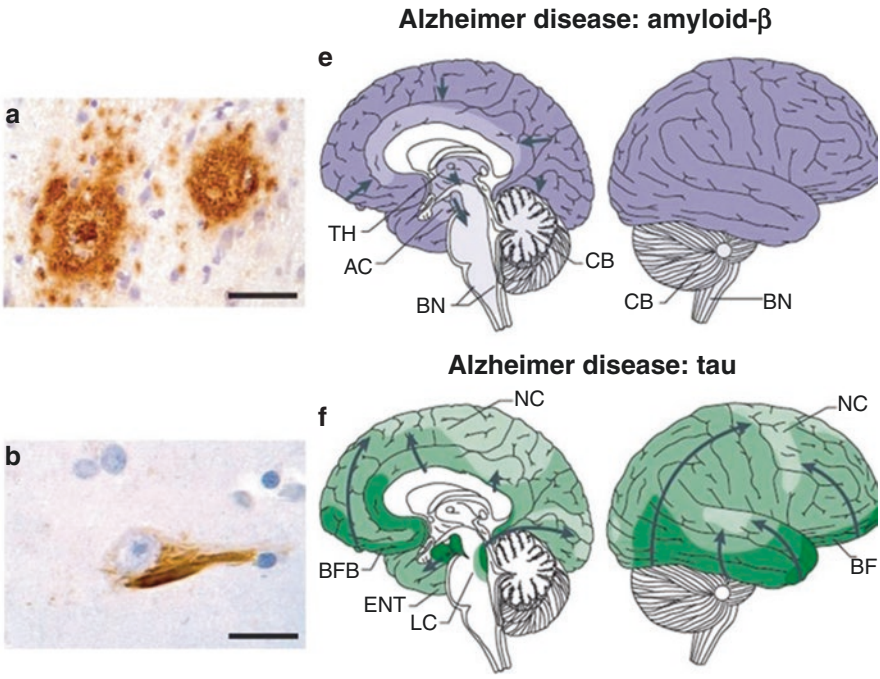


Fig. 9.2 Progressive expansion of amyloid-beta (Aβ) and tau pathology in Alzheimer's disease (AD) brain. (**a**) Aβ plaques in the cortex of an AD patient (50 μm scale bar); (**b**) tau neurofibrillary tangle in a neuron of an AD patient (20 μm scale bar); (**e**) Aβ deposits are first observed in the neocortex and are then detected in all cortical, diencephalic, and basal ganglia structures (in a caudal direction) and in the brainstem, and occasionally in the cerebellum; (**f**) tau aggregates develop in the locus coeruleus, then in the transentorhinal and entorhinal regions, and, subsequently, in the hippocampal formation and in broad areas of the neocortex. Abbreviations: *AC* Allocortex; *BFB* Basal forebrain, *BN* Brainstem nuclei, *CB* Cerebellum, *ENT* Entorhinal cortex, *LC* Locus coeruleus, *NC* Neocortex, *TH* Thalamus. Adapted with permission from Carbonell F et al. (2018) Front Neurol 9:37 under the CC-BY license 4.0 (http://creativecommons.org/licenses/by/4.0). Copyright © 2018 Carbonell, Iturria-Medina and Evans

With regard to inflammation, it has been proven that many neuroinflammatory mediators are upregulated in affected areas of the AD brain, including prostaglandins, complement components, anaphylatoxins, cytokines, chemokines, proteases, protease inhibitors, adhesion molecules, and free radicals (Akiyama et al. 2000). Côté et al. (2012) established a direct association between the prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs), which target cyclooxygenase (COX), and a decreased risk of subsequently developing AD even though several other clinical studies using NSAIDs in AD patients yielded a negative outcome (ADAPT Research Group et al. 2008; Breitner et al. 2011). Initially, the effect of NSAIDs in AD was thought to be attributed to a reduction of inflammation. In 2001, however, it was reported that a subset of NSAIDs reduced $A\beta_{1-42}$ production in cultured cells and mouse brain through a mode of action different from COX inhibition

(Weggen 2001). On the other hand, recent studies have observed that immune checkpoint blockade directed against the programmed death-1 (PD-1) pathway evokes an interferon-γ-dependent systemic immune response, which is followed by the recruitment of monocyte-derived macrophages to the brain. In mice with established AD pathology, this leads to clearance of plaques and improved cognitive performance (Baruch et al. 2016). As a consequence, anti-PD-1 ligand antibodies (immunotherapy) hold promise as a new therapeutic avenue for AD.

Interestingly, the induced neuroinflammation in AD might also lie at the basis of some BPSD, such as depression. For example, the enzyme indoleamine 2,3-dioxygenase (IDO) metabolizes tryptophan, the precursor of serotonin (5-hydroxytryptamine (5-HT)), into kynurenine. Due to neuroinflammation, the IDO activity becomes upregulated, and eventually the kynurenine catabolization further leads to an overproduction of quinolinic acid, the neurotoxic end product of the tryptophan pathway which also contributes to the excitotoxic effects in an AD brain. The altered tryptophan levels consequently affect 5-HT synthesis, which is a neurochemical hallmark in the etiology of depression. Neuroinflammation by upregulating IDO and consequently lowering tryptophan levels has thus been linked with major depressive disorder in AD patients (Dobos et al. 2010). Additionally, CSF levels of the anti-inflammatory cytokine interleukine-10 have also been inversely associated with BPSD in AD patients, of which agitation, depression, and nighttime behavior in particular (Holmgren et al. 2014).

AD is conventionally regarded as a central nervous system disorder, even though various studies implicated that the impact of the disease extends far beyond the brain. For instance, the gut microbiome has a profound impact on the formation of the blood-brain barrier, myelination, neurogenesis, and microglia maturation. The gut-brain axis, therefore, could be an important modifiable pathway in dementia as well (for review, see (Du et al. 2018)).

9.1.3.2 Other Dementia Subtypes

Apart from AD which is the most prevalent dementia syndrome (65% approximately), AD with cerebrovascular disease (AD+CVD), vascular dementia (VAD), dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD), and frontotemporal dementia (FTD) together roughly account for the other 35% (Fig. 9.3) (Small et al. 1997; Mikkelsen et al. 2016).

Below, DLB and FTD are briefly described as they significantly differ from AD concerning their diagnostic criteria, pathogenesis, disease course, and behavioral profiles.

Dementia with Lewy Bodies (DLB)

Dementia with Lewy bodies (DLB) is the third most prevalent primary dementia subtype and is diagnosed according to McKeith et al. (McKeith et al. 2005, 2017). Similar with AD, several core and supportive criteria need to be present in order to establish a clinically acceptable DLB diagnosis. A fourth consensus report of the DLB consortium was established in 2017 (McKeith et al. 2017). The four core criteria are (i) a fluctuating cognition, (ii) recurrent and well-described visual

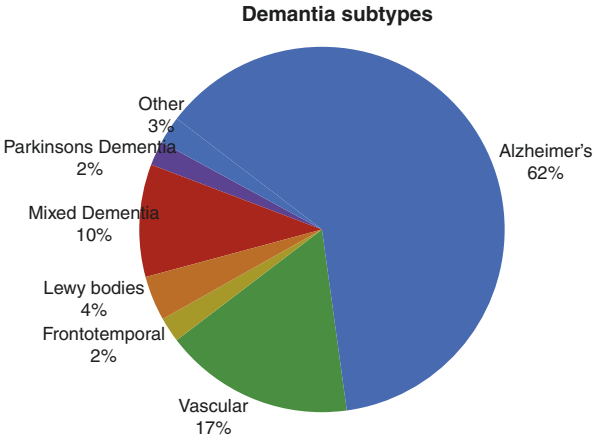


Fig. 9.3 Different etiological diagnoses of dementia. Alzheimer's disease is the most prevalent dementia subtype (±62%), followed by vascular dementia (±17%), Alzheimer's disease + cerebrovascular disease (mixed dementia; ±10%), dementia with Lewy bodies/Parkinson's disease dementia (±6% in total), frontotemporal dementia (±2%), and other dementias (±3%). Reprinted from Mikkelsen et al. (2016) Maturitas 93:108-113, with permission from Elsevier. Copyright © 2016 Elsevier Inc

hallucinations, (iii) REM sleep behavioral disorders (RBD), and (iv) clinical signs of overt parkinsonism (extrapyramidal symptoms (EPS), tremor, rigidity, and hypokinesia). The presence of only two core criteria or one core criterion but with one or more indicative biomarkers is sufficient to diagnose "probable" DLB. "Possible" DLB can be diagnosed if only one core criterion is present or no core criteria but only one or more indicative biomarkers. Some other supportive criteria are autonomic dysfunction, depression, apathy, anxiety, delusional ideation, repeated falls, and severe sensitivity to antipsychotic agents. New in comparison with the 2005 criteria is the inclusion of indicative biomarkers, such as reduced dopamine (DA) transporter (DAT) uptake in basal ganglia demonstrated by SPECT or PET, abnormal (low uptake) of ^{123}iodine-metaiodobenzylguanidine (MIBG) following myocardial scintigraphy, or, polysomnographic confirmation of REM sleep without atonia (McKeith et al. 2017). In addition, supportive biomarkers have been enlisted, such as the relative preservation of medial temporal lobe structures on CT/MRI scan, the generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity, and the cingulate island sign on FDG-PET imaging.

As in the 2005 criteria, the difference between DLB and PDD is solely based upon the temporal sequence of appearance of the extrapyramidal symptoms: DLB should be diagnosed when dementia occurs before (at least 1 year in research studies) or concurrently with parkinsonism. The term PDD should be used to describe dementia that occurs in the context of well-established PD (McKeith et al. 2005, 2017; Geser et al. 2005).

The main pathological characteristic of DLB is the presence of cytoplasmic aggregated inclusions of α-synuclein, generally known as "Lewy bodies" (Vladimir

2007). Synucleinopathies form a group of neurodegenerative disorders that share common pathologic proteinaceous lesions containing aggregated α-synuclein molecules which are deposited in neurons, nerve fibers, or glial cells (Goedert 1999, 2001), often in combination with AD plaques and NFT (McKeith et al. 2017), which frequently hampers differential diagnosis among these dementia syndromes. Specifically in DLB, Lewy bodies precipitate not only in the substantia nigra (pars compacta) of the basal ganglia and LC but also in the neocortex and hippocampus (McKeith et al. 2005). Only when a loss of dopaminergic neurons of 80% or more in the substantia nigra is reached, EPS will set off. Several case studies demonstrated the occurrence of familial DLB cases (Gwinn-Hardy and Singleton 2002) and that Lewy bodies are commonly seen in familial cases of AD as well (Trembath et al. 2003). There are reports of triplications of the α-synuclein (SNCA) gene in DLB, PD, and PDD patients, whereas SNCA gene duplications only seem to be associated with motor PD, suggesting a possible gene dose effect (Singleton and Gwinn-Hardy 2004). However, SNCA gene multiplications were not found in most sporadic DLB cases (Johnson et al. 2004). A study by Guerreiro and colleagues (2016) showed that DLB shares approximately the same amount of genetic determinants with PD as it does with AD, hereby excluding the strong association at the APOE locus.

Frontotemporal Dementia (FTD)

A less frequent and very heterogeneous neurodegenerative disorder is frontotemporal dementia (FTD). Neary et al. (1998) established the diagnostic criteria of among others *behavioral variant* FTD—simply referred to as FTD—which forms one of the three diagnostic entities of "frontotemporal lobar degeneration" (FTLD), together with primary progressive aphasia and semantic dementia (SD). Latter two syndromes have been recategorized into semantic variant primary progressive aphasia and nonfluent/agrammatic aphasia variant. Typical for FTD patients is the very early disease onset compared to AD or DLB, namely, between the age of 45 and 70. At onset of the syndrome, there may typically be a neglect of personal hygiene, disinhibition, loss of insight and judgment, social neglect, and emotional disturbance (i.e., emotional bluntness, impaired control of emotions) in contrast to a comparatively spared memory and spatial abilities (core criteria). A subsequent cognitive impairment is inevitable although in the beginning amnesia remains surprisingly absent. FTD thus initially manifests itself by subtle changes in behavior and character (Neary et al. 1998; De Deyn et al. 2005). Some other typical behavioral characteristics are the expression of stereotypes and changes in sexual behavior, dietary hyperactivity, speech disturbances (echolalia, mutism, logorrhea), and restlessness. From a clinical point of view, FTD is likely to be recognized and distinguished from AD solely due to this distinctive behavioral pattern (De Deyn et al. 2005).

Genetics have a major role in FTLD, with up to 43% of patients having a positive family history. On the neuropathological level, a distinction must be made between tauopathies and non-tauopathies. Tauopathies are caused by a mutation in the *microtubule-associated protein tau* (MAPT) gene (Bancher et al. 1987; Sieben et al. 2012), whereas non-tauopathies can be etiologically defined by mutations in the

progranulin (GRN) (Cruts et al. 2006) and *TAR DNA-binding protein 43* (TDP-43) gene among others (Arai et al. 2006; Neumann et al. 2006). Mutations in the MAPT gene cause cytoplasmic tau to aggregate which leads to the formation of tangles and eventually to neuronal death, especially in frontotemporal cortical areas. This phenomenon is known as Pick's disease, but also progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are classified as tauopathies (FTLD-tau; (Keith 2008)). In addition to GRN and TDP-43, mutations in C9Orf72, TBK1, and VCP genes all cause TDP-43 aggregates (non-tauopathies, FTLD-TDP), leading to a consequent neuronal degradation and dementia syndrome (for review, see (Sieben et al. 2012; Van Mossevelde et al. 2018)). Histopathologically, these aggregates are visible as tau-negative but ubiquitin (U)-positive inclusions so that non-tauopathies are generally categorized as FTLD-U. Approximately 60% of patients with FTLD have protein inclusions that stain positive for U and contain TDP-43 as the major constituent. Four distinct subtypes of FTLD-TDP pathology can be differentiated (A/B/C/D), and TDP-43 inclusions are also present in patients with motor neuron disease. Remarkably, an estimated 15% of all patients with FTD develop amyotrophic lateral sclerosis (ALS), indicating the presence of a disease continuum between FTLD and ALS (Gijselinck et al. 2012).

In addition to FTLD-TDP and FTLD-tau, three more subtypes are identified on the basis of the major protein inclusion constituent: FTLD-FET (a collective term for FTLD with inclusions of the RNA-binding proteins FUS or EWS (also known as EWSR1) or TATA-binding protein-associated factor 2N (TAF15)), FTLD-UPS (featuring inclusions of proteins of the ubiquitin-proteasome system, for instance, in the case of CHMP2B gene mutations), and FTLD-ni (no inclusions) (for review, see (Van Mossevelde et al. 2018)).

9.2 Behavioral and Psychological Signs and Symptoms of Dementia (BPSD)

Besides cognitive disturbances, dementia is characterized by numerous behavioral disturbances too, categorized as *behavioral and psychological signs and symptoms of dementi*a (BPSD) (Reisberg et al. 1987; Finkel et al. 1996) and also referred to as *neuropsychiatric symptoms* (NPS) (Geda et al. 2013). BPSD are a heterogeneous group of behavioral, psychological, and psychiatric disturbances occurring in 50–80% of dementia patients of any etiology (Finkel et al. 1996) and affect almost all individuals with dementia (97%) over the course of the disease (Lanctôt et al. 2017). These behavioral and psychological symptoms are generally classified into seven main subtypes: paranoid and delusional ideation, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbances, and anxieties/phobias (Reisberg et al. 1987). BPSD often lead to a greater amount of caregiver distress, diminished quality of life for both patient and caregiver, greater cognitive impairment (Weamer et al. 2009), premature institutionalization, frequent (re)hospitalizations, and increased secondary morbidity and mortality (Finkel

2000). Last but not least, BPSD also have a significant and increasing socioeconomic impact (Beeri et al. 2002) (Fig. 9.1).

Distinct BPSD syndromes have different neurobiological underpinnings, so understanding the dysfunction or dysregulation of subcortical forebrain and diencephalic and brainstem nuclei that generate or mediate visceral, emotional, motivational, and other psychiatric symptoms will be required. The involvement of, for example, NFT and amyloid plaques in critical brain regions in AD regulating these behaviors, is, therefore, important and needs to be recognized. Understanding of neuropathology is also fundamental for future drug development, where currently approved treatments for mood and psychotic symptoms, such as antidepressants and antipsychotics, may not work because of the lack of target engagement in a degenerating brain (Lanctôt et al. 2017).

From a neurochemical point of view, alterations in central noradrenergic (Engelborghs et al. 2008; Herrmann et al. 2004; Lanari et al. 2006; Matthews et al. 2002), serotonergic (Engelborghs et al. 2008; Garcia-Alloza et al. 2005; Lanctôt et al. 2001; Vermeiren et al. 2014, 2015), and dopaminergic (Engelborghs et al. 2008; Lanari et al. 2006; Vermeiren et al. 2016) neurotransmitter systems and associated receptors proved to play a critical role in BPSD manifestation, irrespective of the dementia subtype (Vermeiren et al. 2016, 2013). Particularly the balance between those different neurotransmitter systems seems to be of importance as it is conceivable, due to the neurochemical complexity and diversity of BPSD, that more than one neurotransmitter system contributes to a particular behavioral syndrome (Lanari et al. 2006). Studying neurotransmitter systems in isolation cannot fully explain changes in behavior, given that many neurotransmitter systems work in conjunction with each other. In spite of this difficulty, the neurochemical mechanisms underlying BPSD are proven to be both BPSD- and dementia-specific (Engelborghs et al. 2008; Vermeiren et al. 2013), so that dementia-specific neurochemical alterations might be found. There is also supportive evidence for amino acids playing a functional role in the neurochemical pathophysiology of BPSD (Engelborghs et al. 2003; Fekkes et al. 1998; Francis 2009; Garcia-Alloza et al. 2006), with, for example, significantly high correlations between CSF taurine levels and depression in AD and CSF glutamate levels and agitation in FTD (Vermeiren et al. 2013).

Engelborghs et al. (2005) showed that different behavioral patterns can be observed depending on the dementia subtype, thereby further stressing that the behavioral assessment itself may help in differentiating between different forms of dementia (Fig. 9.4).

In 1996, Jost and Grossberg (Jost and Grossberg 1996) examined the frequency of BPSD in temporal relationship with the diagnostic progression of AD patients. The authors showed that, for example, depression occurs already 25 months before a proper clinical diagnosis was made in over 50% of patients. Agitation is mostly present some 10 months following the clinical AD diagnosis in over 80% of patients. In contrast to the cognitive symptoms in AD which progressively worsen during its course, BPSD seem different, as some behavioral symptoms are severely present during the early disease stages (e.g., depression, paranoia, diurnal rhythm disturbances) although later on these symptoms might gradually diminish or even

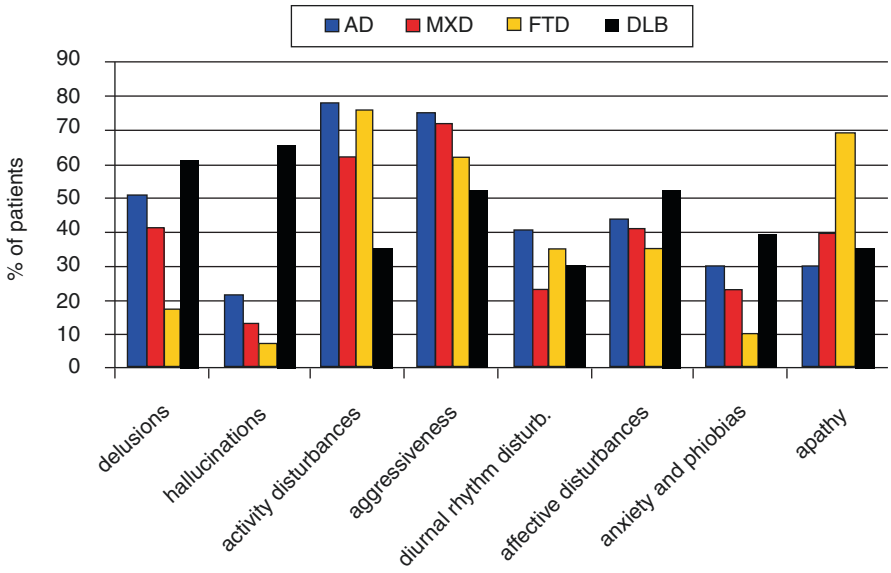


Fig. 9.4 Frequency of dementia-specific BPSD items. This figure shows that, for example, apathy is much more frequent in FTD as compared to AD/MXD/DLB, whereas delusions, hallucinations, and anxieties are less frequently present in FTD compared to DLB. Abbreviations: *AD* Alzheimer's disease, *BPSD* Behavioral and psychological signs and symptoms of dementia, *DLB* Dementia with Lewy bodies, *FTD* Frontotemporal dementia, *MXD* Mixed dementia. Based upon Engelborghs et al. (2005) *Int J Geriatr Psychiatry* 20:1028–1037

completely disappear, to be eventually replaced by other BPSD items (e.g., aggression, hallucinations, wandering). Another investigation regarding the prevalence of specific BPSD in AD was performed by Fernández et al. (2010). The authors concluded that out of a total of 1014 patients, almost all (90%) had BPSD at inclusion, 17% of which reported psychotic outbreaks. The most prevalent symptoms were lack of concentration (56%), tremors (56%), depression (44%), lack of cooperation (36%), and delusions (32%). They also showed that cognitive impairment and BPSD were correlated.

9.2.1 Delusional Ideation and Hallucinations: The Psychotic Syndrome

Approximately more than 40% of dementia patients of any etiology and up to 73% of AD patients suffer from delusional ideation during the disease course (Finkel 2001). The most prominent delusion according to Reisberg et al. (1987) is suspiciousness/paranoia, i.e., the conviction that people are stealing things from the patient. Other frequently occurring delusions are the "one's house is not one's home delusion" or the accusation of infidelity toward their spouse or caregiver. Delusions are frequently associated with verbal and physical aggression which in most cases

leads to an untenable situation at home and premature institutionalization (Deutsch et al. 1991). Deutsch et al. (1991) suggest delusions to be risk factors in patients with probable AD who have moderate-to-severe cognitive impairment.

In patients with AD, psychosis occurs more frequently in women than in men. Some other predisposing factors besides gender for psychotic symptoms are age, severity of illness, and cognitive deterioration (Hirono et al. 1998). Weamer et al. (2009) found that the severity of cognitive impairment was a strong predictor of psychosis in AD patients up to 2 years prior to psychosis onset.

Hallucinations in dementia patients are less frequent than delusions, with a prevalence rate of 12 up to 49% (Swearer 1994). Hallucinations and delusions are characteristic for specifically DLB patients, as shown in Fig. 9.4 (based upon Engelborghs et al. (2005)). A hallucination is the patient's strict conviction of a sensory perception in the absence of sensorial stimulation. Reisberg et al. (1987) made a distinction between visual, auditory, olfactory (smell), and haptic (touch) hallucinations. It is noticeable that hallucinations are more likely to occur in patients with more severe cognitive deterioration compared to patients with mild forms of dementia (Devenand et al. 1997). Moreover, hallucinations are less stressful for dementia patients than delusions so that pharmacological treatment is less mandatory (De Deyn 2004).

AD patients with psychosis have been reported to deteriorate twice as fast as patients without psychotic symptoms (Rosen and Zubenko 1991). Similarly, Scarmeas et al. (2005) studied whether the presence of delusions and hallucinations has predictive value for important outcomes in AD patients, such as cognitive and functional decline. Their results confirmed that the presence of delusions and hallucinations was associated with an increased risk for cognitive and functional decline, institutionalization, and even death.

It is noteworthy that psychosis of AD is a distinct syndrome that is markedly different from, for example, schizophrenia in elderly patients. Numerous research groups have reported potentially relevant clinical, neuropsychological, neurochemical, neurobiological, and neuropathological differences between AD patients with and without psychosis (Jeste and Finkel 2000). In the past, there have been no specific criteria for diagnosing psychosis in AD as a distinct entity. Therefore, Jeste and Finkel have proposed several core criteria in 2000 in order to correctly diagnose the psychotic syndrome in AD (Jeste and Finkel 2000). Characteristic symptoms are the presence of one (or more) visual/auditory hallucination(s) and/or delusion(s). Also, there has to be evidence from the patient's history that these symptoms have not been continuously present prior to dementia onset. The symptoms also must have been present for at least 1 month or longer and have to cause some disruption in the patient's functioning. Moreover, schizophrenia and related psychotic disorders as well as a delirium or other causes (e.g., substance-related) that might have initiated the psychosis need to be excluded. Finally, associated behavioral features such as agitation, negative symptoms, and/or depression might be present as well.

All criteria may also apply to a similar psychotic syndrome associated with other dementias such as DLB, VAD, and MXD.

9.2.2 Agitation and Aggression

Agitation includes inappropriate verbal, vocal, or motor behaviors that, in the opinion of an observer, do not result directly from the needs or confusion of the agitated individual (Cohen-Mansfield and Deutsch 1996). Approximately 80% of dementia patients will suffer from agitation during the disease course. Agitation therefore is one of the most frequently (re)occurring BPSD (Allen and Burns 1995). In 2000, Lyketsos et al. (2000) reported the prevalence of agitation and other BPSD in 329 participants with dementia (the Cache County Study on Memory in Aging, Utah), of which 65% had AD, and concluded that agitation and aggression were present in approximately 24% of dementia patients. Given that the estimates were only considered over 1 month before behavioral assessments and due to the episodic course of this behavioral symptom, Lyketsos et al. (2000) mentioned that these prevalence numbers were an underestimation of the cumulative prevalence which may approach 70–80%. Subsequently, the Cache County Study was resumed in 2003 (Steinberg et al. 2008) in which an incident sample of 408 dementia participants was behaviorally assessed during a 5-year follow-up period. At the end, 42% of dementia participants developed agitation.

In general, agitation mostly occurs in the moderate stages of dementia and less in mild or severe dementia stages (Lyketsos et al. 2000; Cohen-Mansfield et al. 1989). Cohen-Mansfield et al. (1989) make a distinction between physically nonagitated behavior (e.g., restlessness, pacing, cognitive abulia, wandering, inappropriate (dis)robing) and verbally agitated behavior (e.g., negativism, complaining, repetitive sentences or questions, strange noises, unwarranted request for attention).

Aggression has a frequency between 20 and 30% (Allen and Burns 1995) and can be divided into physically aggressive behavior (e.g., hitting, kicking, pushing, scratching, biting) and verbally aggressive behavior (e.g., screaming, cursing) (De Deyn 2004). In general, physically aggressive behavior is more common in male dementia patients compared to females (Cohen-Mansfield and Deutsch 1996). Furthermore, aggression in dementia patients is associated with depression according to Lyketsos et al. (1999).

9.2.3 Diurnal Rhythm Disturbances

Sleep disturbances can be subdivided into difficulties falling asleep, multiple awakenings during sleep, early morning awakenings, or a completely inversed sleep-wake pattern (Prinz et al. 1982). Insomnia in dementia also seems to be the most prominent reason for an eventual institutionalization according to Harper et al. (2001). One specific diurnal rhythm disturbance is *sundowning*, a situation in which patients are relatively calm during the day but as evening falls show an exacerbation of behavioral symptoms, such as pacing, wandering, and repetitive, purposeless activities (cognitive abulia) (Little et al. 1995).

9.2.4 Depression

In AD, depression has a prevalence of 20 (Castilla-Puentes and Habeych 2010) up to 50% (Starkstein et al. 2005). Depression is mostly present in mild-to-moderate AD or even 2 years before the established AD diagnosis (Jost and Grossberg 1996; Alexopoulos et al. 1988). A major depressive episode in dementia is characterized by mood-related signs (anxiety, lack of reactivity to pleasant events, irritability), behavioral symptoms (agitation, retardation (slow movements and speech), loss of interest, physical complaints), physical signs (appetite and weight loss, lack of energy), sleep rhythm disturbances, and ideational disturbances (pessimism, suicidal wishes, poor self-esteem) (Alexopoulos et al. 1988). Besides the behavioral aspects, depression is also characterized by deficits in verbal and visual memory, concentration, and executive functioning (Sierksma et al. 2010). Several research groups have even suggested that depression in general might be a prodrome (i.e., a premonitory symptom indicating the onset of a disease, risk factor) of developing AD (Caraci et al. 2010; Korczyn and Halperin 2009), given the fact that the pathophysiological properties of depression and some etiological hallmarks of AD are related (e.g., increased neuroinflammation, monoaminergic deficiency, increased synaptic neurodegeneration, and altered neurotrophic factors) (Sierksma et al. 2010). Depressed dementia patients also have a higher mortality rate compared to their nondepressed counterparts (Rovner et al. 1991).

9.2.5 Activity Disturbances

According to Reisberg et al. (1987), activity disturbances form a separate entity in the behavioral phenomenology of AD patients among others. Approximately 80% of AD patients suffer from activity disturbances (Engelborghs et al. 2005), which can be best described as a form of physical agitation. Some examples are wandering, purposeless activities (e.g., cognitive abulia, such as repetitive (dis)robing, pacing), and inappropriate activities (inappropriate physical sexual advances, hiding objects, hoarding) (Reisberg et al. 1987). In some cases, activity disturbances are severe enough to require restraint or even result in abrasions (e.g., pacing) or physical harm. Besides AD, FTD patients characteristically suffer from certain types of activity disturbances as well, mainly stereotype movements (e.g., tapping, hand clapping, patting, hand rubbing, wandering a fixed route) and general restlessness (aimless wandering, pacing, fidgeting, inability to sit still) (De Deyn et al. 2005).

9.2.6 Anxieties and Phobias

Although less frequent, anxiety is a psychological symptom in dementia patients which is present in different variants (De Deyn 2004). Anxiety or fear of being left alone and the "Godot syndrome" are two frequent types of anxiety in AD patients (Reisberg et al. 1987). In case of "Godot syndrome," patients repeatedly and

constantly ask questions concerning a completely normal but approaching event such as meeting with the family doctor (Reisberg et al. 1986). This term was firstly described in the late 1980s by Reisberg et al. (1986) and is an extreme form of anxiety in dementia patients and sometimes requires the patient to be accompanied at all times. On the other hand, pacing, stereotype behavior, and restlessness might be physical reflections of a rooted anxiety residing within the patient. A phobia is an anxiety disorder which is disproportional to the actual danger, often being irrational. Examples are fear of traveling, bathing, darkness, and overcrowded places (De Deyn 2004).

9.2.7 Apathy

In the context of dementia, apathy has been defined as a disorder of diminished motivation that persists over time for at least 4 weeks with an additional reduced goal-directed behavior, cognitive activity, and emotions (Robert et al. 2009). These relatively new criteria have been established due to the overlap between apathy and depression among others. Apathy is a common behavioral disorder not only in AD but also in PD, FTD, and stroke (Levy et al. 1998). Results from the *European Alzheimer's Disease Consortium* study in 2007 showed that apathy is the most prominent and persistent neuropsychiatric syndrome in dementia as it occurred in 65% of 2354 AD patients (Aalten et al. 2007). Additionally, it is also present during all stages of the disease (Lyketsos et al. 2011; Robert et al. 2009), and there is a growing body of evidence that it might be indicative of a pre-dementia state (Robert et al. 2009; Ready et al. 2003). More recently, van der Linde et al. (2016) performed a systematic literature review and analyzed the baseline prevalence, persistence, and incidence of 11 BPSD symptoms. In total, 59 studies were included in these analyses. In the end, the authors confirmed that despite heterogeneity across studies in terms of setting, focus, and length of follow-up, apathy was the only symptom with high baseline prevalence, persistence, and incidence during the course of dementia.

9.3 Behavioral Assessment Scales

In order to evaluate this large group of behavioral and neuropsychiatric symptoms in dementia patients, different behavioral assessment scales have been developed throughout the years. The most common are described below, i.e., *Middelheim Frontality Score* (MFS), *Behavioral Pathology in Alzheimer's Disease Rating Scale* (Behave-AD), *Cohen-Mansfield Agitation Inventory* (CMAI), *Geriatric Depression Scale* (GDS), *Cornell Scale for Depression in Dementia* (CSDD), and *Neuropsychiatric Inventory* (NPI). All these scales are very useful assessment tools to identify the behavioral profile of dementia patients or even to distinguish between different types of dementia (De Deyn et al. 2005). The efficacy of novel psychotropic medication in the treatment of BPSD can also be demonstrated by the use of these well-validated and drug-sensitive behavioral scales mentioned above, such as

Behave-AD, CMAI, and NPI (De Deyn and Wirshing 2001). Moreover, these behavioral assessment scales are widely used to study the neuroanatomical and pathophysiological etiology of different behavioral phenotypes in dementia in combination with neuroimaging data.

9.3.1 Middelheim Frontality Score (MFS)

The *Middelheim Frontality Score* (MFS) is a clinical and behavioral assessment tool which measures frontal lobe features and, in contrast to classical behavioral scales, reliably discriminates FTD from AD patients (De Deyn et al. 2005). The MFS is rated by a clinician and is obtained by summating the scores in a standardized fashion on ten different items. Each item is scored either zero (absent) or one (present) yielding a total maximal score of 10. Information is obtained through an interview of the patient and her/his professional and/or main caregiver, clinical files, and behavioral observation. The ten items are (item 1) initially comparatively spared memory and spatial abilities that reflect the neurobehavioral onset of the disease; frequently occurring personality and behavioral changes like (item 2) loss of insight and judgment; (item 3) disinhibition; (item 4) dietary hyperactivity (referring to overeating); (item 5) changes in sexual behavior (hypersexuality as well as the more frequently occurring hyposexuality); (item 6) stereotyped behavior (encompasses all kinds of stereotyped behavior, both simple repetitive behaviors (can also be oral) as complex behavioral routines as wandering); (item 7) impaired control of emotions, euphoria, or emotional bluntness; (item 8) aspontaneity; (item 9) speech disturbances such as stereotyped phrases, logorrhoea, echolalia, and mutism; and, finally, (item 10) restlessness. Although the NPI is able to correctly classify 77% of AD and FTD patients (Levy et al. 1996), the frequently used Behave-AD and CMAI lack sensitivity for FTD as they have been specifically developed for AD patients. The Behave-AD even underestimates BPSD in FTD patients as was shown by Engelborghs et al. (2004): 28 FTD patients had significantly lower Behave-AD total scores compared to 152 AD patients, whereas the Behave-AD global scores (reflecting caregiver burden) were not different between both patient groups. Moreover, Pickut et al. (1997) previously showed that the total MFS scores correlated with severity of bifrontal hyperperfusion on SPECT in FTD.

The discriminatory cut-off score of the MFS is set at a total score of 5 as, respectively, 85.9% and 76.6% of clinically diagnosed FTD and AD patients were correctly classified (De Deyn et al. 2005).

9.3.2 Behavioral Pathology in Alzheimer's Disease Rating Scale (Behave-AD)

In 1987, the *Behavioral Pathology in Alzheimer's Disease Rating Scale* (Behave-AD) was developed to correctly assess and categorize frequently occurring behavioral symptoms of AD patients (Reisberg et al. 1987). The first part of the Behave-AD

comprises 25 items of which each item can be rated from zero (absent) to three (severely present, with emotional and physical component, possibly requiring restricting) with a total maximum score of 75. The second part is the Behave-AD global score which assesses caregiver burden: 0 (not at all troubling to the caregiver or dangerous to the patient), 1 (mildly troubling to the caregiver or dangerous to the patient), 2 (moderately troubling to the caregiver or dangerous to the patient), and 3 (severely troubling to the caregiver or dangerous to the patient). The first 25 items are categorized into 7 behavioral clusters: cluster A (paranoid and delusional ideation: items 1–7), cluster B (hallucinations: items 8–12), cluster C (activity disturbances: items 13–15), cluster D (agitation and aggression: items 16–18), cluster E (diurnal rhythm disturbances: item 19), cluster F (affective disturbances: items 20, 21), and cluster G (anxieties and phobias: items 22–25).

The Behave-AD is a very detailed and relatively simple scale which allows an assessment within a short amount of time (De Deyn 2004). Several studies (Sclan et al. 1996; Patterson et al. 1990) showed that the reliability of the Behave-AD is comparable with those of several widely used cognitive assessment scales, such as the *Mini-Mental State Examination* (MMSE) *(*Folstein et al. 1975*)*. However, one disadvantage of the Behave-AD is its specificity for and usage in exclusively AD patients. Furthermore, only the intensity of the 25 BPSD items is rated (scores 0–3) and not frequency (De Deyn 2004).

9.3.3 Cohen-Mansfield Agitation Inventory (CMAI)

The *Cohen-Mansfield Agitation Inventory* (CMAI) was originally designed for the staff of nursing homes to rate the frequency of agitation and related behaviors in the elderly with cognitive deterioration. This scale assesses 29 types of agitated behavior which are subdivided into three main categories: items 1–10 comprise "aggressive behavior," items 11–21 consist of "physically nonaggressive behavior," and finally items 22–29 are clustered into the category "verbally agitated behavior." Each item is scored depending on its frequency, i.e., from 1 (never) to 7 (several times an hour) (Cohen-Mansfield et al. 1989).

9.3.4 Geriatric Depression Scale (GDS)

The *Geriatric Depression Scale* (GDS) is the eldest scale so far and was designed to estimate depression in non-demented elderly (Yesavage et al. 1983). It takes little or no experience for the investigator to use this scale which consists of 30 questions that are related to depression in the elderly. Each question should be answered with a simple "yes" or "no." A score of 12 or more is indicative of a "light" depression, whereas 18 or more point to moderate depression. Debruyne et al. (2009), using the CSDD as the golden standard, concluded that the GDS-30 is not a reliable screening tool when assessing depressive symptoms in dementia patients but only in patients with MCI and non-demented elderly.

9.3.5 Cornell Scale for Depression in Dementia (CSDD)

The *Cornell Scale for Depression in Dementia* (CSDD) dates from 1988 and is a very useful assessment tool to diagnose depression in dementia (Alexopoulos et al. 1988). The scale is a 19-item clinician-administered instrument that uses information from interviews with both the patient and nursing staff members, a method suitable for dementia patients. Each item is scored based on a three-point scale, i.e., 0 (absent), 1 (mild or intermittent), and 2 (severely present). If it is impossible to rate one of the items, a score remains absent (A: unable to evaluate). All 19 items are subdivided into five main categories:

A. Mood-related signs (anxiety, sadness, lack of reactivity to pleasant events, irritability)
B. Behavioral disturbances (agitation, retardation (slow movements and speech), multiple physical complaints, loss of interest)
C. Physical signs (appetite loss, weight loss, lack of energy)
D. Cyclic functions (diurnal variation of mood, diurnal rhythm disturbances)
E. Ideational disturbances (suicidal ideation, poor self-esteem, pessimism, mood-congruent delusions).

A score of 8 or more is suggestive for the presence of depression (Burns et al. 2004).

9.3.6 Neuropsychiatric Inventory (NPI)

The *Neuropsychiatric Inventory* (NPI) evaluates 12 types of behavioral disturbances that are dementia-specific, i.e., delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria, apathy/indifference, disinhibition, irritability/lability, repetitive purposeless behavior, insomnia/diurnal rhythm disturbances, appetite, or a change in dietary activity (Cummings et al. 1994). The severity and the frequency of these symptoms are rated by a series of questions which are intended for the main caregiver of the patient. The severity score is based on a three-point scale ranging from 1 (mild) to 3 (severe), and the frequency score can vary between 1 (occasionally, less than once a week) and 4 (very frequent, multiple times a day). The scores of each of these 12 behavioral symptoms need to be summed up to obtain a total NPI score. Besides the severity and frequency scores, the level of caregiver distress (emotional burden) of each of the 12 behavioral symptoms requires rating as well. In this case, a scale ranging from 0 (no distress) to 5 (severe and extreme distress) is provided (Kaufer et al. 1998). The total score of "caregiver distress" is yielded by summing up the 12 individual distress subscores.

Because the NPI consists of a gross variety of behavioral symptoms, it is a useful instrument to discriminate between different types of dementia as well as to evaluate the behavioral outcome due to pharmacological interventions (De Deyn 2004; De Deyn and Wirshing 2001). In 2001, a shortened version of the NPI, namely,

NPI-Q (questionnaire), was developed by Kaufer et al. (2000) which facilitates its daily use in a clinical setting. Several other forms of the NPI have also been proposed depending on the informant, such as clinicians (NPI-C) (de Medeiros et al. 2010), or the institutional setting, such as nursing homes (NPI-NH) (Wood et al. 2000). Finally, in 2018, a diary version of the NPI (NPI-Diary) was designed to overcome several shortcomings that are experienced while using the NPI-NH version, such as the tight work schedule of raters in a nursing home setting, resulting in rather arbitrary evaluations, or staff which is undertrained in the domain of neuropsychiatry (Morganti et al. 2018). Another problem is that the NPI is a retrospective caregiver-informant rating (up to 1 month) and that there frequently is insufficient monitoring. For these reasons, the NPI-Diary was created and showed appropriate validity and reliability compared to the NPI-NH, when administered in a highly variable sample, which generally is the case in a healthcare setting (Morganti et al. 2018).

9.3.7 Other Behavioral Assessment Scales

The *Alzheimer's Disease Assessment Scale* (ADAS) is widely used in clinical trials of potential treatments for AD. The cognitive portion of the ADAS (ADAS-Cog) consists of 11 items designed to assess the severity of memory, language, praxis, and orientation impairments. The noncognitive portion of the ADAS (ADAS-Noncog) consists of ten clinician-rated items assessing the severity of depressive symptoms, tearfulness, increased motor activity, hallucinations, delusions, pacing, increased/decreased appetite, agitation, concentration/distractibility, and tremors. Each item is rated on a 1–5 point severity scale, ranging from very mild to severe. The time period for evaluation includes the entire week before the interview (Rosen et al. 1984). An example in which the ADAS-Noncog has been applied to assess the prevalence of BPSD-specific items in AD comes from Fernández et al. (2010).

The *Hamilton Depression Rating Scale* (HDS) is one of the most commonly used depression rating scales. It requires 20–30 min of questions in a semi-structured interview by a trained interviewer and is, therefore, less suitable for usage in people with dementia. It is commonly used in antidepressant drug trials and has a preponderance of psychological rather than physical items (Hamilton 1960).

In 2017, a rating instrument to comprehensively assess the psychopathology in Down syndrome (DS) with or without AD, or with questionable dementia, was developed. In this European multidisciplinary study, the *Behavioral and Psychological Symptoms of Dementia in Down Syndrome* (BPSD-DS) scale identified frequency and severity of behavioral changes taking account of lifelong characteristic behavior in DS individuals. In total, 83 behavioral items in 12 clinically defined sections were evaluated. First exploratory data suggest promising interrater, test–retest, and internal consistency reliability measures. However, further study regarding applicability, reliability, and validity is necessary. Future application of the scale in daily care may aid caregivers to understand changes and contribute to timely interventions and adaptation of caregiving (Dekker et al. 2018).

Another example of a novel scale is the *Abe's BPSD score* (ABS). This swift and simple scoring instrument provides a new simple and quick test for BPSD assessment in mild-to-moderate dementia patients, with a good correlation to NPI but a shorter interview time and with high interrater reliability. A total of ten items are inquired (from wandering, eating or toilet problems, agitation, psychosis, apathy, day-night disturbances, irritability, depression to violent force), with item-specific weighted scores (taking temporal occurrences into account: seldom, occasionally, sometimes, often), varying from 0 to 9, and with a maximum ABS total score of 44 (Abe et al. 2015).

9.4 PET in the Differential Diagnosis of Dementia

Neuroimaging has played an important role in the study and differential diagnosis of dementia over the last 40 years. Positron emission tomography (PET) studies of cerebral metabolism with fluorine-18 (^{18}F)-labeled fluorodeoxyglucose (FDG) and amyloid tracers such as the carbon-11 (^{11}C)-labeled *Pittsburgh Compound-B* (PiB), and, since 2012, ^{18}F-labeled florbetapir, florbetaben, and flutemetamol, have provided invaluable information regarding specific AD-like brain changes ((Johnson et al. 2012); for review, see (Iaccarino et al. 2017)). Even in prodromal and presymptomatic states, PET imaging has emerged as a robust biomarker of neurodegeneration in individuals who were later found to progress to AD (de Leon et al. 2001; Bateman et al. 2012). Bateman et al. (2012), for instance, detected early Aβ deposition in the precuneus of 128 autosomal dominant AD patients measured by PET-PiB nearly 15 years before expected symptom onset, indicating PET imaging to be an essential and reliable imaging tool not only in the differential diagnosis between AD and non-AD dementias but even for asymptomatic disease states. One of the most recent advances of in vivo PET imaging from 2012 onward is the evaluation of tau burden in AD and non-AD. To date, four broad groups of tau PET radioligands are evaluated, i.e., ^{18}F-THK5351, ^{18}F-THK5117/5105, ^{18}F-AV1451/^{18}F-T807 (better known as ^{18}F-flortaucipir), and ^{11}C-PBB3.

Table 9.2 comprises a non-exhaustive list of the most frequently studied radiotracers for both PET- and SPECT-based analysis of AD pathophysiology and AD differential diagnostics (apart from ^{18}F-FDG for PET and ^{99m}Tc-HMPAO for SPECT).

9.4.1 Radioligands and Compounds

Brain FDG-PET primarily indicates synaptic activity. Because the brain relies almost exclusively on glucose as its main energy resource, the glucose analog FDG is suitable as indicator of brain metabolism and, when labeled with ^{18}F (half-life 110 min.), is detected with PET. Studies support the notion that astrocytes play a central role in neuronal glucose consumption. Decrease of ^{18}F-FDG-PET uptake is considered to be a direct index of synaptic dysfunction, which can result from a variety of neuropathological events, including but not limited to altered intracellular

Table 9.2 Most frequently used radiotracers designed for PET- and SPECT-based analysis of AD pathophysiology

Radiotracer	Half-life	Common name	Modality	Target	Category/ condition
^{11}C-PiB	20 min	Pittsburgh Compound-B	PET	Aβ	AD
^{11}C-AZD2184	20 min		PET	Aβ	AD
^{18}F-FDDNP	110 min		PET	Aβ and tau	AD
^{18}F-AV-45	110 min	Florbetapir	PET	Aβ	AD
^{18}F-BAY94-9172	110 min	Florbetaben	PET	Aβ	AD
^{18}F-GE067	110 min	Flutemetamol	PET	Aβ	AD
^{18}F-AZD4694	110 min		PET	Aβ	AD
^{11}C-BF-227	20 min		PET	Aβ	AD
^{11}C-SB-13	20 min		PET	Aβ	AD
^{123}I-SB-13	13.2 h		SPECT	Aβ	AD
^{123}I-IMPY	13.2 h		SPECT	Aβ	AD
^{18}FTHK5105	110 min		PET	Tau	AD/tauopathies
^{18}F-THK5107	110 min		PET	Tau	AD/tauopathies
^{18}F-T807/^{18}F-AV1451	110 min	Flortaucipir	PET	Tau	AD/tauopathies
^{18}F-T808	110 min		PET	Tau	AD/tauopathies
^{11}C-PBB3	20 min		PET	Tau	AD/tauopathies
^{11}C-THK5351	20 min		PET	Tau	AD/tauopathies
^{18}F-THK5351	110 min		PET	Tau	AD/tauopathies
^{11}C-PK11195	20 min		PET	PBR-TSPO	Neuroinflammation
^{123}I-PK11195	13.2 h		SPECT	PBR-TSPO	Neuroinflammation
^{18}F-DPA714	110 min		PET	PBR-TSPO	Neuroinflammation
^{11}C-PMP	20 min	Methylpiperidin	PET	AChE	Neurochemistry
^{18}F-FDOPA	110 min	Fluorodopa	PET	DA	Neurochemistry (dd. PD)
^{11}C-MRB	20 min	Methylreboxetine	PET	NET	Neurochemistry
^{123}I-FP-CIT	13.2 h	Ioflupane—DaTscan	SPECT	DAT	Neurochemistry (dd. PD)
^{123}I-β-CIT	13.2 h		SPECT	DAT	Neurochemistry (dd. PD)
^{123}I-IBVM	13.2 h	Iodobenzovesamicol	SPECT	VAChT	Neurochemistry
^{123}I-IDEX	13.2 h	Iododexetimide	SPECT	mAChR	Neurochemistry
^{123}I-5-I-R91150	13.2 h		SPECT	5-HT$_{2A}$	Neurochemistry

Abbreviations: *5-HT$_{2A}$* Serotonin (5-hydroxytryptamine) 2A receptor, *Aβ* Amyloid-beta, *ACh* Acetylcholine, *AChE* ACh Esterase, *AD* Alzheimer's disease, *DA* Dopamine, *DAT* DA transporter, *dd* Differential diagnosis, *mAChR* Muscarinic ACh receptor, *NET* Norepinephrine transporter, *PBR-TSPO* Peripheral benzodiazepine receptor-translocator protein, *PD* Parkinson's disease, *VAChT* Vesicular ACh transporter. Partly adapted with permission from Arora A and Bhagat N (2016) *Int J Biomed Imaging* 2016:7462014 under the CC-BY license 4.0 (http://creativecommons.org/licenses/by/4.0). Copyright © 2016 Arora A and Bhagat N

signaling cascades and mitochondria bioenergetics, impaired neurotransmitter release, and accumulation of neurotoxic protein species (for review, see (Iaccarino et al. 2017)). Especially the glutamatergic synaptic signaling is responsible for the maintenance of intrinsic, resting (task-independent) activity of the cerebral cortex, which, most of the time, is the brain's main task (Johnson et al. 2012; Sibson et al. 1997). Therefore, ^{18}F-FDG-PET is widely accepted to be a valid biomarker of the overall brain metabolism to which ionic gradient maintenance for synaptic activity is the most principal contributor (Schwartz et al. 1979; Magistretti 2006). The characteristic pattern found in AD generally is a hypometabolism of the temporoparietal cortex (Herholz et al. 2002; Ferreira and Busatto 2011) and specific limbic and association areas, such as the precuneus, posterior cingulate gyri, inferior parietal lobes, posterolateral portions of the temporal lobe, as well as the hippocampus and medial temporal cortices (Foster et al. 1983; Minoshima et al. 1997; Reiman et al. 2005). An asymmetry between both hemispheres is commonly seen in early stages of AD, whereas in a more advanced stage of the disease, usually the prefrontal association areas become affected (Johnson et al. 2012).

A meta-analysis showed that hypometabolism of the inferior parietal lobes and precuneus is the most striking neurological finding on FDG-PET imaging in AD patients compared to non-demented elderly (Schroeter et al. 2009). Moreover, longitudinal neurofunctional imaging studies have demonstrated hypometabolism in the parietal lobe of MCI converters in comparison with those who did not convert to AD (Schroeter et al. 2009). In conclusion, FDG-PET can be useful in cases of diagnostic uncertainty and has even shown to be valuable in distinguishing AD from FTD (Foster et al. 2007). However, it is advisable to always combine FDG-PET findings with imaging data of other neuroimaging or biomarker techniques, as FDG-PET alone does not allow an adequate evaluation of the brain structure (Waldemar et al. 2007). For instance, complementary ^{18}F-FDG- and ^{11}C-PiB-PET scanning improves diagnostic accuracy of AD vs. non-AD from 76 to 94%, as shown by Hellwig et al. (2019). Moreover, the combination of FDG-PET with CSF biomarker analyses of $A\beta_{1–42}$, T-tau, and P-tau_{181P} levels highly improves clinical diagnostic accuracy, of which in particular T-tau deposition in brain is related to temporal, parietal, and frontal hypometabolism in AD (Perani et al. 2016; Chiaravalloti et al. 2018).

The pathological hallmark in the AD brain is the extracellular deposition of senile plaques and Aβ aggregates. Consequently, a second strategy to visualize AD pathology is not based on glucose metabolism, but on a synthesized derivate which in vivo binds Aβ, such as the N-methyl[^{11}C]2-(4′methylaminophenyl)-6-hydroxybenzothiazole, also known as "Pittsburgh Compound-B" (PiB) (Mathis et al. 2002). Amyloid imaging tracer compounds have binding properties for Aβ in the nanomolar range and are derivatives of histological dyes, such as Congo Red, thioflavin S and T, acridine orange, and chrysamine-G, or based on other molecules such as styrylbenzene ((Suhara et al. 2008); for review, see (Adlard et al. 2014)). PET studies using PiB labeled with ^{11}C showed that amyloid deposition already occurs years before the clinical diagnosis of dementia (Chetelat et al. 2010); is related to cortical atrophy rate, as well as cognitive decline (Braskie et al. 2010); and is more present

in MCI converters compared to non-converters (Forsberg et al. 2008). Peretti and colleagues even concluded that regional cerebral blood flow (rCBF) estimates from pharmacokinetic analysis of PiB scans might be a good alternative to an additional FDG-PET scan, thus bypassing the limitations of a dual examination (Peretti et al. 2019). One concern, however, is the short half-life of PiB labeled with ^{11}C (20 min.), which renders its use in some diagnostic clinical settings more difficult. Consequently, attempts were made to develop an amyloid-sensitive, radioactive-labeled Aβ tracer with longer half-life, such as ^{18}F-florbetapir (^{18}F-AV-45) (Choi et al. 2009; Wong et al. 2010), which has been approved by the US Food and Drug Association (FDA) on April 6, 2012, for the clinical evaluation of patients suspected with AD and other related syndromes. Various studies have compared the diagnostic utility of ^{18}F-florbetapir-PET compared to ^{11}C-PiB-PET (Wolk et al. 2012) and the commonly used ^{18}F-FDG-PET (Newberg et al. 2012), concluding that ^{18}F-florbetapir-PET produced comparable results in discriminating AD patients from cognitively normal adults. Next, Doraiswamy et al. (2012) proved that ^{18}F-florbetapir-PET may help in identifying individuals who are at increased risk of progressive cognitive decline. On the contrary, a recent study from Khosravi et al. (2019) concluded that ^{18}F-FDG-PET global quantification is a superior indicator of cognitive performance in AD and MCI patients compared to ^{18}F-florbetapir-PET. Accordingly, the authors still recommend ^{18}F-FDG-PET over amyloid imaging in the evaluation of AD and MCI. A tracer similar to florbetapir is florbetaben (BAY 94-9172). This ^{18}F-PET marker for Aβ imaging proved to have a sensitivity and specificity of 80 and 91% in an AD versus control comparison (Barthel and Sabri 2011). More importantly, ^{18}F-florbetaben could play a substantial role in the differential diagnosis of AD vs. PD(D)/DLB or AD vs. FTD. As an example, the radiotracer demonstrated a lower overall retention in DLB patients in spite of similar involvement of Aβ compared to AD subjects (Villemagne et al. 2011). Last in the series of most commonly used ^{18}F-labeled amyloid PET imaging tracers is ^{18}F-flutemetamol (^{18}F-GE067). Earlier work demonstrated similar findings of ^{18}F-flutemetamol in probable AD and MCI patients relatively to healthy controls with a similar performance as ^{11}C-PiB within the same subjects (Vandenberghe et al. 2010). Additionally, Wolk et al. (2011) demonstrated a high correspondence between immunohistochemical estimates of Aβ levels in brain tissue of seven AD patients who underwent previous biopsy and in vivo quantitative measures of ^{18}F-flutemetamol uptake at the location contralateral to the biopsy site (i.e., right frontal), supporting its sensitivity to detect Aβ and its use in the study and early detection of AD. Taken together, ^{11}C-PiB and ^{18}F-flutemetamol show similar topographical gray matter uptake in AD and cognitively normal participants, and the tracers show comparable group discrimination. The key disadvantage of such a class of ^{18}F-labeled amyloid radiotracers, however, is that they generate greater levels of nonspecific background noise and higher nonspecific uptake in white matter (also visible in elderly controls) in comparison with ^{11}C-PiB (Lowe et al. 2017).

Amyloid in vivo imaging is a very promising approach, with, currently, all three radiotracers (florbetapir, florbetaben, flutemetamol) approved by the FDA for their diagnostic utilities. At the same time, one should keep in mind that amyloid PET

imaging is restricted to specialized centers around the world, even though it seems that it is becoming more and more implemented in the routine diagnostic workup and differential diagnosis of AD patients (Witte et al. 2015).

Besides amyloid deposits, intracellular NFT consisting of tau protein are a pathological feature of AD as well. The development of PET probes for in vivo imaging of NFT has become an active research field from 2012 onward (Ono and Saji 2012). The first ^{18}F-labeled compound that was synthesized in order to bind NFT was ^{18}F-2-(1-(2-(*N*-(2-fluoroethyl)-*N*-methylamino)naphthalene-6-yl)ethylidene)malononitrile (FDDNP) (Agdeppa et al. 2001; Barrio et al. 1999). Interestingly, FDDNP does exclusively bind not only NFT but also senile Aβ plaques. A more recent tau imaging probe is 2-((1*E*,3*E*)-4-(6-((^{11}C-methylamino)pyridine-3-yl)buta-1,3-dienyl) benzo[d]thiazol-6-ol, better known as ^{11}C-PBB3 (Maruyama et al. 2013). Chiotis et al. (2018) have observed that if compared with ^{11}C-labeled THK5351, ^{11}C-PBB3 appeared to preferentially bind to tau deposits with a close spatial relationship to Aβ, whereas the binding pattern of ^{11}C-THK5351 fitted the expected distribution of tau pathology in AD better and was more closely related to downstream disease markers. The latest tau PET tracer is ^{18}F-AV1451/^{18}F-T807, better known as ^{18}F-flortaucipir. This tracer showed high specific binding in AD, moderate binding in Pick's disease and FTD with parkinsonism-17, and low but displaceable binding in CBD, PSP, and non-tau proteinopathies (Sander et al. 2016). Evidence for a non-tau binding site and lack of correlation between tracer binding and antibody staining suggest that reliable quantification of tau load with this tracer is still somewhat problematic.

These first generations of tau tracers often suffer from off-target binding in the basal ganglia, midbrain, thalamus, choroid plexus, and venous sinus, and ^{11}C-THK5351 may even bind monoamine oxidase B in disease-associated brain regions linked to neurodegeneration (Okamura et al. 2018).

Another approach to visualize AD pathology using PET as an imaging tool is the in vivo mapping of altered neurochemical processes which are typical in the AD brain, such as cholinergic denervation (Van Dam and De Deyn 2006). One example is N-^{11}C-methylpiperidin-4-yl propionate, known as ^{11}C-PMP (Kuhl et al. 1999). This radiopharmaceutical is used in PET imaging to determine the activity of the cholinergic neurotransmitter system by acting as a substrate for acetylcholinesterase. Besides the cholinergic neurotransmission, PET imaging with radioligands that are involved with several other neurotransmitter systems or receptors such as substrates for DA or serotonin (5-HT) signaling has provided important insights into several neurodegenerative disorders (Bohnen and Frey 2007) and has even helped in distinguishing AD from DLB and PD (Tatsch 2008). A frequently used radiotracer in this regard is ^{18}F-fluorodopa. As a fluorinated form of levodopa (i.e., the precursor of DA), ^{18}F-fluorodopa-PET is a valid method for assessing the functional state of the nigrostriatal dopaminergic pathway. It is particularly useful for studies requiring repeated measures such as examinations of the course of a disease and the effect of treatment. Studies using ^{18}F-fluorodopa-PET have also distinguished DLB from AD with a sensitivity of 86% and a specificity of 100% (Hu et al. 2000). Another brain region of particular neurochemical interest in AD, PD/DLB, and DS with(out)

AD—also in the study of BPSD—is the LC, which is the brain's main source of norepinephrine (NE) (Herrmann et al. 2004; Vermeiren and De Deyn 2017). Using PET, the NE transporter (NET) can be studied in vivo. In this regard, the most suitable radiotracer is ^{11}C-methylreboxetine (^{11}C-MRB). This compound is derived from reboxetine, primarily used as an antidepressant. Reboxetine is an NE reuptake inhibitor, binds to NET, and thus allows for accurate localization and quantification. So far, ^{11}C-MRB-PET has been used successfully in previous studies investigating the NE system, such as in healthy volunteers (Smith et al. 2014), patients with posttraumatic stress disorder (Pietrzak et al. 2013), PD patients (Sommerauer et al. 2018), and subjects suffering from depression (Yatham et al. 2018). Collectively, results show that ^{11}C-MRB-PET allows for differential characterization of NET concentration in examined NET-rich brain regions, including the LC, and correlates well with the clinical profile (e.g., Hoehn and Yahr staging in PD) (Sommerauer et al. 2018). The first pioneering study that will apply ^{11}C-MRB-PET in AD compared to PD, DS (with)out AD, and healthy controls to examine its potential diagnostic usage is on its way (see Acknowledgments section, JPND-HEROES).

Noteworthy, ^{11}C-PK11195 is the most successful radiotracer for PET-based neuroinflammation studies, since it specifically binds to the 18 kDa translocator protein (TSPO), also known as the peripheral benzodiazepine receptor (PBR). In normal physiological conditions, TSPO has only a basal expression in the microglial cells. However, when the microglia undergo inflammatory activation, PBR-TSPO expression is upregulated, thereby functioning as a putative biomarker for neuroinflammation. In 2001, it was investigated that there was a high localization of the radiotracer in the cingulate cortex (CC), amygdala, fusiform gyrus, and temporoparietal cortex of AD patients compared to aged healthy controls, triggering further investigation ((Cagnin et al. 2001); for review, see (Arora and Bhagat 2016)). The modified version of ^{11}C-PK11195 is ^{123}I-PK11195, with a significant longer half-life (Table 9.2) and is applied in SPECT to study neuroinflammation in dementia (cfr. Sect. 9.6.4).

Similar PET tracers related to all kinds of pathophysiological aspects of AD are enlisted in Table 9.2.

Please visit http://www.clinicaltrials.gov/ to look for ongoing clinical trials that concern the development of novel PET probes related to amyloid and tau imaging, or other neurodegenerative disease markers of interest, for the differential diagnosis of dementia.

9.5 PET Imaging in Neuropsychiatric Disturbances of Dementia

9.5.1 Alzheimer's Disease and Mild Cognitive Impairment

9.5.1.1 Depression

Loss of neurons in the serotonergic raphe nuclei and dysfunction of its nerve terminals in the neocortex have been reported in AD (Mann and Yates 1983; Palmer et al.

1987). Many lines of evidence suggest this serotonin (5-HT) deficiency to be strongly related with mood disorders in dementia patients and non-demented elderly (Sierksma et al. 2010). In vivo imaging studies that used PET have so far focused on 5-HT-receptors in the limbic brain regions associated with cognitive impairment in AD (Kepe et al. 2006; Meltzer et al. 1998). Ouchi et al. (2009) used a set of two different biomarkers in mild-to-moderate stage AD patients with and without depression to investigate the levels of presynaptic serotonergic function and cortical neuronal activity using PET with ^{11}C-DASB (^{11}C-3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile), a specific 5-HT transporter marker, and the more common ^{18}F-FDG-PET. Because the 5-HT transporter is located on presynaptic 5-HT terminals and regulates 5-HT signaling, levels of ^{11}C-DASB binding in these regions thus reflect the activity of presynaptic 5-HT neurons in the dorsal raphe nuclei. Thomas et al. (2006) previously found a marked reduction in the binding of 5-HT transporter levels in the prefrontal cortex of AD patients ($n = 14$) compared to control subjects ($n = 10$) and non-demented depressed subjects ($n = 8$), but not between depressed ($n = 9$) and nondepressed ($n = 5$) AD patients. Contrastingly, Ouchi et al. (2009) observed a negative correlation between ^{11}C-DASB binding potential levels in the subcortical serotonergic projection region (striatum) and GDS scores ($n = 15$) (Spearman rank-order correlation, $P < 0.01$), as well as significantly lower ^{11}C-DASB binding potential levels in AD patients, irrespective of depression, compared to healthy controls ($n = 10$) in the putamen, thalamus, and midbrain ($P < 0.05$). Consequently, Ouchi et al. (2009) suggested that a certain degree of presynaptic 5-HT function in the subcortical 5-HT projection region is compromised in AD patients even before the development of depression. Also, statistical parametric mapping (SPM) correlation analysis showed that glucose metabolism in the right dorsolateral prefrontal cortex was positively associated with the levels of striatal ^{11}C-DASB binding, suggesting that right dorsolateral prefrontal dysfunction in parallel with 5-HT inactivation is also implicated in the progression of emotional and cognitive deterioration in AD.

Holthoff et al. (2005) performed cerebral glucose metabolism measurements applying ^{18}F-FDG-PET in 53 AD patients. Neuropsychiatric symptoms were assessed using the NPI (Cummings et al. 1994), of which depression and apathy were the most frequently encountered of all symptoms. The group of depressed AD patients ($n = 10$) showed hypometabolism in left and right dorsolateral prefrontal regions (Brodmann area (BA) 6 and 45) in comparison with nondepressed AD patients ($n = 10$) ($P < 0.02$) (Fig. 9.5) (Holthoff et al. 2005).

The combination of ^{18}F-florbetapir-PET imaging, to assess brain amyloid load, with ^{18}F-FDG-PET has been attempted by Brendel et al. (2015). The researchers examined depressive symptoms by applying NPI-Q in 371 MCI subjects from the *Alzheimer's Disease Neuroimaging Initiative* (ADNI) study, dividing groups into Aβ-positive (Aβ+, 206 patients) or Aβ-negative (Aβ−, 165 patients) according to the ^{18}F-florbetapir-PET scanning, with a mean follow-up time of 21.5 months. The authors revealed that Aβ+ MCI subjects with depressive symptoms showed higher amyloid load in the left superior temporal gyrus, left uncus, left gyrus parahippocampalis, left insula, and left CC ($P < 0.001$), as well as in the left medial frontal

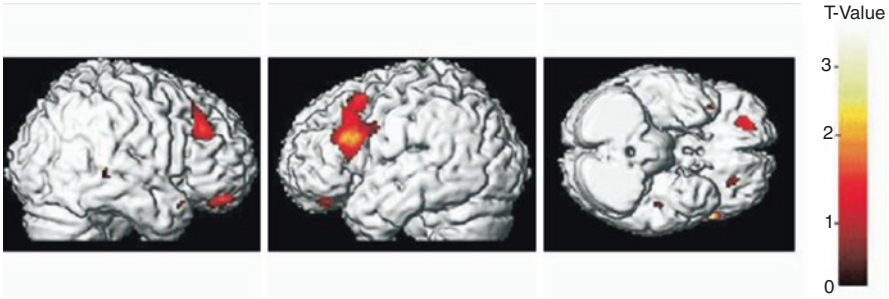


Fig. 9.5 Overlay images of the significant decreases in regional cerebral glucose metabolism in depressed AD patients ($n = 10$) compared to nondepressed AD patients ($n = 10$). Overlay of significant decreases in glucose metabolism by ^{18}F-FDG-PET in left and right dorsolateral prefrontal regions (BA6 and 45) of AD patients with clinically significant depression compared with AD patients free of depression on an MRI template (SPM analysis, $P < 0.05$, corrected). The left image displays the right hemisphere; in the middle, the left hemisphere is displayed; and, finally, the right image visualizes the caudal view of the brain. Abbreviations: *AD* Alzheimer's disease, *BA* Brodmann area, *^{18}F-FDG-PET* ^{18}F-fluorodeoxyglucose positron emission tomography, *MRI* Magnetic resonance imaging. Reprinted from Holthoff VA et al. (2005) Biol Psychiatry 57:412–421, with permission from Elsevier. Copyright © 2005 Elsevier Inc

and rectal gyrus ($P < 0.005$), compared to those without depression. Significantly lower levels of amyloid were found in a small cluster of the right cuneal cortex ($P < 0.001$). Corresponding FDG-PET data showed relative hypermetabolism in the bilateral frontal lobes, as well as in the left fusiform gyrus ($P < 0.001$). Hypometabolism was found in a small cluster of the left cuneal cortex (Fig. 9.6). Among Aβ− MCI subjects with depressive symptoms, small clusters with lower amyloid deposition in bilateral temporal, left precentral, and right inferior frontal gyri were seen compared to nondepressed MCI individuals. Both the depressed MCI subjects and the Aβ+ MCI subjects showed significantly faster progression to AD than their respective counterparts. The fastest progression rate was found in Aβ+ depressed MCI subjects.

In 2016, Ballarini et al. (2016) looked into the metabolic profile of depression in early-onset AD and generally assessed for BPSD using the NPI in 27 early-onset AD subjects (mean age of 58), subclustering the NPI into four subsyndromes (apathetic, hyperactive, affective, and psychotic subsyndromes). The authors further explored whether there was any association between ^{18}F-FDG-PET regional and connectivity-based brain metabolic dysfunctions and subsyndromes. Surprisingly, the affective subsyndrome was correlated with an increase of glucose metabolism in the left and right anterior CC and superior frontal gyrus, extending to the supplementary motor area.

Briefly, it seems that depression in MCI or prodromal/early-onset AD is manifested by a hypermetabolic (Brendel et al. 2015; Ballarini et al. 2016) or hypometabolic state (Holthoff et al. 2005) of frontal cortices and the anterior CC, a contradiction which, perhaps, necessitates further investigation. On the contrary, SPECT studies largely agree on the theory of hypoperfusion in depression in AD

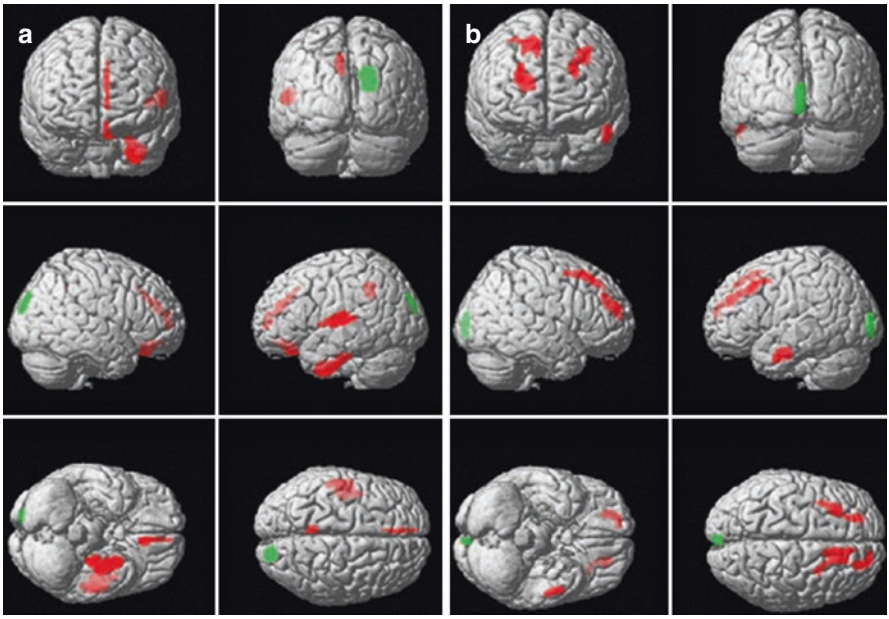


Fig. 9.6 Statistical parametric mapping (SPM) for ^{18}F-Florbetapir-PET (**a**) and ^{18}F-FDG-PET (**b**) in Aβ+ MCI subjects corrected for MMSE score, age, gender, APOE ε4 allelic status, and years of education. Subsyndromally depressed MCI subjects ($N = 65$) are contrasted with nondepressed MCI subjects ($N = 141$). Voxels exceeding a significance threshold of $P < 0.005$ (uncorrected for multiple comparisons, cluster size >100) for increased amyloid levels (**a**) or FDG hypermetabolism (**b**) in depressed MCI subjects are indicated in *red*, while voxels of decreased amyloid levels (**a**) or FDG hypometabolism (**b**) in depressed MCI subjects are indicated in *green*. Both contrasts are rendered on the surface of the standard SPM8 template. Abbreviations: *Aβ* Amyloid-beta, *APOE* Apolipoprotein E, *FDG* Fluorodeoxyglucose, *MCI* Mild cognitive impairment, *MMSE* Mini-Mental State Examination; *SPM* Statistical parametric mapping. Reprinted from Brendel et al. (2015) Eur J Nucl Med Mol Imaging 42:716–724, with permission from Springer. Copyright © 2015 Springer-Verlag Berlin Heidelberg 2015

(cfr. Sect. 9.7.1.1). In this regard, Ashraf et al. (2015) theorized that hypermetabolism in MCI might be indicative of a greater adaptive plasticity as a potential compensatory mechanism before Aβ has been sufficiently deposited.

9.5.1.2 Apathy

In the abovementioned study by Holthoff and colleagues (2005), apathy was rated too by means of the NPI, and it appeared to be one of the most frequent BPSD. The authors further evidenced that the apathetic AD group ($n = 17$) had significant hypometabolism in left orbitofrontal regions (BA10 and BA11) compared to non-apathetic AD patients ($n = 17$) ($P < 0.008$) (Fig. 9.7). In addition to the results of Ballarini et al. (2016) examining depression in early-onset AD (described in Sect. 9.5.1.1), they also found that apathetic subscores were inversely correlated with FDG uptake in the bilateral orbitofrontal and dorsolateral frontal cortex, known to

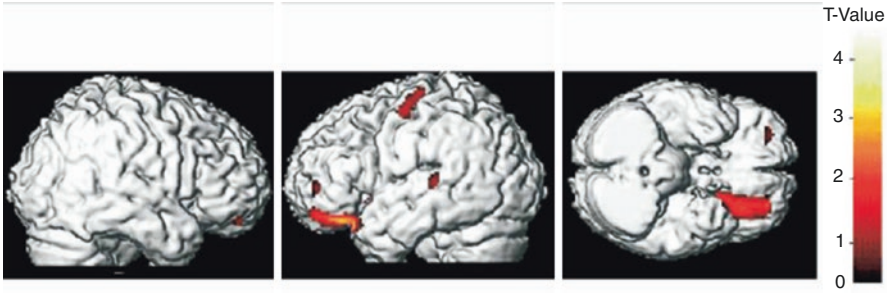


Fig. 9.7 Overlay images of the significant decreases in regional cerebral glucose metabolism in AD patients with clinically significant apathy (n = 17) compared to AD patients free of apathy (n = 17). Overlay of significant decreases in glucose metabolism by ^{18}F-FDG-PET in left orbitofrontal regions (BA10 and 11) of AD patients with clinically significant apathy compared with AD patients free of apathy on an MRI template (SPM-analysis; $P < 0.05$, corrected). The left image displays the right hemisphere; in the middle, the left hemisphere is displayed; and, finally, the right image visualizes the caudal part of the brain. Abbreviations: *AD* Alzheimer's disease, *BA* Brodmann area, *^{18}F-FDG-PET* ^{18}F-fluorodeoxyglucose positron emission tomography, *MRI* Magnetic resonance imaging. Reprinted from Holthoff VA et al. (2005) Biol Psychiatry 57:412–421, with permission from Elsevier. Copyright © 2005 Elsevier Inc

be involved in motivation and decision-making processes. Results are similar to those of Holthoff et al. (2005) and, again, point to the orbitofrontal cortex as an important key brain region that modulates apathetic behavior in AD.

Recently, similar neuroimaging research into apathy has been performed, albeit in MCI subjects. For instance, baseline data from 65 MCI participants (11 with apathy and 54 without) from the ADNI study were analyzed. All participants underwent a comprehensive cognitive and neuropsychiatric assessment, volumetric MRI, and measures of cerebral glucose metabolism applying ^{18}F-FDG-PET. The presence of apathy at baseline was determined by the NPI-Q. Compared with the apathy-free MCI patients, MCI patients with apathy had significantly decreased metabolism in the left and right posterior CC (BA31, $P < 0.001$). The authors further implied that apathy may belong to the spectrum of prodromal AD symptoms, since early metabolic reductions in the posterior cingulate are hypothesized to represent a more specific marker of AD than hippocampal atrophy and hypometabolism (Delrieu et al. 2015).

Similar to depression in AD/MCI, apathy seems to be characterized by a metabolic dysfunction in alike brain regions, i.e., the CC (Ballarini et al. 2016) or dorsolateral frontal/orbitofrontal cortices (Holthoff et al. 2005; Delrieu et al. 2015). The only difference is that, for apathy, a hypometabolic state has been measured thrice following FDG-PET (Holthoff et al. 2005; Ballarini et al. 2016; Delrieu et al. 2015), whereas in depression, both increases and decreases in FDG uptake have been found.

9.5.1.3 Psychosis

As described above, psychosis is a distinct AD syndrome and includes the presence of at least one (or more) hallucination(s) and/or delusion(s) (Jeste and Finkel 2000).

Hirono et al. (2000) studied the neuroanatomical basis of delusions in AD using ^{18}F-FDG-PET to measure cerebral glucose metabolism in 65 mild-to-moderate probable AD patients. The Behave-AD or NPI were used to assess for delusions, categorizing 26 patients as being delusional while 39 as not delusional. Surprisingly, a significant increase in glucose metabolism in the left inferior temporal gyrus and a significant decrease in the left medial occipital region in delusional AD patients were observed when compared to their non-delusional counterparts.

Sultzer et al. (2003) similarly used FDG-PET and identified three specific regions in the right frontal cortex of 25 AD patients which were strongly associated with the *Neurobehavioral Rating Scale* delusion scores, i.e., the right superior dorsolateral frontal region (BA8) (hypometabolism), the right inferior frontal pole (BA10) (hypometabolism), and the right lateral orbitofrontal region (BA47) (hypometabolism), confirming a link between delusional ideation and right hemispheric pathology.

A similar study that examined the link between psychosis in AD and altered brain metabolism was performed by Koppel et al. (2014). In this study, 21 ADNI participants with AD who developed psychotic symptoms during the study but were not psychotic at baseline were matched with 21 participants with AD who never became psychotic during the study period, and mean brain ^{18}F-FDG-PET cerebral metabolic glucose rates by regions of interest (ROI) were compared. Additionally, 39 AD participants with active psychosis at the time of image acquisition were matched with 39 participants who were never psychotic during the study period, and mean brain FDG-PET cerebral metabolic glucose rates by ROI were, again, compared. The authors found no regional brain metabolic differences between those with AD destined to become psychotic and those who did not become psychotic. There was, however, a significant reduction in mean orbitofrontal brain metabolism in those with active psychosis.

Reeves et al. (2009) tested if delusions were associated with striatal DA D2/D3 receptor function in AD. The investigators used in vivo ^{11}C-raclopride-PET imaging (^{11}C-RAC-PET) in 23 patients with mild-to-moderate probable AD who underwent behavioral assessment by means of the NPI. They found that the mean ^{11}C-RAC-PET binding potential levels for striatal DA D2/D3 receptors were higher in AD patients with (n = 7 of which 5 were men) than without (n = 16 of which 6 were men) delusions. When women were excluded from the analysis, striatal ^{11}C-RAC-PET binding potential levels were still higher in delusional male AD patients compared to male AD subjects without delusions (P = 0.05). Furthermore, these results were comparable with the dopaminergic D2/D3 receptor availabilities of drug-naïve schizophrenia patients.

9.5.1.4 Agitation

Only one study so far has looked into the neurobiological correlates of agitation in AD using PET, in which a total of 85 outpatients with mild-to-moderate AD were recruited from the *VA Greater Los Angeles Healthcare System Geropsychiatry Outpatient Program (*Weissberger et al. 2017*)*. A cross-sectional investigation was conducted of the relationship between cerebral glucose metabolism measured via

^{18}F-FDG-PET and agitated symptoms from the NPI. Two empirically derived clusters of agitation symptoms were investigated: an *agitation factor*, comprising agitation/aggression and irritability/lability items of the NPI, and a *behavioral dyscontrol factor*, comprising elation/euphoria, disinhibition, aberrant motor behavior, sleep, and appetite items of the NPI. Mean cerebral metabolism for patients who scored positively on each of the two factors was compared with mean cerebral metabolism for those who did not. Patients with AD who scored positively on the *agitation factor* showed reduced glucose metabolism of the right temporal, right frontal, and bilateral CC. In contrast, the *behavioral dyscontrol factor* did not show specific neurobiologic correlates. These results warrant further study and confirmation.

9.5.1.5 Other Behavioral Disturbances

It becomes clear from the collective PET neuroimaging evidence that psychiatric and behavioral symptoms in dementia are not random consequences of diffuse brain illness, but are fundamental expressions of regional cerebral pathological events (Sultzer 1996). Tanaka et al. (2003) showed that a dysfunction of the striatal dopaminergic D2 receptor metabolism, characterized by significantly lowered ^{11}C-RAC-PET binding potential levels, is manifested in AD patients with more severe Behave-AD *Frequency Weighted Severity Scale* scores (Monteiro et al. 2001) compared to AD patients without BPSD. This study, however, comprised no more than ten AD patients and only reported Behave-AD total scores.

Ng et al. (2017) performed a longitudinal observation of 115 cognitively normal individuals stratified by hallmark AD biomarkers to identify individuals with preclinical AD with the highest risk of progression to clinical AD and tested the hypothesis that BPSD are associated with metabolic abnormalities in limbic regions and predict conversion. Both ^{18}F-florbetapir-PET and phosphorylated CSF tau biomarkers were used for stratification. Furthermore, regression and voxel-based regression models evaluated the relationships between baseline BPSD measured by the NPI and baseline and 2-year change in metabolism measured by ^{18}F-FDG-PET. Collectively, the researchers found that the magnitude of BPSD is linked to a transient metabolic dysfunction in limbic networks that are vulnerable to early AD pathophysiology in individuals with preclinical AD. Initially, individuals with preclinical AD with higher NPI scores had higher FDG uptake in the posterior CC, ventromedial prefrontal cortex, and right anterior insula at baseline, but high NPI scores predicted subsequent hypometabolism in the posterior CC over 2 years only in the individuals with preclinical AD. Moreover, this metabolic shift was driven by the sleep/nighttime behavioral disorders and irritability components of the NPI.

Apart from depression and apathy subsyndromes (cfr. Sects. 9.5.1.1 and 9.5.1.2, respectively), Ballarini et al. (2016) also rated the hyperactivity subsyndrome cluster of the NPI in 27 early-onset AD patients and, subsequently, performed interregional correlation analysis to explore metabolic connectivity following FDG-PET. These hyperactivity subsyndrome scores were associated with increases in glucose metabolism in the superior frontal gyrus and anterior CC with a left hemispheric predominance.

Unfortunately, besides depression, apathy, agitation, and psychosis in AD or MCI, no in vivo PET imaging studies have been performed yet with regard to aggression, diurnal rhythm disturbances, disinhibition, or anxiety.

9.5.2 Other Dementia Subtypes

Rackza et al. (2010) examined behavioral deficits in 17 FTLD patients (diagnoses consisted of FTD ($n = 10$) and SD ($n = 7$)) using ^{18}F-FDG-PET imaging. Behavioral deficits were assessed using the NPI. Total NPI scores were significantly correlated with hypometabolism in various frontomedial regions, the left anterior middle frontal gyrus, the left anterior and superior insula, and the left inferior temporal gyrus. Imaging results were based mainly on apathy, disinhibition, and appetite changes because these behavioral disorders occurred most frequently in this cohort. Moreover, Peters et al. (2006) indicated that the known cerebral metabolic impairment in FTLD patients specifically affects areas specialized in emotional evaluation. This Belgian study obtained PET imaging and NPI behavioral data from 41 FTLD patients from specialized European PET centers around the world. The investigators primarily found decreased posterior orbitofrontal cortical activity to be related with both apathy and disinhibition, which neuroanatomically also corresponds to the hypometabolic pattern of apathy in AD or MCI (cfr. Sect. 9.5.1.2).

Results of a more recent PET imaging study investigating the neuroanatomy and pathophysiology of BPSD in FTD patients were reported by Schroeter et al. (2011). In total, 13 FTLD patients underwent ^{18}F-FDG-PET imaging after being behaviorally scored applying the NPI. The researchers performed a conjunction analysis across the common neural correlates of the three most relevant behavioral disorders as identified in the single regression analysis. All three behavioral disorders, i.e., apathy, disinhibition, and eating disorders, were related to mainly frontomedian hypometabolism. Afterward, a disjunction analysis aimed to specifically identify the neural correlates of these three relevant behavioral disorders individually: disinhibition was correlated with hypometabolism in both anterior temporal lobes, anterior hippocampi, left amygdala, left anterior and superior posterior insula, caudate head, and bilaterally lateral and posterior orbital gyri. Smaller clusters were detected additionally for disinhibition in the right superior middle insula, postcentral gyrus, left superior frontal gyrus, and posterior thalamus ($P < 0.001$); apathy was related to hypometabolism in, most remarkably, the ventral tegmental area and left inferior and middle temporal gyrus, whereas eating disorders were finally associated with the right inferior, middle, and superior frontal gyri with a same statistical threshold (Schroeter et al. 2011).

Lastly, PET imaging studies in DLB patients with BPSD, although sparse, have been performed as well. The first study investigated visual hallucinations in 14 DLB patients compared to 7 DLB patients without such visual hallucinations by means of ^{18}F-FDG-PET imaging (Perneczky et al. 2008). The imaging results revealed hypometabolic regions at the right occipitotemporal junction and in the right middle frontal gyrus only in the DLB group with visual hallucinations, suggesting that

hypometabolism in visual association areas rather than in the primary visual cortex might be involved in psychosis in DLB (Perneczky et al. 2008). Also, ^{18}F-FDG-PET data in ten DLB patients with delusions revealed a hypometabolism of the right middle frontal gyrus (BA9) and pars triangularis of the right inferior frontal gyrus (BA45) in comparison with non-delusional DLB patients (n = 11) (Perneczky et al. 2009). The delusion frequency and severity subscores of the NPI within the past 4 weeks prior to the examination were used to distinguish between delusional and non-delusional DLB patients. A hypometabolism of the right middle frontal gyrus (BA9) thus seems to be associated not only with visual hallucinations but also with delusions in DLB patients.

On the whole, psychosis seems more confined to right hemispheric pathologic disturbances in both DLB and AD, irrespective of PET or SPECT imaging (cfr. Sects. 9.5.1.3 and 9.7.1.3).

9.6 SPECT in the Differential Diagnosis of Dementia

The other commonly used nuclear gamma ray-emitting imaging modality besides PET which can provide functional information about the pathophysiological processes of neurodegenerative diseases is single-photon emission computed tomography (SPECT). It is well recognized that PET has a higher resolution, sensitivity, less artefact, and better quantitative capacity than SPECT; however, SPECT imaging is cheaper and more practical as a routine clinical diagnostic procedure, and SPECT scanners are widely installed in most hospitals (Kung et al. 2004). Limitations of a dual PET tracer approach, on the contrary, are the increased radiation exposure and costs. Another advantage of SPECT is the longer half-life of utilized radiotracers (^{123}I, 13.2 hours; or the technetium isotope ^{99m}Tc (^{99m}Tc), 6.06 h), so there is no requirement for an on-site cyclotron and a specialized radiochemistry facility. Such tracers are normally produced at a commercial scale (Arora and Bhagat 2016).

9.6.1 ^{99m}Tc-HMPAO-SPECT

For the differential diagnosis in dementia, the most commonly applied tracer is ^{99m}Tc-HMPAO (hexamethylpropyleneamine oxime, also known as exametazime). The technetium isotope ^{99m}Tc has a half-life of 6.06 h and is bound to HMPAO which allows ^{99m}Tc to be taken up by the brain tissue rapidly in a manner proportional to the brain's blood flow. Many research during the last decade has indicated that ^{99m}Tc-HMPAO-SPECT is very valuable not only in establishing an (early) AD diagnosis (Bonte et al. 2006; Nagao et al. 2006) but also in distinguishing between different types of dementia (Pickut et al. 1997; Charpentier et al. 2000; Rollin-Sillaire et al. 2012) or between very early AD/MCI and normal aging (Nagao et al. 2006).

Pickut et al. (1997) studied the discriminative use of ^{99m}Tc-HMPAO-SPECT in 21 FTLD versus 19 age- and severity-matched AD patients. The researchers found

significantly more bilateral hypoperfusion of parietal lobes in the AD patients as compared to more pronounced bifrontal hypoperfusion in FTLD patients. This bifrontal hypoperfusion was afterward identified by stepwise logistic regression as the most significant contributing parameter to correctly classify FTLD versus AD patients on SPECT. Comparable with Pickut et al. (1997), Charpentier et al. (2000) examined 20 probable AD and FTD patients by means of ^{99m}Tc-HMPAO-SPECT imaging and detected 5 specific variables after the bivariate and multivariate analyses with the highest predictive value rate for the differential diagnosis between both neurodegenerative disorders, i.e., right median frontal-, left lateral frontal-, left parietotemporal-, and left temporoparietal-occipital areas as well as MMSE scores. Rollin-Sillaire et al. (2012) evaluated the contribution of ^{99m}Tc-HMPAO-SPECT imaging to the differential diagnosis of dementia in 48 neuropathologically confirmed patients with a degenerative (AD or FTLD) or vascular dementia. SPECT-based diagnoses were then compared with clinical and neuropathological diagnoses. Compared with clinical diagnoses alone, SPECT imaging improved the specificity of the etiological diagnosis in degenerative dementia, although its sensitivity was not as good as that of the clinical diagnosis. Furthermore, for AD and FTLD patients, the agreement between the clinical and SPECT-based diagnoses was always confirmed by neuropathological assessment, again indicating that ^{99m}Tc-HMPAO-SPECT is very helpful in the differential diagnosis of dementia.

One last ^{99m}Tc-HMPAO-SPECT study quantified the heterogeneity of cerebral perfusion on SPECT images in elderly controls (n = 31) and very mild AD patients (n = 75) by using a three-dimensional fractal analysis (Nagao et al. 2006). Especially the posterior limbic fractal dimension significantly differed between very early AD and control persons so that authors concluded that ^{99m}Tc-HMPAO-SPECT imaging of the posterior limbic region (consisting of the hippocampal-amygdaloid complex, thalamus, a part of the anterior/posterior CC, and precuneus) combined with 3D fractal analysis may be useful in objectively distinguishing patients with very early AD and MCI from healthy elderly.

9.6.2 ^{123}I-IMP-SPECT

Another frequently administered SPECT imaging radionuclide to differentially diagnose dementia patients is the intravenous injection of N-isopropyl-p-^{123}I-iodoamphetamine (^{123}I-IMP). Combined with magnetic resonance imaging (MRI), Goto et al. (2010) were able to distinguish patients with mild DLB (n = 19) from those with AD (n = 19) with a high level of accuracy. More particularly, they found a significantly lower striatal volume on MRI plus a lower occipital SPECT ratio in the DLB group as opposed to AD patients. These results, therefore, point to a strong and added value of MRI combined with ^{123}I-IMP-SPECT imaging when distinguishing AD from DLB patients.

Hanyu et al. (2010) used the similar ^{123}I-IMP-SPECT imaging technique in 24 rapidly progressing and 24 slowly progressing AD patients based on annual MMSE score changes and assessed the possible relationship between the rate of cognitive

decline and the initial and follow-up rCBF patterns. At the initial evaluation, the rapidly progressing AD group had greater rCBF deficits mainly in the parietotemporal, frontal, and left posterior cingulate regions compared to the slowly progressing AD group. Moreover, follow-up SPECT data of the rapidly progressing AD group showed a significant rCBF reduction in widespread regions, including parietotemporal and frontal lobes, while in the slowly progressing AD group, rCBF patterns were reduced in rather small and more scattered regions of the parietal, temporal, and limbic lobes. Based on these results, Hanyu et al. (2010) suggested that rCBF deficits in specifically parietotemporal, posterior cingulate, and frontal brain regions are associated with subsequent rapid cognitive decline in AD.

9.6.3 SPECT Imaging with Cholinergic and Monoaminergic Radioligands

Altered neurochemical processes in AD have been described extensively throughout the years. One well-known example is the cholinergic denervation in cerebral AD pathology (Mash et al. 1985) which already occurs in very mild or even presymptomatic stages of the disease. Using a sensitive in vivo cholinergic neuron marker in combination with regular SPECT imaging might, therefore, be useful in establishing a very early AD diagnosis (Boundy et al. 1997) or in studying the involvement and alteration of cholinergic activity in AD brain (Boundy et al. 2005; Mazère et al. 2008).

Mazère et al. (2008) used a specific marker of the vesicular acetylcholine transporter, namely, ^{123}I-iodobenzovesamicol (^{123}I-IBVM), combined with SPECT imaging to image cholinergic activity in very early AD patients ($n = 8$ with MMSE scores of 23.8 ± 1.6). In comparison with eight age-matched control subjects (28.3 ± 1.3), the researchers found a significant decrease in ^{123}I-IBVM binding (47–62%) in the CC and parahippocampal-amygdaloïd complex of AD patients. These patterns, however, appeared to be independent of atrophied areas. These results suggest that a cholinergic degeneration already occurs in the very early stages of AD and that it could be associated with cognitive impairment. As a result, the imaging of cholinergic neurons by applying ^{123}I-IBVM-SPECT might also be an effective approach to identify potential cholinergic treatment responders. With regard to non-AD dementias, Mazère et al. (2017) recently evaluated the effectiveness of ^{123}I-IBVM-SPECT in the fundamental study of cholinergic pathways in DLB. The authors found that compared to healthy volunteers ($n = 12$), binding potential values for DLB patients ($n = 11$) were significantly lower in the Ch4 terminal regions of the anterior CC and the superior and inferior parietal cortices, in the Ch5 terminal region of the thalamus, and in the striatum. They concluded that alterations in cholinergic transmission in the anterior CC could be closely associated with the development of apathy in DLB.

Another cholinergic radioligand combined with SPECT to visualize cholinergic brain activity, is ^{123}I-iododexetimide (^{123}I-IDEX), which has shown to effectively bind muscarinic acetylcholine receptors (mACh) (Muller-Gartner et al. 1992).

Possible alterations in mACh levels were evaluated by Boundy et al. (2005) in early clinical AD patients (n = 11) compared to ten age- and gender-matched control subjects. In this study, ^{123}I-IDEX was combined with the previously described ^{99m}Tc-HMPAO-SPECT technique. Boundy et al. (2005) examined a deficit of ^{123}I-IDEX binding in the posterior CC of the mild AD group using a voxel-based approach with SPM99 software. In parallel with previous results of Mazère et al. (2008), this study provides further evidence for the involvement of altered cholinergic activity in the posterior cingulate region in early AD. Moreover, SPM99 found no deficits on ^{99m}Tc-HMPAO-SPECT scans, suggesting that neither atrophy nor hypoperfusion were involved in the reduced ^{123}I-IDEX-binding. Based on this evidence, Mazère et al. (2008) suggested that cholinergic changes in AD might proceed alterations in rCBF patterns. Already in 1997, Boundy et al. (1997) indicated that the use of ^{123}I-IDEX combined with ^{99m}Tc-HMPAO-SPECT might be discriminative enough to be used in the early diagnosis of AD.

The discriminative use of radio-iodinated monoaminergic SPECT ligands might be another efficient approach to distinguish between AD patients and cognitively healthy volunteers. Versijpt et al. (2003a) assessed this possibility by studying the binding potential of ^{123}I-5-I-R91150, a ^{123}I-labeled 5-HT$_{2A}$ receptor antagonist. ^{123}I-5-I-R91150-SPECT images of 9 AD patients revealed a generally decreased neocortical binding potential with a significant reduction in orbitofrontal, prefrontal, lateral frontal, cingulate, sensorimotor, parietal inferior, and occipital regions in comparison with SPECT images of 26 healthy control subjects. Furthermore, Versijpt and colleagues found an age-related decline in 5-HT$_{2A}$ receptor binding potentials, following which they stressed the necessity for inclusion of age-matched study samples (Versijpt et al. 2003a).

Finally, several other monoaminergic SPECT ligands have been developed to distinguish AD from DLB patients based on the fact that (i) severe nigrostriatal neurodegeneration in DLB occurs to greater extent than in AD and (ii) clinical symptoms show significant overlap, particularly in early stages of the disease (McKeith et al. 2017). As a consequence, the differential diagnosis between both conditions might be very challenging (Tatsch 2008). Multiple examples of monoaminergic SPECT ligands targeting the dopaminergic neurotransmitter system are given by Tatsch (2008), of which ^{123}I-β-CIT (^{123}I-2beta-carbomethoxy-3beta-(4-iodophenyl)tropane) and ^{123}I-ioflupane(FP)-CIT have shown to be most promising in correctly categorizing AD and DLB. Both ^{123}I-β-CIT and ^{123}I-FP-CIT-SPECT imaging modalities measure presynaptic striatal DA transporter (DAT) levels, which were always found to be significantly lower in DLB patients compared to AD patients. In contrast, corresponding monoaminergic SPECT ligands which targeted postsynaptic DA receptors showed to be much less efficient in differentiating DLB from AD patients. Kasanuki and colleagues (Kasanuki et al. 2017) investigated the clinical relevance of ^{123}I-FP-CIT-SPECT in prodromal DLB and concluded that mean striatal specific binding scores of both prodromal and clinical DLB patients were significantly lower than those of AD patients. Moreover, among the related nonmotor symptoms, duration of olfactory dysfunction and RBD demonstrated a negative correlation with striatal specific binding scores in prodromal DLB. Again,

this shows that the combination of SPECT with other disease-related biomarkers is preferred to increase the diagnostic specificity in (prodromal) DLB, in this case ^{123}I-FP-CIT-SPECT combined with measures of olfactory dysfunction/RBD.

Of note, ^{123}I-FP-CIT-SPECT is more familiar under the tradename of "DaTscan." The main advantage of ^{123}I-ioflupane is that a steady state allowing SPECT imaging is reached at 3 hours after a single bolus injection of the radioligand compared with 18–24 hours of ^{123}I-β-CIT. Evidence shows that ^{123}I-ioflupane uptake in the basal ganglia is markedly reduced in DLB compared to AD patients (Walker et al. 2002). Nowadays, ^{123}I-ioflupane-SPECT is widely used in clinical routine for the differential diagnosis between PD and essential/dystonic tremor or for clinical suspicion of psychogenic parkinsonism or parkinsonism secondary to drugs, although it might also be valuable to differentiate between DLB and AD patients. In general, DaTscan favors the diagnostic workup of PD-related disorders (Antonini 2007).

9.6.4 SPECT Imaging of Neuroinflammation

As mentioned before, inflammation in AD primarily contributes to neurodegeneration and is acknowledged to be a primary source of pathology. Consequently, SPECT imaging of neuroinflammation in AD brain might also be useful to differentially discriminate between AD patients and control subjects. One example comes from Versijpt et al. (2003b), who studied neuroinflammation in AD by using the radioligand ^{123}I-PK11195 with SPECT imaging. PK11195 is an isoquinoline carboxamide that selectively binds to PBR-TSPO which are expressed on microglia. Additionally, PK11195 becomes upregulated under inflammatory circumstances. The authors compared the SPECT images of ten AD and nine control subjects and showed that the mean ^{123}I-PK11195 uptake was increased in nearly all neocortical regions of AD patients; however, statistical significance was only achieved in the frontal and right mesotemporal regions.

As a result, PK11195 may be considered a valuable cellular disease activity marker for the in vivo evaluation of microglial inflammation in AD, using both PET and SPECT.

9.6.5 SPECT Tracers Imaging Aβ Plaques

The development of PET as well as SPECT tracers for Aβ imaging represents an active area of radiopharmaceutical design. Finding a suitable radioligand is, however, very challenging as Aβ plaques are not homogenous and contain multiple binding sites for structurally different compounds (Valotassiou et al. 2010). One good example comes from Kung et al. (2004), who developed 6-iodo-2-(4′-dimethylamino-)phenyl-imidazo[1,2]pyridine (IMPY) and 4-N-methylamino-4′-hydroxystilbene (SB-13) as ligands for targeting amyloid plaques. The researchers firstly evaluated in vitro binding properties of these two potential Aβ-imaging agents in temporal, parietal, and cerebellar cortex of AD patients (n = 4) and control

persons (n = 4). When labeled with ^{125}I or H-3, ^{125}I-IMPY and ^{3}H-SB-13-SPECT, respectively, showed an abundant in vitro binding capacity with high binding affinities for Aβ plaques in all affected brain regions of AD patients compared to very low specific binding in cortical tissue of control brain homogenates. These properties suggest that both ligands are valuable in quantifying and localizing amyloid plaque burden in living AD patients if labeled with ^{11}C or ^{123}I, even though their use warrants further analysis (Chen et al. 2015).

Please visit http://www.clinicaltrials.gov/ to see ongoing clinical trials concerning the development of novel SPECT probes related to amyloid imaging or other neurodegenerative disease markers of interest for the differential diagnosis of dementia. As mentioned previously, Table 9.2 summarizes the most frequently used radiotracers for SPECT- and PET-based analysis of AD pathophysiology (apart from ^{18}F-FDG for PET and ^{99m}Tc-HMPAO for SPECT).

9.7 SPECT Imaging in Neuropsychiatric Disturbances of Dementia

During the last two to three decades, much SPECT-related research regarding neuropsychiatric disturbances in dementia has been performed. In general, literature comprises more SPECT- than PET-related BPSD studies for the period 1990–2010, whereas from 2010 onward, more PET studies have emerged. Of all BPSD, depression, apathy, and psychosis in AD have been examined the most. Besides, activity disturbances, agitation/aggression, and sleep disorders have also been the subject of SPECT research in AD, in addition to the study of psychosis and apathy in DLB and FTD patients.

9.7.1 Alzheimer's Disease

9.7.1.1 Depression

One of the first studies that dealt with mood disorders in AD was published by Galynker et al. (2000) who examined the relationship between rCBF patterns and negative symptoms in AD patients (n = 25). The AD group was subdivided in a high- (more negative symptoms) (n = 12) and low (less negative symptoms) severity group (n = 13). Each patient underwent ^{99m}Tc-HMPAO-SPECT. Categorization of negative symptoms was performed by means of the *Scale for the Assessment of Negative Symptoms*, the HDS, and the *Positive and Negative Symptom Scale*. Authors observed a significantly lower rCBF pattern in the dorsolateral prefrontal cortex bilaterally (right, P = 0.002, and left, P = 0.02), the main right frontal cortex (P = 0.02), and CC (P = 0.022) of the high-severity AD group compared to the low-severity group. Results point to a significant association between negative symptoms and hypofrontality in AD. Somewhat later in 2003, Liao et al. (2003) tested the hypothesis that depression in AD is the result of a specific cerebral pathogenesis rather than a diffuse event, as was previously shown by Galynker et al. (2000). In

total, 43 AD patients received a behavioral assessment with the HDS and underwent ^{99m}Tc-HMPAO-SPECT imaging. An inverse correlation was found between depression scores and cerebral perfusion in the bilateral anterior and posterior cingulate gyri and precuneus, which was in agreement with Galynker et al. Surprisingly, no hypoperfusion in (pre)frontal cortices of depressed AD patients was identified.

Akiyama et al. (2008) scrutinized previous results and used the so-called easy Z-score imaging system (eZIS) combined with ^{99m}Tc-ethyl-cysteinate dimer (ECD)-SPECT imaging, another frequently used radioligand (ECD) which binds the technetium isotope ^{99m}Tc, to investigate if hypoperfusion in prefrontal cortex or CC is associated with depression in AD. Depression scores were based on the NPI depression items, so in total 44 AD patients were subdivided into 26 depressed and 19 nondepressed AD subjects. Data from eZIS-^{99m}Tc-ECD-SPECT scans revealed that mean Z-scores of the left prefrontal cortex in the depressed AD group were significantly higher ($P < 0.0125$) than those in the nondepressed group. Moreover, there were no significant differences in Z-scores of the right prefrontal cortex or in the bilateral anterior CC between the two groups, which is in contrast but also in agreement with previous studies who found hypoperfusion in either CC alone (Liao et al. 2003) or in the prefrontal cortex as well as in the CC (Galynker et al. 2000). Also in 2008, Levy-Cooperman and colleagues (Levy-Cooperman et al. 2008) used the CSDD with a cut-off score of 8 or more as being indicative for depression to dichotomize depressed ($n = 27$) from nondepressed ($n = 29$) AD patients with the same ^{99m}Tc-ECD-SPECT technique combined with MRI. Similarly, this study aimed to determine neural correlates of depressive symptoms in 56 AD patients who met the criteria for probable AD. Results showed a hypoperfusion in the right superior and bilateral middle frontal ($P < 0.005$), left superior frontal ($P < 0.05$), and anterior cingulate gyri ($P < 0.005$) of depressed AD patients compared to nondepressed patients. SPM analyses also revealed a significantly lower perfusion in bilateral dorsolateral and superior prefrontal cortex of depressed AD patients (right, $P < 0.005$, and left, $P < 0.05$), which is consistent with previous reports that suggested that the prefrontal cortex and CC are involved in affect and emotional regulation in AD.

Finally, in 2010, Kataoka et al. (2010) again used ^{99m}Tc-ECD-SPECT but afterward analyzed all SPECT images with *3D stereotactic region of interest template* (3DSRT) software to compare rCBF ratios of each brain segment between depressed ($n = 17$) and nondepressed AD patients ($n = 18$). Depression scores were based on the Japanese version of the NPI depression subscale, and AD patients had mild-to-moderate AD according to DSM-IV criteria. The authors found that perfusion ratios (rCBF patterns) on 3DSRT images of the left callosomarginal segment, i.e., left prefrontal cortex, were significantly lower ($P < 0.05$) in the depressed AD group than those of the nondepressed group. In comparison with their own previous study where they used eZIS-^{99m}Tc-ECD-SPECT instead of 3DSRT-^{99m}Tc-ECD-SPECT (Akiyama et al. 2008), current results remained consistent, thus suggesting that frontal dysfunction is associated with the expression of depressive symptoms in AD patients.

9.7.1.2 Apathy

Apathy is closely related to depression as it is one of the main components of the CSDD (lack of reactivity to pleasant events, loss of interest (Alexopoulos et al. 1988)) to decide whether or not AD patients might be depressed. Therefore, it is very likely that the same affected brain ROI in depressed AD patients (prefrontal cortex, CC) might be comparable with those of apathetic AD patients on SPECT.

The first study that agrees with this hypothesis comes from Benoit et al. (1999) who studied regional cerebral perfusion with ^{99m}Tc-ECD-SPECT in 20 apathetic AD patients rated by the apathy subscale of the NPI. Authors indeed revealed that the apathy NPI scores were correlated with a right cingulate deficit, whereas MMSE scores positively correlated with the left temporoparietal area. A comparable study in 2002 from Benoit et al. (2002) used ^{99m}Tc-ECD-SPECT imaging again, but this time in combination with SPM99 analysis. Brain perfusion patterns were compared between apathetic (n = 15) and non-apathetic AD patients (n = 15), as well as healthy control subjects (n = 11). SPECT data indicated that compared to healthy subjects, the apathy-free AD subgroup had significantly lower cerebral perfusion of the inferior temporal and occipital regions. In contrast, the apathy subgroup had significantly decreased perfusion of the left anterior cingulate, right inferior medial, and left orbitofrontal gyrus and right gyrus lingualis. When both AD groups were compared, a significantly lower perfusion in BA8, BA9, and BA10 (bilateral medial frontal gyri) was observed in the apathetic AD group but not in the group free of apathy. On the other hand, apathetic AD patients tended toward a decreased perfusion in the anterior CC, even though this finding did not reach statistical significance.

Benoit et al. (2004) further assessed apathy in AD by making a distinction between the separate behavioral, cognitive, and emotional aspects of apathy, using the *Apathy Inventory*. Thirty AD patients were included, and brain perfusion was once more measured with ^{99m}Tc-ECD-SPECT and SPM99 analysis. Lack of initiative scores was negatively associated with perfusion in the right anterior CC, whereas lack of interest scores was negatively associated with perfusion in the right middle orbitofrontal gyrus. Lastly, emotional blunting scores inversely correlated with perfusion in the left superior prefrontal dorsolateral cortex.

Similarly as with Benoit et al. (2004), Robert et al. (2006) also studied the two major dimensions of apathy, i.e., lack of initiative and lack of interest, by using the *Apathy Inventory* combined with ^{99m}Tc-ECD-SPECT and SPM99 analysis in 19 AD subjects presenting this type of behavioral phenomenology compared to 12 AD subjects who did not. On the whole, AD patients with lack of initiative and interest showed a significantly lower perfusion in the right anterior CC than AD patients without such specific behavior (P = 0.00012). These parallel results, however, are not surprising as they both resulted from the same research group and were derived from a rather small subgroup of patients. Nonetheless, this is yet another confirmation of the CC to be involved in the pathophysiological processes of apathy in AD brain.

One last study that relates to apathy, as well as depression, in AD, originates from Kang and colleagues (2011). A rather large number of patients, namely, 81,

were enrolled in this prospective study. ^{99m}Tc-HMPAO-SPECT was performed to evaluate rCBF patterns, and according to the NPI subscores for apathy and depression, unfortunately only nine were classified as clinically depressed and nine as clinically apathetic. In addition, 18 more nondepressed and non-apathetic AD patients were classified as an age- and MMSE score-matched disease control group. Kang and colleagues found that depressed AD patients had a significantly lower perfusion in the right orbitofrontal and inferior frontal gyri than nondepressed AD patients, while apathetic AD patients displayed a hypoperfusion in the right amygdala; temporal, posterior cingulate; and right superior frontal, postcentral, and left superior temporal gyri compared to non-apathetic AD patients. Also, when the rCBF patterns were correlated with NPI subscores in the total group of 81 AD patients, depression subscores negatively associated with perfusion in the left inferior frontal and right middle frontal gyri, whereas apathy subscores inversely correlated with perfusion in the right temporal and right medial frontal gyri.

In conclusion, much evidence resulting from not only SPECT but also PET imaging uniformly suggests that mainly (pre)frontal areas as well as the anterior/posterior CC are involved in the cerebral pathophysiology of depression and apathy in AD.

9.7.1.3 Psychosis

Already in 1994, Starkstein et al. investigated whether delusions in AD were associated with dysfunction in specific brain areas (Starkstein et al. 1994). In total, 45 probable AD patients received ^{99m}Tc-HMPAO-SPECT, and delusions were assessed by the *Present State Examination* so that patients were subdivided in delusional (n = 16) or non-delusional (n = 29). The most common delusion was "paranoia," which was present in 75% of AD patients besides hypochondriac-, grandiose-, and infidelity-type delusions. Four patients also suffered from *Capgras* (impostors) and two from *Cotard* syndrome (delusions of deformity of body parts). Imaging results only revealed that delusional AD patients had a bilateral hypoperfusion in inferior and temporal lobes compared to non-delusional subjects. However, the mixture of different types of delusions might have accounted for the lack of laterality and loss of frontal significance (Ismail et al. 2012).

Somewhat later, Ponton et al. (1995) included 15 initially non-delusional AD patients who underwent SPECT scanning and psychometric testing with the *Alzheimer's Disease Assessment Scale*. Procedures were repeated 1 year later, when 6 out of the original 15 AD patients had developed several types of delusions. When comparing the original baseline SPECT data between delusional (n = 6) and non-delusional (n = 9) subjects, the investigators found that delusional patients already had a significantly higher perfusion in the right hemisphere, particularly in the inferior and superior temporal gyrus, the temporoparietal area, the Broca's area, the prefrontal region, and the primary visual cortex. Afterward, when comparing SPECT data which were yielded at year one between both subgroups, a lower perfusion in the right temporal region was observed in the delusional group compared with those who did not develop any type of delusion. Ponton et al. (1995), subsequently, were the first to suggest that specifically right temporal lobe dysfunction

might predict the onset of delusions in AD. Staff et al. (1999) were also able to identify a relationship between right hemispheric hypoperfusion, namely, in right frontal and limbic regions, and delusions in 18 probable AD patients compared to 15 AD patients who were free of delusions using ^{99m}Tc-HMPAO-SPECT with SPM. The same goes for Fukuhara et al. (2001), who investigated a very specific type of delusions, i.e., delusion of theft, in only nine age- and cognitive-matched AD patients by means of ^{99m}Tc-HMPAO-SPECT imaging and SPM. AD patients with delusions of theft showed a significant hypoperfusion in right medial posterior parietal region compared to patients without such delusions, indicating that right parietal dysfunction may play a role in producing this type of delusions in AD.

Nakano et al. (2006a) obtained similar results, also using ^{99m}Tc-HMPAO-SPECT, when examining the relationship between delusions and rCBF in AD. This time, however, SPECT data of 64 probable AD patients were compared to a group of 76 age-matched controls. Delusions were assessed by the NPI delusion subscale following which AD patients were categorized into delusional (n = 25) and non-delusional (n = 39), without any significant difference between age and MMSE scores. Neuroimaging results showed that, when compared to healthy volunteers, AD patients had significantly decreased perfusion in the posterior cingulate gyri, precuneus, and parietal association cortices. In comparison with non-delusional AD subjects, the delusional one's displayed a significantly decreased perfusion in the prefrontal cortex, anterior cingulate gyri, inferior to middle temporal cortices, and parietal cortex with a right hemispheric predominance ($P < 0.01$).

In 2010, Matsuoka et al. studied the relationship between brain perfusion and associated delusion severity in individuals with AD, using SPECT and NPI (Matsuoka et al. 2010). In total, 35 patients entered this study of which 14 suffered from delusions, whereas 21 did not. The delusion subscale scores of the NPI were negatively correlated with rCBF patterns in the right anterior insula ($P < 0.01$) when the total AD group was taken into account (n = 35). However, rCBF patterns in the right anterior insula were not significantly decreased in delusional AD patients when compared to non-delusional patients. The authors suggest that although it may not be responsible for the onset of delusions, the right anterior insular dysfunction may be responsible for exacerbation of these symptoms.

SPECT imaging has also been used to investigate gender differences in regional perfusion in the brains of psychotic AD patients. For instance, Moran et al. (2008) assessed cerebral perfusion of 51 probable AD patients with psychosis (16 males, 35 females) compared to 52 nonpsychotic probable AD patients (19 males, 33 females). The researchers used the Behave-AD scale to rate the presence or absence of psychosis within 1–2 weeks of ^{99m}Tc-HMPAO-SPECT imaging. The authors concluded that perfusion was lower in female patients with psychotic symptoms in right infero-lateral prefrontal cortex and in inferior temporal regions compared to female patients without such symptoms. In contrast, perfusion was higher in male patients with psychotic symptoms in the right striatum compared to nonpsychotic male subjects. Comparison groups did not differ in age nor dementia severity, which was estimated by the MMSE. These results support the role of right hemispheric prefrontal and lateral temporal cortex in psychosis of AD in women, but not in men,

and raise the possibility that there might be a gender-related regional specificity in the pathophysiology of psychosis in AD.

As distinct from delusions, SPECT studies examining the neuropathophysiology of hallucinations are very limited. For instance, Mori et al. (2006) investigated rCBF changes in a case of AD with music hallucinations compared to a control AD group ($n = 747$). The patient was a 73-year-old right-handed woman who developed AD at the age of 69. ^{99m}Tc-HMPAO-SPECT imaging data revealed that rCBF of the case was significantly increased in the left superior temporal and left angular gyrus compared to control persons. This specific profile thus could be relevant to the neuroanatomical basis of music hallucinations.

In summary, delusions in AD seem to be primarily associated with right hemispheric pathology as was shown not only by SPECT but also by PET imaging data (cfr. Sect. 9.5.1.3). More neuroimaging research, however, is mandatory with regard to hallucinations in AD.

9.7.1.4 Activity Disturbances

Wandering is a common activity disturbance in AD and one of the most exhausting for the caregiver (Rolland et al. 2003). For the moment, only Rolland et al. (2005) tried to study the brain's possible underlying physiological processes of wandering behavior in AD patients. For this purpose, they used ^{99m}Tc-ECD-SPECT and NPI. SPECT scans were then compared between AD subjects with ($n = 13$) and without ($n = 13$) wandering behavior. Despite similar clinical dementia severity based on MMSE scores, wanderers exhibited a more severely reduced rCBF in the left parietotemporal lobe than AD patients without wandering behavior. SPM analysis further revealed a reduced rCBF in the left middle temporal gyrus (BA21) and left parahippocampal gyrus (BA37). Unfortunately, these results did not confirm the authors' hypothesis of the involvement of the supervisory role of the frontal lobes and neither seemed to be associated with a dysfunction of the spatial navigation located in the right parietal cortex nor with a disorder of perception or reality, which should have involved the right temporal lobe. In contrast, wandering in AD, as physical activity and aberrant motor behavior, might enhance an extensive cortico-subcortical network interaction.

9.7.1.5 Agitation and Aggression

Nakayama et al. (2017) analyzed the effect of galantamine on BPSD and caregiver burden and treated a total of 50 mild AD patients for 12 weeks, followed by NPI scoring at baseline and follow-up. ^{123}I-IMP-SPECT was performed at baseline. In the end, the authors could not find any significant improvement of NPI scores after treatment. Baseline comparison of rCBF SPECT between agitated vs. non-agitated AD patients based on the NPI subitems, however, demonstrated increased perfusion in the right prefrontal cortex in the agitated subgroup. In one patient of this subgroup who underwent multiple SPECT scannings at 20 and 56 months after commencement of galantamine treatment, the increase in the rCBF of the right prefrontal lobe disappeared at 20 months but, unfortunately, reappeared 36 months thereafter, suggesting that the magnitude of rCBF increase in this area may affect a patient's

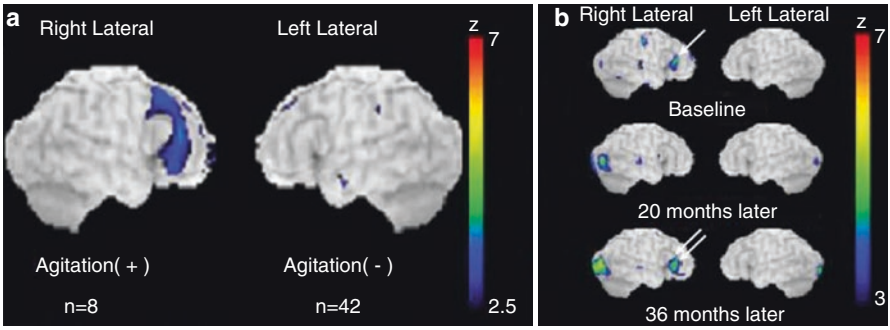


Fig. 9.8 Statistical parametric map on a surface standard anatomical image following ^{123}I-IMP-SPECT in agitated vs. non-agitated mild AD subjects. The map reflects regions with significantly higher blood flow in the group with agitation at baseline than without. The differences were found in the right lateral prefrontal cortex (**a**). The maps show the changes of rCBF in a 67-year-old female patient. The maps reflect regions with significantly high blood flow compared with normal controls. The increased region in the right lateral prefrontal cortex at baseline decreased 20 months after commencement of galantamine treatment but had reappeared in 36 months (**b**). Abbreviations: *AD* Alzheimer's disease, *rCBF* Regional cerebral blood flow. Reprinted from Nakayama S et al. (2017) J Alzheimer's Dis 57:267–273, with permission from IOS Press. Copyright © 2017 IOS Press

response to galantamine (Fig. 9.8). The agitated subgroup only consisted of 8 AD patients (compared to 42 non-agitated patients), so the observed results should be interpreted with caution.

Another very common behavioral disturbance in AD is aggression. So far, only two studies have investigated regional brain perfusion in dementia patients with this specific behavioral phenomenology.

The first study of Hirono et al. (2000) used a group of ten mixed dementia (MXD) patients, i.e., AD+CVD, with and without aggression based on the NPI subscale of aggression. As imaging technique, ^{99m}Tc-HMPAO-SPECT was applied, and MXD patients with aggression revealed a significant hypoperfusion in the left anterior temporal cortex ($P < 0.001$) in addition to the bilateral dorsofrontal and right parietal cortex.

The second study of Lanctôt and colleagues (Lanctôt et al. 2004) was slightly different, as they used 30 aggressive and 19 nonaggressive AD patients who were rated by the Behave-AD and underwent ^{99m}Tc-ECD-SPECT instead of ^{99m}Tc-HMPAO-SPECT. This time, diagnoses were made according to the NINCDS-ADRDA criteria for probable AD, thereby excluding vascular pathology. Unfortunately, SPECT scanning had to be performed only within 3 months of their behavioral assessments, which is a rather large interval. Compared with nonaggressive patients, the aggressive subjects displayed hypoperfusion in the right and left middle temporal ROI ($P = 0.02$ for both). Supplementary SPM analysis further revealed a right middle medial temporal hypoperfusion in the aggressive AD group ($P = 0.008$). This region includes the hippocampus, parahippocampus, and posterior amygdala and corresponds to BA28, BA35, and BA36. The authors, therefore,

suggested that the right middle medial temporal region is an important neural correlate of aggression in AD, which is somewhat comparable with Hirono et al. (2000), who also identified the temporal cortex as an important key factor in the onset of aggression, although in this case the hypoperfusion was located in the left hemispheric temporal region.

9.7.1.6 Sleep Disorders

Sleeplessness in AD is one last behavioral variant besides depression, apathy, psychosis, activity disturbances, and agitation/aggression which has been explored in the neuroimaging field of AD. Noteworthy, literature contains only one related SPECT study so far (Ismail et al. 2009).

In this study of Ismail et al. (2009), authors aimed to investigate the possible association of regional cerebral perfusion and sleep loss in AD. A group of 55 AD patients was characterized as having or not having nocturnal sleep loss based on standardized AD scales assessing sleep over the previous 4 weeks. Regular ^{99m}Tc-ECD-SPECT imaging scans were performed when patients were in a relaxed, wakeful state. Afterward, SPM5 analysis was performed to compare brain perfusion across both groups. In addition, the two AD groups were also compared with a healthy control group of the same age and gender. Results showed increased perfusion in the right middle frontal gyrus (BA9) ($P = 0.016$) in AD patients suffering from nocturnal sleep loss as opposed to patients who were free of sleep loss. Comparison with the normal control subjects indicated that the hyperperfusion in the right middle frontal gyrus among AD patients with sleep loss was not supreme, given the fact that the hyperperfusion of this region which was found in the healthy control group after AD patients with sleep loss versus control group comparison could not be exceeded. Authors thus concluded that in mild-to-moderate AD, relative hyperperfusion (rather than absolute hyperperfusion) of the right middle frontal gyrus might be associated with reports of sleeplessness in AD. Furthermore, this region might play an important role in the regulation of sleep.

9.7.1.7 Other Behavioral Disturbances

The cingulate island score (CIS) indicates the Z-score ratio of the posterior CC relative to the medial occipital area and has been evidenced to be useful for differentiating DLB from AD (Imamura et al. 1997). It reflects the preservation of glucose metabolism in the mid- or posterior cingulate. Only recently, Yasuno et al. (2019) looked into the potential association between BPSD and CIS by applying ^{99m}Tc-ECD-SPECT in 17 early-stage AD patients and 13 amnestic MCI subjects combined into one single group. ^{99m}Tc-ECD-SPECT images acquired from all patients were converted, and the CIS was determined by using the easy Z-score imaging system. A significant correlation between CIS and the NPI-Q was identified, with the increase in CIS reflecting the relative decrease in posterior CC perfusion. Afterward, based on a CIS of 0.39, patients with and without (i.e., NPI-Q score = 0) BPSD were correctly classified with a sensitivity and specificity of 72.2% and 75.0%, respectively. The authors concluded that CIS may not only be useful in

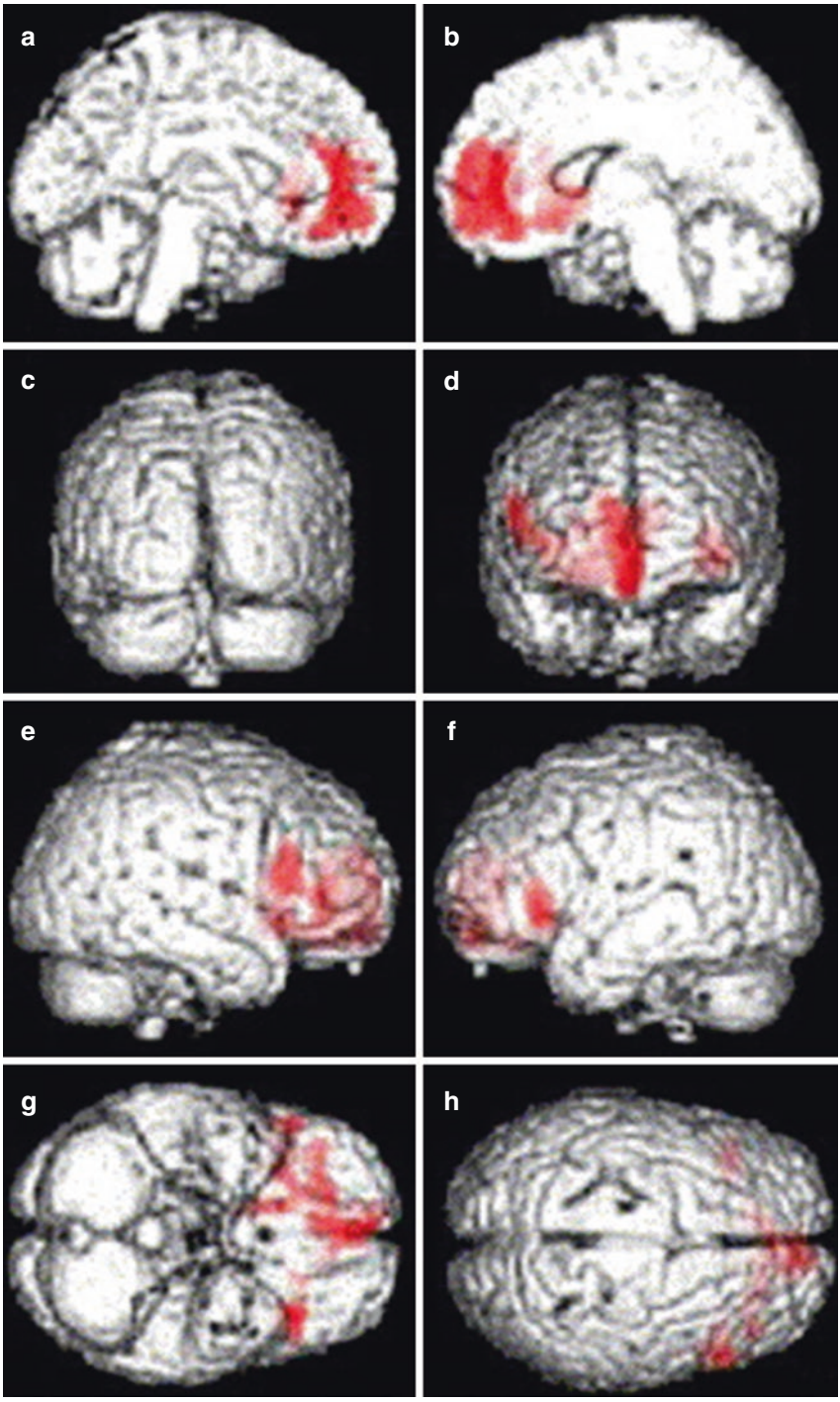
discriminating DLB from AD subjects, but that it can also be a valuable and clinically effective tool indicating vulnerability to BPSD at the prodromal to early stages of AD.

9.7.2 Other Dementia Subtypes

Personality changes such as antisocial behavior are a prominent part of the behavioral symptomatology in FTD patients. This topic was studied by Nakano et al. (2006b) who assessed 22 FTD patients with the NPI and categorized five types of antisocial behavior (stealing, traffic accident (e.g., hit and run), physical assault, sexual comments or advances, public urination). These antisocial behaviors were rated independently by three different geriatric psychiatrists who had not been given the information of the SPECT images. A control group of 76 healthy volunteers was included also, and both groups underwent ^{99m}Tc-ECD-SPECT and SPM99 analysis. Compared to controls, FTD patients showed a significant reduction of rCBF in the widespread frontal cortical areas (such as the superior, middle, and inferior frontal gyri), as well as in subcortical structures (particularly thalamus and caudate nuclei). A subsequent correlation analysis further revealed that antisocial behavioral symptoms were associated with reduction of the rCBF in the orbitofrontal cortex, BA47, BA32, the right caudate nucleus, and the left insula of FTD patients, suggesting that mainly a functional decline of the orbitofrontal cortex in FTD patients is related to antisocial behavior (Fig. 9.9). This conclusion is not surprising at all, given the fact that orbitofrontal cortex dysfunction is mostly associated with disinhibition, facetiousness, sexual and personal hedonism, and lack of concern for others (Nakano et al. 2006b).

The study of Roselli et al. in 2009 targeted BPSD symptoms in 18 well-characterized DLB patients and measured striatal DAT levels by ^{123}I-FP-CIT-SPECT imaging (DaTscan) after NPI assessment (Roselli et al. 2009). Imaging data showed a significant correlation between decreased DAT levels and visual hallucinations. Although no other correlations were observed, delusions, apathy, and depression were also inversely correlated to decreased caudate DAT levels when putamen and caudate nucleus were considered separately. Hence, these results provide important evidence on the involvement of mesocortical dopaminergic pathways in neuropsychiatric symptoms in DLB, such as delusions, apathy, and depression.

Fig. 9.9 Results of SPM analyses displaying rCBF patterns that correlated with antisocial behavioral scores in FTD patients ($n = 22$). Representation in stereotaxic space of cerebral regions that correlated with antisocial behavioral scores in FTD patients ($n = 22$) displayed on a 3D surface anatomical template ($P < 0.005$, not corrected for multiple comparisons). Images show that antisocial behavioral symptoms are, in particular, associated with reduction of rCBF in the orbitofrontal cortex. Views are medial right (**a**), medial left (**b**), posterior (**c**), anterior (**d**), right lateral (**e**), left lateral (**f**), inferior (**g**), and superior (**h**). Abbreviations: *FTD* frontotemporal dementia, *rCBF* Regional cerebral blood flow, *SPM* Statistical parametric mapping. Reprinted from Nakano et al. (2006a) Neuroimage 32:301–306, with permission from Elsevier. Copyright © 2006 Elsevier Inc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Furthermore, ^{99m}Tc-HMPAO-SPECT imaging in 14 DLB patients with hallucinations showed a significant inverse correlation between brain perfusion in the midline posterior CC and hallucination severity, as was illustrated by O'Brien et al. (2005).

Finally, Nagahama et al. (2010) utilized ^{99m}Tc-HMPAO-SPECT imaging and found that visual hallucinations in DLB patients (n = 100) were related to hypoperfusion in the left ventral occipital gyrus and bilateral parietal areas, whereas delusions were rather associated with hypoperfusion in the right rostral medial frontal cortex, left medial superior frontal gyrus, and bilateral dorsolateral frontal cortices. Based on these results, the authors concluded that visual hallucinations in DLB may be related to a dysfunction of parietal and occipital association areas, while delusions may rather be associated with dysfunctions of the frontal cortex. The latter statement fully agrees with similar PET research of Perneczky et al. (2008) (cfr. Sect. 9.5.2).

9.8 Concluding Remarks

PET and SPECT neuroimaging techniques have played an important role in the differential diagnosis of dementia over the past three decades. They have both provided invaluable information regarding characteristic pathophysiological changes during the course of AD. Presently, both imaging modalities have proven to be crucial to most efficiently facilitate dementia diagnosis, indicate disease staging, visualize plaque burden, as well as monitor the effects of disease-modifying therapies. However, recent developments evinced that it is best to combine both *state-of-the-art* imaging techniques with other biomarkers of disease to considerably enhance differential dementia diagnostics, such as CSF $A\beta_{1–42}$, T-tau, and P-tau_{181P} measurements. PET and SPECT also work very complementary. In the last 6 years, a lot of tau radiotracers have emerged, in addition to improved ligands for amyloid pathology. A future challenge will be to continue developing novel radioligands which target different and unique aspects of the etiology of dementia, so that patients might be even more adequately diagnosed, perhaps in an asymptomatic or prodromal phase

With regard to BPSD, PET and SPECT have repeatedly shown that depending on the behavioral phenomenon and dementia subtype, BPSD such as depression, apathy, or psychosis are the result of a very specific, cerebral pathophysiology rather than a diffuse brain event. Evidence resulting from not only SPECT but also PET imaging uniformly suggests that mainly (pre)frontal areas and anterior/posterior CC are involved in the cerebral pathophysiology of depression and apathy in AD and MCI, even though both hypermetabolic and hypometabolic states have been reported, potentially due to early compensatory mechanisms in MCI. Delusions in AD and both delusions and visual hallucinations in DLB seem to be primarily associated with right hemispheric pathology, as was shown by SPECT and PET research. For agitation in AD, only one SPECT and one PET study have been performed so far, with contradictory results—but with a consensus on brain regions—measuring

increased perfusion or reduced glucose metabolism, respectively, in prefrontal and temporal cortices. As for aggression, hypoperfusion in the temporal cortex has been indicated among others, following a handful of SPECT studies in AD, without confirmatory evidence of alike PET research. A general remark is that for PET-related BPSD research, studies were hitherto mostly confined to ^{18}F-FDG as the standard radiotracer, so combinations of various tracers are preferred in future studies, similar as in Ng et al. (2017).

By and large, this shows that more PET and SPECT neuroimaging research is mandatory with special attention to activity disturbances, anxieties, hallucinations, diurnal rhythm disturbances, and aggression/agitation to fully characterize the pathophysiology of each of these neuropsychiatric disturbances in not only AD but also other dementia subtypes, such as FTD and DLB.

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Part III

Anxiety Disorders

PET and SPECT Studies in Anxiety Disorders

10

Vanda Faria, Mats Fredrikson, and Tomas Furmark

Contents

Abstract

Neuroimaging studies using PET and SPECT to evaluate neurofunctional differences between patients with anxiety- and stress-related disorders and healthy controls were reviewed. At rest, patients with social anxiety disorder display increased serotonin synthesis rate and upregulated serotonin transporter expression, whereas

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studies targeting dopamine have yielded mixed results. Posttraumatic stress disorder is associated with a compromised benzodiazepine receptor function. In panic disorder, both benzodiazepine receptors and serotonergic (5-hydroxytryptamine 1A ($5HT_{1A}$)) receptors are downregulated. Across the anxiety disorders, there is downregulation of both benzodiazepine and $5HT_{1A}$ receptors. Symptom provocation studies, where regional cerebral blood flow is measured, support that activity in the brain's fear circuit is altered with increased reactivity in the amygdala, the midbrain, and possibly also the insular cortex, whereas activity in emotion-regulating areas in the prefrontal cortex such as the subgenual anterior cingulate cortex and the orbitofrontal cortex is compromised in the symptomatic state, predominantly in phobic disorders. Some studies demonstrate a coupling between individual differences in neurotransmission and fear network activity. Treatment studies suggest that reductions of neural activity in the amygdala may be a final common pathway for successful therapeutic interventions, thereby linking neurotransmission to plasticity in the core fear network of the brain.

10.1 Anxiety, Genes, and Environment

Anxiety involves a subjective experience of fear and apprehension associated with physiological reactions and avoidance or escape behavior. When the intensity or the frequency of anxiety reactions compromises quality of life, an anxiety disorder is diagnosed. Anxiety problems are prevalent and costly and induce significant suffering. Epidemiological studies show that the lifetime prevalence of any anxiety disorder is almost 30% with roughly twice as many women than men being affected (Kessler et al. 1994, 2005, 2012). Anxiety may come out of the blue like in panic disorder (PD), result from memory activation as in posttraumatic stress disorder (PTSD), be elicited by environmental triggers like in social anxiety disorder (SAD) and specific phobia (SP), or be determined by internal worry cues as in generalized anxiety disorder (GAD). These, together with obsessive-compulsive disorder (OCD), were the principal diagnostic categories for the anxiety disorders in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*) (American Psychiatric Association 1994). The current version of DSM, i.e., *DSM-5*, differs from *DSM-IV* in many respects. For example, OCD falls under "obsessive-compulsive and related disorders" and is diagnosed separately from the anxiety syndromes now including the new entity of "hoarding disorder." Also, PTSD has its own category called "trauma and stressor-related disorders" including acute stress and adjustment disorders. Beside these differences, anxiety disorders in *DSM-5* now include separation anxiety disorder and selective mutism, both previously classified in the section "Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence." In this chapter, we will focus on DSM-5 anxiety- and stress-related disorders including SP, SAD, GAD, PD, and PTSD. In all these disorders, anticipation of feared events or situations causes negative affect and eventually leads to their avoidance.

10.1.1 Anxiety Etiology

Recent etiological theories of anxiety capitalize both on inborn and acquired mechanisms but to a different extent. Anxiety disorders tend to cluster in families (Tillfors et al. 2001a), most likely reflecting common genetic and not environmental factors (Hettema et al. 2001). There are two independent genetic factors in anxiety disorders: the first associated predominantly with PD, GAD, and agoraphobia, while the second mainly influences specific phobias (Hettema et al. 2005). Genetic factors account for a moderate proportion of around 30–40% of the variance in the anxiety disorders. Thus, environmental factors also contribute to fear and anxiety; particularly unique rather than commonly shared environmental factors influence anxiety development rendering gene-environmental interactions pivotal.

Fear conditioning, a plausible candidate mechanism both for the acquisition of anxiety and for mediating gene-environmental interactions, is moderately heritable in the range of 35–45% (Hettema et al. 2003). In addition, there is tentative evidence that fear conditioning to stimuli like snakes and spiders that often trigger fear has a higher heritability than conditioning to neutral stimuli like circles and triangles (Hettema et al. 2003). In early research, some candidate genes for fear conditioning have been identified in humans (Garpenstrand et al. 2001; Lonsdorf et al. 2009), and certain moderately heritable personality traits may also act as vulnerability factors for the development of anxiety. Although previous twin studies were suggestive of a moderate heritability for anxiety disorders (Hettema et al. 2003), genome-wide association studies have struggled to identify genes significantly associated with these disorders (Sharma et al. 2016). On the other hand, anxiety disorders are considered stress-related. Evidence from animal studies suggests a strong role for stress on the epigenetic control of the hypothalamic–pituitary–adrenal (HPA) axis and stress-related brain responses. Neuroepigenetics may explain individual variations in the likelihood of environmental disturbances and consequently anxiety-related disorders (Bartlett et al. 2017).

10.2 Anxiety and Brain Imaging

Initial brain imaging studies of mental disorders that used tools like PET and SPECT focused on schizophrenia and depression and were performed in the resting state. In the second wave of imaging studies, i.e., activation studies, cognitive and emotional tasks were used to activate certain brain areas in order to isolate and localize the task-related processes. Symptom provocation studies were carried out in an attempt to define dysfunctional regions related to anxiety. Most of the second-wave studies utilized tracers like [^{18}F]fluorodeoxyglucose (FDG) and [^{15}O]oxygen to determine glucose metabolism and regional cerebral blood flow (rCBF). In the anxiety disorders, a number of provocation studies have been published in specific phobia and SAD (Ahs et al. 2009, Åhs et al. 2017; Carlsson et al. 2004; Fredrikson et al. 1993, 1995; Rauch et al. 1995, 1996; Tillfors et al. 2001b, 2002; Van Ameringen et al. 2004; Veltman et al. 2004; Wik et al. 1996, 1997) as well as in PTSD (Barkay et al. 2012; Bremner et al. 1999a, b; Britton et al. 2005; Fischer et al. 1966; Liberzon

et al. 1999; Nardo et al. 2011; Pissiota et al. 2002; Shin et al. 1997, 1999, 2004; Zubieta et al. 1999). There are at least 24 published studies from the early 1990s to 2019 that have used PET or SPECT tracers to determine activity in brain areas responsive to symptomatic challenge in the situationally elicited anxiety disorders, SP, SAD, and PTSD and that also have described activations in the three-dimensional Montreal Neurological Institute (MNI) or Talairach and Tournoux (1988) space. Several additional studies use emotional probes other than symptom provocation such as aversive facial and affective pictures to elicit affective and/or perceptual processes (Bergman et al. 2014; Fusar-Poli et al. 2009; Sergerie et al. 2008; Sabatinelli et al. 2011). Also, other challenges like anticipation of anxiety-inducing pentagastrin administration have been studied using PET (Boshuisen et al. 2002). There are additional studies that have used pharmacological and physiological perturbations to induce anxiety in healthy individuals and patients like the cholecystokinin tetrapeptide (CCK4) (Eser et al. 2009; Schunck et al. 2006) and carbon dioxide (CO_2) challenge (Ponto et al. 2002).

Studies have been mixed with respect to activation patterns. Because physiological alterations besides their anxiety-inducing properties also have peripheral effects, the CNS alterations are less straightforward to interpret as compared to studies that have used psychological procedures to induce anxiety. Some studies have also imaged behavioral and pharmacological treatment effects (cf. Fredrikson et al. 1995; Furmark et al. 2002; Peres et al. 2007; Lindauer et al. 2008; Sakai et al. 2006). Also, in the area of imaging genetics, candidate genes for anxiety and learning have been related to brain function using neuroimaging tools (cf. Bergman et al. 2014; Winterer et al. 2005; Bigos and Weinberger 2010).

10.2.1 Anxiety, Symptom Provocation, and the Fear Network

We have previously performed a meta-analysis of increased and decreased brain activity as a function of symptom provocation in specific and social phobia on the one hand and PTSD on the other (Fredrikson and Faria 2013). Both phobias and PTSD are characterized by the fact that environmental factors elicit anxiety. Thus, symptom provocation can be accomplished through psychological means rendering them comparable in terms of anxiety induction methods.

Both in phobias and in PTSD, rCBF in the amygdala and the midbrain increases reliably across studies. Also, the insular cortex tends to be activated, while hippocampus activity is not increased, neither in phobia nor in PTSD, perhaps reflecting the noncognitive nature of situationally elicited fear and anxiety (Ray and Zald 2012). In other words, cues may activate an amygdala-localized memory trace (Agren et al. 2012) while not taxing context-dependent memory representation in the hippocampus. In the phobic disorders, as a function of fear, activity in the anterior cingulate cortex (ACC) increases but decreases in the orbitofrontal cortex, whereas in PTSD, this pattern is not observed. Like in rodents, the human fear network is likely to encompass the amygdala, the insula, the hippocampus, the anterior cingulate cortex, the orbitofrontal prefrontal cortex, and the periaqueductal gray of

the midbrain (Shin and Liberzon 2010). A consistent finding is that the amygdala, the insular cortex, and the midbrain seem involved in generating emotional distress and that areas in the prefrontal cortex, to a certain extent, seem to inhibit negative affect possibly by regulating the amygdala. The anterior cingulate cortex covaries both with the inhibition and expression of anxiety (see also Etkin et al. (2011)). The orbitofrontal and the ventromedial prefrontal cortices and the subgenual part of the ACC have all been attributed anxiety-reducing properties. For phobias, the orbitofrontal cortex may be central because symptom provocation results in reduced orbitofrontal cortex activity coupled with enhanced amygdala activation and symptomatic treatment with cognitive behavioral therapy (CBT) increases orbitofrontal activity (cf. Peres et al. 2007) while amygdala reductions are observed at the same time (cf. Furmark et al. 2002). We suggest that part of the experience of losing emotional control during phobic anxiety is also related to reduced activity in the orbitofrontal cortex.

The third wave of brain imaging studies using symptom provocation designs is today almost exclusively performed using functional magnetic resonance imaging (fMRI) rather than PET and SPECT. They are beyond the scope of this chapter but have been reviewed elsewhere (e.g., Bandelow et al. 2016; Brühl et al., 2014; Etkin and Wager 2007; Goossen et al., 2019; Hughes and Shin 2011). It should be noted that increased activity in the fear circuit is not restricted to conditions of symptom provocation but occurs also in response to nontraumatic but distressing cues in PTSD (Gold et al. 2011) and in the resting state in patients with PD (Sakai et al. 2005), perhaps reflecting a disorder-related vulnerability factor or a scar resulting from repeated anxiety activation. Longitudinal research is needed to determine this. Collectively, it can be concluded that parts of the fear circuit in patients with situationally elicited anxiety disorders are hyperactive. This may be a mechanism accounting for increased autonomic and endocrine drive present in anxiety-disordered patients (Ahs et al. 2006), as well as behavioral manifestations of anxiety (Laukka et al. 2011).

10.2.2 Anxiety and Neurotransmission

Brain imaging studies in anxiety disorders have also characterized neurochemistry in the resting state. An advantage of PET and SPECT is the virtually unlimited potential for using organic compounds like ^{18}F, ^{15}O, ^{13}N, and ^{11}C serving as radioisotopes enabling determination of brain perfusion, metabolism, and neurochemistry. The whole-brain coverage is excellent; the meaning of the signal is well understood, making baseline measurements possible and allowing for comparisons of differences between individuals at rest. An additional focus of this paper is to perform a comprehensive review of differences in brain neurochemistry between patients with anxiety- and stress-related disorders and healthy controls as revealed by PET and SPECT imaging. We searched PubMed and crossed each disorder with each imaging technique like "positron emission tomography OR PET OR single-photon emission computed tomography OR SPECT AND generalized anxiety disorder OR

social anxiety disorder OR (specific OR simple) phobia OR posttraumatic stress disorder" to retrieve references. We also extracted studies by using the reference list of resulting publications. From 1994 to 2019, several have used PET or SPECT tracers to determine dopamine and serotonin neurotransmission with ligands probing, for example, dopamine-D_2 and $5HT_{1A}$ receptors as well as dopamine and serotonin reuptake transporters. Also, activity in the neurokinin 1/substance P (NK1/SP) system and benzodiazepine (BZD) receptors has been imaged. With one exception, all neurochemical studies have been performed in the resting state. Table 10.1 details the main findings for GAD (n = 3 studies), SP (n = 1), SAD (n = 12), PD (n = 15), and PTSD (n = 10).

Most studies have been performed in PD, and data suggest that BZD receptors are downregulated even though conflicting evidence exists. Also, $5HT_{1A}$ receptors are downregulated in PD. Data for the serotonin transporter in PD are inconclusive since one study report enhanced and another attenuated reuptake of serotonin. One study reported similar dopamine transporter availability in the striatum of patients with PD and healthy controls.

Social anxiety disorder is the second most investigated condition. A reduced D_2 receptor binding potential was initially suggested, but one study failed to demonstrate differences between striatal regions of patients and controls. Also with respect to dopamine reuptake mechanisms in SAD, data are inconclusive because one study reported higher, one lower, and one similar uptake activity in SAD patients when compared to controls. These were mainly SPECT studies, but by using relatively more specific and sensitive PET methodology, we recently demonstrated elevated dopamine transporter availability in SAD correlating with symptom severity in the amygdala, hippocampus, and putamen (Hjorth et al. 2019). A more consistent pattern emerges for serotonin since three studies indicate increased availability of serotonin transporters in thalamic and striatal regions. This appears true also for the ventral striatum/nucleus accumbens, and interestingly, there is evidence of higher co-expression of serotonin and dopamine transporters in fear- and reward-related brain regions in SAD (Hjorth et al. 2019). Two studies also report increased serotonin synthesis capacity in SAD in limbic and basal ganglia regions. Increased synthesis could, in turn, result from downregulation of inhibitory raphe $5HT_{1A}$ autoreceptors as reported by Lanzenberger et al. (2007). Taken together, these findings may indicate an overactive presynaptic serotonin system in socially anxious individuals.

In PTSD, BZD receptors appear downregulated even though there is conflicting evidence with studies not showing differences between patients and controls. For GAD, there are still too few studies to draw any general conclusions, but suggestive evidence of downregulated BZD receptors exists. Studies are lacking also for specific phobia, but there are indications that alterations in the NK1/SP system activity may characterize one or several anxiety disorders including specific phobia. There are only a few studies investigating NK1/substance P system activity. One study in PTSD reported widespread decreased binding of an NK1 receptor ligand at rest, while another one noted increased NK1 binding in the amygdala in patients. Co-expression of NK1 receptors and serotonin transporters was suggested to be

Table 10.1 Neurochemical alterations in the anxiety disorders based on PET and SPECT studies

First author (year)	Neurofunction	Patients/controls	Imaging/ligand	Main results
Neurochemical alterations in GAD, as compared to controls, based on PET and SPECT studies				
Tiihonen et al. (1997a, b)	GABA/BZD	GAD (10♀) HC (10♀)	SPECT: [^{123}I] NNC-13-8241	↓ TP (L)
Maron et al. (2004a, b)	SERT	GAD (7) HC (7)	SPECT: [^{123}I] nor- β-CIT	= Midbrain 5HTT – Corr with symptom severity in pts
Lee et al. (2015)	DAT/SERT	GAD (12) HC (12)	SPECT: [^{99m}Tc] TRODAT-1 [^{123}I]ADAM	↓ DAT striatum (GAD)
Neurochemical alterations in SP, as compared to controls, based on PET and SPECT studies				
Michelgård et al. (2007)	NK1/SP	SP (16) HC (0)	PET: [^{11}C] GR205171	↓ Amygdala uptake during anxiety provocation – Corr with symptom severity
Neurochemical alterations in SAD, as compared to controls, based on PET and SPECT studies				
Tiihonen et al. (1997a, b)	DAT	SAD (11) HC (28)	SPECT: [^{123}I] β-CIT	↓ Striatum 0 – Corr
Schneier et al. (2000)	D_2	SAD (10) HC (10)	SPECT:[^{123}I] iodobenzamide	↓ Striatum – Corr (trend) with LSAS
Lanzenberger et al. (2007)	$5HT_{1A}$	SAD (12) HC (18)	PET: [^{11}C] WAY-100635	↓ Amygdala, ACC, insula, raphe 0 – Corr
Schneier et al. (2008)	D_2	SAD + OCD (7) OCD (8) HC (8)	SPECT: [^{123}I] - IBZM	↓ Striatum (SAD) – Corr KSP detachment
van der Wee et al. (2008)	SERT/DAT	SAD (12) HC (12)	SPECT: ^{123}I-β-(4-iodophenyl)-tropane	↑ SERT thalamus ↑ DAT striatum 0 – Corr
Schneier et al. (2009)[a]	DAT/D_2	SAD (17) HC (13)	SPECT: [^{123}I] β-CIT PET: [^{11}C] raclopride	= DAT, D_2 (baseline and after challenge) 0 – Corr
Moriyama et al. (2011)	DAT	Parkinson + SAD (11) Parkinson (21)	SPECT: TRODAT-1	+ Corr with symptom severity in the putamen and N Caud
Frick et al. (2015a, b)	5HT synthesis	SAD (18) HC (17)	PET: [^{11}C]5-HTP	↑ Amygdala, raphe nuclei, caudate nucleus, putamen, hippocampus, and ACC + Corr with symptom severity in the amygdala

(continued)

Table 10.1 (continued)

First author (year)	Neurofunction	Patients/controls	Imaging/ligand	Main results
	SERT	SAD (26) HC (17)	PET: [^{11}C] DASB	↑ Raphe nuclei, caudate nucleus, putamen, thalamus, and insula – Corr with symptom severity in dorsal ACC
Frick et al. (2015b)	NK1	SAD (17) HC (17)	PET: [^{11}C] GR205171	↑ amygdala 0 – Corr
Furmark et al. (2016)	5HT synthesis	SAD (18) HC (6)	PET: [^{11}C]5-HTP	↑ Hippocampus, globus pallidum, and putamen 0 – Corr
Plavén Sigray et al. (2017)	D_2	SAD (12) HC (16)	PET: [^{11}C] FLB457	↑ OFC ↑ dlPFC + Corr with symptom severity in OFC
Hjorth et al. (2019)	DAT	SAD (27) HC (43)	PET: [^{11}C]PE2I	+ Corr with symptom severity in the amygdala, hippocampus, putamen ↑ Amygdala, hippocampus, striatum (trend)
	SERT		PET: [^{11}C] DASB	↑ Nucleus accumbens ↑ Amygdala, hippocampus, striatum, thalamus, insula (trend) 0 – Corr
	SERTxDAT co-expression			↑ Amygdala, striatum, thalamus ↓ Dorsomedial thalamus 0 – Corr
Neurochemical alterations in PD, as compared to controls, based on PET and SPECT studies				
Schlegel et al. (1994)	GABA/BZD	PD (10) Epileptic pts. (10)	SPECT: [^{123}I] iomazenil	↓ FC, occipital, TP
Kaschka et al. (1995)	GABA/BZD	PD + depression (9) Dysthymic (9)	SPECT: [^{123}I] iomazenil	↓ Inferior TP, inferior FC, (rCBF-related) ↓ Medial inferior TP ↓ left TP (not rCBF-related)

Table 10.1 (continued)

First author (year)	Neurofunction	Patients/controls	Imaging/ligand	Main results
Kuikka et al. (1995)	GABA/BZD	PD (17) HC (17)	SPECT: [^{123}I] iomazenil	↑ R > L-ratio in pts. ↑ TP
Brandt et al. (1998)	GABA/BZD	PD (12) most on meds HC (9)	SPECT: [^{123}I] iomazenil	↑ Supraorbital cortex (R) ↑ Temporal cortex (R) - Trend correlation with STAI in HC 0 – Corr in pts
Malizia et al. (1998)	GABA/BZD	PD (7) HC (8)	PET: [^{11}C] flumazenil	↓ Globally most pronounced in OFC + insula (R)
Bremner et al. (2000a, b)	GABA/BZD	PD (13) HC (16)	SPECT: [^{123}I] iomazenil	↓ Hipp, precuneus ↓ PFC in panic attackers – Corr symptom severity in PFC
Maron et al. (2004a, b)	SERT	PD (8) PD remission (8) HC (8)	SPECT: [^{123}I] nor- β-CIT	↓ midbrain, TP, thalamus – Corr with symptom severity Clinical improvement = normalization, except in the thalamus
Neumeister et al. (2004)	$5HT_{1A}$	PD (16) with comorbid Agoraphobia (6) HC (15)	PET: [^{18}F] FC WAY	↓ ACC, PCC, raphe
Sullivan et al. (2005)	$5HT_{1A}$	MDD + PD (7) MDD (21) HC (0) MDD with vs. without comorbid PD	PET: [^{11}C] WAY-100635	↓ TP, ACC, PHG, hipp in comorbid PD – Corr anxiety
Cameron et al. (2007)	GABA/BZD	PD (11) HC (21)	PET: [^{11}C] flumazenil	↓ Insula (R + L) 0 - corr
Hasler et al. (2008)	GABA/BZD	PD (15) HC (18)	PET: [^{11}C] flumazenil	↓ PFC, frontal, temporal, parietal ↑ Hipp – Corr with symptom severity in hipp + Corr with symptom severity in dPFC

(continued)

Table 10.1 (continued)

First author (year)	Neurofunction	Patients/controls	Imaging/ligand	Main results
Nash et al. (2008)	$5HT_{1A}$	PD (9) PD remission (7) HC (9)	PET: [^{11}C] WAY-100635	↓ Raphe, OFC, TP, amygdala 0 – Corr
Fujimura et al. (2009)	SERT	PD (14) HC (14)	PET: [^{18}F] SPA-RQ	↓ In widespread areas including the amygdala
Maron et al. (2010)	DAT	PD (7) PD remission (7) HC (7)	SPECT: [^{123}I] nor- β-CIT	↓ Striatum ↑ Striatum current vs. remitted – Corr DAT with symptom severity
Maron et al. (2011)	SERT	PD ♂ (5) PD ♀ (6) HC ♂ (12) HC ♀ (12)	PET: [^{11}C] MADAM	♂ ↑ Raphe, cortex (in 13 out of 20 studied regions ↓ Hipp ♀ = 0 - corr
Neurochemical alterations in PTSD, as compared to controls, based on PET and SPECT studies				
Bremner et al. (2000a, b)	GABA/BZD	PTSD (13) HC (13)	SPECT: [^{123}I] iomazenil	↓ PFC (BA 9) + Corr with symptom severity
Fujita et al. (2004)	GABA/BZD	PTSD (19) HC (19)	SPECT: [^{123}I] iomazenil	= – Corr with childhood trauma Scores in pts
Bonne et al. (2005)	$5HT_{1A}$	PTSD (12) HC (11)	PET: [^{18}F] FC WAY	=
Liberzon et al. (2007)	μ-Opioid receptors	PTSD (16) Trauma exposed HC (14) HC (15)	PET: [^{11}C] carfentanil	Trauma exposed: ↓ Ext amygdala, NAcc, dFC, insula ↑ OFC PTSD: ↓ ACC 0 – Corr
Czermak et al. (2008)	Nicotinic acetylcholine receptors (β_2 subunit)	PTSD (10 HC (10)	SPECT: [^{123}I] 5-1A-85,380	↑ MTP + Corr with reexperience
Geuze et al. (2008)	GABA/BZD	PTSD (9) Trauma-exposed HC (11)	SPECT: [^{11}C] flumazenil	↓ Cortex, hipp, thalamus
Fujimura et al. (2009)	NK1/SP	PTSD (14) HC (14)	PET: [^{18}F]-SPA-RQ	↓ In widespread areas
Murrough et al. (2011)	SERT	PTSD (15) HC (15)	PET: [^{11}C] AFM	↓ Amygdala – Corr symptom severity
Frick et al. (2016a, b)	SP/NK1	PTSD (16) HC (16)	PET: [^{11}C] GR205171	↑ Amygdala 0 – Corr

Table 10.1 (continued)

First author (year)	Neurofunction	Patients/controls	Imaging/ligand	Main results
	SERT		PET: [^{11}C] DASB	↑ Precentral gyrus, posterior cingulate cortex – Corr with symptom severity in the amygdala
	SP × SERT co-expression			↓ Putamen, thalamus, insula, and lateral orbitofrontal gyrus – Corr with symptom severity
Reuveni et al. (2018)	BZD	PTSD (12) HC (15)	PET: [^{11}C] flumazenil	↑ Caudal ACC and precuneus + Corr symptom severity and BZD binding in the mid-insular and anterior insular cortices

[a]i.v. D—amphetamine to induce dopamine release

lower in PTSD patients and correlated with symptom severity in several brain regions (Frick et al. 2016a, b). In specific phobia, one study report reduced NK1 receptor availability during an anxious state. Individual differences in subjective fear during symptom provocation were related to uptake with highly fearful individuals having a lowered uptake in the amygdala, indicating a reduction in NK1 receptor availability and hence suggestive of enhanced endogenous substance P release (Michelgård et al. 2007). Similar to PTSD, patients with SAD, as compared to healthy subjects, have increased NK1 receptor availability in the amygdala (Frick et al. 2015a, b). Moreover, pharmacological blockade of the NK1 receptor resulted in anxiety reductions of a similar magnitude as those achieved through citalopram treatment, and both treatments attenuated amygdala reactivity to symptomatic challenge in patients with SAD (Furmark et al. 2005), suggestive of a mechanistic role for the NK1/substance P system in anxiety. Increased NK1 availability in the amygdala has also been demonstrated to be associated with anxious traits and introversion in healthy individuals (Hoppe et al. 2018).

Across studies, the most consistent result is that BZD receptor binding is reduced in limbic and frontal areas in patients with panic disorder with a similar pattern for PTSD and possibly GAD. Also, monoaminergic neurotransmission seems altered both in SAD and PD consistent with reduced $5HT_{1A}$ receptor availability. There is insufficient data to evaluate specific phobia with respect to integrating and segregating neurotransmission patterns.

Reductions in BZD receptor activity occur most frequently in limbic and frontal areas both for PD and PTSD. Monoaminergic alterations, both in serotonergic and dopaminergic neurotransmissions, are often localized in the limbic system.

Reflecting tracer binding properties, monoaminergic alterations are located also in the striatum and the midbrain raphe, areas rich in dopamine and serotonin, respectively. The altered neurotransmission dynamics in the limbic and frontal parts of the brain concur with studies determining rCBF and FDG in the resting state (Molina et al. 2010; Kim et al. 2007; Bonne et al. 2003; Mirzaei et al. 2001; Semple et al. 1993, 2000), which also are characterized by an altered perfusion and metabolism in the limbic and frontal areas (see Table 10.2 for a summary of studies). There has been little work on resting-state PET and SPECT in recent years, presumably due to the fact that resting-state fMRI has emerged as a substantial field in neuroimaging.

Table 10.2 Alterations in glucose metabolism or regional cerebral blood at rest in anxiety disorders based on PET and SPECT studies

First author, year	Neurofunction	Patients/ controls	Imaging/ ligand	Main results
Semple et al. (1993)	rCBF	PTSD (6) (comorbid cocaine-abuse) HC (7)	PET: $[^{15}O]H_2O$	↑ trend for OFC
Semple et al. (2000)	rCBF	PTSD (−) (comorbid cocaine-abuse) HC (−)	PET: $[^{15}O]$ butanol	↓ FC
Mirzaei et al. (2001)	rCBF	PTSD (8) HC (8)	SPECT: $[^{99m}Tc]$ HMPAO	Ratio only – More left lateralized and heterogeneous in pts
Bonne et al. (2003)	rCBF	PTSD (11) HC (11) Trauma-exposed HC (17)	SPECT: $[^{99m}Tc]$ HMPAO	↑ CBL (L + R), BA4, 6, 22, 19, 37 Vs trauma-exposed HC ↑ CBL (L + R), 20, 21, 40, 3, 4 (HC) Vs trauma-exposed HC + Corr symptomatology in CBL and visual cortex
Kim et al. (2007)	rCBF	PTSD (19) HC (19)	SPECT: $[^{99m}Tc]$ HMPAO	↓ thalamus (R) + corr symptom severity ↑ superior parietal (R) + corr symptom severity
Bisaga et al. (1998)	Glucose	PD♀ (6) HC♀ (6)	PET: $[^{18}F]$FDG	↑ Hipp, parahipp ↓ Inferior parietal, superior temporal
Evans et al. (2009)	Glucose	SAD (15) HC (10)	PET: $[^{18}F]$FDG	↓ ACC vmPFC ↑ vmPFC after tiagabine 3–6 mg GABA reuptake inhibitor
Molina et al. (2010)	Glucose	PTSD (15) HC (6)	PET: $[^{18}F]$FDG	↓ Acc, precuneus (BA 7), insula, hipp, FC, PDF, visual cortex, verbal areas ↑ Fusiform, temporal, occipital, precuneus (BA 31), CBL

Table 10.2 (continued)

First author, year	Neurofunction	Patients/ controls	Imaging/ ligand	Main results
Kim et al. (2012)	Glucose/rCBF	PTSD♀ (12 SPECT & PET) HC♀ (10 SPECT; 15 PET)	SPECT: $[^{15}O]H_2O$ PET: $[^{18}F]FDG$	rCBF: ↓ hippocampus, basal ganglia Glucose: ↓ hippocampus, superior temporal, precentral gyri
Ramage (2016)	Glucose	PTSD danger traumas (19) PTSD non-danger traumas (26) HC soldiers (26) HC civilians (24)	PET: $[^{18}F]FDG$	↑ Amygdala (PTSD with danger traumas compared to HC) ↑ Precuneus (PTSD non-danger traumas compared to danger traumas PTSD) ↑ Precuneus, dACC ↓ l amygdala (PTSD with danger traumas) ↑ Precuneus ↓r amygdala (PTSD non-danger traumas)
Zandieh et al. (2016)	Glucose	PTSD (9) HC (10)	PET: $[^{18}F]FDG$	↓ Occipital lobe in 6 of the 9 PTSD, temporal lobe in 1 of the 9 PTSD, caudate nucleus in 5 of the 9 PTSD ↓ posterior cingulate cortex, parietal and frontal lobes in 2 of the 9 PTSD
Baeken et al. (2018)	Glucose	MDD with GAD (22) MDD without GAD (15) HC (15)	PET: $[^{18}F]FDG$	↑ Parahippocampus (MDD in comparison with HC) ↓ frontotemporal and parietal cortices (MDD in comparison with HC) ↑ dmFC (MDD patients without GAD)

10.2.3 Anxiety Treatment and Brain Function

For certain disorders and some neural functions, there are also treatment studies. For example, Spindelegger et al. (2009) treated patients with PD comorbid with SAD with selective serotonin reuptake inhibitors (SSRIs) for 12 weeks and reported a decrease in $5HT_{1A}$ availability. Because the binding in patients initially is lower than in controls, the causative role of $5HT_{1A}$ receptors in determining anxiety symptomatology remains uncertain. It is not clear if there is cross talk between the monoaminergic systems or if the ligands fail to selectively mirror only one system. For example, Warwick et al. (2012) reported an increased dopamine transporter (DAT) binding in the caudate and putamen after 12 weeks of escitalopram treatment in patients with SAD suggesting serotonergic influences on dopamine signaling. Thus, the interpretation of alterations in neurotransmission in anxiety disorders is probably not unidimensional and restricted to one brain function but multidimensional and related to multiple mechanisms.

10.3 Multiple Mechanisms Mediating Anxiety

Altered neurotransmission could represent a primary vulnerability factor or a secondary scar resulting from repeated anxiety experiences which in turn could modulate the activity of the fear network in the brain (Shin and Liberzon 2010). For example, Hariri and co-workers reported a negative correlation between $5HT_{1A}$ receptor density and BOLD reactivity to emotional pictures in normal healthy volunteers. Fisher et al. (2006) and Kienast et al. (2008) demonstrated positive relations between serotonin and dopamine functions and amygdala BOLD reactivity to negative stimuli. Also, after pharmacologic treatment, reduced serotonin synthesis rate correlated with attenuated stress-related activity in the amygdala in patients with SAD (Frick et al. 2016a, b). This is in line with a modulating role for the monoaminergic system with respect to fear network activity. Also data in patients with specific animal phobia support that the NK1/SP system in the brain modulates activity in the amygdala. Ahs et al. (2009) reported a positive correlation between anxiety ratings and increased amygdala rCBF, while Michelgård et al. (2007) observed a corresponding negative correlation between anxiety ratings and NK1 receptor availability suggesting a potential coupling between fear circuit network activity reflected in rCBF and neurotransmission in the NK1/SP system. Neurochemical modulation of the central nervous system activity is further supported by imaging genetic studies linking monoaminergic polymorphisms to emotionally determined amygdala reactivity (Domschke and Dannlowski 2010; Munafò et al. 2008) and to modulation of intrinsic couplings within the fear network (Pezawas et al. 2005). One implication of the hypothesis that the monoaminergic and other neurotransmission systems modulate fear circuit activity is that all treatments targeting specific neurochemical systems should influence symptomatology through activity in the fear network. A couple of studies from our and other laboratories are consistent with this notion because reductions in anxiety achieved through administration of SSRI and NK1 receptor antagonism both attenuated amygdala reactivity in SAD (Furmark et al. 2002, 2005; Faria et al. 2012; Phan et al. 2013). In addition, in PTSD, prefrontal activity was enhanced by SSRI (Fernandez et al. 2001) with similar findings reported by Fani et al. (2011). Attenuation of amygdala reactivity may be a final common pathway for anxiety reductions irrespective of treatment modality. Effective CBT in SAD and specific phobia reduce amygdala reactivity (Furmark et al. 2002; Lipka et al. 2014). Also, responders but not nonresponders, to placebo administration in a randomized controlled trial evaluating pharmacological anxiolytics for SAD, had reduced amygdala reactivity (Furmark et al. 2008; Faria et al. 2012).

A parsimonious working hypothesis is that both psychological and pharmacological interventions work through altering fear network activity either by bottom-up mechanisms reducing amygdala and insula activity directly or through prefrontal top-down control of fear-initiating areas (Faria et al. 2014). The hypothesis that neurotransmission is tightly coupled to fear network activity also implies that effective CBT is mediated by alterations in the neurochemistry of the brain, as supported by initial evidence (Cervenka et al. 2012).

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Neurobiology of Posttraumatic Stress Disorder

11

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Abstract

This chapter illustrates the functional and anatomical alterations that occur in patients affected by posttraumatic stress disorder (PTSD). Most of these studies have been carried out over the last three decades with advanced neuroimaging techniques and have contributed significantly to describ the model of neurobiological changes underlying PTSD, implying an unbalance between hyperactivation of the amygdala following a traumatic event and the resulting inhibitory action of the prefrontal cortex. The findings of neuroimaging studies in most of the regions whose functional and anatomical changes account for PTSD symptoms will be described as well as the implication of these changes in the disorder of the three main brain connectivity networks.

11.1 PTSD

This disorder was first defined by DSM-III in 1980. It is a dysfunctional learning disorder with memory deficits and mood dysregulation (APA 2013). This leads to a fear-conditioned response and stressful events elicited by internal or external stimuli associated with the traumatic circumstance. This is relived in the form of flashbacks with an involuntary review of the event, concomitant autonomic reactions, and negative sensations. The oppressive tendency to relive the trauma leads to the avoidance of what they remember, irritability and emotional and social withdrawal. In the description of PTSD provided by DSM-5, the symptomatic cluster included negative alterations such as mood, memory, and cognition disorders, all linked to hippocampal dysfunction (Vasterling et al. 1998). The recurrent traumatic memory behaves like a new experience destabilizing homeostasis which activates the brain networks involved in the response to fear causing a generalized autonomic reaction throughout the body. It is estimated that PTSD has a lifetime prevalence in the general population of 1–9%, making it the fourth most common psychiatric disorder (Breslau 2001; Kessler 2000; Wittchen et al. 2012). Darves-Bornoz et al. (2008) interviewed more than 20,000 people in some European countries, finding a prevalence of PTSD of just over 1%, with the highest percentage of people affected in the Netherlands (over 2.5%) and the lowest in Spain (0.6%).

Beginning in the 1990s, the neurobiological correlates of what was called a shell-shock syndrome were progressively unveiled by studies that began in the military hospitals of the United States who took care of Vietnam War veterans, which presented severe psychically disabling symptoms. These studies, together with similar research focusing on functional alterations in abused women and adolescents, have shown that psychological trauma can cause functional alterations in specific brain areas associated with the onset of PTSD symptoms. By increasing the number and quality of functional and anatomical studies, metabolic and morphological damage was highlighted during the symptomatic phase of the disorder, and a specific role was assigned to each area involved in the complex mechanism underlying the processing of emotions. In order to study functional variations in real time during the

symptomatic phase, the so-called scripts have been used (drawings, images, or sounds associated with the trauma to be studied). The administration of a script in PTSD aims to activate the areas involved in the altered mnemonic process that leads to the review of the trauma suffered and to verify how the various positive and negative feedback mechanisms can allow their correct processing. The commonly used strategy is to compare the brain activations associated with a resting state or the administration of neutral stimuli with those that occur during the administration of the script (Francati et al. 2007).

To allow an activation that is compatible with the temporal resolution of the instrument (which differs for different imaging modalities), the script should be administered at different times: few minutes before and after the administration of the radiopharmaceutical in SPECT and PET (Bremner 2006; Pagani et al. 2007). The temporal resolution of fMRI, NIRS, and EEG allows the detection of activation areas even with stimuli lasting a second or less, but even in this case, it is also advisable to administer the script for a prolonged period of time that allows the complete activation of the areas involved in the process to be studied (Ohtani et al. 2009; Pagani et al. 2011; Taber et al. 2003). Another factor to consider is that in severely traumatized and/or anxious patients, even a neutral stimulus may elicit significant functional variations. This could lead to inconsistent conclusions when PTSD studies are compared that used different scripts and resting conditions or that recruited patients with nonhomogeneous clinical traits. In an interesting study, Nardo et al. (2011) considered cortical activation elicited by listening to an autobiographical script of their own traumatic experience and correlated changes in brain areas with the scores of neuropsychological tests used for screening patients with PTSD. The high topographical correspondence between the changes in blood flow in these two cases indirectly validated both the script and the employed tests (Impact of Event Scale and WHO-10 Wellbeing), encouraging their use in PTSD.

The triggering of symptoms through these paradigms is particularly useful for outlining the functional anatomy of the traumatic memories that characterize PTSD since in pathological conditions local variations in response to specific tasks can highlight dysfunctions of the neural processes involved. In this regard, it has been widely demonstrated by numerous studies that exposure to an autobiographical traumatic script, whether through sound or visual or simple narrative concerning the trauma suffered, is a valid approach to elicit a functional response in specific brain areas in PTSD (Francati et al. 2007). When real-time neuroimaging studies are allowed by the technical developments and the methodological features of the instruments (fMRI, EEG, NIRS) this become more feasible and suitable for investigating the neurobiology of emotions. Over the years, the functional and structural alterations underlying the PTSD symptomatology have been highlighted. This has been possible through the various protocols for the trauma review by using the scripts, although with different instruments and cohorts of different patients. Most of these studies converge in identifying alterations in specific regions of the central nervous system associated with clinical symptoms, allowing to ascribe to each process specific areas involved in the processing of emotions and psychological trauma.

11.2 PTSD and Neuroimaging Studies

Numerous meta-analyses indicate that PTSD is associated with dysfunctions in different brain regions, such as the hippocampus, the amygdala, the prefrontal cortex (PFC), the anterior cingulate cortex (ACC), the insula, and many others (e.g. Etkin and Wager 2007; Garfinkel and Liberzon 2009; Hayes et al. 2012a; Simmons and Matthews 2012). All these regions are part of a brain network involved in key processes including fear conditioning, the regulation of threatening stimuli, top-down control of emotional responses, and the evaluation of contextual information (Hayes et al. 2012b). Numerous structural MRI studies have shown that some regions consistently show changes in the volume and density of gray matter in PTSD. Furthermore, functional neuroimaging studies converge in describing variations in both limbic and cortical areas during the re-living of trauma in PTSD patients (Francati et al. 2007). All these studies have identified the hippocampus, the amygdala, and the mPFC as the most involved regions in the pathophysiology of PTSD. The following paragraphs will present the main results of structural and functional neuroimaging studies conducted over the past 25 years in this area, structured, for greater clarity, by brain region.

11.3 Regions Implicated in PTSD

11.3.1 Hippocampus

The hippocampus is a brain region involved in the processing of semantic and autobiographical memories, in the regulation of stress and emotions and the processing of fear, involved in context evaluation.

The first researchers who highlighted the involvement of this region in PTSD were Bremner et al. (1995a), who found a reduction in the volume of the hippocampus associated with PTSD following war trauma compared to healthy controls. Starting from this research, many other studies have reported a volumetric reduction of the hippocampus not only in PTSD associated with war trauma but also in other forms of PTSD, ranging from subjects exposed to trauma to individuals with chronic PTSD (Gilboa 2015; Kitayama et al. 2005; Woon et al. 2010). In most studies, the hippocampus of subjects with PTSD has a lower volume than that of healthy volunteers and that of traumatized but not symptomatic subjects (Kitayama et al. 2005; Smith 2005). As with all neuroimaging studies, these differences are more evident when considered with high-resolution MRI, in which volume differences of up to 20% can be appreciated (Karl et al. 2006), for example, using methods such as diffusion tensor imaging (DTI), which also allows to examine the microstructural architecture (Waltzman et al. 2017).

Many studies have linked this volume reduction to visible memory deficits in PTSD patients and in particular to intrusive symptoms characterized by flashbacks and nightmares (Bremner et al. 1995b; Brewin et al. 2009, 2010; Corcoran and Maren 2001; Eichenbaum 2000; Liberzon and Sripada 2008; Scaglione and Lockwood 2014; Tischler et al. 2006; Vythilingam et al. 2005), although other

research has not confirmed these results (Lindauer et al. 2006; Neylan et al. 2004; Stein et al. 1997; Woodward et al. 2009).

Furthermore, not all studies have found consistent results regarding the link between reduced hippocampal volume and PTSD. Some systematic reviews and meta-analyses have shown a reduction in both right and left hippocampal volume in PTSD patients compared to control subjects (Ahmed-Leitao et al. 2016; Kitayama et al. 2005; O'Doherty et al. 2015; Smith 2005) and to subjects exposed to trauma who did not develop PTSD (Karl et al. 2006).

Woon et al. (2010) have instead suggested that exposure to a traumatic event in itself, even in the absence of PTSD, may be associated with a reduction in hippocampal volume; in fact, they found that individuals with PTSD differ from individuals exposed to trauma who did not develop PTSD solely because of a greater reduction in the right portion of the hippocampus, while there is no difference between these two groups of subjects with regard to the left side or the entire hippocampus.

A recent study has shown how microscopic-level analysis (by using DTI) of hippocampal tissue allows to highlight alterations of the brain tissue even before the onset of atrophy and neuronal degradation at the macroscopic level in this region, hypothesizing that this exact alteration at the microstructural level may be the hippocampal correlate of PTSD (Waltzman et al. 2017). Furthermore, it is still to be clarified whether the reduction in volume often observed in PTSD subjects is an effect of the chronic secretion of cortisol caused by the disorder (as suggested by studies conducted on animals; see Crochemore et al. (2005)) or whether it is already present before the onset of the disease in vulnerable individuals with a high individual risk of developing PTSD (Apfel et al. 2011; Gilbertson et al. 2002; van Rooij et al. 2015a, b). On the other hand, some studies have reported a standard hippocampal volume in subjects with PTSD, leaving open the etiopathological interpretation of its reduction (Freeman et al. 2006; Jatzko et al. 2006).

Functional studies have shown increased activity of both right and left hippocampus in patients with PTSD compared to healthy controls and individuals exposed to trauma without PTSD (Geuze et al. 2008; Thomaes et al. 2009; Werner et al. 2009; Whalley et al. 2008). A recent study conducted by Tural et al. (2018) confirmed these results, showing in particular an altered activation in the right portion of the hippocampus compared to the left one in subjects with PTSD compared to subjects exposed to trauma without PTSD, thus replicating the structural results previously found by Woon et al. (2010). Finally, other studies have shown a direct positive correlation between hippocampal activation and the severity of PTSD symptoms (Osuch et al. 2001; Shin et al. 2004).

11.3.2 Amygdala

Since the first functional neuroimaging studies on PTSD, an increased activity of the amygdala in symptomatic subjects has been highlighted (Bremner et al. 1995b; Van Der Kolk et al. 1997; Rauch and Shin 1997). The amygdala is involved in processes related to the response to external threats and plays a central role in the

processing of the fear-conditioned response (Davis and Whalen 2001; Morris et al. 1998; Phelps and LeDoux 2005). Many studies have identified a pattern of increased activation of the amygdala in subjects with PTSD compared to control subjects (Francati et al. 2007; Patel et al. 2012), hyperactivation that would seem to explain the failure to extinguish the fearful stimuli, a common component in the clinical presentation of PTSD (Shin et al. 2006). Several studies have shown an increased responsiveness of the amygdala, which leads to an exaggerated reaction to both ambiguous and threatening stimuli (Herry et al. 2007; Sander et al. 2003). The amygdala is strongly involved in the interpretation of the stimuli's emotional value and plays a crucial role in fear-response mechanisms. Patients with PTSD are particularly sensitive to the potential threats associated with the trauma immediately coming from the surrounding environment and often suffer from a fear conditioning associated with a pathological hyperactivation of the amygdala, which occurs mainly in the presence of ambiguous or negative stimuli.

The degree of amygdala activation is also correlated with the severity of PTSD symptoms and anxiety symptoms (Scaglione and Lockwood 2014; Shin et al. 2006; Weber et al. 2013). Specifically, a hyper-responsivity of the amygdala was detected during the presentation to war veterans of traumatic autobiographical narratives (Rauch et al. 1996; Shin et al. 2004) and sounds associated with combat (Liberzon et al. 1999; Pissiota et al. 2002). In patients with PTSD, the amygdala is hyperactive not only with affective material closely related to the trauma originating the disorder but also with other stressful stimuli such as the presentation of frightful or angry faces, and this hyperactivation has been directly correlated with the severity of symptoms and the general status of anxiety (Fredrikson and Furmark 2003). However, in some studies involving patients with PTSD, no activation of the amygdala was detected during the symptomatic phase (Bremner et al. 1997). Furthermore, it is important to note that amygdala hyperactivation is not a specific correlate of PTSD, as it has also been detected in other anxiety disorders (Etkin and Wager 2007).

As far as volumetric data is concerned, to date, there is no clear evidence of an alteration of the amygdala related to PTSD (Shin et al. 2006). Multiple studies conducted on homogeneous groups have shown a reduction in the volume of the amygdala associated with PTSD (Kuo et al. 2012; Matsuoka et al. 2003; Morey et al. 2012). In their meta-analysis conducted in 2006, Karl et al. (2006) showed that in PTSD subjects, there was a reduced right amygdala compared to healthy controls. Another meta-analysis conducted in 2009 (Woon and Hedges 2009), however, showed different results, as no difference was detected in the volume of the amygdala (both right and left) among children with PTSD following abuse and healthy children. In an interesting study, Pechtel et al. (2014) found instead an increase in the volume of the right amygdala in adult subjects exposed to childhood maltreatment compared to non-exposed subjects. They also showed that trauma exposure between the ages of 10 and 11 had the greatest impact on the volume of the right portion of the amygdala. Finally, a recent systematic review (Ahmed-Leitao et al. 2016) showed a reduction in the amygdala (both right and left) in adult subjects with PTSD secondary to childhood maltreatment. This may indicate that the reduction in amygdala volume is more pronounced in PTSD secondary to childhood

maltreatment than PTSD due to other types of trauma. This data is also in line with the fact that exposure to childhood maltreatment, regardless of the onset of PTSD, may influence the abnormal development of the amygdala. Studies have documented an increased amygdaloid volume in children exposed to adverse experiences such as maternal depression and institutionalization (Lupien et al. 2011; Mehta et al. 2009; Tottenham et al. 2010).

11.3.3 Prefrontal Cortex

Another finding commonly highlighted in neuroimaging studies on PTSD is a hypoactivation of the prefrontal cortex (PFC) and in particular of the medial prefrontal cortex (mPFC), which includes the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC).

MPFC is implicated in the processing of internally generated emotional stimuli and the regulation of states of arousal. The OFC is a crucial area for the integration of emotional and decision-making information to promote problem-solving and planning. The ACC is involved in the process of fear extinction through amygdala modulation.

Normal brain function is supported by a complex feedback loop between cortical and subcortical systems that functions as a dynamic balance between a survival-oriented bottom-up activity and a top-down activity aimed at planning and directing behaviors (Scaglione and Lockwood 2014). This balance is often altered in PTSD since mPFC hypoactivation contributes to the loss of top-down emotional regulation (Patel et al. 2012). In other words, the decreased responsiveness of mPFC leads to a partial deficit of its normal inhibitory activity on the amygdala (Etkin and Wager 2007).

It has therefore been hypothesized that this dysregulation underlies a series of altered neurocognitive processes in PTSD, such as fear conditioning, fear extinction, and emotional regulation dysfunctions. Furthermore, the lack of contextualization connected to mPFC dysfunction plays an important role in memory deficits and the altered sense of reality typical of PTSD (Scaglione and Lockwood 2014).

In various PTSD neuroimaging studies during listening to autobiographical traumatic scripts (Britton et al. 2005; Lindauer et al. 2004; Pagani et al. 2005) or combat sounds and images (Bremner et al. 2003; Shin et al. 2004), a decreased activation of mPFC under stress was consistently reported. Also, in PTSD, mPFC activation was found to be inversely related to symptom severity (Britton et al. 2005; Shin et al. 2004). Many studies have reported a reduction in the volume of mPFC in PTSD (Shin et al. 2006). An alteration of mPFC gray matter has been shown in patients with PTSD compared to controls exposed to trauma without PTSD (Nardo et al. 2013), and it is associated with the severity of hyperarousal symptoms (Weber et al. 2013).

Concerning the ACC, multiple neuroimaging studies have shown that the involvement of this region in PTSD is also due to the lack of regulation that ACC exerts on the amygdala (O'Doherty et al. 2015; Rauch et al. 2006; Shin et al. 2001). Volumetric studies performed on the basis of voxels (Chen et al. 2006; Li et al. 2014), both with

manual segmentation (Woodward et al. 2006) and software-assisted analysis (Cohen et al. 2006), also converge in reporting a reduction of gray matter in ACC in PTSD subjects (Bing et al. 2013; Karl et al. 2006; O'Doherty et al. 2015). This cortical reduction is associated with the severity of PTSD symptoms (Bing et al. 2013), contributing to reduced fear extinction and working memory deficits of PTSD patients.

11.3.4 Amygdala and Prefrontal Cortex

There are extensive mutual connections between the amygdala and the prefrontal cortex (PFC), particularly with the medial and orbitofrontal areas. PFC, under physiological conditions, modulates the emotional response inhibiting the amygdala function by extinguishing the conditioned response to anxiogenic stimuli, and its reduced functioning can provoke the symptomatology of PTSD (Francati et al. 2007).

PFC glutamatergic afferents project onto GABA synapses causing an important inhibitory stimulus on the amygdala. In particular, left prefrontal activation facilitates two processes simultaneously: (i) it positively reinforces short-term behavioral memory processes, and (ii) it inhibits the amygdala so that the time process of positive affects is enhanced while that of negative affects is limited in time. This, as we will see, implies a lower depolarization of the amygdala's postsynaptic neurons allowing the stimulus to be properly processed. Left mPFC lesions prolong the maintenance of response to adverse conditions, confirming that mPFC under physiological conditions inhibits the amygdala by actively causing fear conditioning extinction. In the absence of this inhibitory input, the amygdala remains activated and continues to maintain a high level of adverse response.

For this reason, patients with PTSD, in the absence of a correct and prompt inhibition of the amygdala by the mPFC, show a pathological response to negative emotions and exhibit a reduced extinction of fear conditioning (Milad and Quirk 2002; Orr et al. 2000; Peri et al. 2000; Quirk et al. 2000; Rothbaum et al. 2001).

Evidence from functional neuroimaging studies suggests that circuit dysfunction that includes the amygdala and ventromedial prefrontal cortex (vmPFC) may be the underlying mechanism of PTSD (Francati et al. 2007; Patel et al. 2012; Rauch et al. 2006; Sartory et al. 2013). In fact, in healthy subjects, the intentional suppression of negative emotions and the extinction of fear are associated with an increase in vmPFC activity and a reduction in amygdala activity (Delgado et al. 2008; Milad et al. 2009), while in subjects with PTSD, vmPFC tends to be hyporesponsive, and the amygdala is excessively hyperreactive, suggesting a dysfunction of this circuit. Some studies have indeed observed an altered connectivity between the amygdala and the cortical regions in PTSD patients, represented by an increased "down-top" inhibitory feedback of the amygdala on the mPFC and a lower regulation of the amygdala by the dorsolateral PFC (Kelmendi et al. 2017).

Although most studies have shown the changes described above, other studies have found different results, for example, a hyperactivation of mPFC during script administration (Sachinvala et al. 2000; Zubieta et al. 1999). These discrepancies can

originate from differences between the various study methodologies (different spatial resolution of the various techniques or cohorts of patients and healthy controls different in nature and number) and the paradigms used to induce symptoms.

11.3.5 Insula

The insula is involved in the processing of negative emotions and the regulation of the autonomic nervous system. The anterior insula contains a center of emotional awareness and is part of a network that generates self-awareness, processing the feelings subjectively perceived within a unified and conscious representation (subjective feeling).

The posterior insula contains a body interoception center, to which all the affective body perceptions (sensory aspects of emotions) and the evaluation of bodily signals (body awareness) belong.

Several functional and structural studies have consistently demonstrated the involvement of the anterior or posterior insula (or both) in the pathophysiology of PTSD (Liberzon et al. 2003; Lindauer et al. 2008; King et al. 2009; Nardo et al. 2011; Osuch et al. 2001; Paulus and Stein 2006; Whalley et al. 2008). Insular hyperactivity has been observed not only in PTSD but also in social anxiety disorder, specific phobia, and obsessive-compulsive disorder and during normal fear conditioning (Etkin and Wager 2007; Rauch et al. 1997), indicating a hyper-responsiveness of a network responsible for generating the fear response (Doruyter et al. 2014).

Increased activity in the anterior insula is related to fear processing or other negative emotional responses to stimuli that trigger posttraumatic symptoms, suggesting the existence of a dysfunctional emotional regulation system (Etkin and Wager 2007). The hyperactivity of the posterior insula is correlated to the activation of somatic representations of the traumatic experience (dissociated memories), which remain unintegrated and fail to reach the declarative memory. This interpretation is in line with a view of PTSD as a memory deficit characterized by reliving unintegrated traumatic memories (Van Der Kolk et al. 1997). Studies found that patients with PTSD showed greater activation in the insula during the script (Hopper et al. 2007; Lindauer et al. 2008) and during an emotional memory recovery task (Whalley et al. 2008). In a study by Nardo et al. (2011), increases in cerebral blood flow in both anterior and posterior insular cortices were detected in PTSD subjects during symptom activation. These results suggest that the intrusive symptoms, the feeling of reliving the traumatic event and avoiding behaviors, are associated with an altered activity both in the posterior and anterior insula, thus showing a dysregulation both at interoceptive level (dissociated somatic memories) and at the level of emotional awareness. Another study reported an association between flashbacks and activation of sensory areas of the insula (Whalley et al. 2013).

Finally, a recent study analyzed the functional connectivity of the insula in patients with PTSD during resting state compared to healthy subjects (Zhang et al. 2016a), highlighting a reduction in functional connectivity between the anterior insula and ACC and reduced functional connectivity between the posterior right

insula, the left inferior parietal lobe, and the postcentral gyrus in PTSD patients. These results suggest that the decrease in functional connectivity of the insula is implicated in the abnormal regulation of emotions and the processing of somatosensory information in patients with PTSD.

Finally, from a structural point of view, a reduction of the gray matter of the insula has been highlighted by several studies (Chen et al. 2009; Nardo et al. 2010) and by a recent meta-analysis (Meng et al. 2016) and was found to be related to the severity of the experienced trauma (Nardo et al. 2010).

11.3.6 Broca's Area

The Broca's area is responsible for creating semantic representations of personal experiences to translate them into conveyable language and restructure them cognitively. Some studies have shown that PTSD subjects encounter difficulties in synthesizing, classifying, and integrating the traumatic memory, or rather the different fragments of memories, into a complete narrative (Hull 2002; Van Der Kolk et al. 1997). It was shown that subjects with PTSD show decreased regional cerebral blood flow (rCBF) in the Broca's area when they are exposed verbally (Rauch et al. 1996; Shin et al. 1997a) or visually (Shin et al. 1997b) to their trauma. These neurobiological correlates indicate a partial deactivation of the Broca's area in PTSD subjects, which could explain the patients' difficulty in correctly describing and positioning the traumatic experience in the semantic memory (Hull 2002; Van Der Kolk et al. 1997).

11.3.7 Retrosplenial Cortex

The retrosplenial cortex is a part of the posterior cortex of the midline involved in the cognitive and affective processes of self-referential evaluation and autobiographical memory (Vann et al. 2009). This area also shows an abnormal function in patients with both acute and chronic PTSD (Daniels et al. 2011; Eckart et al. 2011; Piefke et al. 2007). A meta-analysis conducted by Sartory et al. (2013) summarized the results of studies on PTSD patients compared to healthy controls, highlighting a significant activation of the retrosplenial cortex and the precuneus in response to stimuli associated with trauma in the former. This suggests that this area could represent the neural basis of intrusive symptoms and feelings related to reliving the traumatic event. Recent studies on rodents support this hypothesis, showing that the recovery and extinction of stress-related memories depend on the retrosplenial cortex (Corcoran et al. 2011, 2015) and therefore dysfunctions in this region may contribute to failure in fear extinction in PTSD subjects.

11.3.8 Thalamus

Functional neuroimaging studies have also frequently highlighted the involvement of the thalamus in patients with PTSD. The thalamus is involved in the transmission of external sensory information to different areas of the cerebral cortex and of the

limbic system. Data from several neuroimaging studies have shown that patients with PTSD have a significant deactivation of the thalamus, showing an alteration of thalamocortical connectivity (Lanius et al. 2001, 2003; Yin et al. 2011), concerning the severity of symptoms related to reexperiencing the traumatic event (Kim et al. 2007). Because of its functional nature, an interruption of thalamus activity could lead to the misinterpretation of external stimuli (Francati et al. 2007). Also, it could be implicated in the increase of fear-based feelings, in the failure to extinguish the traumatic memory, which in turn remains intensified and underlies the dissociative symptoms and classic flashbacks of PTSD (Lanius et al. 2001). It is indeed possible to hypothesize that high levels of hyperarousal during the traumatic experience may lead to an alteration of the processing of sensory information by the thalamus, which in turn would cause an alteration of the transmission of sensory information to the PFC, around the cingulate gyrus, to the amygdala, and to the hippocampus. A recent study has also highlighted altered connections between the thalamus and other brain areas, such as the frontal gyrus and the insula (Zhang et al. 2016b), which could determine dysfunctions in cognitive-emotional processing found in PTSD patients. Recent research has also highlighted thalamus atrophy connected to stress exposure in an animal model (Yoshii et al. 2017), which, however, still needs to be confirmed in human subjects.

11.3.9 Caudate Nucleus

The caudate nucleus is also implicated in the neural circuit of psychological responses to trauma. The caudate nucleus, which is part of the striatum, is widely involved in the reward anticipation system and its response. Several studies have found abnormal functioning of the caudate nucleus in subjects with PTSD (Elman et al. 2009; Sailer et al. 2008; Vythilingam et al. 2009) but also in subjects with depression (Eshel and Roiser 2010) and substance abuse (Volkow et al. 2011). A common clinical feature in these disorders is anhedonia and hyporesponsiveness to positive stimuli, thus suggesting that an altered functioning of the caudate nucleus may explain the common aspects of these disorders and be connected to the alteration of the reward system. In an fMRI study, Lanius et al. (2004) showed greater functional connectivity from the right posterior cingulate and occipital and parietal lobe to the right caudate in PTSD subjects, while trauma exposed without PTSD subjects had not developed PTSD had greater connectivity in the left caudate nucleus.

Researches who have investigated alterations in the volume of the caudate nucleus have reported mixed results. Some studies have found a reduction in the volume of the caudate nucleus linked to exposure to early stress (Cohen et al. 2006) and to the presence of posttraumatic symptoms in the absence of PTSD diagnosis (Herringa et al. 2012) and in subjects with diagnosis of PTSD (Filipovic et al. 2011; Sussman et al. 2016). Other studies have instead highlighted an increase in the volume of the right portion of the caudate nucleus associated with the PTSD diagnosis (Looi et al. 2009), while many others have shown no association (Chao et al. 2014; Douglas 1995; Morey et al. 2017). These differences could be due to the small number of subjects examined and to the different methods that were used. Recently,

thanks to an MRI scan with DTI, an alteration of the caudate nucleus tissue was noted in subjects with PTSD (Waltzman et al. 2017) even in the absence of a clear atrophy of this region.

11.3.10 Cerebellum

The cerebellum is a neural structure responsible for motor control, voluntary movement, balance, and associative learning. In recent decades, the involvement of this brain structure in higher cognitive functions such as sensory processing, attention, verbal working memory, and processing of emotions has been highlighted (Bergmann 2000; Schmahmann 2010). The cerebellum is mutually interconnected with different parts of the brain such as the brain stem, limbic areas, cerebral cortex, and frontal lobes and can be considered as an important associative area (Bergmann 2008). Several studies have also highlighted the involvement of this region in the pathophysiology of PTSD (see Carletto and Borsato 2017). The first studies that have investigated the role of the cerebellum in this disorder have detected alterations in the functioning of the left cerebellar hemisphere (Osuch et al. 2001) and of the cerebellar vermis (Anderson et al. 2002; Pissiota et al. 2002) in PTSD patients.

Two meta-analyses showed reduced activation of the cerebellum both during resting state and following a task to induce symptoms (Hayes et al. 2012a; Koch et al. 2016). An interesting study conducted on PTSD subjects resulting from child maltreatment (Baldacara et al. 2011) confirmed the results of previous studies in children and adolescents with PTSD (Carrion et al. 2009; De Bellis and Kuchibhatla 2006) and provided evidence of volume reduction in adults with PTSD compared to controls exposed to traumatic events that did not develop PTSD. This volume reduction in the left hemisphere and the cerebellar vermis was found to be associated with the magnitude of the symptoms. Furthermore, this study found an association between these volume reductions and early traumatic experiences, suggesting that cerebellar changes could be a consequence of an alteration in the cerebellar neurodevelopment resulting from exposure to early traumatic events, which would involve an increased risk of developing PTSD in adulthood. Two other neuroimaging studies have instead reported a volumetric increase in the cerebellum in PTSD subjects (Sui et al. 2010; Sussman et al. 2016) compared to subjects exposed to trauma without PTSD. The age of the subjects at the time of the traumatic event and the age of the PTSD onset could explain the discrepancy between the results of the previously described studies.

Recently, Holmes et al. (2018) conducted a study aimed at simultaneously investigating the morphology and connectivity of the cerebellum in a sample of subjects with PTSD compared to healthy subjects, highlighting a reduction in both volume and functional connectivity of this brain region. In addition to identifying these structural and functional alterations, this study also showed a correlation between the functional connectivity of the cerebellum and the severity of the four clusters of posttraumatic symptoms, suggesting a nonspecific role of the cerebellum in the PTSD symptomatology. Another very recent study (Rabellino et al. 2018) found

alterations in functional connectivity between different parts of the cerebellum and different brain regions involved in emotional regulation, somatosensory processing, and memory recovery, thus emphasizing that there are distinct patterns of altered connectivity between the cerebellum and other brain regions in PTSD patients with and without dissociative symptoms (for an in-depth explanation of these differences, please refer to the paragraph on PTSD and dissociative symptoms).

11.4 Connectivity Studies

As explained so far, the traditional pathophysiological model of PTSD suggests a loss of top-down inhibition of the prefrontal cortex (which includes the anterior cingulate cortex, the ventromedial frontal gyrus, and the orbitofrontal cortex) on the amygdala, which consequently remains hyperreactive. This results in a failure to extinguish fear, a hypo-modulation of emotional components, that underlies intrusive symptoms, and hyper-arousal. Furthermore, the reduction in volume and functionality of the hippocampus is related to memory deficits and contextualization and fear extinction issues, typically found in PTSD (Lanius et al. 2011; Rauch et al. 1996). In recent years, however, this fronto-limbic model has received some criticism, as it only focuses on one of the central aspects of PTSD, namely, the response to fear (Liberzon and Garfkinkel 2009), not considering the role of multiple other areas involved in this disorder. Furthermore, it is now evident that an analysis dedicated to specific regions may be inadequate to understand the complex neurobiology underlying psychiatric disorders, including PTSD (Negreira and Abdallah 2019; Tursich et al. 2015).

Therefore, neuroimaging studies have attempted to identify different sets of functionally connected brain regions, referring to the "triple network" model of psychopathology proposed by Menon (2011). The application of this model to the study of cerebral pathophysiology of PTSD allows to incorporate a series of brain regions that in the classical model were excluded (Negreira and Abdallah 2019) and to demonstrate how the connectivity analyses provide new information on the dysfunctional architecture of PTSD subjects' brains (Abdallah et al. 2019). Menon's triple network model is based on the hypothesis that the cognitive and affective symptoms of psychiatric disorders may emerge from dysfunctions of large-scale neural network connectivity. The three neural networks identified include the default mode network (DMN), the salience network (SN), and the central executive network (CEN).

The DMN spatially extends over important regions of the posterior cingulate cortex, the medial prefrontal cortex, and the medial temporal lobe, including the hippocampus (Buckner et al. 2008). DMN is involved in self-referential, introspective, and autobiographical memory processes. In a functionally consistent manner, it is more active in the resting state and is hypoactivated during goal-oriented activities. In individuals with PTSD, DMN was found to be hypoactivated and poorly interconnected (Akiki et al. 2018; Chen and Etkin 2013; Daniels et al. 2011; Jin et al. 2014; Patel et al. 2012; Peterson et al. 2014; Sripada et al. 2012; Tursich et al.

2015; Yin et al. 2011), showing an association with dissociative, intrusive, and avoidance symptoms (Akiki et al. 2017; Tursich et al. 2015).

The SN involves the insula, the dorsal anterior cingulate cortex, and the amygdala, is implicated in the response to the subjective evaluation of the stimuli, and regulates the transition between CEN activation and DMN activation (Akiki et al. 2017; Goulden et al. 2014). The studies that have investigated it have shown how in PTSD an altered connectivity of the SN compromises this regulation function of the other two networks' activity, resulting in a dysfunctional threshold of salience evaluation of the perceived stimuli and therefore in a state of constant hypervigilance (Brown et al. 2014; Patel et al. 2012; Sripada et al. 2012), associated with hyperarousal symptoms (Tursich et al. 2015).

The CEN, which is anchored mainly in the dorsolateral prefrontal cortex, is known to activate purpose-driven behaviors in high-level cognitive activities such as planning, working memory, and top-down emotional regulation. Therefore, the disconnection of this network highlighted in PTSD reflects a loss of modulation on the fear/threat detection circuits and a deficit in cognition and executive functions (Jin et al. 2014; Patel et al. 2012; Sripada et al. 2012).

In summary, in PTSD, there is a hyperactivation of the SN and a hypo-modulation of the CEN and the DMN (Abdallah et al. 2019; Patel et al. 2012). Although these results largely overlap with the classical fronto-limbic model of PTSD (e.g., data related to hyperactivation of the amygdala are consistent with a hyper-responsive SN (Sripada et al. 2012)), the experts believe that the triple network-based model allows a better understanding of the different endophenotypes of PTSD and comorbidities with other disorders (Abdallah et al. 2019; Akiki et al. 2017).

11.5 PTSD and Dissociative Symptoms

As already described in the previous paragraphs, the neural correlates of people who have been exposed to traumatic experiences can vary significantly; in fact, not all patients with PTSD exhibit the same patterns of brain activation in response to scripts that elicit the traumatic response (Frewen and Lanius 2006; Hopper et al. 2007; Lanius et al. 2002). In 2002, Lanius and collaborators were the first to notice that about 70% of patients with PTSD reported having relived their traumatic experience during the script, showing an increase in heart rate during this task, while the remaining 30% of subjects reported experiences of derealization and depersonalization and a feeling of emotional detachment, without any significant increase in heart rate (Lanius et al. 2002). Dissociation is a prevalent symptom of PTSD (Putnam et al. 1996), present in about 15–30% of subjects (Stein et al. 2013; Wolf et al. 2012), and it involves an interruption or discontinuity in the usually integrated functions of consciousness, memory, identity, emotion, perception, and body awareness, which manifest themselves as symptoms of depersonalization and derealization (American Psychiatric Association 2013). Therefore, several studies (Lanius et al. 2006, 2010a, b, 2012; Nardo et al. 2013) have focused on investigating these differences at a neurobiological level. Thus, it was possible to identify two subtypes of

PTSD: that of "hyper-arousal and hyper-activation," characterized by emotional hypo-modulation and prevalent intrusive symptoms and flashbacks, and the "dissociative" one, characterized by emotional hyper-modulation, with depersonalization and derealization symptoms (Lanius et al. 2010a, b). These two subtypes are associated with different patterns of activation of brain regions: a reduction in volume and reduced activity of mPFC and ACC, associated with an increased activation of the amygdala, are confirmed in the "hyper-arousal and hyper-activation" subtype; instead the dissociative typology reveal an inverse functioning: the mPFC and the lateral prefrontal cortex (lPFC) show hyperactivation and an increase of gray matter, while the activity of the amygdala is reduced. Therefore, the emotional hypo-modulation typical of the "hyper-arousal" (or non-dissociative) subtype, linked to the reduction of mPFC activation and an increase in amygdala responsiveness, is consistent with the data highlighted by most of the neuroimaging studies on PTSD and the classical PTSD model, based on a lack of regulation by a hypofunctional PFC on a hyperreactive amygdala. The dissociative PTSD subtype is instead characterized by a greater activation of the prefrontal regions (mPFC, ACC, frontal medial gyrus, inferior frontal gyrus, superior and medial temporal gyrus, occipital lobe, parietal lobe) (Lanius et al. 2002) and by a hypoactivation of the limbic regions, which entail a hyper-modulation of emotions. This hyper-modulation can be conceived as an attempt to defend from extreme and overwhelming levels of activation, which involves the inhibition of the regions devoted to emotional processing, giving rise to dissociative symptoms. The study by Felmingham and collaborators (2008) provided further support to this hypothesis, showing a different activation of the limbic regions in individuals with the dissociative PTSD type during the explicit and implicit processing of stimuli linked to fear. In fact, during the explicit processing of these stimuli, subjects with dissociative PTSD showed a hyperactivation of the cortical regions compared to subjects with PTSD without dissociation, confirming the hyper-modulation pattern. During implicit processing, the patients with dissociative PTSD showed a hyperactivation in the limbic regions (amygdala, insula, and right thalamus), thus suggesting that the dissociation could be a regulation strategy that is implemented to manage situations of extreme arousal through the inhibition of the limbic system.

Other studies have further confirmed the differences between the two subtypes of PTSD, identifying different patterns of activation and connectivity of the insula (Hopper et al. 2007; Nicholson et al. 2016), cerebellum (Rabellino et al. 2018) and temporal lobe (Hopper et al. 2007; Lanius et al. 2002, 2005), autonomic responses mediated by the periaqueductal gray matter (Harricharan et al. 2016; Nicholson et al. 2017), and the involvement of the opioid system and endocannabinoids (Lanius et al. 2018). For more information on this subject, please refer to the recent work by van Huijstee and Vermetten (2018) and Lanius et al. (2018). Finally, the functional differences described so far have been further confirmed by two studies, which have shown structural alterations in the two subtypes of PTSD. A study conducted by Nardo et al. (2013) highlighted how the dissociative traits associated with PTSD are related to volumetric patterns different from those observed in subjects with PTSD without dissociative traits. In the former, an increase in neuronal density in mPFC

was observed, which was not present in patients with greater hyper-excitation, in which instead a decrease was observed. The authors suggested that the increase in neuronal density and volume of gray matter in subjects with dissociative traits may result from the increased PFC activation over time, the functions it processes, and therefore the regional dendritic and synaptic branching, which is not present in the PTSD characterized by emotional hypo-modulation and chronic depression (Nardo et al. 2013). Another study that investigated the differences in brain volume morphology between patients with dissociative and hyper-aroused PTSD showed that individuals with dissociative PTSD exhibited an increase in the volume of gray matter in the fusiform gyrus and a reduction in gray matter in the right inferior temporal gyrus compared to patients with non-dissociative PTSD (Daniels et al. 2016), also showing a positive correlation between the severity of dissociative symptoms and the volume of gray matter in the right middle frontal gyrus, a region implicated in inhibitory regulation of emotional overexcitement. These volumetric alterations can therefore be interpreted as the structural counterpart of the functional alterations found in the studies described above. These findings further supports the model proposed by Lanius et al. (2010a, b), according to which subjects with hyper-excitatory PTSD show a functional reduction in the prefrontal regions (emotional hypo-modulation), while subjects with dissociative PTSD show greater prefrontal inhibition of limbic regions (emotional hyper-modulation).

11.6 Conclusions

The main objective of the neuroimaging studies in psychiatry conducted over the last three decades has been not only to identify the anatomic-functional variations present in the various pathologies but to broaden our knowledge of the neurobiological mechanisms associated with the related psychotherapeutic treatments. This has been possible, thanks to the use of various approaches and different methods (neuropsychology, PET, SPECT, RM/fMRI, and more recently EEG) and in the identification of morphological and/or functional variations of the central nervous system at different levels (neuropsychological, cerebral perfusion, neuronal density, and electrical activity) before and after the execution of various psychotherapies. Concerning PTSD, the limbic hyperactivation observed in symptomatic patients goes hand in hand with frontal cortical hypofunctionality, resulting reduced inhibition of the amygdala reaction to fear.

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Neuroimaging in PTSD-Related Psychotherapies

12

Marco Pagani, Sara Carletto, and Marco Cavallo

Contents

Abstract

Neuroimaging studies conducted in PTSD patients who have undergone various psychological treatments have provided evidence of modifications in cerebral blood flow (single-photon emission computer tomography, SPECT; positron emission tomography, PET; functional magnetic resonance imaging, fMRI), neuronal volume and density (magnetic resonance imaging, MRI), and, more recently, brain electric signal (electroencephalography, EEG). The purpose of this chapter is to review the results of functional and structural changes being reported in PTSD treatments during the period from 1999 to 2019, in order to integrate the psychotherapy outcome with the essential neurobiological data.

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12.1 Introduction

Post-traumatic stress disorder (PTSD) is a clinical condition that may affect victims of major psychological trauma and is one of the major causes of mental suffering. Initially defined in DSM-III in 1980, PTSD is a dysfunctional learning disorder with derangement of memory and mood regulation, leading to a fear-conditioned response elicited by internal or external cues associated with the traumatic situation that is recalled in flashbacks with involuntary vivid replays, concomitant autonomic reactions, and negative feelings. This oppressive tendency to re-experience the trauma leads to avoidance of reminders, irritability, and social and emotional withdrawal (American Psychiatric Association 1994). The recurring traumatic memory acts as a new traumatic experience that activates the brain networks engaged in fear response, thus resulting in the body's emotional reactions of autonomic arousal. It is estimated that in the general population of the United States, there is a lifetime prevalence of PTSD of 1.3–9% (Breslau et al. 1991; Kessler 2000; Breslau 2001; Davidson et al. 2002), which makes PTSD the fourth most common psychiatric disorder (Breslau et al. 1991). A large survey conducted in six European countries (Belgium, France, Germany, Italy, Spain, and the Netherlands) via face-to-face interviews administered to 21,425 participants showed that the general prevalence of PTSD was 1.1%. The highest prevalence was reported in the Netherlands (2.63%), whereas the lowest was found in Spain (0.56%) (Darves-Bornoz et al. 2008).

Recent studies have shown that psychological trauma can cause anatomical and functional changes in specific areas of the brain associated with the onset of PTSD symptoms. As a result, metabolic and morphological changes in the brain can be identified during the symptomatic phase of the disease, and each area involved in the complex mechanism underlying the processing of emotions and psychological traumas can play a specific role.

Functional and structural studies have shown significant neuropathological alterations in patients with PTSD, particularly during the autobiographical reliving (i.e., "script") of the trauma. The first of these studies, included in a review by Bremner (2007), led to the identification of metabolic and morphological changes occurring in the brain when the disease becomes symptomatic, thus helping us to associate functions to specific areas involved in the processing of emotions and psychological traumas.

Symptom provocation paradigms are an extremely useful and powerful way of delineating the functional anatomy of the traumatic memory that characterizes PTSD. Changes in local activations in response to specific tasks point to neural processing dysfunctions. In this respect autobiographical trauma script exposure (Pavic et al. 2003; Lindauer et al. 2004; Pagani et al. 2005) or audio and visual trauma-related stimuli (Liberzon et al. 1999; Zubieta et al. 1999) proved to be a valid approach to elicit cerebral blood flow (CBF) changes in PTSD, and improved technical and methodological features have made neuroimaging studies particularly suitable in in vivo investigations of the neurobiology of emotions. Since in neuroimaging studies the activations upon a traumatic script administration are often compared to the state of the brain during the administration of a neutral script, it is

worth noting that the latter might be experienced by some patients as a new unknown procedure resulting in an increased stress level. Such variable has to be considered since it might differ from one investigation to the next biasing the comparison of the results. To some extent, the above factors are responsible for inconsistency across PTSD research results along with the heterogeneity of methodologies and recruited subjects.

In the review by Francati et al. (2007), in which functional studies on PTSD were compared, on average SPECT studies included a larger sample of patients (16 as compared to 9 for PET, and fMRI, studies) and investigated a broader spectrum of traumatic events. In fact, the lower spatial and time resolution of SPECT as compared to PET and fMRI implies, in order to obtain statistically reliable results, to recruit larger cohorts of subjects. Moreover, of the reviewed ^{99m}Tc-HMPAO SPECT studies, 4 out of 8 did not include combat-related or sexual abuse traumas, whereas this was true for only 5 out of 30 PET and fMRI studies. Whereas in the past most PTSD studies were carried out on veterans and abused women and children, now there is a tendency to investigate traumas more related to daily life and social stress: such differences in patients' samples might also impact on the cross-comparison of the findings.

Neuroimaging research has helped to identify the brain regions that may play a key role in the pathophysiology of PTSD: the amygdala, the medial prefrontal cortex (mPFC, including rostral anterior cingulate cortex and ventral medial frontal gyrus), and the hippocampus. The amygdala appears to be involved in the response to threat-related stimuli (Morris et al. 1998; Whalen et al. 1998; Davis and Whalen 2001) and plays an active role in the process of fear conditioning (LeDoux 2000; Davis and Whalen 2001) In this respect, its hyperactivation is invariably associated with PTSD (Orr et al. 2000; Peri et al. 2000). The mPFC, in physiological conditions, inhibits the hyperactivation of the amygdala reducing the effect of psychological traumas. Upon lack of such inhibition, the pathological firing of the amygdala causes in turn pathological activations of several brain regions accounting in the end for PTSD symptoms. Lastly, a further region often involved in PTSD pathophysiology is the hippocampus. The hippocampus processes declarative and autobiographic memories, and its dysfunction results in an incorrect transfer and processing of the traumatic memories in the neocortex (Eichenbaum 2000; Corcoran and Maren 2001).

However, mounting evidence suggests that the original model should be more complex than expected and should also take into due account the role played by additional neural structures, such as the dorsal anterior cingulate cortex and the insula (Shin and Liberzon 2010).

The purpose of this chapter is to present and briefly discuss significant English language articles published in the last 20 years (indexed in PubMed 1999–2019) regarding cerebral changes in patients diagnosed with PTSD for whom the neurobiological effects of various psychotherapies have been investigated by neuroimaging techniques, mostly by SPECT and structural MRI. Very recent EEG investigations will also be presented to reinforce the hypotheses suggested by previous functional neuroimaging studies. Initially, the first investigations on this topic will be considered. Then, we will focus on recent studies, before concluding, by reviewing briefly a subset of studies focusing on neural patterns associated with psychotherapy outcomes.

12.2 Neuroimaging in PTSD Psychotherapies

12.2.1 First Studies (1999–2012)

Neuroimaging techniques have been used in the attempt to shed light on the neurobiological correlates of various psychotherapies revealing their neurobiological effects. An extensive review (Roffman et al. 2005) analyzed 14 functional neuroimaging investigations designed to measure the effects of psychotherapies on brain function. Despite a positive clinical outcome and the significant effect of behavioral, cognitive-behavioral, and interpersonal therapies on brain functions, neuroanatomical changes were largely inconsistent both within disorders and within psychotherapies making impossible to draw any well-structured conclusion. However, the studies under review were conducted on a variety of experimental paradigms, methodologies, and psychotherapies, but most importantly they looked at groups of patients falling within the whole spectrum of psychiatric diagnoses, ranging from major depression to phobias and schizophrenia. Such heterogeneity accounts for the failure to identify plausible and convergent physiological mechanisms in the treatments under investigation. Consequently, this chapter will include only those articles which relate to neuroimaging investigations of psychotherapies used to treat PTSD.

The first study in which SPECT was used in psychotherapy research dates back to 1999, the year in which Levin et al. (1999) published a case report on a subject with PTSD treated with eye movement desensitization and reprocessing (EMDR). Upon recall of the traumatic event, SPECT showed a cerebral blood flow increase after therapy in the anterior cingulate and left frontal lobe. Unfortunately, despite extensive discussion of the positive clinical and neuropsychological outcome following the EMDR therapy, the authors only mentioned the functional effects and the design of the SPECT study (a within-subject comparison), but no details were given about the type of camera, the camera resolution, or the methodology applied for image analysis and for statistical testing. However, notwithstanding the above-mentioned inadequacy, this study paved the way for subsequent studies which demonstrated the feasibility of investigating brain physiology during the reliving of trauma.

A few years later, Lansing et al. (2005) investigated six psychologically traumatized police officers, before and after EMDR therapy. When the traumatic event was recalled, it was found that, after the disappearance of the clinical and psychological signs of PTSD, blood flow decreased significantly in the occipital lobe, left parietal lobe, and posterior frontal lobes, and perfusion increased significantly in the left inferior frontal gyrus. The study was conducted with a high-resolution SPECT camera and with an acceptable statistical threshold, considering the low number of subjects and the experimental nature of the investigation. The most relevant results were a parallel decrease in perfusion in regions hyperaroused during the symptomatic phase and an increased blood flow in the inferior frontal cortex after EMDR. These findings indirectly confirmed the impact of EMDR on the neurobiology of PTSD, thus reversing the reduced prefrontal cortex control over amygdalae.

By using structural magnetic resonance imaging, Bryant et al. (2008a) investigated the relationship between treatment response in PTSD and the volume of the rostral anterior cingulate cortex in three groups: patients with PTSD ($n = 13$), traumatized control subjects ($n = 13$), and healthy controls ($n = 13$). Patients with PTSD underwent a brief treatment with cognitive-behavioral therapy (CBT, eight sessions) and were then divided into two sub-groups: responders ($n = 7$) versus nonresponders ($n = 6$). MRI data showed that better response to CBT was associated with larger rACC volume, while nonresponders presented a significantly smaller rACC volume. Moreover, responders had a rACC volume comparable to that of controls. The authors interpreted the results by stating that larger rACC volume may allow patients to better regulate fear during CBT and subsequently to benefit more from the psychological treatment received.

Considering the limited amount of literature available about such a compelling issue, i.e., the changes occurring in the brain in association with psychotherapies in general and the related disappearance of symptoms, our research group at the Karolinska Hospital, Sweden, attempted to identify the neurobiological events occurring at functional and anatomical level during EMDR therapy. These studies formed part of a large research project on PTSD covering Stockholm public transportation employees who had experienced a 'person-under-train' incident or an assault at work (Högberg et al. 2007; Högberg et al. 2008, clinical studies; Pagani et al. 2005; Pagani et al. 2007; Nardo et al. 2011, SPECT studies; Looi et al. 2008; Looi et al. 2009; Nardo et al. 2010, MRI studies). In all the above investigations, the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al. 1997) was applied as a clinical diagnosis benchmark. On the other hand, data originating from interview-based and self-rating scales constituted the basis for psychological assessment. The project was inspired by a meta-analysis of 61 outcome trials for PTSD in which patients were treated with pharmacological and psychological therapies such as behavioral therapy, EMDR, relaxation training, hypnotherapy, and dynamic therapy (Van Etten and Taylor 1998). The study concluded that the best psychological therapies were CBT and EMDR and that these psychotherapies were more effective than drug therapy. Thirty-two percent of patients on drugs discontinued treatment, compared with 14% of patients treated with psychological therapies. A further meta-analysis came to the conclusion that EMDR and exposure therapies had a positive clinical outcome in the treatment of PTSD (Davidson and Parker 2001) and Bradley et al. (2005) reported that PTSD symptoms improved in more than half of the patients who completed treatment with CBT or EMDR. However, in all such studies, patients were monitored for less than 12 months, and Bradley et al. (2005) pointed out the lack of long-term follow-up. This deficiency was overcome by Högberg et al. (2008), who reported a positive outcome from EMDR therapy up to 3 years after the last session.

The preliminary results from Lansing et al. (2005) were confirmed in a larger SPECT study that investigated cerebral blood flow changes following EMDR psychotherapy (Pagani et al. 2007). Fifteen patients were scanned before and after therapeutic intervention, and to increase the reliability and robustness of the study, a control group of 22 non-symptomatic subjects, suffering from the same trauma,

were included in the study. This latter methodological caveat is of great relevance, since it minimizes possible biases in the results due to psychological heterogeneity between the two groups. Furthermore, a very strict statistical threshold was applied accepting the risk of false negatives due to type II statistical errors. When comparing patients with the control subjects, the significant group difference found before therapy (Fig. 12.1) disappeared after treatment. Furthermore, following therapy the responders showed significant CBF normalization in parieto-occipital lobes, visual cortex, and hippocampus and an increased CBF in the lateral prefrontal cortex. These results were confirmed a few years later by an MRI study highlighting in nonresponders before EMDR therapy the decreased gray matter density in roughly the same limbic and cortical structures (Nardo et al. 2010).

Taken together the results of the latter two studies indicate that the decrease in regional blood flow following successful EMDR therapy was associated with the remission of symptoms such as flashbacks, intrusive and stressful memories, hallucinations, and persistent trauma reliving at somatic level. On the other hand, EMDR normalized the capability to retrieve important aspects of the trauma and improved attention levels and sense of self. Furthermore, the activation of the

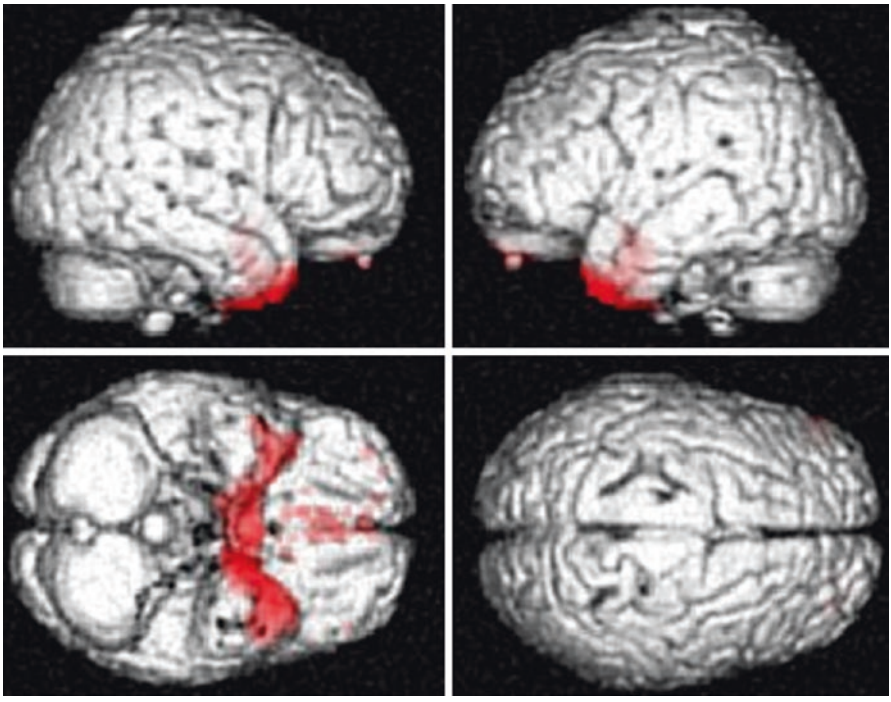

Fig. 12.1 Three-dimensional rendering of voxels reflecting higher tracer distribution in patients before EMDR (n = 15) as compared to controls (n = 27). The statistically significant differences are highlighted. The first row represents the lateral aspect of the right (on the left) and of the left (on the right) hemispheres; the second row represents the inferior (on the left) and the superior (on the right) aspects of the brain (Nardo et al. 2011)

prefrontal cortex, which has been shown to inhibit the limbic system in response to psychological stimuli that resemble the traumatic event, recovered its inhibitory role, reducing the hyperactivation of subcortical structures and the corresponding cortical hyperarousal.

The latest SPECT EMDR study included two patients suffering from a psychological traffic trauma (Oh and Choi 2007). After EMDR, the authors found an increase in cerebral perfusion in the bilateral dorsolateral prefrontal cortex and a decrease in the temporal association cortex. In addition, the SPECT scans were compared to those of a non-traumatized control group, and the findings were in line with the above indicating a tracer uptake normalization following EMDR therapy. As Levin's first study showed, also in this case, the significance of the results is reduced by the extremely low number of patients included in the sample, as well as by relatively poor statistics. However, this study also confirmed the general neurobiological effect of EMDR, with a tendency to restore cortical control over the hyperaroused subcortical limbic structures.

In 2007 a SPECT study of 16 PTSD patients, before and after cognitive restructuring therapy, reported during a script-driven provocation paradigm after successful outcome a higher activation in cortical (temporal, parietal, and prefrontal lobes) and subcortical (thalamus) regions in the left hemisphere (Peres et al. 2007). This investigation was also performed using a low statistical threshold, and the results should be viewed with caution. The same group investigated by fMRI were three groups of policemen: 12 were given exposure-based therapy and cognitive restructuring, 12 were in waiting list, and 12 were symptoms-free (Perez et al. 2011). An increased mPFC and a concomitant decrease of amygdala activity associated with symptoms attenuation were found after psychotherapy in the symptomatic group weakening the sensory content of the traumatic memories while strengthening their cognitive component.

In the following year, Lindauer et al. (2008), using brief eclectic psychotherapy (BET), investigated the cerebral blood flow in ten traumatized police officers using SPECT and reported that, after psychotherapy with a positive clinical outcome, the activation found during the script listening at baseline was significantly lowered in the middle frontal gyrus. Furthermore, treatment efficacy, as measured by scores measuring PTSD symptoms, correlated positively with CBF in temporal and frontal cortex. However, this study was performed with a low-resolution SPECT camera and statistical differences thresholded at a pretty liberal level. The same group published a study in 2005 in which, using MRI, the same subjects showed a lack of volumetric changes following BET (Lindauer et al. 2005). However, hippocampi were found to be smaller in patients than in traumatized controls, a finding often reproduced in PTSD research. The question of whether this anatomical condition is a trait (present before traumas) or a state (following the trauma) characteristic has not been clarified yet. In addition, due to a lack of follow-up, the study did not conclusively shed light on the effects of therapy on the subcortical structures. In fact, the relatively short duration of therapy (4 months) and the minimal time elapsed between the end of psychotherapy and the MRI (about a week) may not have been long enough to produce detectable anatomical changes, as such changes may occur only after a longer interval following successful treatment.

In summary, from 1999 to 2012, a body of research has been carried out on humans to evaluate psychotherapies effectiveness, and a number of studies were focused on revealing their functional substrates despite difficulties arising from both time and spatial resolution of the implemented techniques. The neurobiological grounds for psychotherapies effectiveness in the treatment of PTSD have been supported by SPECT studies showing that, after comparing the brain activity before and after therapy, significant changes in blood flow occur mainly in limbic areas and the prefrontal cortex. Overall, the results of these studies indicate a posttreatment reversal of the prefrontal and limbic abnormalities, which were clearly recognized at pretreatment and are a frequent neuroimaging finding in patients with PTSD. In fact, despite the rather low spatial resolution of SPECT, the increased blood flow found posttreatment mainly in the right middle inferior temporal gyrus may reflect a higher control over the amygdala and an increased stabilization of the pathological brain hyperactivation, resulting in a reduction in somatosensory symptoms of anxiety.

12.2.2 Recent Studies

Zantvoord and collaborators were the first to carry out a systematic review limited to randomized controlled trials concerning the neurobiological effects of trauma-focused cognitive behavioral therapy (TF-CBT) and eye movement desensitization and reprocessing (EMDR) (Zantvoord et al. 2013). In this review, 23 publications were analyzed, which reported the results of 16 different trials. The results revealed a relative lack of studies that, until then, had used neuroimaging techniques to investigate the pre-post effects of psychotherapeutic interventions. In fact, the nine studies that had investigated TF-CBT led to partially inconclusive results although highlighting a general tendency to a reduction in amygdala activity and an increase in posttreatment mPFC activity. None of the studies included in the review had instead investigated the effects of EMDR with neuroimaging methods, further emphasizing the need for efficacy research in this area. In contrast, studies that took physiological effects into consideration showed less ambiguous results. Both in the studies that used the TF-CBT (in comparison with control groups without treatment) and in those that had investigated the EMDR (in comparison with control groups who had received other treatments), a reduction of the posttreatment physiological reactivity was found. In particular, the observed reductions in heart rate, systolic pressure, and electromyography reactivity indicated a reduction in physiological reactivity to traumatic stimuli.

In a systematic review shortly thereafter, Thomaes and colleagues investigated the effect of treatments for PTSD on structural and functional neural changes (Thomaes et al. 2014), analyzing both randomized controlled trials and those with a pre-post design. They included 15 studies, which described both pharmacological and psychotherapeutic interventions, 4 of which were specific to PTSD resulting from childhood abuse. With regard to pharmacological treatments, the results of the three studies included in the review showed an improvement in the structural

abnormalities (increase in hippocampal volume) posttreatment both in PTSD linked to adult trauma and in PTSD resulting from childhood abuse. However, the increase in hippocampal volume was associated with an improvement in memory deficits only in one study, indicating the need for a deepening of this aspect in other studies. Regarding the effects of psychological interventions, this review examined nine studies that analyzed the functional effects of interventions such as CBT, EMDR, and BEP during a posttreatment symptom challenge task. In patients with PTSD related to adult trauma, a reduction in amygdala activation was observed after treatment, and a parallel increase in the functionality of the dorsolateral prefrontal cortex, ACC, and hippocampus, all consistent with the classic model of PTSD on fear conditioning, was found. On the contrary, in the study that investigated the effects of treatment on PTSD resulting from complex childhood trauma, a different pattern of functioning was noted, not detecting any change in the amygdala and instead observing a reduction in activations in the dorsolateral prefrontal cortex, ACC, and insula, after treatment indicating how patients with complex PTSD may not respond favorably to types of treatment that have been found effective for PTSD related to adult trauma. This could be due to the presence of dissociative symptoms, which are mostly seen in subjects exposed to childhood trauma (abuse or neglect). It is therefore essential to continue to investigate the neurobiological correlates of dissociative PTSD and complex PTSD (recently recognized as a separate clinical diagnosis by ICD-11) and the effects at the neural level of the related psychotherapeutic treatments, since the treatments usually used for the classic forms of PTSD seem to be only partially effective (Corrigan and Hull 2015a, b; Karatzias et al. 2019).

More recently, Helpman et al. (2016) investigated the associations between treatment efficacy and alterations in brain structures, focusing on rostral anterior cingulate cortex (rACC) volume. The authors found that following prolonged exposure (PE) treatment, PTSD remitters exhibited cortical thinning and volume decrease in the left rACC compared with PTSD non-remitters and controls, suggesting that PE treatment for PTSD, by reducing negative trauma associations, could promote stable morphological changes in rACC. This pattern of results at least in part contradicts findings from Boukezzi et al. (2017), who aimed to determine whether symptoms improvement in PTSD was associated with gray matter (GM) density changes of brain structures. The first group ($n = 11$) was treated with eye movement desensitization and reprocessing therapy and recovered from symptoms. The second group ($n = 7$) included patients which followed a supportive therapy and remained symptomatic (wait-list group). Both groups were scanned prior to therapy (T1), 1 week and 5 months after the end of therapy (T3). Voxel-based morphometry was used to track GM density evolution. It showed a significant group-by-time interaction effect between T1 and T3 in prefrontal cortex areas: this interaction effect was associated with a GM density increase in the recovery group as compared to the wait-list group. Symptoms recovery was then associated with GM density enhancement of cerebral areas typically involved in emotional regulation.

Butler et al. (2018) investigated morphological changes in combat-related PTSD after psychotherapy, focusing on hippocampal gray matter. After a first neuroimaging assessment, the treatment group received multimodal psychological therapy for

approximately 6 weeks, and then both treatment and control groups completed a second neuroimaging assessment. ROI analysis was used to investigate gray matter volume in the hippocampus and amygdala. The small experimental group ($n = 6$) showed a significant increase in hippocampal volume and a nonsignificant trend toward an increase in amygdala volume following therapy, while no change was observed in the small control group ($n = 9$). This study provides preliminary evidence for increase in gray matter volume in the hippocampus in response to therapy for combat-related PTSD.

In a detailed literature review of mindfulness treatments for PTSD, Boyd et al. (2018) concluded that there is considerable overlap between main neurobiological models of PTSD and imaging findings in mindfulness studies. Mindfulness-based treatments have the potential to target emotional *undermodulation* (associated with hyperarousal and intrusion symptoms) and *overmodulation* (associated with dissociative symptoms) and may be effective in increasing activity in prefrontal regions and reducing activity in limbic regions (e.g., amygdala) to effectively target intrusion and hyperarousal symptoms. See Fig. 12.2 for details.

Lastly, a very recent selective review (Szesko and Yehuda 2019) considered magnetic resonance imaging studies that have been used to monitor treatment response to cognitive-behavioral therapy or prolonged exposure in PTSD. Overall, they demonstrated abnormalities in processing involving the salience network, including the amygdala, anterior cingulate cortex, and insula. In PTSD, increased attention to environmental cues may lead to hypervigilance and abnormal action monitoring for the detection of threatening stimuli and to a reduced capacity to integrate emotional and sensory stimuli appropriately. Successful psychotherapy treatments seem to involve the ability to downregulate amygdala activity to trauma-related stimuli through improved regulation of attention by the anterior cingulate cortex and of internal emotional states mediated by the insula.

12.2.3 Outcome Studies

A few studies have investigated the mechanisms through which PTSD patients get benefit from psychological treatments. Thus, the essential clinical topic of identifying positive predictors for treatment response is currently being investigated from a neuroimaging point of view as well. The response to fearful and neutral facial expressions in 14 patients was investigated by Bryant et al. by fMRI. Greater amygdala and anterior cingulate cortex activation before therapy predicted the poor response to CBT found in seven of them (Bryant et al. 2008b). The authors concluded that the excessive amygdala response to fear may reflect difficulty in managing anxiety reactions elicited during CBT, and this factor may limit optimal response to therapy. In an interesting literature review examining neural correlates of psychotherapeutic treatment of PTSD investigated by SPECT or fMRI, Malejko et al. (2017) found that successful psychotherapy in PTSD was frequently associated with decreased activity in the amygdala and the insula, as well as increased activity in the dorsal anterior cingulate cortex (dACC) and hippocampus. Interestingly,

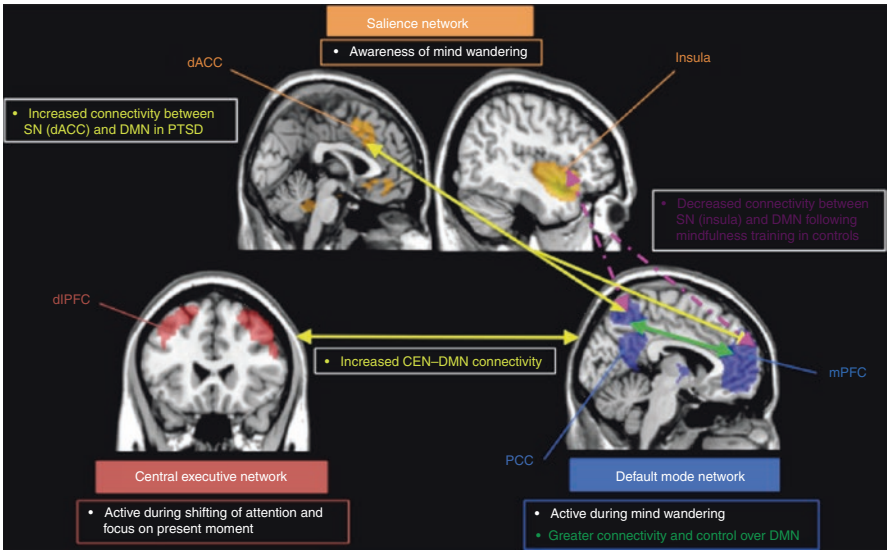

Fig. 12.2 Summary of findings suggesting that mindfulness may lead to restoration of functioning of the salience network (SN, shown in orange), central executive network (CEN, shown in red), and default mode network (DMN, shown in blue). Increased connectivity within networks is depicted by solid green lines, increased connectivity between networks is depicted by solid yellow lines, and reduced connectivity between networks is depicted by dashed pink lines. Emerging work has indicated greater functional connectivity within the DMN during rest among meditators when compared with controls and among veterans with post-traumatic stress disorder (PTSD) following mindfulness intervention, suggesting that it may restore DMN connectivity and appropriate self-referential processing in those with PTSD. Increased CEN–DMN connectivity was also reported and may reflect increased ability to shift between internal and external loci of attention. Mixed findings of both increased and decreased DMN–SN connectivity following mindfulness intervention have been reported, depending on the region of the SN. Increased dorsal anterior cingulate cortex (dACC)–DMN connectivity was reported following mindfulness intervention for PTSD, which may suggest increased capacity for attentional shifting from internal to external stimuli (dACC implicated in executive control). In contrast, reduced SN (insula)–DMN connectivity was reported among controls, which may result in reduced hyperarousal symptoms and increased self-referential processing if findings were replicated in individuals with PTSD. *dlPFC* Dorsolateral prefrontal cortex, *mPFC* Medial prefrontal cortex, *PCC* Posterior cingulate cortex (*Boyd* et al., J Psychiatry Neurosci 2018;43:7–25)

significant dACC activity prior to treatment emerged as a positive predictor for treatment response, whereas elevated amygdala and insula pretreatment activities were typically associated with treatment failure, thus confirming the results of Thomaes et al. (2014). This reduction of activation in limbic regions and increased activation in posttreatment cortico-frontal regions may represent the biological correlate of the recovery of top-down inhibitory control of cognitive areas on the emotional regions of the limbic system that led to bottom-up dysfunctional processes before treatment. Not having identified substantial differences between the different types of treatment for PTSD may be due to the fact that the changes observed at the neural level correspond more strongly to changes and improvements in clinical

symptoms than to the different techniques that promote these changes and therefore to the common elements of the different types of treatment.

Colvonen et al. (2017) examined various biomarkers as predictors of evidence-based PTSD psychotherapy outcomes. Results provide preliminary evidence that the integrity of specific structural and functional neural systems involved in affecting fear learning and extinction, cognitive restructuring, information and emotional processing, and interoceptive monitoring such as anterior cingulate cortex, hippocampus, and insula, when coupled with other biomarkers (such as glucocorticoid sensitivity and metabolism, heart rate, gene methylation, and certain genotypes), predicted the quality of response to PTSD psychological treatment.

Suarez-Jimenez et al. (2019) investigated whether anterior hippocampal volume would predict affect-focused treatment outcome. Thirty-five patients with PTSD and 24 with panic disorder underwent MRI scan before randomization to affect-focused or exposure-based treatments. Anterior and posterior hippocampal volumes were regressed with clinical outcome measures. For affect-focused treatments, but not exposure-based treatments, anterior hippocampal volume predicted clinical improvement as smaller volume correlated with greater affect-focused treatment improvement, while posterior hippocampal volume did not. These preliminary results suggest that treatment outcome can be potentially predicted by anterior hippocampus volume, even if larger studies should target this crucial clinical issue before reaching any general conclusion.

In summary, in the last years, various studies provided evidence of the role played by the prefrontal and limbic structures in patients with PTSD. When an effective psychotherapy treatment is provided to patients, at a neural level, one can observe a diminished activity of limbic correlates associated with an increased activity of prefrontal cortex, suggesting that, as treatment proceeds effectively, patient's emotions, memories, and thoughts tend to be less under the regulation of subcortical structures and more under control of prefrontal areas. Volume and perfusion of these crucial structures (such as hippocampus, amygdala, and anterior cingulate cortex) have been recently proposed as possible predictors for treatment response in PTSD. These findings provide convergent evidence about clinical improvement by showing that psychotherapies have a significant impact on brain activity too and that the acquired pattern of brain activity due to the effective psychotherapy treatment is consistent with a significant reduction of post-traumatic and altered mood symptoms. Future neuroimaging studies should focus on the clarification of mechanisms through which biomarkers are associated with treatment outcomes. We still do not know how structural and functional activity of brain areas correlate to, or perhaps interfere with, successful or unsuccessful psychotherapy. No single neural structure works in isolation; thus, using functional connectivity analyses to examine the interaction of multiple regions involved in cognitive and emotional processes distorted in PTSD will likely be useful in understanding neural correlates of effective psychotherapy. Evidence available to date strongly suggests the need to continue to investigate the neurobiological effect of the different types of traumatic events, the age of exposure to them, and individual genetic and biological variables in order to be able to understand which psychological treatments may be more appropriate for each patient.

With a view to personalizing care, it is also essential to involve patients in the decision-making process; as shown by a recent study on PTSD subjects, the fact of receiving the patient's preferred treatment is associated with better clinical results and better adherence to treatment (Zoellner et al. 2019).

However, none of the functional neuroimaging studies performed by SPECT has succeeded in investigating PTSD and its related psychotherapies with accurate time resolution. In fact, the firing of brain neurons responding to psychotherapy-induced stimuli, along with the effects of such stimuli on brain activation/deactivation, was recorded only before and after treatment. This has restricted the findings to static conditions without describing in detail the dynamics of regional neuronal synchronization during psychotherapy sessions, an essential step in the comprehension of their functional mechanism. One of the tools that may help to overcome this limiting methodological factor is electroencephalography (EEG), resulting in a time resolution of milliseconds and having an acceptable capability to identify the sources of activity in the 3D brain space, especially with a medium- to high-density array of electrodes.

A new series of investigation about this topic had been carried out, based on online EEG monitoring of the functional response during psychotherapy (Pagani et al. 2011, 2012). To allow the experiment to be as patient-friendly as possible, the EEGs in a group of patients affected by major psychological trauma were recorded in a private practitioner's quiet room. The activation of the human cortex in "live mode" throughout the EMDR session was compared between traumatized individuals in the acute phase and after clinical recovery. The comparison between the patients' EEGs recorded during the first and the last EMDR sessions showed a significantly greater activation during the latter in the temporo-parietal-occipital cortex mainly on the left side (Pagani et al. 2012). In patients after therapy, a significant decrease in the fast alpha and gamma components of the activation present at the first EMDR session in the orbitofrontal and anterior cingulate cortex was also observed. These changes may suggest a better cognitive and sensorial (visual) processing of the traumatic event during the autobiographic reliving after successful EMDR therapy. At this stage, as an effect of successful trauma elaboration, the visual images of the event are processed and stored in primary and associative visual cortex and likely decoupled from the emotional memory of faces and bodies linked to the event, typically processed by fusiform gyrus.

Beginning from these premises, Trentini et al. (2015) used high-density EEG (hdEEG) to explore the impact of EMDR on a sample of school-aged children with histories of early and prolonged maltreatment, considering neural responses to adults' facial emotions, as well as the levels of traumatic distress and emotional-adaptive functioning. Before EMDR, hdEEG showed similar significantly higher activity on the right medial prefrontal and frontotemporal limbic regions, shifting toward the left medial and superior temporal regions after the conclusion of the intervention. These changes were associated with the decrease of depressive and traumatic symptoms and with the improvement of emotional-adaptive functioning over time. Consistent with the results of previous research on traumatized adults (Pagani et al. 2012), this study indicated that, after EMDR, children used higher-order cognitive resources while processing emotion expressions.

In another study Pagani et al. (2015) used EEG to compare the neuronal activation during the bilateral stimulation phase between the first (T0) and the last (T1) session of EMDR in two distinct groups of psychologically traumatized patients, recruiting patients that faced traumatic events in daily life as well as patients suffering of chronic PTSD following a natural catastrophe, also in comparison with healthy controls. In all patients the cortical activation shifted from anterior PFC at T0 to fusiform and lingual cortex at T1, speaking in favor of an EMDR-related response to reliving the traumatic event normalizing toward the one found in healthy controls at T0. In the chronically exposed patients' subgroup both before and after EMDR therapy, such changes were less intense, suggesting a lower functional response to traumatic exposure during time. This might be explained by the environmental context in which all patients could share with the community the traumatic experience.

Finally, a recent EEG study (Carletto et al. 2019) investigated the efficacy of an EMDR intervention compared to a supportive treatment in women with breast cancer-related PTSD. The results showed a greater clinical efficacy of EMDR treatment compared to standard supportive treatment. Women who underwent EMDR therapy had a remission of post-traumatic and depressive symptoms, while women who underwent standard supportive treatment showed only a partial or no reduction in these symptoms. The results of the evaluations carried out by EEG corroborated the clinical results, showing greater changes after EMDR therapy in the left angular gyrus and in the right fusiform gyrus, areas corresponding to the ones found to activate post-therapy in the previous EEG studies. As in Pagani et al. (2012), the restored activity of these regions after successful EMDR could facilitate an elaboration at higher cognitive level of the images related to the traumatic event, allowing better processing and contextualization.

In our opinion, the importance of these studies lies not only in the validation, through a different functional neuroimaging technique, of the results obtained with SPECT and PET but also in the critical importance of PTSD-related psychotherapy research. Being able to perform EEG studies in a quiet and cozy environment helps to avoid biases caused by patient discomfort and possible psychological constraints (i.e., claustrophobia, anxiety, panic, etc.) which can occur in a fMRI scanner (Mazard et al. 2002). In this respect a very recent study has used PET to investigate in 15 military veterans suffering from PTSD brain metabolism before and after EMDR, finding a significant activation of precuneus post-therapy (Rousseau et al. 2019). The importance of the study derives from the novel use of virtual reality as script to elicit an emotional response in PTSD patients and from the rediscovery of metabolic PET as a means to perform activation studies in alternative to the use of the more uncomfortable and complex fMRI investigations (Pagani et al. 2019).

12.3 General Discussion

One of the aims of the functional studies carried out over the last 20 years in PTSD has been to broaden our knowledge about the neurobiological mechanisms underlying successful psychotherapy. This has been pursued via various methodologies to

identify the pathophysiological changes occurring in the brain following psychotherapy by neuropsychological, blood perfusion, neuronal density, and electrical activation studies. This exciting journey has helped to confirm the association between clinical outcomes and changes in brain functions and structures following psychological treatment and has also confirmed the feasibility of real-time monitoring of cortical activations during therapy. The significant normalization of these patterns of activation when symptoms disappear can be interpreted as a neurobiological correlate of clinical recovery. This supports the hypothesis of a shift of emotional and cognitive processing from limbic to cortical regions with an overwhelming cognitive and sensory role occurring when the memory retention of the traumatic event can move from an *implicit* subcortical to an *explicit* cortical status, with different regions participating in an effective processing of traumatic experience.

In general, limbic hyperactivation in PTSD patients is paralleled by cortical hypofunction, resulting in a lack of inhibition of reaction to fear from amygdala and lack of adequate attenuation of peripheral sympathetic and hormonal responses to stress. It had been proposed that such hyperperfusion and hyperactivity of limbic and paralimbic regions be related to stress-induced long-term potentiation between amygdala and periaqueductal gray through the N-methyl-D-aspartate-mediated pathway, once a sufficient amount of glutamate is released following stressful events. Chronic PTSD is often associated with long-term pharmacological treatments and/or alcohol and substance abuse, which further affect brain structure and function and confound the results of the investigations. In this respect, the choice of an appropriate control group is a critical factor in neuroimaging analysis. Subjects exposed to psychological trauma but not developing PTSD clinical symptoms are likely to be the best candidates. In this case, CBF distribution differences between groups will be related to the psychological disorder itself and will allow to gain a major understanding of this critical neural factor.

12.4 Conclusions

The main objective of neuroimaging studies in PTSD conducted over the last 20 years had been not only to identify its anatomic-functional correlates but also to broaden our knowledge of the neurobiological mechanisms associated with the related psychotherapeutic treatments. This has been possible, thanks to the use of approaches and methods this chapter focused on (i.e., mainly SPECT, MRI, and more recently EEG) to investigate morphological and/or functional brain changes before and after the execution of various psychotherapies.

In general, the limbic hyperactivation observed in symptomatic patients goes hand in hand with frontal cortical hypo-functionality, resulting in a reduced inhibition of the amygdala reaction to fear. The studies here described have shown that after effective psychotherapeutic treatments (mainly CBT and EMDR), there is a normalization of these patterns of activation associated with a reduction in symptoms that can reasonably be interpreted as neurobiological correlates of clinical recovery. This evidence supports the hypothesis of a migration of cortical activity

mainly from subcortical regions more emotionally connoted to neocortical regions more involved in cognitive and sensory processes, which proceeds in parallel with a more explicit elaboration of the traumatic experience that would therefore cease to be solely relegated to the field of reduced awareness (Pagani et al. 2013). Studies have also demonstrated the feasibility of real-time monitoring of cortical activation during therapy, opening up new horizons for a more thorough and neurobiological understanding of the mechanisms of action of psychotherapies (Carletto et al. 2017; Pagani et al. 2017). This compelling journey allowed us to confirm the preliminary evidence of a relevant association between patients' clinical status and changes in brain structure and function following effective psychotherapeutic treatments, urgently calling to foster this essential field of applied clinical research.

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Neuroimaging of Obsessive-Compulsive Disorder: Insights into Serotonergic Mechanisms

13

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Abstract

The neurobiology of obsessive-compulsive disorder (OCD) is not well understood. The clinical benefits of selective serotonin-reuptake inhibitors (SSRIs) have implicated serotonin, but a clear understanding of its role in symptom onset, aggravation, and resolution remains elusive. Some progress has come from studies using positron emission tomography (PET). PET studies with α-[11C]methyl-L-tryptophan suggest that OCD patients, relative to healthy controls, have elevated brain serotonin synthesis capacity. This increase becomes greater following treatment with either cognitive behavior therapy or an SSRI. A similar phenomenon has been observed in most PET studies targeting the serotonin transporter. Compared to healthy controls, OCD patients commonly exhibit decreased serotonin reuptake potential, a group difference that can also enlarge following treatment. Some of these serotonergic alterations might be unique to OCD. Finally, contrasting with what is seen in those with OCD, brain serotonin synthesis capacity is decreased in people who have difficulty regulating impulsive behaviors, such as those with borderline personality disorder and a history of suicide attempts. Together, these observations raise the possibility that elevated serotonergic tone may be an attempt to inhibit OCD symptoms, a mechanism of "braking" or "resistance" that becomes more effective with treatment.

13.1 Overview

Obsessive-compulsive disorder (OCD) is characterized by frequent and persistent obsessive thoughts and/or compulsive behaviors causing marked distress and disability. The disorder often starts in late childhood or in early adulthood (Anholt et al. 2014) and affects up to 3% of the population (Fineberg et al. 2012). Yet, OCD currently lacks universally effective treatments, leading many cases to be misleadingly labeled "treatment refractory." This term falsely implies that non-responders are inherently less treatable, rather than communicating that a reliable treatment for these patients is not yet available. Among the treatments that are available, the best-established are drug therapy with selective serotonin-reuptake inhibitors (SSRIs) and specialty cognitive behavior therapy (CBT) (Hirschtritt et al. 2017).

Randomized controlled trials (RCTs) have shown that SSRIs and CBT yield clinically significant symptom reduction or remission in roughly 25% of patients, a partial response in 35%, and no significant improvement in 40% of the patients. The

exact figures depend on a number of factors including the definition of satisfactory response (Öst et al. 2015; Pallanti and Quercioli 2006).

Adding to the complexity, OCD is a highly heterogeneous disorder with multiple symptom profiles (McKay et al. 2004; Sookman et al. 2005). Types of obsessions include intrusive thoughts, mental images, impulses, and fears. Types of compulsions include mental rituals such as counting and behavioral rituals such as checking or washing. This diversity has led many researchers to investigate the potential benefits of categorizing OCD subtypes. Subtypes have been proposed that involve purely compulsions or a mix of obsessions and compulsions (Rodgers et al. 2015), as have subtypes based on the presence or absence of various comorbid disorders, including Tourette syndrome (Brander et al. 2019) and mood and anxiety disorders (Nestadt et al. 2003). Growing evidence also supports early-onset and late-onset subtypes of OCD (Kim et al. 2019a; Taylor 2011). Each subtype may be driven by different neurobiological mechanisms. Obtaining a better understanding of the pathophysiology underlying OCD symptom presentations is crucial to inform the development and refinement of effective treatment strategies.

13.1.1 Hypothesized Braking System Model of OCD

OCD can be conceptualized as a disorder that begins with a loss of control, whether perceived or real, that triggers the formation of coping rituals. Strikingly, most patients with OCD are aware of the irrationality of their own thoughts and behaviors, yet their symptoms persist to a maladaptive extent. A central inhibition system designed to modulate these symptoms may come into play, but the patient's perceived failure to regain control persists, rendering these responses highly inflexible. The brain's natural "braking system" may therefore be left unable to catch up with the dysfunctional mechanisms driving the obsessions and compulsions. Although speculative, it is possible that behavioral and drug therapies strengthen these inhibitory mechanisms with the support needed to successfully reduce OCD symptoms. Our understanding of the pathways and neurotransmitters involved in this hypothesized neural system remains primitive.

13.2 Neurobiology

13.2.1 Brain Circuits

Over the past few decades, neuroimaging studies of people with OCD have provided evidence of alterations in cortico-striato-thalamo-cortical (CSTC) circuits. Within these circuits, the orbitofrontal cortex, anterior cingulate, and caudate nucleus have been identified with particular consistency (Aouizerate et al. 2004; Menzies et al. 2008). Early positron emission tomography (PET) imaging studies identified, to varying degrees, increased glucose metabolic rates in each of these brain regions (Baxter et al. 1987; Brody et al. 1998; Nordahl et al. 1989). Subsequent

studies indicated that symptom reduction following SSRI or CBT treatment was associated with decreased glucose metabolism and cerebral blood flow in the orbitofrontal cortex and caudate (Baxter et al. 1992; Benkelfat et al. 1990). These reductions in CSTC activity were recently confirmed in a meta-analysis of 14 PET and single photon emission computed tomography (SPECT) studies conducted between 1990 and 2017 (van der Straten et al. 2017).

The identified brain regions in OCD do not function in isolation. Early PET studies found that activity levels in CSTC sites were highly correlated in patients, much more so than in healthy volunteers (Schwartz 1997). Evidence of abnormally high connectivity between CSTC circuit nodes has also been observed in resting-state functional magnetic resonance imaging (fMRI) studies (Beucke et al. 2013), with normalization (decreased connectivity) occurring following successful treatment (Dunlop et al. 2016). Indeed, the relatively rare use of deep brain stimulation to treat OCD also reduces fronto-striatal hyper-synchrony, and the magnitude of these decreases is associated with the degree of symptom reduction (Figee et al. 2013). Evidence of a causal link also comes from studies in mice showing that optogenetic modulation of CSTC circuitry can both generate and eliminate OCD-like behaviors (Ahmari et al. 2013; Burguière et al. 2013).

Although some inconsistent findings suggest an even more complex picture of the involvement of CSTC activity and connectivity (Busatto et al. 2000; Posner et al. 2014; Rubin et al. 1992), the weight of current evidence suggests that dysfunction within these circuits drives OCD symptoms. Antidepressants and CBT may help to diminish this dysfunction, possibly by supporting neurobiological mechanisms already influencing these circuits. However, our understanding of the specific neurobiological processes contributing to dysfunction within these circuits, as well as those helping to control this dysfunction, is still in its nascency.

13.2.2 Neurochemistry

Multiple neurotransmitters have been implicated in OCD, including glutamate, oxytocin, dopamine, and, most prominently, serotonin (Barr et al. 1992; Goodman et al. 1990a; Leckman et al. 1994; Pittenger et al. 2011). The involvement of any one neurotransmitter in OCD neuropathology is likely to include interactions with other neurotransmitter systems. For example, glutamate may play an important role given preliminary evidence that glutamate modulators, such as ketamine and N-acetylcysteine, can improve obsessive-compulsive (OC) symptoms (Li et al. 2020; Rodriguez et al. 2013). This requires more study. The present chapter provides an update on the larger, though still challenging, literature on serotonin and, to a lesser extent, dopamine.

13.2.2.1 Serotonin

The neurotransmitter serotonin, also known as 5-hydroxytryptamine (5-HT), projects from its cell body region in the raphe nuclei to sites throughout the CSTC circuit (Graybiel and Ragsdale 1983; Jacobs 1994). Serotonin has received particular attention largely based on the preferential effectiveness of SSRIs (e.g., fluvoxamine,

sertraline, fluoxetine, paroxetine, and citalopram) and the tricyclic antidepressant clomipramine to reduce OC symptoms. These antidepressants inhibit serotonin reuptake by blocking the binding of 5-HT to the serotonin transporter (SERT) and have been shown to reduce symptoms in most cases of OCD (Jackson et al. 1994; Kronig et al. 1999; McDonough and Kennedy 2002; Montgomery et al. 2001). In comparison, antidepressant drugs that primarily influence other neurotransmitters, such as norepinephrine, have shown either little or no clinical benefit in OCD (Goodman et al. 1990b; Insel et al. 1983). The link between the clinical benefit of SSRIs and serotonergic alterations underlying OCD symptoms, however, appears to be indirect, with effects of extended (Benkelfat et al. 1989) but not transient (Berney et al. 2006) 5-HT changes implicated. The similar efficacy of CBT raises the possibility of an overlapping effect on the serotonergic system, but there is a paucity of studies testing this. Thus, although SSRIs and CBT are the treatments of choice for OCD, the exact process through which 5-HT alleviates OCD symptoms remains unknown.

Interest in a relation between 5-HT and OCD was also stimulated by an early study examining cerebral spinal fluid (CSF) concentrations of the primary 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA). Thorén et al. (1980) reported that, following 3 weeks' treatment with clomipramine, a significant improvement in OCD symptoms correlated strongly with greater decreases in CSF 5-HIAA. Patients who responded to treatment showed significantly higher pre-treatment CSF 5-HIAA levels than non-responders and healthy controls. However, later studies were unable to reliably identify abnormal baseline measures of 5-HIAA and other peripheral markers of 5-HT function in OCD (Insel et al. 1985; Leckman et al. 1995).

A second research strategy that implicated a role of 5-HT in OCD employed pharmacological challenges. These studies found that administration of the 5-HT_{1D} receptor-specific agonist sumatriptan or the non-specific 5-HT receptor agonist meta-chlorophenylpiperazine (mCPP) could worsen OC symptoms (Gross-Isseroff et al. 2004; Zohar et al. 1987), with the latter effect prevented by prior treatment with clomipramine (Zohar et al. 1988). However, these findings too have not been reliably replicated (Goodman et al. 1995; Ho Pian et al. 1998; Stein et al. 1999). One partial explanation might be that 5-HT is ubiquitous throughout the brain, eliciting a complex array of excitatory and inhibitory influences, whereas its role in OCD is likely to be limited to particular neural pathways. As such, although pharmacological challenge studies, as well as peripheral and CSF measurements of 5-HT, hint at serotonin's involvement, they fail to identify pathway-specific mechanisms related to the expression or alleviation of OC symptoms. Since the experimental induction of transient decreases in serotonergic tone does not alter OC symptoms (Berney et al. 2006), they most likely do not depend solely on short-term changes in presynaptic 5-HT availability.

In the years since Thorén et al.'s 1980 observations, the techniques for studying serotonergic mechanisms in the brain have improved. Neuroimaging advancements in the past few decades have allowed us to probe OCD with more precision and depth than before, providing us with the tools we need to uncover crucial pieces of the OCD puzzle. This noted, despite encouraging progress in some realms, a

comprehensive and unequivocal understanding of serotonin's role in OCD has yet to emerge.

PET and SPECT imaging can map, *in vivo*, brain regional availabilities of the SERT and 5-HT receptors. The majority of PET and SPECT studies have found SERT binding to be low in CSTC related brain regions in those with OCD compared to healthy controls (Hesse et al. 2005, 2011; Matsumoto et al. 2010; Reimold et al. 2007; Stengler-Wenzke et al. 2004; Zitterl et al. 2006). Following treatment with clomipramine, SERT availability decreases further (Zitterl et al. 2008), most probably reflecting medication binding to SERT sites. Similarly, reduced SERT availability within the CSTC circuitry compared to healthy controls has been observed following treatment with the SSRI, escitalopram (Kim et al. 2016; Müller-Vahl et al. 2019). The literature contains a few discrepant findings, though, and both increased (Müller-Vahl et al. 2019; Pogarell et al. 2003) and normal pre-treatment SERT binding availabilities (Simpson et al. 2003) have been reported. Some of the variability in findings might reflect the inclusion of heterogeneous, non-drug-naïve samples of patients and comorbid Tourette syndrome.

Serotonin receptor distribution has also been investigated using PET and SPECT imaging, though there is less consistency than has been seen in the SERT literature. One [^{18}F]altanserin study identified greater 5-HT$_{2A}$ receptor binding in the caudate nuclei of OCD patients compared to healthy controls, which remained unaltered following SSRI treatment (Adams et al. 2005). Other studies, however, using [^{11}C]MDL100907, showed reductions in 5-HT$_{2A}$ postsynaptic receptor availability in frontal, temporal, and parietal cortices in OCD patients compared to healthy controls (Perani et al. 2008) or no significant differences in 5-HT$_{2A}$ receptor availability (Simpson et al. 2011). The precise mechanisms underlying these potential abnormalities are unclear.

PET and SPECT evidence implicating 5-HT in OCD has been complemented in recent years by (i) human genetic association studies and (ii) rodent models of OCD. In candidate gene studies, polymorphic variations of the *SERT* gene or *HTR2A* receptor gene have been associated with some consistency with the OCD diagnosis (Grünblatt et al. 2018; Sinopoli et al. 2017; Taylor 2016) and CSTC regional volumes among OCD patients (Atmaca et al. 2011; Sinopoli et al. 2019). Additional support comes from compelling rodent models of OCD: *SAPAP3* knockout mice exhibit cortico-striatal synaptic defects (Welch et al. 2007) and elevated 5-HT metabolites across the CSTC circuitry (Wood et al. 2018). Considered collectively, the accumulating evidence from across modalities provides strong support for a serotonergic mechanism in OCD.

13.2.2.2 Dopamine

Serotonin's influence on OCD symptoms might intersect with dopamine (Goodman et al. 1992, 1990a). Although inconsistencies also exist in this literature, accumulating studies suggest that dopamine neurotransmission may be overactive in the basal ganglia of OCD patients (Denys et al. 2004b). For example, SPECT studies have

identified greater dopamine transporter binding ratios in the basal ganglia (Kim et al. 2003; van der Wee et al. 2004) and lower dopamine receptor binding in the striatum, relative to controls (Denys et al. 2013, 2004a; Figee et al. 2014), raising the possibility that OCD patients have elevated extracellular dopamine levels in these areas.

More notably, whereas monotherapy with dopamine antagonist antipsychotics has not shown much promise (McDougle et al. 1995), combination therapy with both SSRIs and antipsychotics has been more successful, especially in the treatment of patients who allegedly do not respond to SSRIs alone and for some OCD subtypes (McDougle 1997; McDougle et al. 1990; Metin et al. 2003). Furthermore, successful SSRI treatment has been shown to increase striatal D_2 receptor binding (Moresco et al. 2007). Responders and non-responders to SSRI may, however, require different neurochemical changes for therapeutic benefit. Illustrating this idea, in a [^{123}I]iodobenzamide SPECT study of treatment refractory OCD patients, deep brain stimulation of the bilateral nucleus accumbens led to decreased striatal $D_{2/3}$ receptor availability, suggesting the induction of striatal dopamine release, which was associated with symptom improvement (Figee et al. 2014). Dopamine may act synergistically with 5-HT, affecting the etiology and treatment of OCD. However, the exact mechanism(s) by which this conjunction of effects is made operative is not known, motivating further study.

13.3 Dimensions Vs. Diagnosis

Whereas studies associating dysfunctional circuits and neurotransmitter systems with a diagnosis of OCD offer some insight into its neurobiology, the substantial clinical heterogeneity and variability in neurobiological findings highlights the need for a more refined phenotypic characterization. “Core” symptoms may be present in the majority of OCD patients, whereas other symptoms may be unique to its specific clinical presentation. As such, our understanding of OCD etiology may benefit from the disorder’s decomposition into a broad array of dimensions. Each OCD subtype is likely comprised of dimensions, such as impaired inhibition, maladaptive perseveration, dysfunctional habit formation, rigid monitoring and control, and many more. Since both hyperactivity (Baxter et al. 1988; Lacerda et al. 2003; Saxena et al. 2004) and hypoactivity (Busatto et al. 2000; Rubin et al. 1992) of the orbitofrontal cortex and striatum have been found in OCD, the relationship between activity in these areas and symptoms may involve complex dysregulation(s) with increased activity for certain OCD dimensions, but decreased activity for others. Because links between dimensions and OCD may only exist for some clinical presentations, interpretations of findings that relate specific dimensions to specific neurobiological mechanisms should be made with caution. Still, a large body of neuroimaging studies examining associations with OCD dimensions has accumulated in recent years.

In particular, deficits in behavioral and cognitive flexibility are common in OCD, and patients who display high levels of behavioral and/or cognitive rigidity may

have difficulty shifting their responses or learning associations in changing contexts. Indeed, various studies have indicated decreased orbitofrontal cortex and striatal activity in OCD patients compared with controls during reversal learning tasks (Chamberlain et al. 2008; Remijnse et al. 2006; Robbins et al. 2019). Animal models of reversal learning have shown that 5-HT, but not dopamine, was crucial in the orbitofrontal cortex and that dopamine, but not 5-HT, was more relevant in the caudate (Clarke et al. 2011). More recently, Apergis-Schoute et al. (2017) showed that impaired reversal learning in individuals with OCD was accompanied by an absence of ventromedial prefrontal cortex activity in response to safety cues during learning. Although it is unlikely that OCD consists solely of a reversal learning deficit, the study of this potential dimension has helped illuminate the complexities of fronto-striatal, 5-HT, and dopamine mechanisms that might underlie some of the behavioral *dimensions* in OCD.

Other dimensions have been studied in a similar manner, including error processing, response inhibition, and OC symptoms themselves. Hyperactivity in the anterior cingulate cortex and ventral frontal areas in response to errors (Stern et al. 2011) and elevated activity in the pre-supplementary motor area during impaired response inhibition (de Wit et al. 2012) have been reported in patients with OCD. The importance of these dimensions to OCD pathology has become increasingly apparent in recent years. A meta-analysis of >200 patients with OCD and >200 healthy controls found (i) regional hyperactivity and hypoactivity during error processing and response inhibition in OCD patients, including hyperactivity within the anterior cingulate cortex, pre-supplementary motor area, and frontal cortices during error processing, (ii) hyperactivity within the premotor cortex during response inhibition, and (iii) hypoactivity within CSTC circuitry during response inhibition (Norman et al. 2019). Finally, aggressive and sexual/religious symptoms in OCD patients have been associated with heightened amygdala activation in response to fearful faces (Via et al. 2014). While these features are relevant to OCD neuropathology, they may not be specific to OCD, and their value as potential transdiagnostic dimensions of psychopathology needs to be tested.

The heterogeneity that exists within a diagnosis of OCD is also relevant to the serotonergic system. For example, Hesse et al. (2011) investigated a group of drug-naïve patients using the PET [^{11}C]DASB ligand, taking age of onset (<18 years of age vs. ≥18 years of age) and a variety of other factors into account. Relative to controls, only late-onset patients exhibited reduced SERT binding in limbic areas, including the striatum, hippocampus, and amygdala. This finding suggests that early-onset and late-onset OCD subtypes could involve different serotonergic mechanisms. Another PET study using the [^{11}C]-P943 ligand (Pittenger et al. 2016) found that 5-HT$_{1B}$ receptor availability did not differ in OCD patients compared to healthy controls, but patients and controls did exhibit different regional correlations with sensorimotor gating (prepulse inhibition), a process that is impaired in patients with OCD (Ahmari et al. 2012). Lastly, sleep quality could represent another dimension of OCD that maps onto serotonergic function, as 5-HT plays an important role in regulating sleep (Cespuglio 2018; Liu and Borjigin 2006), and some OCD patients suffer from sleep disturbances (Donse et al. 2017). More studies examining

the role of specific clinical features in 5-HT variability among OCD patients are needed.

13.4 α-[^{11}C]MTrp

The PET tracer α-[^{11}C]methyl-L-tryptophan (α-[^{11}C]MTrp) has been used over the past two decades to study regional 5-HT synthesis in a variety of patient populations (Chugani et al. 2001, 1999; Pfund et al. 2002). During 5-HT synthesis, the 5-HT precursor tryptophan is converted into 5-hydroxytryptophan (5-HTrp), which is then metabolized into 5-HT. It has been shown that levels of tryptophan correlate with levels of 5-HT (Cohen et al. 1995), and that increasing the availability of tryptophan can increase the rate of 5-HT synthesis (Ashcroft et al. 1965; Fernstrom and Wurtman 1971). α-[^{11}C]MTrp is an analog to tryptophan, and its rate of accumulation has been found to index rates of 5-HT synthesis (Chugani and Muzik 2000). An overview of the pathway of tryptophan in comparison to that of α-[^{11}C]MTrp is illustrated in Fig. 13.1. α-[^{11}C]MTrp is able to cross the blood brain barrier (Diksic et al. 2006), after which it enters serotonergic neurons and is converted to α–methyl-5-hydroxytryptophan (α-M5-HTrp), which is then converted to α–methylserotonin (α-M5-HT). α-M5-HT cannot cross the blood–brain barrier and is not degraded by monoamine oxidase (MAO) (Missala and Sourkes 1988), therefore allowing it to accumulate in the brain. The main difference between α-[^{11}C]MTrp and tryptophan is that the former is not incorporated into protein (Diksic et al. 1990). The α-[^{11}C]MTrp net trapping constant (*K** value, mL/g/min) is calculated using the net blood-to-brain clearance of the tracer and is used to estimate regional rates of 5-HT synthesis.

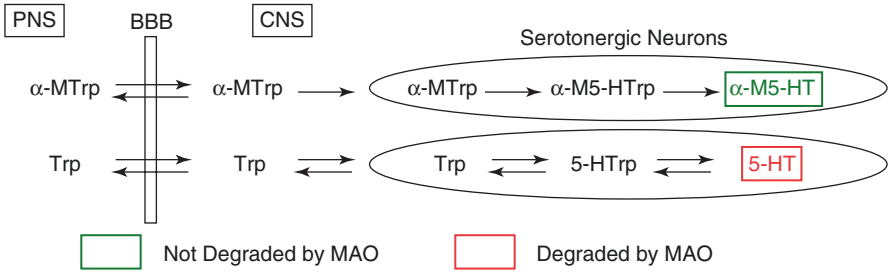

Fig. 13.1 A schematic of the similar metabolic pathways of the serotonin (5-HT) precursor tryptophan (Trp) and the analogous radioisotope α-[^{11}C]methyl-L-tryptophan (α-[^{11}C]MTrp). *PNS* Peripheral nervous system, *CNS* Central nervous system, *BBB* Blood–brain barrier, *α-M5-HTrp* α-methyl-5-hydroxytryptophan, *α-M5-HT* α-methylserotonin, *5-HTrp* 5-hydroxytryptophan, *5-HT* Serotonin, *MAO* Monoamine oxidase

Table 13.1 The demographics of both OCD patients and healthy controls in a study by Berney et al. (2011)

Characteristics	OCD patients (n = 21)	Controls (n = 21)
Age in years		
Mean (SD)	34.0 (8.6)	34.0 (9.6)
Range	18–53	20–56
Gender	15M/6F	15M/6F
Early-onset OCD	11	N/A
Predominant compulsion		
Washing	10	N/A
Checking	11	N/A
History of MDE	6	0
History of substance abuse	1	0
Past SSRI treatment	2	0
Mean Y-BOCS score (SD)	23.6 (5.3)	N/A
Mean BDI score (SD)	13.2 (9.3)	1.4 (2.2)
Mean plasma free Trp	8.4 (3.7)	8.9 (3.8)
Concentration, nmol/L (SD)		

OCD Obsessive-compulsive disorder, *M* Males, *F* Females, *N/A* Not applicable, *MDE* Major depressive episode, *SSRI* Selective serotonin reuptake inhibitor, *Y-BOCS* Yale-Brown Obsessive Compulsive Scale, *BDI* Beck Depression Inventory, *Trp* Tryptophan. Adapted from Berney et al. (2011)

13.4.1 Baseline Measurements of Serotonin Synthesis in OCD

Using the α-[^{11}C]MTrp tracer, Berney et al. (2011) compared regional K^* values in unmedicated OCD patients (n = 21) with those of age- and gender-matched healthy controls (n = 21) (Table 13.1). All patients were without current comorbid disorders and reported never having used the alleged SERT-inhibiting neurotoxic substances 3,4-methylenedioxymethamphetamine (MDMA) or 3,4-methylenedioxyamphetamine (MDA). Patients with a past history of depression secondary to OCD were included, but no significant correlations were found between K^* values and Beck Depression Inventory (BDI) scores, suggesting that this was not a confounding variable. Regions of interest focused on sites within CSTC circuitry, including cortical areas, such as the orbitofrontal cortex and anterior cingulate, and subcortical areas such as the caudate.

Overall, OCD patients showed significantly higher K^* values in the right hippocampus and left inferior temporal gyrus and did not show significantly lower K^* values in any of the regions of interest. When the analyses were restricted to males (n = 15 in each group), OCD patients showed significantly higher K^* values in bilateral caudate nucleus than controls. Symptom severity correlated positively with the estimates of 5-HT synthesis in both the temporal cortex and right caudate.

These findings suggest that some OCD patients, relative to healthy controls, have elevated rates of 5-HT synthesis in brain regions such as the hippocampus, temporal cortex, and caudate. Although this study alone could not establish whether elevated 5-HT synthesis in limbic and striatal regions reflects a primary or secondary

compensatory event, these findings raise the possibility of a failed attempt by the inhibitory system to regain control.

Some support for this interpretation of the α-[^{11}C]MTrp data has been provided by a recent resting-state fMRI study. The investigators measured functional connectivity of the 5-HT cell body region, the raphe nucleus, in a large sample of OCD patients (n = 102), compared to matched healthy controls (n = 101) (Kim et al. 2019b). In line with our α-[^{11}C]MTrp results (Berney et al. 2011), patients with OCD had greater functional connectivity between the raphe nuclei and temporal cortices, including the inferior/middle temporal gyri, hippocampus, and caudate, compared to controls. Greater functional connectivity between the raphe nuclei and left temporal gyrus correlated with higher OCD symptom severity (Kim et al. 2019b).

The evidence of altered α-[^{11}C]MTrp trapping in the temporal cortex is also of interest given the brain structure's roles in memory formation and preservation (Bayley et al. 2005). It has been speculated that OCD patients with predominantly checking compulsions have altered meta-memory (van den Hout and Kindt 2003). Among individuals performing an experiment with disinformation distractors, there is evidence that those with reduced memory confidence exhibit more checking behaviors (Alcolado and Radomsky 2011; Cuttler et al. 2013; Radomsky and Alcolado 2010). OCD "checkers" might also have dysfunctional memory self-monitoring; that is, they have decreased confidence in their memory capability reflecting higher standards instead of poor memory, per se (Macdonald et al. 1997).

13.4.2 The Effects of Treatment on Serotonin Synthesis in OCD

As a follow-up to Berney et al. (2011), we investigated potential changes in brain regional 5-HT synthesis rates following CBT and drug therapy for OCD (Lissemore et al. 2018). Patients were randomly assigned to 12 weeks of either bi-weekly CBT sessions (n = 8) or daily doses of sertraline (n = 8). See Table 13.2 for a summary of patient demographic and clinical characteristics. CBT included cognitive therapy for symptom-related difficulties such as dysfunctional beliefs and intolerance of distress, exposure and response prevention, and behavioral experiments, with therapist assistance in naturalistic environments (e.g., home, work) as needed. Sertraline doses were gradually increased to a maximum of 200 mg, and the mean ± SD daily dose received was 133 ± 52 mg/day. Both brain-wide and volume of interest analyses were performed. Significant improvement in symptom severity was observed in both treatment modalities (see Fig. 13.2), with six patients in the sertraline group and four in the CBT group showing either substantial or partial responses to treatment (a minimum 25% decrease in Y-BOCS scores) (Mataix-Cols et al. 2016; Pallanti and Quercioli 2006).

Among patients who responded to CBT or sertraline, treatment led to increased α-[^{11}C]MTrp trapping globally, including within CSTC circuitry and in regions previously found to have high α-[^{11}C]MTrp trapping prior to treatment compared to controls (Berney et al. 2011). The marked increases in α-[^{11}C]MTrp trapping were absent in non-responders, suggesting that dysfunction in the non-responders may

Table 13.2 The demographic and clinical characteristics of obsessive-compulsive disorder (OCD) patients treated with either selective serotonin reuptake inhibitor (SSRI) or cognitive behavior therapy (CBT)

Characteristics	SSRI Group (n = 8)		CBT Group (n = 8)	
Age in years				
Mean (SD)	33.4 (8.5)		33.7 (9.5)	
Range	18–45		23–53	
Gender	6M/2F		6M/2F	
Early-onset OCD	5		5	
Predominant compulsion				
Washing	4		4	
Checking	4		4	
History of mood disorder	3		2	
History of substance abuse	0		0	
Past SSRI treatment	1		0	
	Pre-Tx	***Post-Tx***	***Pre-Tx***	***Post-Tx***
Mean Y-BOCS score (SD)	23.6 (5.6)	14.7 (8.2)	23.0 (4.4)	15.8 (7.5)
Mean BDI score (SD)	14.1 (11.2)	7.6 (9.5)	9.8 (4.5)	6.9 (6.0)
Mean plasma free Trp concentration, nmol/L (SD)	9.8 (1.7)	9.3 (2.1)	10.3 (2.6)[a]	8.4 (1.4)[a]

M Males, *F* Females, *Pre-/Post-Tx* Pre-/post-treatment, *Y-BOCS* Yale-Brown Obsessive Compulsive Scale, *BDI* Beck Depression Inventory, *Trp* Tryptophan
Adapted from Lissemore et al. (2018)
[a]Data missing for one participant

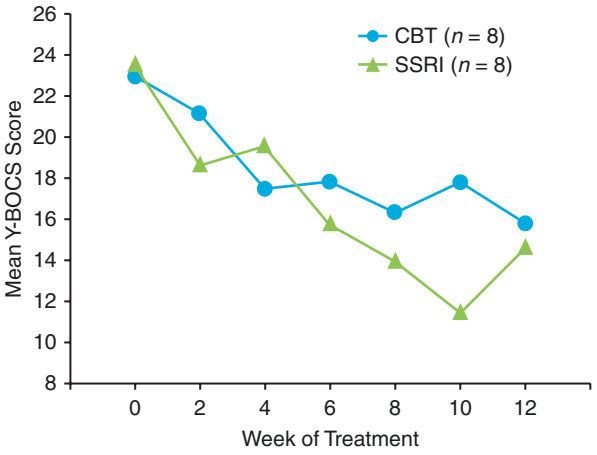

Fig. 13.2 Significant decreases in symptom severity were observed in OCD patients treated with 12 weeks of either cognitive behavior therapy (CBT) or the selective serotonin reuptake inhibitor (SSRI), sertraline. From Lissemore et al. (2018)

well be differentially mediated (Fig. 13.3). The increases in regional 5-HT synthesis tended to be restricted to the right side of the brain; whether such asymmetry is meaningful or relevant is not known, as this effect could reflect on sample size, and may "disappear" with a larger sample studied for a longer period of time. Considering the relationship between reduced SERT expression and increased serotonergic neurotransmission (Mathews et al. 2004; Zhao et al. 2009), these α-[^{11}C]MTrp PET

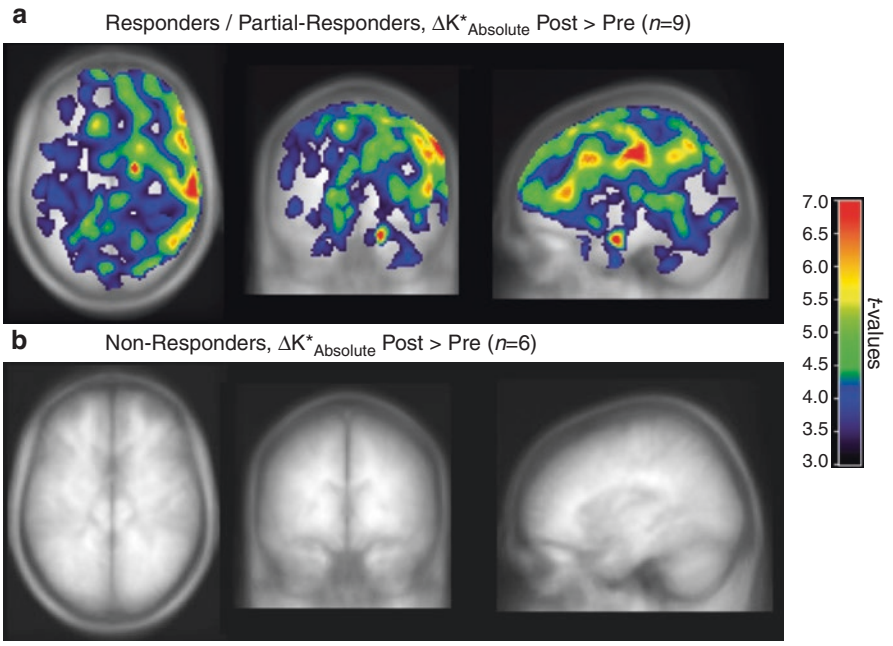

Fig. 13.3 Maximum intensity projections of the *t*-values (SPM12: $p < 0.005$ and $k = 50$ voxels) for the differences in absolute K^* values between the pre- and post-treatment conditions. (**a**) Pre-post treatment increases of K^* values in responders and partial-responders to either SSRI treatment or CBT (>25% decrease in Y-BOCS scores). (**b**) Absence of any significant pre-post treatment increases in K^* values in those patients who did not respond to either treatment (<25% decrease in Y-BOCS scores). From Lissemore et al. (2018)

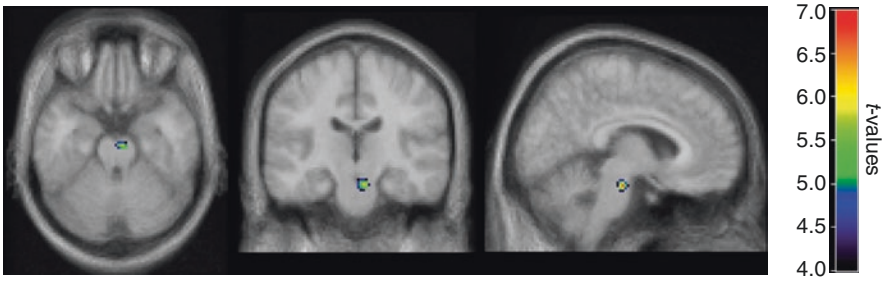

Fig. 13.4 Statistical parametric maps (SPM12) demonstrating a positive correlation between pre-treatment K^* values in the raphe nuclei and symptom improvement after CBT or SSRI treatment. From Lissemore et al. (2018)

findings of (i) elevated 5-HT synthesis capacity at baseline and (ii) further increases with treatment are in line with previous PET and SPECT findings of reduced SERT in OCD patients at baseline and further reductions with treatment (Kim et al. 2016; Zitterl et al. 2008).

Pre-treatment tracer trapping (K^*) values in the rostral raphe nuclei also correlated positively with OCD symptom improvement, independently of treatment modality. The higher the 5-HT synthesis in these nuclei before treatment, the more patients benefitted from either CBT or sertraline treatment (see Fig. 13.4). The ability of pre-treatment 5-HT synthesis capacity to predict response to treatment is consistent with the proposed braking system hypothesis. Overall, the findings suggest that increased central serotonergic neurotransmission contributes to further coping, increasing the ability to apply a brake against obsessions and compulsions.

13.4.3 Comparisons of α-[^{11}C]MTrp Findings Across Psychiatric Populations

Of particular interest within the framework of dimensional traits is to compare α-[^{11}C]MTrp data from patients with OCD to those from patients who have difficulty regulating impulsive behaviors, such as borderline personality disorder (BPD) (Leyton et al. 2001) or a history of multiple suicide attempts (Leyton et al. 2006). Indeed, it has been proposed that OCD and impulse-control disorders can be conceptualized as being on an impulsive-compulsive spectrum (Berlin and Hollander 2014; Fineberg et al. 2010; Potenza et al. 2009).

First, in all three studies of treatment-free patients, the case-control comparison (OCD-controls; suicide attempters-controls; BPD-controls) yielded no significant group differences in global α-[^{11}C]MTrp trapping (K^*), with the effect sizes all small to moderate (Cohen's $d = 0.43$, 0.50 and 0.48, respectively).

Second, whereas regional K^* values were consistently *higher* in patients with OCD compared to healthy volunteers, those with impulse-control disorders generally had *lower* regional K^* values. The specific brain regions where K^* values most robustly differed from the controls overlapped only in part (OCD vs. controls, right hippocampus, inferior temporal gyrus, and striatum; suicide attempters vs. controls, orbitofrontal and medial prefrontal gyrus; and BPD vs. controls, widespread cortical differences including medial frontal gyrus, anterior cingulate gyrus, temporal gyrus). The effect sizes for each of the three case-control comparisons were again similar. For example, the average Cohen's d effect size in regional K^* value was 1.03 for the OCD patients-controls comparison and 1.15 for the suicide attempters-controls comparison. Both effect sizes can be interpreted as large.

Third, all three studies reported very strong associations between regional K^* values and symptom severity. In the participants with BPD, K^* values were negatively correlated with behavioral impulsivity, in both men and women, in the medial prefrontal cortex, anterior cingulate, and striatum. Effect sizes for the associations between regional K^* values and impulsivity in BPD patients are estimated to be large based on the reported standardized scores ($Z \geq 3.0$, $p < 0.01$). In OCD patients, the average correlation between K^* values in the temporal gyrus and total Y-BOCS scores was |0.70|. In the study of suicide attempters, the average correlation between K^* values in the orbitofrontal/medial prefrontal gyrus and degree of lethal intentionality was |0.84|. These latter two correlations correspond to a Cohen's d of 1.96 and 3.09, respectively. While both effect sizes can be interpreted as very large, the effect

sizes are moderately higher for suicide attempters than for OCD patients (Cohen's $q = 0.35$, interpreted as an intermediate effect size difference).

Overall, these findings suggest that 5-HT synthesis rates are more closely related to symptom severity than diagnostic categories. Such observations support the need for a more nuanced investigation of clinical dimensions and eventual subtypes in the neurobiological characterization of psychiatric disorders, including OCD.

13.5 Concluding Remarks

PET and SPECT, together with genetic association studies and animal models of OCD, continue to provide evidence of a serotonergic mechanism, particularly within CSTC circuitry. In spite of numerous findings, some of which were reviewed here, one must recognize that those many contributions cannot fully elucidate the details within the multiple OCD etiologies. Several etiological pathways and mechanisms, responsible for diverse phenotypic expressions, are likely to be encountered. For example, serotonergic involvement in OCD is likely to include complex interactions with other neurotransmitters, such as dopamine, and future research into neurotransmitter interactions will be critical. Additionally, longer-term CBT is required for many patients to optimize symptom reduction, and, indeed, this was offered to patients in our α-[^{11}C]MTrp study described above. Further research could usefully examine effects following longer treatment durations (Sookman 2016).

The present research also suggests that, rather than contributing to OC symptoms directly, the serotonergic system acts to control symptoms. As such, prior to treatment, it is proposed that this system is working inefficiently and therefore unable to successfully inhibit symptoms. Clinical improvement following either behavioral or drug therapy may arise from a stimulation of serotonergic neurotransmission that gradually improves the ability to control symptoms, thus producing a therapeutic response. The source of these symptoms that elevated 5-HT function is proposed to control remains to be found. Heightened serotonergic tone in OCD contrasts with the dampened tone observed in disorders characterized by impulsivity, suggesting that the proposed "serotonergic braking system" may be engaged specifically in those with OC symptoms.

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Part IV

Psychosis and Cognitive Disorders

Dopamine and Response to Antipsychotic Medication

14

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Abstract

The precise molecular basis of schizophrenia is not completely understood. In this chapter, we will describe and examine the evidence from PET and SPECT imaging findings on the key role that dopamine, the neurotransmitter most strongly associated with schizophrenia, plays in its pathophysiology. We will review the evidence for presynaptic dopamine pathway dysfunction, which is most apparent in the associative striatum and involves abnormal elevations of dopamine synthetic capacity, dopamine release and synaptic dopamine levels. This dysfunction is well correlated with the increased likelihood, onset and worsening severity of schizophrenia. Furthermore, this association appears to be crucial in relation to the therapeutic response to dopamine antagonists.

Here, in addition we review the evidence for the mechanism of action of current antipsychotics, by examining the roles that pre- and postsynaptic dopamine modulation play in their clinical efficacy. Furthermore treatment resistance, current understanding about its neurological underpinnings and treatment strategies will be outlined. Finally, we explore the dopamine and non-dopaminergic mechanisms of potential novel therapies.

14.1 Introduction

Despite the significant advances in schizophrenia research, the principal biological changes that underpin the aetiology, symptomology and clinical course of the disorder are incompletely understood. The dopamine hypothesis of schizophrenia (Carlsson and Lindqvist 1963; Davis et al. 1991; Howes and Kapur 2009) has been instrumental in providing a theoretical framework and platform for further scientific research into understanding of how antipsychotic medications work and, consequentially, of the mechanisms that underlie the disease process itself. However, despite this important work, up to one-third of patients do not respond to first-line dopamine antagonists (Lindenmayer 2000; Hasan et al. 2012), of which most do not respond to the only licensed second-line agent, clozapine (Kane et al. 1988; Chakos et al. 2001; Lieberman et al. 1994). The gap in our understanding of the neurochemical changes that underpin schizophrenia's pathophysiology forms a large barrier to the development of novel, more effective and more tolerable treatment, which is even more true for treatment-resistant illness. Notwithstanding this, recent work has begun to disentangle the mechanisms that underpin treatment response and resistance. In this chapter we outline the neurochemical evidence, from positron emission tomography (PET) and single-photon emission [computed] tomography (SPE[C]T) neuroimaging, for dopamine dysfunction in schizophrenia, particularly in relation to treatment response. In addition, we focus on potential novel pharmacological treatments for schizophrenia. While this chapter is focused on dopamine and treatment response, a comprehensive understanding of this subject requires the incorporation of research from several closely related areas, which are not directly linked to PET and SPECT neuroimaging and are, therefore, beyond the scope of this manuscript.

14.2 The Role of Dopamine in the Pathogenesis of Schizophrenia

Despite its several revisions (Howes and Kapur 2009; Toda and Abi-Dargham 2007), the dopamine hypothesis of schizophrenia is one of the longest surviving concepts in psychiatry. It posits that presynaptic dopaminergic dysfunction is the key final common pathway that underlies the development of psychosis (Howes and Kapur 2009). As a theory, it began fortuitously after the development of chlorpromazine (Charpentier et al. 1952) and observation of its efficacy when treating people with schizophrenia (Delay et al. 1952), in the 1950s. The findings that antipsychotic medication increases the metabolism of dopamine (Carlsson and Lindqvist 1963; Carlsson et al. 1957) and that its clinical potency is associated with its affinity for the dopamine receptor (Seeman and Lee 1975; Seeman et al. 1976; Creese et al. 1976), suggested that the pathophysiology of schizophrenia itself, a neurobiological disorder, could be explained by hyperdopaminergia in the brain. Through progress in the use of in vivo neuroimaging techniques, specifically positron emission tomography (PET) and single-photon emission [computed] tomography (SPE[C]T), regional differences in dopaminergic dysfunction were directly determined; predominantly frontal hypodopaminergia and subcortical hyperdopaminergia, which, respectively, have been linked to the negative and positive symptoms of the disorder (Davis et al. 1991). Recent advances from preclinical and human neuroimaging, genetic, and molecular biological studies of antipsychotic treatment response, demonstrated that the neurobiology of treatment response is far more complicated, involving several other neurotransmitter pathways including those of glutamate, GABA, acetylcholine and serotonin (Girgis et al. 2019; McCutcheon et al. 2019). In the following sections, in some detail, we present evidence predominantly from the molecular imaging studies.

14.2.1 Evidence from Early in Vitro Research

In the 1950s and 1960s, in vitro research provided first evidence for the dopamine involvement in pathophysiology of schizophrenia. Carlsson and colleagues demonstrated that in mice, the selective administration of 3,4-dihydroxyphenylalanine, precursor to dopamine, counteracted the phenotypic effects of reserpine, while 5-hydroxytryptophan, precursor to serotonin, did not (Carlsson et al. 1957), suggesting that reserpine and dopamine share an antagonistic relationship. In their seminal work, they further showed that the administration of chlorpromazine and haloperidol stimulated the turnover of DA in the brains of mice, which gave rise to dopamine hypothesis of schizophrenia (Carlsson and Lindqvist 1963). The hypothesis received indirect support from observations that (a) the clinical potency of antipsychotics is associated with their affinity for the postsynaptic dopamine receptors (Seeman and Lee 1975; Seeman et al. 1976), the mechanism of which is mediated via dopamine receptor blockade (Van Rossum 1966; Horn et al. 1975); (b) psychoactive stimulants, such as amphetamines, can both cause psychotic symptoms in

healthy individuals and worsen the symptoms in schizophrenic patients (Connell 1957; Berman et al. 2009; Curran et al. 2004); and (c) while there wasn't an increase in dopamine neuronal densities (Bogerts et al. 1983), dopamine neurotransmitter concentrations and dopamine D2 receptor densities were increased, albeit modestly, in post-mortem samples of people with schizophrenia (Bird et al. 1979; Cross et al. 1981).

However, subsequent research, that addressed the failure of hyperdopaminergia to account for the neurobiology of negative and cognitive symptoms, indicated that these symptoms are related to a deficit in cortical DA transmission. Thus, the hypothesis was revised to incorporate both the subcortical (striatal) hyperdopaminergia and cortical (frontal) hypodopaminergia (Davis et al. 1991). Their coexistence in schizophrenic patients has been directly supported by several PET and (SPECT) studies (Abi-Dargham et al. 1998, 2002).

14.2.2 The Investigations of Dopamine Receptors in Schizophrenia

In the last three decades, PET and SPECT neuroimaging have provided direct evidence of dopamine dysregulation in schizophrenia studies, enabling direct measurement of different aspects of dopamine transmission in a human brain, in vivo.

Due to its high-density concentration of the D2 receptor, extensive dopaminergic connections to other brain regions and the central role it is believed to play in the pathophysiology of schizophrenia (Davis et al. 1991), the striatum has attracted particular attention (McCutcheon et al. 2019). It receives inputs from the majority of the cortex (Hunnicutt et al. 2016; Averbeck et al. 2014) and acts as a vital centre for integrating and processing information in the brain. Animal research has shown that it is divided into four main subdivisions, which are based on observed segregation of various corticostriatal pathways, namely, the limbic, associative, sensorimotor (Alexander and Crutcher 1990) and caudal divisions (Hunnicutt et al. 2016). While it has been acknowledged that these pathways overlap (Chung and Deisseroth 2013), the subdivisions are functionally independent. There is now robust evidence, from PET neuroimaging findings, that implicates defective dopaminergic regulation in the associative striatal subdivision, in patients with schizophrenia (Howes et al. 2009, 2013; Kegeles et al. 2010; Mizrahi et al. 2012; Egerton et al. 2013). These studies were synthesised in a recent meta-analysis which revealed an association of large effect size between dopamine dysregulation and the associative striatum (Hedges' $g = 0.73$), and a medium effect size with the sensorimotor striatum (Hedges' $g = 0.54$) (McCutcheon et al. 2017).

While dopamine has been identified as a neurotransmitter of interest, it was not clear exactly which process, along its pathway of synaptic transmission, was functioning abnormally. Attention was initially focused on the striatal D2 receptor, since post-mortem research had indicated that it was expressed in higher densities in the brains of patients with schizophrenia compared to control groups without schizophrenia (Bird et al. 1979; Cross et al. 1981). However, these post-mortem findings

struggled to account for changes due to chronic antipsychotic administration, which had been shown to upregulate the expression of dopamine receptors (Owen et al. 1979).

The use of high-resolution PET and SPECT neuroimaging has provided much clarity. Farde and colleagues (Farde et al. 1990) examined D2 receptor binding using PET and [^{11}C]-raclopride in 18 drug-naïve patients with schizophrenia and 20 healthy controls. They demonstrated that, in contrast with the aforementioned post-mortem research, there was no difference in receptor density or affinity between the two groups. The synthesis of over two decades of PET and SPECT research has led to a gradual downplaying of the role that D2 receptor density changes play in schizophrenia (Laruelle 1998; Zakzanis and Hansen 1998; Weinberger and Laruelle 2001), with the most recent meta-analyses, of over 50 studies, finding no evidence for an elevation in drug-naive patients (Howes et al. 2012; Brugger et al. 2019), and a small effect size for previously treated patients (Cohen's $d = 0.28$) (Howes et al. 2012). Likewise, no evidence, for elevated striatal dopamine D1 receptor densities, has been found (Howes et al. 2012).

Although dopamine D1/D2 receptor densities may not be altered in schizophrenia, animal studies suggest that there may be a change in dopamine D2 receptor function. D2 receptor high-affinity states are functional while low-affinity states are not. Preclinical studies suggest that in schizophrenia there may be a preponderance of high-affinity compared to low-affinity D2 receptor states (Seeman 2011). Unfortunately, the research investigating this in humans is limited. While preliminary in vivo work using radiotracer [^{11}C]-(+)-PHNO found no supporting evidence for an association between dopamine receptor affinity state and schizophrenia *(*Graff-Guerrero et al. 2009a*)*, research suggests that [^{11}C]-(+)-PHNO may not be high-affinity state selective (Seeman 2012). Future research in humans, using a radiotracer that is able to differentiate between dopamine receptor high−/low-affinity states, is therefore warranted.

The implications of these dopamine receptor density findings provide two important lines of inquiry. (A) May the locus of dopaminergic dysfunction lie in its presynaptic control? (B) If dopamine D2 receptors densities are not altered, what underlies the clinical efficacy of current licensed antipsychotic medication, which blocks the same receptors? The former question will be addressed now, while the latter will be explored in a following section of this chapter, **'**PET and SPECT findings in Treatment-Responsive Schizophrenia'.

14.2.3 Presynaptic Dopamine Regulation and Positive Symptoms

The dopamine transporter (DAT) reduces synaptic dopamine levels by transporting it back into the presynaptic terminal, see Fig. 14.1. Aberrations to this process could result in overzealous, or insufficient, dopamine reuptake, resulting in reduced or elevated synaptic dopamine levels, respectively. Howes and colleagues (Howes et al. 2012) meta-analysed 11 studies investigating a possible association between DAT dysfunction and schizophrenia, totalling 152 patients and 132 healthy

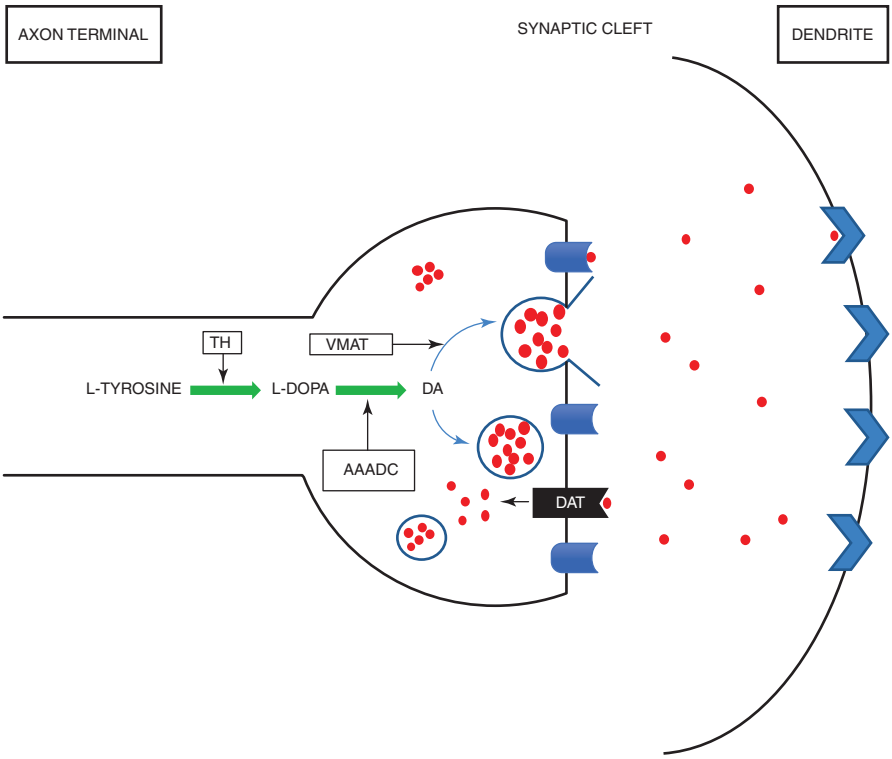

Fig. 14.1 Schematic presentation of presynaptic dopamine regulation (Leung et al. 2019). Conversion of largely dietary 4-hydroxyphenylalanin (L-tyrosine) to L-3,4 dihydroxyphenylalanine (L-DOPA) is the first step in a complex pathway of dopamine (DA) synthesis. L-tyrosine is converted to L-DOPA by tyrosine hydroxylase (TH). Aromatic L-amino acid decarboxylase (AAADC) then acts on L-DOPA to convert it to dopamine (DA). Along with the presynaptic autoreceptors, the DA uptake transporter (DAT) plays an important role in maintaining extracellular homeostasis by increasing cytoplasmic DA levels via the reuptake of extracellular DA. From the cytoplasm the majority of DA is stored in specialised synaptic vesicles by the vesicular monoamine transporter (VMAT) and is ready for release upon arrival of the action potential

controls, and found no evidence for such a relationship ($d = -0.34$, 95% CI −0.75 to 0.07, $z = -1.64$, $p = 0.10$). Their finding has been replicated in further meta-analyses (Brugger et al. 2019; Fusar-Poli and Meyer-Lindenberg 2013a; Chen et al. 2011), suggesting that DAT dysfunction plays no role in the pathophysiology of schizophrenia. Dopamine synthesis capacity (DSC) is measured using radiotracer [^{18}F]-DOPA which, after its decarboxylation to [^{18}F]-dopamine, is stored in the presynaptic vesicles.

This process particularly occurs in the striatum, since the vesicles are rich in AAADC, see Fig. 14.1. The accumulation of [^{18}F]-dopamine reflects the rate of decarboxylation of endogenous L-DOPA to dopamine, i.e. a measure of dopamine synthesis, and is quantified as the influx constant *Ki*, which is relevant, given the interest in the relationship between DSC and schizophrenia (Sonnenschein and

Grace 2020). The association between DSC and schizophrenia is one of the most replicated findings in schizophrenia research, with the most recent meta-analysis including 65 studies of dopamine dysregulation, a total of >900 patients and >900 controls (Brugger et al. 2019). Brugger and colleagues (Brugger et al. 2019) have robustly demonstrated that mean DSC is elevated in patients with schizophrenia compared to controls (SMD = 0.65; $p = 0.004$). Similar evidence for an increase in dopamine release capacity was also found (SMD = 0.66; $p = 0.03$). Due to a paucity of studies investigating DSC in drug-naive patients alone, they carried out a subgroup analysis of the combined group of drug-naive/treatment-responsive patients and found strong evidence for its elevation, with a large effect size (Hedges' $g = 0.75$; $p = 0.0004$), and again a similar effect size was found for dopamine release capacity (Hedges' $g = 0.66$; $p = 0.03$). Studies are conflicted regarding the effect of antipsychotic medication on DSC with some suggesting it causes an increase (McGowan et al. 2004; Vernaleken et al. 2006), while others suggest that there is no effect (Laruelle and Abi-Dargham 1999; Jauhar et al. 2019). However, McCutcheon and colleagues (McCutcheon et al. 2017), in their meta-analysis, have shown that the association between DSC and schizophrenia remains present when examined in drug-naive patients alone (Hedges' $g = 0.78$; $p < 0.001$), while a similar effect size can be observed in treatment-responsive patients separately (Hedges' $g = 0.64$; $p < 0.001$), which suggests that DSC changes occur independent of antipsychotic treatment.

Neuronal capacity to release dopamine into the synaptic cleft (DRC) can be estimated by measuring the binding of radiotracers such as [^{11}C]-raclopride or [^{123}I]-IBZM, which compete with endogenous dopamine to bind at dopamine receptors. Therefore, an increase in DRC, such as after a pharmacological challenge, leads to a fall in radiotracer receptor binding (Egerton et al. 2010). In combination with above radiotracers, alpha-methyl-p-tyrosine (AMPT), a tyrosine hydroxylase inhibitor, can be used to index synaptic dopamine levels, as administration of the inhibitor leads to a reduction in the levels of synaptic dopamine, which can be observed, using molecular neuroimaging, as an increase in radiotracer receptor binding. As with DSC, there is strong evidence for an increase in both DRC (McCutcheon et al. 2017; Howes et al. 2012; Brugger et al. 2019) and dopamine synaptic levels (Kegeles et al. 2010) in schizophrenia. In the most recent meta-analysis, examining six and three studies, respectively, both DRC (Hedges' $g = 0.66$; $p = 0.03$) and dopamine synaptic levels (Hedges' $g = 0.78$; $p = 0.0006$) were elevated with large effect sizes (Brugger et al. 2019).

Interestingly Brugger and colleagues (Brugger et al. 2019) have, to our knowledge, conducted the first meta-analysis to demonstrate strong evidence for inter-individual variability of striatal dopamine D2/3 receptor (VR = 1.26; $p < 0.0001$) and DAT (VR = 1.31; $p = 0.01$) in patients with schizophrenia compared to healthy controls. This variability was not found for DSC or dopamine release capacity, suggesting that these latter factors may be common to all with treatment responsive schizophrenia and may be necessary in the pathophysiology of schizophrenia. The heterogeneity of dopamine D2/3 receptor and DAT concentrations may represent the presence of different dopaminergic subgroups within schizophrenia, which may

correlate with different underlying neurobiologies, clinical subtypes or treatment-response profiles (Amato et al. 2018) and may offer a clue for novel ways to individualise dopamine-modifying treatments in the future. This is a potentially exciting development that requires further study.

Through more nuanced analysis, striatal presynaptic dopamine dysfunction has been studied via a dimensional approach. In schizophrenia, factor analysis of symptoms has identified five dimensions: positive, negative, cognitive, disorganised and affective (Dutta et al. 2007). Research has demonstrated that presynaptic striatal dopaminergic hyperactivity is positively associated with the presence, and increased severity, of positive symptoms in schizophrenia, while on the other hand, there seems to be no relationship with negative or cognitive symptoms (Jauhar et al. 2017a, 2018a). Analogously, while an association has been found in other non-schizophrenic disorders, where positive symptoms are predominant, such as bipolar affective disorder with psychosis (Fig. 14.2), temporal lobe epilepsy with psychosis and schizotypy (Jauhar et al. 2017a; Yung et al. 2003; Reith et al. 1994; Abi-Dargham et al. 2004), as well as in amphetamine challenge/dopamine depletion paradigms (Laruelle et al. 1999; Abi-Dargham et al. 2000), no relationship has been identified in non-psychotic disorders (Reith et al. 1994; Yatham et al. 2002; Martinot et al. 2001; Turjanski et al. 1994; Ernst et al. 1997) nor in measures of affective illness in those with schizophrenia (Howes et al. 2009; Laruelle et al. 1999). Furthermore, a positive association has also been demonstrated between striatal dopamine hyperactivity and those at ultra-high risk of developing psychosis (UHR) (Howes et al. 2009; Egerton et al. 2013), with a higher *Ki* correlating well with positive symptom severity and eventual development of the disorder (Howes et al.

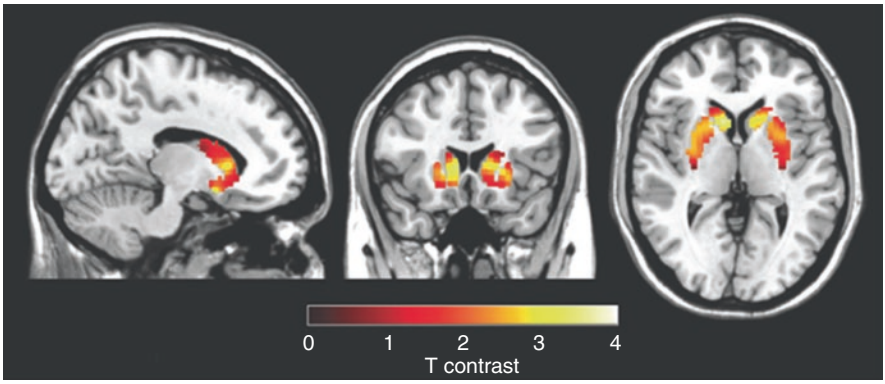

Fig. 14.2 *Voxelwise comparison of striatal dopamine synthesis capacity in the bipolar psychosis group relative to the control group (*Jauhar et al. 2017a*).* Increased striatal dopamine synthesis capacity was evident in the bipolar psychosis group ($n = 22$) relative to the control group ($n = 22$). The colour bar shows the t statistic. The most significant increase was in the right caudate (peak at Montreal Neurologic Institute coordinates $x = 8$, $y = 10$, $z = -8$; t statistic = 3.96, familywise-error corrected $P = 0.03$). The image was thresholded at $p < 0.001$ (uncorrected) using a striatal mask (for illustration purposes only). The t statistics for the striatal region are overlaid on a standard structural template in sagittal (left), coronal (middle), and axial (right) views

2011). It has also been shown to reduce in patients whose positive symptoms are in remission (Avram et al. 2019), which, when taken with the UHR findings together, suggests that it may play a causal role in triggering the onset of a psychotic disorder/acute psychosis. However, studies in family members of patients with schizophrenia have been contradictory (Huttunen et al. 2008; Shotbolt et al. 2011), indicating that more research is needed to help understand this variability. Putting these findings together, striatal dopamine hyperactivity is most closely related to the positive symptoms dimension, it occurs across psychotic disorders and not just in schizophrenia, and it may be a putative marker for psychosis onset and severity. Even in spite of the latter assertion, we have robust evidence presynaptic terminals of the dorsal striatum and are the key sites of dopaminergic abnormality in psychosis, which in reality may represent its role in the pathogenesis of schizophrenia (Howes and Kapur 2009). Taken together, there is quite robust evidence that, increased presynaptic dopaminergic activity in the dorsal striatum is involved in the neurobiology of schizophrenia and that this is independent of the effects of antipsychotic medication on dopamine metabolism.

14.2.4 Presynaptic Dopamine Regulation and Cognitive Impairment/Negative Symptoms

Alongside striatal dysfunction, frontal hypodopaminergia is thought to be responsible for the cognitive and negative symptoms that are experienced in schizophrenia (Davis et al. 1991). Several mechanisms have been proposed to explain these links (Goldman-Rakic 1994; Tamminga 2006), and while there is evidence linking striatal presynaptic dopamine dysfunction with cognitive impairment (Howes et al. 2009; McGowan et al. 2004; Meyer-Lindenberg et al. 2002), imaging evidence associating prefrontal dopamine dysfunction has been limited thus far.

The first parameter of frontal dopamine transmission to be directly measured using *molecular imaging* studies was D1 receptor availability. The studies investigating this in schizophrenia appear to be somewhat conflicting (Takano 2018), with studies showing decreased (Okubo et al. 1997), equivalent (Karlsson et al. 2002), and increased levels (Abi-Dargham et al. 2002, 2012) compared to controls. This discrepancy may be explained by the different radiotracer specificities that were used to bind to the D1 receptor ([^{11}C]-SCH23390 vs [^{11}C]-NNC112), their cross-connectivity with the serotonin receptor (Ekelund et al. 2007) and potential differences in the population groups that were studied. Abi-Dargham and colleagues (Abi-Dargham et al. 2012) examined the relationship by comparing drug-naïve (n = 12) and drug-free (n = 13) patients with schizophrenia to healthy subjects (n = 40). They observed that D1 upregulation occurred in the drug-naïve patients (linear mixed model, $F(1,34) = 7.3$, $p = 0.01$) with no difference between drug-free and healthy subject groups. Interestingly, findings by studies using [^{11}C]-SCH23390 PET imaging (Takahashi et al. 2008; Takahashi 2013), found that the relationship between cognitive impairment and dopamine D1 receptor binding was described by a U-shaped curve, with reduced performance in the Wisconsin Card Sorting test

observed at the extremes of receptor density concentration. They also observed a task-dependent variability in dopamine D1 and D2 receptor prefrontal activity, along with evidence of hippocampal involvement. This suggests that the relationship between dopamine D1 receptor activation and cognition is likely to involve several pathways, be task specific and may require a dynamic dopaminergic input, where *too much* or *too little* prefrontal D1 receptor stimulation hampers cognitive performance. This assertion is consistent with preclinical models (Okubo et al. 1997; Seamans and Yang 2004; Eshel and Tian 2014).

Another aspect of extrastriatal synaptic dopamine transmission that has gathered interest, in schizophrenia research, is dopamine release. A multimodal PET/fMRI study (Slifstein et al. 2015), was the first in humans to examine cognition in the context of prefrontal dopamine release. The authors studied the relationship between prefrontal amphetamine-induced dopamine release, measured using dopamine-binding potentials, working memory and regional blood-oxygen-level-dependent (BOLD) activation by comparing 20 patients with schizophrenia and 21 matched healthy controls. They observed that there were no differences in baseline dopamine-binding potential measures between patients and controls. However, the authors found that after amphetamine administration, controls had more pronounced changes in dopamine-binding potential measures (mean[SD] = −7.5%[11.4%]; $p = 0.01$), compared to patients (mean[SD] = 1.8%[11.1%]), when completing working memory tasks. This observation was most specifically observed in the dorsolateral prefrontal cortex (DLPFC) (mean[SD]: patients = 1%[7%]; controls = −5%[7%]; $p = 0.01$). They also observed that the change in dopamine-binding potential was associated with blood-oxygen-level-dependent (BOLD) activation ($\beta = 52.9$; $t31 = 2.211$; $p = 0.03$). These findings suggest that an individual's working memory capabilities, may, at least in part, be correlated with the association to cerebral perfusion, in the DLPFC, and DRC.

Interestingly, dopamine release in the patient group did not predict working memory performance (Slifstein et al. 2015). To explain this, the authors suggest that, as with cerebral perfusion, working memory might also be governed by dynamic, as opposed to static, changes in DRC (Eshel and Tian 2014), which are not observable using the study's methodology. Combining these findings, there is some evidence that cognitive impairment in schizophrenia may be correlated with dysfunctional dopamine activity in the prefrontal cortex. This seems to occur at the extremities of dopamine D1 receptor activity (Okubo et al. 1997; Takahashi et al. 2008; Takahashi 2013; Seamans and Yang 2004; Eshel and Tian 2014) and may be associated with blunted fluctuations in dopamine release responses (Slifstein et al. 2015). This relationship seems to be complex, and while there is evidence that implicates the striatum in cognitive impairment (Howes et al. 2009; McGowan et al. 2004; Meyer-Lindenberg et al. 2002), the direction of causality remains unclear (Howes et al. 2011; Fusar-Poli et al. 2010). As current antipsychotic medications are not effective at treating cognitive impairment and negative symptoms (Nasrallah et al. 2011), and their burden contributes to a large proportion of disability in schizophrenia (Ho et al. 1998), this is an under-researched area of highly significant clinical need.

In summary, the advent of PET/SPECT imaging has vastly advanced our ability to manipulate and observe in vivo neurochemical changes in the brain. The evidence presented so far in this chapter, supports the major tenets of the third iteration of the dopamine hypothesis (Howes and Kapur 2009) that the focus of striatal dopamine dysfunction has been moved from the dopamine D2 receptor to its presynaptic regulation, especially increased DSC, DRC and synaptic dopamine levels; this dysfunction likely occurs specifically at the associative striatum; and that rather than just schizophrenia, this dysregulation may be related, to psychosis as a dimensional entity, and may therefore be applicable to other psychotic disorders (Jauhar et al. 2017a; Reith et al. 1994; Abi-Dargham et al. 2004). This helps to explain the role of antipsychotic medication in treating a wide range of psychotic disorders, not just schizophrenia. The role that high striatal dopamine D2 receptor affinity states and receptor/DAT heterogeneity contribute to the disorder is yet to be delineated, as is imaging evidence, to explain the mechanism behind cognitive and negative symptoms.

14.3 Challenges to the Dopamine Hypothesis of Schizophrenia

While the hypothesis has several strengths; it has drawn criticism for suggesting that dopaminergic dysregulation is on the causal pathway leading to schizophrenia. It has been argued that the observed association between schizophrenia, and presynaptic dopamine dysfunction may be confounded by drug use or environmental stress (Moncrieff 2009; Hengartner and Moncrieff 2018), which have both been shown to lead to schizophrenia (Murray et al. 2008; Pruessner et al. 2004) and may do so via mechanisms other than through the dopamine system (Sulzer et al. 2005; McEwen et al. 2015).

However, ascertaining causality is difficult (Hill 1965), especially in observational studies, which govern the majority of neuroimaging findings in this field. However, as detailed in a previous section, the evidence for presynaptic dopamine abnormalities is robust (Howes and Kapur 2009), reproducible (McCutcheon et al. 2017; Brugger et al. 2019; Meyer-Lindenberg 2013b), commands a large effect size (McCutcheon et al. 2017; Brugger et al. 2019; Meyer-Lindenberg 2013b), observes a biological gradient (Howes et al. 2009; Jauhar et al. 2017a, 2018a), is specific (Yung et al. 2003; Turjanski et al. 1994; Ernst et al. 1997), seems to display a temporal relationship (Howes et al. 2011; Avram et al. 2019), is present in prodromal states (Howes et al. 2009; Egerton et al. 2013) and shows analogous consistency with animal models (Sonnenschein and Grace 2020). Furthermore much of the above research has sought to limit the effect of environmental stressors or substances as confounders, e.g. by studying cross-diagnostic comparisons of individuals who are likely to have more background similarities with individuals with schizophrenia, such as those with equally distressing, non-psychotic disorders [e.g. (Reith et al. 1994; Yatham et al. 2002). We argue that while various studies have implicated other neurotransmitters in the development of, and possible targets for

treating, schizophrenia, like glutamate, acetylcholine and serotonin (Girgis et al. 2019; McCutcheon et al. 2019; Sonnenschein and Grace 2020), the role of dopamine seems to remain key (Kaar et al. 2019) and is the most widely replicated (McCutcheon et al. 2017; Brugger et al. 2019; Meyer-Lindenberg 2013b). Notwithstanding this, further studies would provide better knowledge about the interplay between the different neurochemical and neuroinflammation pathways that lead to schizophrenia, which would enrich the current model.

Following on from this, the hypothesis does not account for the fact that about a third of patient symptoms are resistant to dopamine blockade (Lindenmayer 2000; Hasan et al. 2012), the primary mechanism of action of current antipsychotic medication nor does it explain the superior efficacy of clozapine for these patients (Kane et al. 1988; Kahn et al. 2018). The following section will explore responses to antipsychotic medication and provide an insight into potential new therapeutic targets in schizophrenia.

14.4 Dopamine and Treatment Response

14.4.1 PET and SPECT Findings in Treatment-Responsive Schizophrenia

In the decade following their development, chlorpromazine and reserpine where used in parallel to treat schizophrenia, in Europe and North America, respectively (Healy 2009). Although, there is substantial evidence to support the theory that *presynaptic* striatal dopamine dysregulation plays a substantial role in the pathophysiology of schizophrenia, there is a clear pathophysiological mismatch: all licensed antipsychotic medications act *postsynaptically*. They have all been modelled as functional analogues to first chlorpromazine, and later clozapine, resulting in mechanisms of action that are primarily focused on downstream postsynaptic dopamine receptor blockade to varying degrees (Kapur et al. 2004). Here, we outline the evidence from PET and SPECT imaging studies that have investigated the mechanism mediating antipsychotic clinical efficacy and outline the emerging evidence for targeted presynaptic dopamine modulation, by existing and potential novel antipsychotic drugs.

14.4.2 Blockade of Dopamine D2 Receptors and Clinical Response

It was initially unclear which receptors mediated the clinical response to antipsychotics, since they act on several neurotransmitters in the brain, including serotonin, acetylcholine, noradrenaline and histamine (Kaar et al. 2019). The use of PET and SPECT neuroimaging has helped signify the importance of the dopamine D2 receptor. While seminal in vitro studies indicated that the clinical potency of antipsychotic drugs might be associated with their affinity at postsynaptic dopamine

receptors (Seeman and Lee 1975; Seeman et al. 1976; Creese et al. 1976); using [^{11}C]-raclopride PET imaging, Farde and colleagues were the first to show that at clinical doses, antipsychotic medications were associated with high affinities for the dopamine D2/3 receptor (Farde et al. 1989). Subsequently, several molecular imaging studies have shown that treatment response, usually determined by reductions in psychotic symptoms as rated on the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987), is directly correlated with antipsychotic affinity for the postsynaptic dopamine D2/3 receptor (Farde et al. 1992; Wolkin et al. 1989; Pilowsky et al. 1993).

These results were further supported by double-blind PET studies (Nordstrom et al. 1993; Kapur et al. 2000), the largest of which examined 22 drug-naïve patients diagnosed with first-episode psychosis (Kapur et al. 2000). In this study, they demonstrated that daily administration of haloperidol was significantly associated with treatment response when >65% postsynaptic dopamine D2/3 receptors were occupied. Furthermore, they also showed that >72% and >78% receptor occupancies significantly predicted the onset of hyperprolactinaemia and EPSEs, respectively (Kapur et al. 2000). In combination with the earlier molecular imaging findings and subsequent replication through further research (Uchida et al. 2011; Stone et al. 2009), it was established that, with the exception of clozapine and the dopamine receptor partial agonists, all antipsychotic medications must reach a therapeutic threshold of 60–80% postsynaptic dopamine D2 receptor occupancy in order to achieve clinical efficacy (Kaar et al. 2019). D2 receptor occupancy levels <60% are associated with a subtherapeutic response, and occupancy levels >80% are associated with the significant development of extrapyramidal, hyperprolactinaemic side effects, without much added therapeutic benefit. Exceptions to this rule are clozapine and partial agonists, such as aripiprazole and cariprazine, which achieve about 40% (Farde et al. 1992; Kapur et al. 1999; Nordstrom et al. 1995) and 80+% (Girgis et al. 2016a; Gründer et al. 2008; Mamo et al. 2007; Yokoi et al. 2002) D2 receptor occupancy, respectively, at clinically effective doses. These findings had significant translational impact as they demonstrated that (a) at lower doses than were previously thought, sufficient saturation of 65–70% of dopamine receptors and clinical responsiveness, can be achieved; (b) higher doses of medication worsened adverse effects without providing additional therapeutic benefit; and (c) a meaningful proportion of patients are treatment resistant and do not respond to dopamine-blocking medications, despite adequate levels of postsynaptic D2 receptor occupancy.

Second-generation antipsychotic agents (SGAs), such as olanzapine and risperidone, were developed as an attempt to mimic the action of clozapine (Seeman and Tallerico 1998), following observations that it was superior at treating refractory patients with schizophrenia (Kane et al. 1988). Although the division between SGAs and first-generation antipsychotic agents (FGAs) is and can be problematic (Kapur and Mamo 2003), it has provided a useful way of grouping these two classes of medication. With the exception of the drugs mentioned previously, at clinical doses both classes of medication demonstrate >60% occupancy of the dopamine D2 receptor (Kaar et al. 2019). While the landmark prospective Clinical Antipsychotic Trial of Intervention and Effectiveness (CATIE) and Cost Utility of the Latest

Antipsychotic Drugs in Schizophrenia Study (CUtLASS) investigations showed that, apart from clozapine, SGAs and FGAs do not differ in clinical efficacy (Lieberman et al. 2005; Jones et al. 2006), more recent work suggests that any treatment superiority with SGAs is marginal at best (Leucht et al. 2013).

SGAs were believed to differ in efficacy and side effects from FGAs due to their high-relative affinities for the serotonin-2A (5-HT_{2A}) receptor compared to the dopamine D2 receptor (Kaar et al. 2019; Kapur et al. 1995). Through PET investigation, it has since been demonstrated that some FGAs have comparable affinities for the 5-HT_{2A} receptor (Mamo et al. 2007; Natesan et al. 2006) and that neither the use of selective 5-HT_{2A} antagonists (de Paulis 2001) nor the ratio of 5-HT_{2A} to D2 receptor blockade (Kapur et al. 1999, 1998; Nyberg et al. 1993), seem to correlate with treatment response. Nevertheless, a characteristic that differentiates SGAs from FGAs, with the exception of risperidone and amisulpride, is their ability to dissociate more quickly from the dopamine D2 receptor (Kapur and Seeman 2000, 2001). Firstly, this was evidenced from PET/SPECT findings which showed that both quetiapine and clozapine have <30% dopamine D2 occupancy levels at 24 hours post-administration, despite having initially achieved therapeutic dopamine D2 occupancy thresholds immediately post-administration (Kapur et al. 2000b; Gefvert et al. 1998; Jones et al. 2000). Secondly, intermittent, as opposed to sustained, occupancy of the dopamine D2 receptor leads to reduced rates of tardive dyskinesia (Kashihara et al. 1986; See and Ellison 1990; Csernansky et al. 1990; Masuda et al. 1982), which suggests that a more intermittent pattern of receptor occupancy is less able to produce tolerance and upregulation of D2 receptors, compared to a more sustained pattern. And, thirdly, administration of olanzapine, clozapine and quetiapine has been showed to lead to a rapid and temporary-only increase in prolactin secretion (Kapur et al. 2000b; Turrone et al. 2000). Combining these findings, SGAs rapidly and transiently occupy the dopamine D2 receptor. This explains their reduced tendency, compared to FGAs, to produce hyperprolactinaemia and motor side effects (Kapur and Seeman 2001).

The precise mechanism of action of antipsychotic drugs remains unknown. Studies to date suggest that, in psychotic illness, antipsychotics diminish the hyperactive, dopamine-dependent, motivational salience that is applied to irrelevant stimuli, thus leading to decrease in the intensity of positive psychotic symptoms (Kapur 2003; Kapur et al. 2005a). Up until the 1980s, the onset of this treatment response, termed clinical latency, was believed to take several weeks to manifest. However, the increased use of PET and SPECT neuroimaging in research has provided more refined estimates. It has been demonstrated that the clinical latency, mediated through depolarisation block (Grace et al. 1997), is in fact much shorter (Howes et al. 2009; Agid et al. 2003; Catafau et al. 2006; Kapur et al. 2005b; Leucht et al. 2005). A large meta-analysis by Agid and colleagues (Agid et al. 2003) of nearly 8000 patients, demonstrated that symptom reduction does occur during the first 2 weeks of treatment, which may in fact represent the greatest reduction in symptoms over a whole treatment period (Nordstrom et al. 1993). In addition, while high D2 receptor occupancy at 48 h is associated with a greater clinical response within 2 weeks (Catafau et al. 2006), improvements in psychotic symptoms have been

observed in the first 24 h of treatment (Agid et al. 2003; Kapur et al. 2005b; Leucht et al. 2005). Furthermore, on a molecular level, therapeutic D2 receptor saturation has been shown to occur within hours of drug administration (Nordstrom et al. 1992). Taken together, these findings suggest that postsynaptic D2 receptor occupancy and clinical response share a dose-response and temporal association, with the former predicting the latter, therefore contributing to the growing body of evidence suggesting that this relationship is causal in nature.

14.4.3 Presynaptic Regulation of Dopamine

It is widely reported that presynaptic dysregulation, specifically increases in DSC, DRC and synaptic dopamine concentrations, is central to pathogenesis of schizophrenia. It is therefore well acknowledged that through D2 receptor blockade, antipsychotic medications seem to work downstream of the main dopaminergic pathology, by dampening the resultant effects of presynaptic dysfunction but neither targeting nor normalising the abnormalities themselves (Leung et al. 2019). PET and SPECT preclinical findings have provided, however, contradictory evidence, indicating that antipsychotics may also affect the presynaptic modulation of dopamine function (Amato et al. 2019). Furthermore, it has been suggested that the mechanism of treatment response is more complex, than just direct postsynaptic D2 receptor antagonism, and is likely to involve several functionally interconnected components of the dopamine transmission (Amato et al. 2019). For instance, it has been observed that the increase in extracellular dopamine concentrations during treatment (Amato et al. 2018, 2011; Abi-Dargham et al. 2000; Samaha et al. 2007; Caravaggio et al. 2019) is more substantial than that which postsynaptic D2 receptor antagonism could account for on its own (Bunney et al. 1973; Chiodo and Bunney 1983; Amato et al. 2017; Santiago and Westerink 1991). Consequently, the effect of antipsychotic medication on DSC, DRC and DAT via blockade at D2 autoreceptors has been extensively researched.

Early in vitro and in vivo animal studies found that acute administration of antipsychotic drugs led to an increase in DSC (Vernaleken et al. 2006; Ito et al. 2009; Gründer et al. 2003; Eisenberg et al. 2017). While some, cross-species comparisons with humans have demonstrated no change (Jauhar et al. 2019; Mamo et al. 2004), other studies have shown that DSC can either increase (Vernaleken et al. 2006; Ito et al. 2009; Gründer et al. 2003; Eisenberg et al. 2017) or decrease (Gründer et al. 2003) in response to antipsychotic treatment, with either effect observed to be associated with treatment response (Vernaleken et al. 2006; Ito et al. 2009; Gründer et al. 2003; Eisenberg et al. 2017). While preliminary preclinical findings have implicated the enzyme tyrosine hydroxylase (TH) and its mediation of dopamine D2 autoreceptor and DAT activity (Jones et al. 1998; Rocha et al. 1998; Dickinson et al. 1999; Salvatore et al. 2016), further research is required to explore the apparently contradictory findings and delineate the mechanism that may govern this relationship.

In healthy individuals, the homeostatic regulation of synaptic dopamine concentrations and its resultant occupancy of postsynaptic receptors is managed through a negative feedback loop under presynaptic dopamine autoreceptor and DAT control (see Fig. 14.1. Although, there is substantial support for an increase in DRC in schizophrenia, there is no evidence that DAT densities are abnormal (Howes et al. 2012; Brugger et al. 2019; Fusar-Poli and Meyer-Lindenberg 2013a; Meyer-Lindenberg 2013b). Research has shown that DRC reduces in response to treatment (Roth 1984) and that antipsychotics directly block the DAT (Seeman and Lee 1974; Iversen et al. 1976; Miller and Friedhoff 1979; Meiergerd et al. 1993; Suaud-Chagny et al. 1995; Lee et al. 1997; Siebert et al. 2000). Linking the two, it has been hypothesised that antipsychotic DAT blockade prompts a reduction of extracellular dopamine reuptake, without affecting DAT densities (Meiergerd et al. 1993; Rothblat and Schneider 1997). This has been putatively posited to lead to the net increase in the synaptic dopamine concentrations, which triggers rebound dopamine autoinhibition that have been observed in multiple studies (Amato et al. 2018, 2011; Samaha et al. 2007; Caravaggio et al. 2019). Exploring this further, Amato and colleagues used PET imaging to investigate the relationship between D2/3 receptor blockade, DAT availability and treatment response in rats, using [^{18}F]-Fallypride and [^{18}F]-FP-CMT respectively (Amato et al. 2018). The rats received haloperidol and they were followed up until treatment failure. Interestingly, they found that while behavioural response to treatment was directly associated with postsynaptic D2 receptor occupancy, it was also associated with suppression of DAT availability. Conversely, at treatment failure, rats showed an increase in DAT availability and a reduction in extracellular dopamine concentrations, despite postsynaptic D2 occupancy remaining high at 69%. Similar findings have been replicated elsewhere (Samaha et al. 2007; Amato et al. 2011) and suggest that, at least in rodents, treatment efficacy may in part be mediated by changes to extracellular dopamine and DAT availability, independent of postsynaptic receptor blockade.

The mechanism that governs this relationship is not currently clear. Under the aberrant salience model (Kapur 2003; Kapur et al. 2005a), the presence of relevant, pleasurable or aversive stimuli induces a release of dopamine. The release of dopamine triggers the attachment of salience to the stimuli, leading to heightened attention. In schizophrenia, it is hypothesised that as a result of the presynaptic dysregulation, phasic dopamine hyperactivity occurs in the absence of relevant stimuli. Hyperactive dopamine release, therefore, coincides with the presence of normally irrelevant stimuli, which as a result, have motivational salience attached. These newly salient stimuli are perceived as being abnormally pleasurable or aversive and drive the observed psychotic behaviour, which has been supported by findings that phasic dopamine release is increased during psychosis (Abi-Dargham et al. 2002, 2000; Laruelle et al. 1999, 1996; Heinz 2002; Grace 1991). Antipsychotic blockade at the DAT reduces uptake of dopamine into the presynaptic vesicles, therefore allowing extracellular dopamine to accumulate (Seeman and Lee 1974; Iversen et al. 1976; Miller and Friedhoff 1979; Meiergerd et al. 1993; Heinrichs and Zakzanis 1998). This additional accumulation in baseline levels of extracellular dopamine in schizophrenia (Howes et al. 2012) reduces the threshold that is required

to trigger neuronal autoinhibition, via the stimulation of presynaptic autoreceptors by endogenous dopamine. Essentially, antipsychotic medications may, in addition to postsynaptic D2 antagonism, act their clinical response by lowering the presynaptic autoinhibition threshold, via blockade of the DAT. Although this hypothesis is largely based on animal data, a correlation between changes in the concentration of extracellular dopamine and treatment has been also shown in humans (Abi-Dargham et al. 2000). However, replication is required in future fine-grained and stratified clinical schizophrenia studies that need to primarily address individual differences in the availability of DAT (Brugger et al. 2019) that may be able to predict treatment response.

14.4.4 Implications for Novel Dopaminergic Agents

There is an ongoing interest in exploring the therapeutic potential of drugs that target non-D2, dopamine receptors. Development of D2/3 agonist radiotracer [^{11}C]-(+)-PHNO has allowed the effect and distribution of D2 and D3 receptors to be studied separately (Wilson et al. 2005). The D3 receptor is involved in cognitive, social, and motor processing (Gross and Drescher 2012) and is found in higher densities in the ventral striatal and mesolimbic areas, than the D2 receptor (Gurevich and Joyce 1999). It has up to a 20-fold higher affinity for dopamine than D2 (Freedman et al. 1994; Sokoloff et al. 1992; Seeman et al. 2005) and in preclinical studies, selective D3 antagonists have reduced cognitive impairment (Laszy et al. 2005; Millan et al. 2007; Sigala et al. 1997) and improved motor function (Gyertyán and Sághy 2004; Sautel et al. 1995; Waters et al. 1993). This indicates that D3 antagonism may play a role in treating negative symptoms. However, while an elevation in D3 receptor densities has not been found in patients with schizophrenia (Graff-Guerrero et al. 2009b) and further studies suggest that selective D3 antagonism is not an effective strategy for treating schizophrenia (Redden et al. 2011), it has been proposed that clinical efficacy may be governed by achieving a specific balance between D2 and D3 antagonism (Girgis et al. 2016a). The development of Cariprazine, a newer antipsychotic drug (McCormack 2015), which is a D3-preferrential partial dopamine D2/D3 agonist (Girgis et al. 2016a), supports this theory by showing promise in safely treating schizophrenia (Debelle et al. 2015; Kane et al. 2015; Nemeth et al. 2017a, b; Chhatlani et al. 2018) and maintaining remission (Correll et al. 2019).

The dopamine D1 receptor is believed to play a role in the management of working memory and executive function (Goldman-Rakic 1994; Tamminga 2006) and, thus the abnormalities in prefrontal D1 receptor densities are associated with impairments in cognitive performance in patients with schizophrenia (Abi-Dargham et al. 2002; Okubo et al. 1997; Karlsson et al. 2002; Takahashi et al. 2008; Takahashi 2013). At clinically effective doses, although current antipsychotic drugs occupy the D1 receptor to varying degrees, ranging from 0% with haloperidol to 60% with clozapine (Farde et al. 1992; Nordstrom et al. 1995; Tauscher et al. 2004), the contribution of D1 antagonism for adequate treatment response is yet to be determined. So far, neither the poorly tolerated selective D1 receptor antagonists (Karlsson et al.

1995) nor the better tolerated selective D1 receptor agonists (George et al. 2007; Girgis et al. 2016b; Rosell et al. 2015) have proved effective as treatment strategies.

Dopamine D4 receptors are found in similar regions of the brain as D2 receptors. Early interest into their possible role in pathophysiology of schizophrenia stemmed from the findings that clozapine uniquely demonstrates a higher affinity for the D4 rather than D2 receptor (Van Tol et al. 1991) and from post-mortem findings, which suggested that D4 receptor densities were raised in schizophrenia (Seeman et al. 1993). Since then, although there have been mixed attempts at repeating these findings (Murray et al. 1995; Reynolds and Mason 1994), selective D4 antagonists, such as sonepiprazole (Corrigan et al. 2004) and L-745,870 (Kramer et al. 1997), have failed to show a clinical treatment response in humans.

Drugs that primarily target presynaptic dopamine modulation have shown promise as non-D2 receptor antagonist treatment options. Reserpine, which is an extract from *Rauvolfia serpentina*, was first used in the 1950s and is an unlicensed but effective antipsychotic (Healy 2009). Unlike licensed antipsychotic drugs, it acts by inhibiting the vesicular monoamine transporter (VMAT) (Braun 2006; Yaffe et al. 2018) see (Fig. 14.1), therefore reducing the amount of dopamine that is stored for release into the synapse. Unfortunately, the fact that VMAT is also found in other monoamine neurons has limited its use, as reserpine administration can lead to significant adrenergic side effects. Similarly, alpha-methyl-p-tyrosine, an inhibitor of tyrosine hydroxylase, has been shown to reduce psychotic symptoms (Abi-Dargham et al. 2000). However, as with reserpine, alpha-methyl-p-tyrosine is poorly tolerated because it also affects non-dopaminergic neurons. This highlights the need for development of novel specific presynaptic agents.

Dopamine D2 autoreceptor activation reduces the release of synaptic dopamine and subsequent neuronal firing (Suaud-Chagny et al. 1991; Mercuri et al. 1997). Apomorphine, which is thought to be a partial D1 and D2 receptor agonist (Newman-Tancredi et al. 2002), has been observed to have contrasting effects on dopamine levels at different doses, with low doses preferentially activating D2 autoreceptors, and higher doses activating postsynaptic D2 receptors (Meltzer 1980; Zetterström and Ungerstedt 1984; Torstenson et al. 1998). In a [^{18}F]-DOPA PET clinical study on 12 healthy participants, Jauhur and colleagues (Jauhar et al. 2017b) preliminarily showed that the administration of low-dose apomorphine has a regulatory effect on DSC and that this effect is dependent on an individual's baseline DSC level. They observed that after apomorphine administration, DSC reduced in participants who usually had high baseline levels and that it increased in participants who usually had low baseline levels. While extending earlier findings from [^{11}C]-DOPA PET studies in rhesus monkeys (Torstenson et al. 1998) and humans with Parkinson's disease (Ekesbo et al. 1999) by helping to ascertain the action of apomorphine healthy individuals, the findings from this study indicate that low-dose apomorphine, via the stimulation of D2 autoreceptors, may stabilise DSC during hyperactive dopaminergic states, such as during an episode of acute psychosis (McCutcheon et al. 2017; Howes et al. 2012; Brugger et al. 2019). While the therapeutic implications of this

theory have been supported by evidence from early trials, which showed that apomorphine can be efficacious in treating schizophrenic symptoms (Tamminga et al. 1978), later trials failed to replicate this (Tamminga 2002). Issues with desensitisation and the use of comparatively higher doses of apomorphine have been offered as possible explanations for the contrasting results of these later trials (Jauhar et al. 2017b) and, adjusting for these conditions, future investigation of the role of partial dopamine agonists in dopamine regulation is warranted.

14.5 PET and SPECT Findings in Treatment-Resistant Schizophrenia

By helping to transfer care from the asylum to the community, the advent of antipsychotic medication revolutionised the treatment of schizophrenia. We now have a better understanding about the aetiological factors that lead to development of the disorder and, especially, the role that dysfunctional dopaminergic signalling plays in this (Howes and Murray 2014). Despite this, there remains a significant knowledge gap. As observed in the works of Kraepelin and others (Kraepelin et al. 1921), the notion of a more severe and enduring form of schizophrenic illness has existed for at least a century. Although exact estimates range from one-fifth up to one-half (Essock et al. 1996; Lieberman 1999; Elkis 2007), it is generally accepted that about a third of patients with schizophrenia do not respond to first-line antipsychotic treatment (Lindenmayer 2000; Hasan et al. 2012), up to 84% of whom may already be treatment-resistant by the time they have presented to services (Demjaha et al. 2017). This is particularly critical because treatment resistance is strongly associated with more severe psychopathology, more severe cognitive impairment, poorer psychosocial adjustment and higher health costs (Ascher-Svanum et al. 2007; Iasevoli et al. 2016). For this heterogenous group (Lieberman et al. 1993; Levine et al. 2012), clozapine is the only evidence-based pharmacological agent (Taylor and Duncan-McConnell 2000; McEvoy et al. 2006; Lewis et al. 2006), however, even this superior antipsychotic treatment is only effective in approximately 50% of patients (Kane et al. 1988; Chakos et al. 2001; Lieberman et al. 1994). There is therefore an urgent need for a new and effective class of antipsychotic agents; however, the precise molecular abnormality that governs treatment resistance remains unknown. Here, we outline the available evidence from PET and SPECT studies that have shed some light on the underlying mechanisms of treatment-resistant schizophrenia (TRS). We explore the implications of these findings on the aetiology of the disorder and detail the evidence for current and future strategies for pharmacological treatment.

14.5.1 Definition of Treatment-Resistant Schizophrenia

In spite of growing evidence that the presence and severity of negative symptoms may be more useful as markers of treatment resistance (Demjaha et al. 2017),

definitions of TRS have tended to focus on the presence of positive symptoms. Symptoms must persist despite therapeutic trials of two separate antipsychotic drugs, taken at adequate doses and for adequate durations of time. Different interpretations of these criteria have been proposed by several clinical bodies – including the National Institute for Health and Clinical Excellence (NICE) (National Collaborating Centre for Mental Health UK 2014), American Psychiatric Association (APA) (Lehman et al. 2004), the Schizophrenia Patient Outcome Research Team (PORT) (Buchanan et al. 2010) and the World Federation of Societies of Biological Psychiatry Guidelines (WFSBP) (Hasan et al. 2012). The multitude of, and differences between, these interpretations has meant that different definitions are used in the literature, with investigators using tighter or wider criteria, depending on their study aims and outcomes (Howes et al. 2016). The use of inconsistent definitions can lead to delays in recognition and treatment of treatment-resistant illness and limits the validity and comparability of research studies. This, for example, may help to account for the wide variation in the reported prevalence rates of TRS, which ranges from 0 to 76% (Suzuki et al. 2011). To address this issue, the International Treatment Response and Resistance in Psychosis Group (TRRIP) developed operationalised criteria, following a systematic review of the literature, which stipulates strict minimum requirements of: ≥2 trials of sequential antipsychotic drugs; plasma-levels confirmed drug adherence rates of ≥80%; drug doses of ≥600 mg chlorpromazine equivalence, treatment durations of ≥6 weeks per drug; persistence of moderate symptom severity (positive, negative or cognitive symptoms); and/or moderate functional impairment, as recorded on standard rating scales (Howes et al. 2016). The authors note that to remain current, the criteria should evolve and adapt with future revisions to reflect forthcoming research findings. This has been a welcome addition that should help to improve the validity and clinical usefulness of research in this field.

14.5.2 Dopamine and Treatment-Resistant Schizophrenia

It was not until the 1990s, with the use of molecular imaging, that researchers began to examine in vivo neurochemical features of TRS. After the seminal study by Farde and colleagues, which demonstrated that clinical doses of antipsychotics were associated with high levels of striatal dopamine D2 blockade (Farde et al. 1989), Pilowsky and colleagues (Pilowsky et al. 1993) used (Kapur et al. 1995)-IBZM SPET neuroimaging to compare dopamine D2 receptor availabilities between patients with schizophrenia treated with haloperidol (10 responders and 8 non-responders) and 20 healthy controls. Importantly, they demonstrated that there was no difference in striatal D2 receptor availabilities between the responder and non-responder groups, reinforcing findings from previous smaller studies (Wolkin et al. 1989; Coppens et al. 1991). Along with this discovery, findings that high antipsychotic D2 receptor occupancy levels of 95% failed to treat refractory illness (Coppens et al. 1991) and that fewer than 5% of patients who had already failed two non-clozapine antipsychotics, responded to a third (Agid et al. 2010), provided

foundational evidence that in this group of patients, poor treatment response was not due to differences in drug dosing, drug delivery or drug metabolism, but, rather, due to a variance in its pathophysiology. As outlined earlier, there is robust evidence that presynaptic dopamine changes are fundamental to the downstream pathophysiology of schizophrenia. The findings above, coupled with discoveries that greater presynaptic dopamine dysregulation is correlated with treatment response (Abi-Dargham et al. 2000) and that clozapine, which does not demonstrate appreciable dopamine D2 blockade (Van Tol et al. 1991), is the most efficacious medication for TRS (Kane et al. 1988), suggested that dopaminergic dysfunction may not play a significant role in the pathophysiology of TRS (Leung et al. 2019; Howes and Kapur 2014; Nucifora Jr et al. 2018).

To examine this, Demjaha and colleagues used [^{18}F]-DOPA uptake PET neuroimaging to examine the relationship between treatment resistance and striatal DSC (Demjaha et al. 2012). DSC was measured using the influx rate constant (Ki^{cer}), in patients with schizophrenia (12 responders and 12 non-responders), and the results were compared to 12 healthy controls. Consistent with previous research (Abi-Dargham et al. 2000; Ottong & Garver 1997; Duncan et al. 1993; Kim et al. 2017), the authors demonstrated that treatment-responsive patients had higher striatal Ki^{cer} values, when compared to non-responders (effect size = 1.11, $p = 0.02$ corrected) and healthy volunteers (effect size = 1.12, $p = 0.02$ corrected). Furthermore, these differences were most marked in the associative striatum (non-responders: effect size = 1.31, $p = 0.008$ corrected; healthy volunteers: effect size = 1.24, $p = 0.01$ corrected), the subdivision of the striatum with the most robust evidence supporting its role in the pathogenesis of schizophrenia (Kegeles et al. 2010; Mizrahi et al. 2012; Egerton et al. 2013; Howes et al. 2013). The most striking finding, however, was the lack of significant difference in striatal Ki^{cer} values between non-responders and healthy volunteers. This was the first study to provide direct evidence that DSC may be unaltered in non-responders, providing some of the first explanations for non-efficacy of dopamine blockade for this treatment group. The authors were amongst the first to suggest that TRS may be a neurobiologically distinct form of illness. Kim and colleagues expanded this work by studying DSC in patients with TRS, who had responded to clozapine (Kim et al. 2017), and therefore had comparably low symptom severities compared to the treatment-responsive cohort. They showed that clozapine responders ($n = 12$), had lower striatal Ki^{cer} values than treatment responders to first-line antipsychotics ($n = 12$) (mean difference in $Ki^{cer} = -1.1 \times 10^{-3}$, SE = 0.28×10^{-3}, df = 95.0, $p < 0.001$), which suggests that this difference in DSC between the two groups may reflect different neurochemical pathophysiologies and is not related to illness severity.

In both studies, all patients were chronically medicated so it remained unclear whether this may have affected results. While there is currently inconclusive evidence about what effect chronic antipsychotic treatment has on DSC (Jauhar et al. 2019; Ito et al. 2009; Gründer et al. 2003; Eisenberg et al. 2017; Mamo et al. 2004), preclinical studies have suggested that chronic treatment may cause upregulation of dopamine D2 receptors, leading to breakthrough dopamine supersensitivity, which can lead to a delayed failure to respond to treatment (Samaha et al. 2007; Ginovart

et al. 2009). Research suggests that this pattern of treatment resistance characterised by schizophrenia symptoms that initially respond to first-line medication but ultimately develop resistance may represent about 16% of the TRS population (Demjaha et al. 2017), though this remains to be confirmed. To account for the possible confounding effects of chronic treatment, Jauhur and colleagues (Jauhar et al. 2018b) conducted a 6-month prospective [^{18}F]-DOPA PET study, to examine DSC in relation to treatment response. The authors recruited 26 patients with first-episode psychosis (FEP)—initially either drug-naïve, drug-free (included after a medication washout period) or treated for a maximum of 2 weeks—and compared them to 14 healthy volunteers. In line with previous findings by Demjaha and colleagues (Demjaha et al. 2012), they documented higher striatal Ki^{cer} values in treatment responders (mean $Ki^{cer} = 13.45 \times 10^{-3}$, SD $= 0.78 \times 10^{-3}$) compared to non-responders (mean $Ki^{cer} = 12.12 \times 10^{-3}$, SD $= 0.93 \times 10^{-3}$, $p = 0.004$), with a large effect size (Cohen's $d = 1.55$, $p = 0.01$). These data confirmed that TRS may indeed be a neurobiologically separate disease entity from treatment-responsive schizophrenia. Moreover, this study also lent support to the work by Abi-Dargham and colleagues (Abi-Dargham et al. 2000) by providing evidence that presynaptic dopamine dysfunction is correlated with treatment response at 6 months follow-up. In addition to the finding that VMAT inhibition is not an effective treatment strategy in TRS (Remington et al. 2012), such studies have provided preliminary evidence that, unlike in responsive illness, presynaptic dopamine dysfunction does not play a significant role in the pathophysiology of TRS (Leung et al. 2019; Nucifora Jr et al. 2018; Nakajima et al. 2015; Mouchlianitis et al. 2016a). This implies that other neurotransmitter pathways may be abnormal in TRS.

14.5.3 Glutamate and Treatment-Resistant Schizophrenia

In recent years, various lines of evidence have highlighted that glutamatergic pathway dysfunction may potentially be the source of neurochemical imbalance in TRS (Egerton et al. 2012; Demjaha et al. 2014; Mouchlianitis et al. 2016b; Iwata et al. 2019). Glutamate and its metabolite, glutamine (Shank and Aprison 1981), are measured in vivo using proton magnetic resonance spectroscopy (^{1}H-MRS) and elevated concentrations have been found in the medial temporal lobe, basal ganglia and thalamus, in schizophrenia (Merritt et al. 2016). While a review of the ^{1}H-MRS imaging literature is beyond the scope of this chapter, a series of multimodal neuroimaging studies, coupling PET and ^{1}H-MRS, have yielded promising findings in the field of TRS research.

By conducting ^{1}H-MRS neuroimaging on the participants that had taken part in their original study, which has been described above (Demjaha et al. 2012), Demjaha and colleagues showed that, relative to healthy controls, treatment responders ($n = 8$) exhibited no change in Anterior Cingulate Cortex (ACC) glutamate concentrations ($t16 = 0.29$, $p = 0.77$) compared to healthy participants, while non-responders ($n = 6$) exhibited an increase ($t14 = 2.80$, $p = 0.01$, effect size = 1.68) (Demjaha et al. 2014). These results have been replicated in some (Mouchlianitis et al. 2016b) but

not all (Gillespie et al. 2017; Vita et al. 2019) studies. Demjaha and colleagues' findings have been subsequently extended in a PET and ^{1}H-MRS multimodal study, to address the potential effects of chronic illness and treatment, with a larger sample of FEP patients ($n = 28$) (Jauhar et al. 2018b). In this study, they demonstrated that that treatment response in patients with psychosis, as defined by reductions in scores on the PANSS-positive rating scale, and striatal DSC were both inversely correlated with ACC glutamate concentrations (R^2 = 0•16, $r = -0.4$, $\beta = -1•71 \times 10^{-4}$, SE = 7•63 × 10^{-5}, p = 0•03). This relationship remained significant after possible confounders were added to the model (p = 0•015). Also, there was weak evidence for an association between treatment response, in patients with psychosis, and striatal DSC (R^2 = 0•14, β = 2546, SE = 1217, p = 0•046), which was lost when confounders were added to the model (p = 0.089). The link between ACC glutamate concentration and striatal DSC lends further support to the hypothesis that treatment response in schizophrenia may be related to an inverse relationship between cortical glutamate and presynaptic dopamine. The finding that there was no association between striatal DSC and treatment response may represent a Type II error and more research to explore this is indicated.

Causal inferences cannot be drawn from these cross-sectional studies, and it is not clear what governs the observed glutamate-dopamine relationship. Evidence from PET clinical studies have shown that ketamine-induced N-methyl-D aspartate receptor (NMDAR) blockade results in increased striatal dopamine release and dopamine concentrations, in response to a challenge (Kegeles et al. 2000; Vollenweider et al. 2000; Kokkinou et al. 2018). Carlsson and colleagues proposed that glutamate may influence dopamine neuronal firing either directly via "accelerator" stimulation or indirectly via GABA interneuronal "brake" inhibition (Carlsson et al. 2000, 2001). According to the model, reduced glutamate activity (acting through the indirect pathway and mediated, in part, via striatal and thalamic control) leads to a decline in GABA interneuron inhibition, and a resultant increase of dopamine neuronal firing. This pathway functions via a negative feedback loop, with the increase in dopamine activity leading to an increase in glutamate concentrations, and a subsequent decrease in dopamine activity (Leung et al. 2019). Currently, from a synthesis of the current neurochemical data, we speculatively propose that, the indirect pathway is the dominant glutamate-dopamine pathway in TRS, which may explain the above findings that DSC remains at physiological levels, despite elevated glutamate concentrations in TRS. Though speculative, the implications of this hypothesis are intriguing. It may explain why TRS does not respond to dopamine blockade and indicates that non-dopaminergic neurotransmitters like glutamate, GABA and endocannabinoids have exciting potential as targets for novel treatments. The hypothesis also indicates that treatment-responsive and treatment-resistant schizophrenia may arise from different neurobiological aetiologies. Nonetheless, this hypothesis requires further validation through future research.

14.5.4 Clozapine and Treatment-Resistant Schizophrenia

In the 1958, clozapine was synthesised as a compound from a group of tricyclics, mimicking the structure parent drug, imipramine (Crilly 2007). Therapeutic results from initial animal and human trials in the 1960s were mixed and its disinclination to cause EPSEs, thought at the time to be a necessary marker of antipsychotic efficacy (Van Rossum et al. 1970; Stephens 1990), meant that its reception was marked by a substantial degree of doubt and scepticism. As such, clozapine was not considered a particularly viable pharmacotherapeutic option for treating schizophrenia for at least the decade following its development (Crilly 2007). Its disfavour was cemented in 1975 when Idanpaan-Heikkila and colleagues reported nine cases of fatal agranulocytosis (Idanpaan-Heikkila et al. 1975). Concern about agranulocytosis coupled with initial doubts about its efficacy led to a halt in clinical trials and slowing down of its use worldwide, until the now landmark multicentre study, conducted by Kane and colleagues in 1988 (Kane et al. 1988). The researchers entered 268 patients with schizophrenia, who had failed a trial of haloperidol, into a 6-week randomised double-blind trial, comparing the efficacy of clozapine with chlorpromazine. They noticed that clozapine outperformed chlorpromazine, 30% vs 4% ($p < 0.001$), in achieving the pre-determined treatment-response criteria. They also noticed that, unlike with chlorpromazine, treatment response in clozapine was achieved more quickly, being noticeable within the first week, and involved reductions in negative as well as positive symptoms. These findings caused a remarkable shift to the psychopharmacological landscape and were instrumental in cementing clozapine's dominance, over other antipsychotic medication, for treating schizophrenia and its refractory subset.

Several decades later, clozapine is still the most efficacious antipsychotic medication for treating schizophrenia (Leucht et al. 2013; Taylor and Duncan-McConnell 2000; Lewis et al. 2006; Siskind et al. 2016) and TRS (Kahn et al. 2018; McEvoy et al. 2006; Okhuijsen-Pfeifer et al. 2018). In the CATIE phase I investigation, 1493 patients with schizophrenia were randomised to receive either risperidone, quetiapine, perphenazine, ziprasidone or olanzapine for 18 months (Lieberman et al. 2005). In the phase II arm of the study, 99 patients that had failed to respond to any of the previous medication were randomised to trial either another one of the initial antipsychotic agents or clozapine (McEvoy et al. 2006). They observed that (1) clozapine was superior to other agents in prolonging time to discontinuation because of treatment failure; (2) and that at 3 months, PANSS-total scores had decreased in more patients treated with clozapine than risperidone and quetiapine, though this was not the case compared to olanzapine.

Likewise, in the CUtLASS investigation, 136 patients with TRS were randomised to receive clozapine or an SGA (olanzapine, risperidone, quetiapine or amisulpride) and followed up for 1 year (Lewis et al. 2006). The investigators found that (1) at 1-year follow-up, patients treated with clozapine had lower PANSS-total scores; and (2) at 12 weeks follow-up, patients treated with clozapine reported having significantly more substantial improvements to their mental health than the other patients. Clozapine's superiority has also been replicated in more recent,

shorter-duration trials (Kahn et al. 2018; Leucht et al. 2013; Siskind et al. 2016; Okhuijsen-Pfeifer et al. 2018).

It is worth noting that, although blinding has been undertaken where possible, all of these studies utilised an open-label approach to clozapine testing. Due to its side effects and monitoring requirements, efficacy studies tend not to blind clozapine treatment. In a meta-analysis, where only double-blinded RCTs were included, researchers found that clozapine was not superior to SGAs (Samara et al. 2016). This was likely due to the study's exclusion of significant non-blinded trials, such as the large prospective CATIE and CUtLASS investigations described above. In addition to this, responders to the results of the meta-analysis have noted that double-blinded RCTs are more likely to include patients who are less unwell than non- or partially blinded studies, which introduces a sampling bias (Kane and Correll 2016). Furthermore, the meta-analysis did not use a standard definition of TRS, limiting the validity of its results.

14.5.5 Therapeutic Targets for Treatment-Resistant Schizophrenia

Despite decades of research, clozapine's exact mechanism of action remains elusive. Unlike other licensed antipsychotic medication, clozapine shows a marked preference for dopamine D4, rather than D2, receptor blockade (Van Tol et al. 1991). Post-mortem research, showing that D4 receptor densities were raised in schizophrenia (Seeman et al. 1993), provided early promise that the D4 receptor may the source of clozapine's therapeutic dominance. Unfortunately, attempts to replicate this were inconclusive (Murray et al. 1995; Reynolds and Mason 1994) and subsequent clinical trials of selective D4 receptor antagonists have been unsuccessful in treating symptoms (Corrigan et al. 2004; Kramer et al. 1997).

Following on from this, clozapine's appreciable 5-HT_{2A} receptor antagonism garnered a lot of interest (Meltzer 1989) and led to the development of SGAs like olanzapine, risperidone and quetiapine (Seeman and Tallerico 1998). However, observations from PET studies that olanzapine and risperidone displayed near 100% 5-HT_{2A} receptor blockade at subtherapeutic doses (Kapur et al. 1999, 1998) discouraged confidence in its importance for producing treatment response. Selective 5-HT_{2A} antagonists have thus far failed to be effective treatments in schizophrenia (de Paulis 2001). In spite of this, post-mortem findings that cortical 5-HT_{2A} receptor densities are reduced in schizophrenia (Selvaraj et al. 2014) have promoted investigation into the antipsychotic potential of 5-HT_{2A} inverse agonists (Meltzer et al. 2012). For instance, the 5-HT_{2A} inverse agonist, pimavanserin, has shown great promise in the treatment of Parkinson's disease psychosis (Bozymski et al. 2017), and exciting recent results tentatively suggest that it may be a useful in treating clozapine-resistant illness too (Nasrallah et al. 2019).

As with D4 and 5-HT_{2A} antagonism, clinical trials attempting to mimic the potential therapeutic benefit of clozapine's potent action at the histamine receptors

(H1-H4) (Humbert-Claude et al. 2012) have thus far yielded unsuccessful results (Kishi and Iwata 2015; Jarskog et al. 2015).

Recent TRS neurochemical imaging studies have implicated glutamate dysfunction in the pathogenesis of schizophrenia (Egerton et al. 2012; Demjaha et al. 2014; Mouchlianitis et al. 2016b; Iwata et al. 2019), and it has been noted that clozapine's mechanism of action may be linked to this (Abekawa et al. 2006, 2007), possibly acting as a partial agonist at the NMDAR (Schwieler et al. 2008). Trials of selective partial agonists, such as D-cycloserine, and co-agonists, such as D-serine, at the NMDAR have thus far followed a pattern of showing significant early promise in small studies but unequivocal or negative results when examined in larger clinical trials (Girgis et al. 2019). The most promise has come from allosteric group II metabotropic glutamate receptor (mGluR2/3) modulators, such as pomaglumetad, which are thought to indirectly reduce dopaminergic activity (Sonnenschein and Grace 2017). A phase II trial of pomaglumetad demonstrated impressive results in reducing PANSS-total, positive and negative scores, compared to placebo (Patil et al. 2007) in patients with schizophrenia. These results were comparable with those gained by patients in the olanzapine arm of the study, though pomaglumetad was better tolerated. While follow-up studies have so far been unequivocal or negative (Downing et al. 2014; Kinon et al. 2011; Stauffer et al. 2013), post hoc analysis suggests that pomaglumetad may be effective in particular population subgroups (Kinon et al. 2015).

Taken together, researchers have not been able to identify the key factors that contribute to clozapine's therapeutic dominance, and efforts to mimic its mechanism of action, possibly excepting mGluR2/3 modulation, have thus far been disappointing. The development of new non-clozapine medications is important because clozapine's substantial side effect burden and requirement for close blood monitoring form a barrier to its prescription (Verdoux et al. 2018) and are likely to contribute to its underuse (Shah et al. 2018), as well as the delay in initiating the only evidence-based treatment for TRS (Patel et al. 2014). This delay has important clinical ramifications as it is associated with a diminished treatment efficacy, an increase in hospitalisations and an increased use of adjunctive electroconvulsive therapy (ECT) (Shah et al. 2018; Harrison et al. 2010; Yoshimura et al. 2017; Üçok et al. 2015).

Furthermore, up to half of TRS patients are also resistant to clozapine (Kane et al. 1988; Chakos et al. 2001; Lieberman et al. 1994), termed ultra-resistant schizophrenia (URS). Treatment of this cohort remains a challenge and several therapeutic strategies have been trialled, mainly focusing on the pharmacological augmentation of clozapine with a more D2-selective antipsychotic, a mood stabiliser, an antidepressant or glutamatergic drugs. A recent systematic metareview of 21 meta-analyses and systematic reviews concluded that there is a paucity of high-quality evidence in this field (Wagner et al. 2019). Poor study design and inconsistent definitions for clozapine resistance limited the quality and generalisability of the studies. The authors noted that the best quality evidence, which comes from low-quality studies, provides some support for the pharmacological use of first- or second-generation antipsychotics as adjuncts to clozapine. Augmentation of

clozapine is, in theory, a useful mechanism of treating URS because it employs drugs that are already in use, with known dosing regimens and side effect profiles. Unfortunately, evidence for their efficacy in URS is poor at best.

As the potential benefits of drugs that target non-dopaminergic pathways, like pomaglumetad and pimavanserin, are yet to be determined, more high-quality research is needed to meet the unrealised clinical need in TRS and URS therapeutic management.

14.6 Conclusion

In this chapter, we have outlined the molecular evidence, from PET and SPECT neuroimaging, that explores the relationship between presynaptic dopamine dysfunction and schizophrenia, with particular focus on treatment response. In addition, we have highlighted that the locus of dysfunction appears to be in the associative, and not limbic, region of the striatum. Furthermore, pathological elevations in DSC, DRC and synaptic dopamine levels are well replicated as correlates of schizophrenic illness and are associated with the development, and worsening severity, of the disorder. We argue that while there is evidence that other aberrant neurotransmitter pathways may be involved in the pathophysiology of schizophrenia, the robust findings that have been outlined in this paper provide strong evidence that dopamine dysregulation remains key and may play a causal neurochemical role in the development of the disorder. Replication of existing studies with larger-sized, longitudinal cohorts of UHR and drug-naïve FEP patients would further enrich this model.

While it has been well evidenced that a therapeutic threshold of 60–80% postsynaptic dopamine D2 receptor blockade is necessary for current antipsychotics to achieve their clinical response, emerging evidence, from animal studies, suggests that antipsychotic activity at the DAT may also mediate treatment response, independent of postsynaptic D2 receptor blockade. This warrants further exploration. Furthermore, while agents that solely block non-D2 postsynaptic receptors have not proved to be clinically effective in trials so far, cariprazine, a recently licensed, D3-preferrential, partial dopamine D2/D3 agonist, has shown great promise as a novel treatment for achieving and maintaining remission.

Unlike with positive symptoms, since the advent of molecular neuroimaging, relatively limited progress has been made in our understanding about the pathophysiological changes that underpin the cognitive and negative deficits of schizophrenia. Current research suggests that there may be dynamic changes in dopamine regulation, possibly via changes D1 postsynaptic receptor activation, in the DLPFC. Additionally, studies suggest that these changes may correlate with regional changes in blood perfusion, though it has thus far proved challenging to fully capture and characterise these findings using current neurochemical imaging methods. Furthermore, frontal brain region interactions with the hippocampus and striatum have been implicated in mediating cognitive deficits, in schizophrenia, though again this is not well understood. As a consequence of our limited understanding, these

symptoms are poorly treated by current antipsychotics. There is emerging evidence of beneficial effects of low-dose amisulpride as well as cariprazine in this group (Krause et al. 2018). However, future trials are required to determine the most effective and tolerable treatment for these symptoms. As the presence of these symptoms seems to be associated with more severe functional and disease outcomes, and the fact that there are no currently licensed treatments, there is a desperate clinical need to develop the literature in this area.

The majority of patients with TRS appear to be resistant from the onset of their disorder. Even though clozapine is the only effective pharmacological agent for up to half of this population group, adequate treatment is delayed by an average of 5 years. While barriers to clozapine initiation include physician and patient concerns about blood monitoring and adverse effects, under-recognition may also play a significant role. The recent development of an operationalised definition of TRS, by the TRRIP group, aims to standardise the characterisation of the disorder. In doing so, it will hopefully homogenise the recognition of the disorder, improve the quality of research and facilitate the timely initiation of clozapine. The neurochemical mechanisms that underlie TRS are not well understood but recent findings that glutamate levels, and not DSC, are abnormally elevated in TRS, indicate that this, and possibly other, neurotransmitter pathways are abnormal in treatment-resistant illness. Furthermore, while efforts are being made to understand the mechanism of action of clozapine, it has been postulated that its efficacy may be mediated by its activity at serotonin, muscarinic, histaminergic or NMDA receptors. Based on this knowledge, there is great interest in identifying pharmacological agents, which may be better tolerated, cause fewer adverse events and prove as least as effective as clozapine. Several pharmacological agents have been developed to target the aforementioned receptors. The most promising of these have been mGluR2/3 modulator, pomaglumetad, and 5-HT_{2A} inverse agonist, pimavanserin, which have demonstrated acceptable tolerability and efficacy in treating TRS, respectively.

PET and SPECT neuroimaging have helped cement our understanding about the key role that striatal dopamine regulation plays in salience and reward, and how its dysregulation contributes to the chronic and complex condition such as schizophrenia. The literature detailing the workings of current and potential antipsychotic drugs is expanding rapidly, although, for it to meet the clinical needs of our patients, our methods need to be more nuanced and fine-tuned to the biological intricacies that define cognitive impairment, negative deficits and treatment resistance (Demjaha 2018). Through this approach, academics may be able to develop more effective clinical tools that can accurately predict those that are most likely to develop schizophrenia, and of individuals with schizophrenia, those that will or will not respond to dopamine blockade, so that the appropriate treatment can be administered accordingly.

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Acetylcholine Imaging in Psychosis

15

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Abstract

Core symptoms of psychosis include delusions, hallucinations, motor symptoms, and cognitive impairments. The cholinergic system has been increasingly implied in the pathophysiology of psychotic disorders. PET and SPECT imaging can be useful tools to increase our insight in the role of the neurotransmitter acetylcholine in psychosis. In this chapter we will first globally describe cholinergic neurotransmission and the function of the nicotinic and muscarinic receptors. Second, we will provide an overview of PET and SPECT studies examining the cholinergic system in psychosis. Finally, we will briefly discuss the results of these studies as well as future directions.

Abbreviations

Ach	Acetylcholine
AcCoa	Acetyl-coenzyme A
AChE	Acetylcholinesterase
AChE-Is	Acetylcholinesterase inhibitors
AD	Alzheimer's disease
α-BTX	α-Bungarotoxin
BP_{ND}	Binding potential nondisplaceable
ChAT	Choline acetyltransferase
Cho	Choline
CNS	Central nervous system
DLPFC	Dorsolateral prefrontal cortex
[^{18}F]FEOBV	[^{18}F]fluoroethoxybenzovesamicol
[^{18}F]ASEM	[^{18}F]-JHU82132; 3-(1,4-diazabicyclo[3.2.2]nonan-4-yl)-6-^{18}F]fluorodibenzo[*b*,*d*]thiophene 5,5-dioxide)
2-[^{18}F]F-A-85380	2-[^{18}F]fluoro-3-(2(*S*)azetidinylmethoxy)pyridine
[^{3}H]QNB	[^{3}H](R)-3-quinuclidinylbenzilate
[^{123}I]-IDEX	[^{123}I]-iododexetimide
[^{123}I]-IBVM	[^{123}I]-iodobenzovesamicol
[^{123}I]5-IA-85380	[(123)I]-5-iodo-3-[2(S)-azetidinylmethoxy]pyridine)
mAChRs	Muscarinic acetylcholine receptors
MRS	Magnetic resonance spectroscopy
nAChRs	Nicotinic acetylcholine receptors
OFC	Orbitofrontal cortex
PD	Parkinson's disease
PET	Positron emission tomography
PNS	Peripheral nervous system
SPECT	Single-photon emission computed tomography
VAChT	Vesicular acetylcholine transporter

15.1 Introduction

Psychosis spectrum disorders, schizophrenia being the most severe form, are highly disabling psychiatric disorders characterized by positive (delusions, hallucinations), negative (blunted affect, anhedonia), motor, and cognitive symptoms. The prevalence of psychotic disorders is estimated at approximately 3% in the Western population, (Perälä et al. 2007) and the World Health Organization (WHO) estimates the direct costs of schizophrenia alone in Western countries at 1.6–2.6% of total healthcare expenditures (Chong et al. 2016). Current pharmacological treatments reduce positive symptoms, but do not target negative and cognitive symptoms and are accompanied by (severe) side effects (e.g., parkinsonism). However, alleviation of only positive symptoms often does not lead to functional recovery. Research suggests that, with current treatment, less than 15% of patients fully recover in terms of daily/social functioning (Remington et al. 2016). Therefore, there is an urgent need for treatment of negative and cognitive symptoms. However, the biological mechanisms underlying these symptoms remain largely unknown. A growing body of evidence implicate the cholinergic system in the pathology of psychosis, in particular cognitive symptoms (Carruthers et al. 2015; Raedler et al. 2007). Numerous studies have shown that receptor antagonist compounds targeting the central cholinergic system, such as scopolamine, can induce learning and memory problems, whereas cholinergic receptor agonists as well as acetylcholinesterase inhibitors (AChE-Is) can enhance these functions (Everitt and Robbins 1997; Fibiger 1991). Therefore, it has been suggested that development of pharmacological treatment targeting the cholinergic system could improve cognition in psychosis. However, in order to develop effective medication, more insight is necessary into the precise role of the cholinergic system in psychotic disorders. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are highly useful tools as these imaging techniques allow for chemical characterization of the cholinergic system in vivo. Although choline containing compounds can be measured with magnetic resonance spectroscopy (MRS), at present no other noninvasive neuroimaging techniques are available.

15.2 Cholinergic Neurotransmission

Acetylcholine (Ach) is the first discovered neurotransmitter and plays a role in many central nervous system (CNS) functions, including motor function, sleep, learning, and memory (Sofuoglu and Mooney 2009). Ach is synthesized in the presynaptic nerve terminal from a reaction between acetyl-coenzyme A and choline (Cho) and catalyzed by choline acetyltransferase (ChAT), an enzyme primarily expressed by cholinergic neurons, and stored in the synaptic vesicles (Sofuoglu and Mooney 2009; Sarter and Parikh 2005). Ach is released into the synaptic cleft where it is degraded into the inactive metabolites Cho and acetate by acetylcholinesterase

(AChE) (Sarter and Parikh 2005). Subsequently, Cho is transported back into the axon terminal for synthesis of more Ach (Sarter and Parikh 2005). Ach binds to two major classes of cholinergic receptors: nicotinic (ionotropic) and muscarinic (metabotropic) receptors.

15.2.1 Nicotinic Receptors

Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channel (inotropic) receptors with fast responses and excitatory effects (Sofuoglu and Mooney 2009; Dani and Bertrand 2007). Nicotinic receptors are expressed both in the peripheral nervous system (PNS) and the CNS and composed of ligand binding subunits, α_2–α_{10} (Jones et al. 2012), and structural subunits, β_2–β_4 (Gu 2002). Nicotinic AChRs are localized at post-, pre-, peri-, and extra-synaptic sites of cholinergic and other neurons (Dani and Bertrand 2007). Presynaptically located nAChRs regulate release of endogenous ACh (Sofuoglu and Mooney 2009; Jones et al. 2012), whereas postsynaptic nAChRs contribute a small minority of fast excitatory transmission, and non-synaptic nAChRs influence neuronal excitability, thereby modulating multiple neurotransmitter systems (Dani and Bertrand 2007). Their ability to modulate activity-dependent events underlies nAChR involvement in fundamental aspects of synaptic plasticity, attention, learning, and memory (Dani and Bertrand 2007; Albuquerque et al. 1997). Disruptions in central nicotinic modulated cholinergic transmission have been implicated in a variety of disorders including schizophrenia (Dani and Bertrand 2007; Jones et al. 2012).

15.2.2 Muscarinic Receptors

Muscarinic acetylcholine receptors (mAChRs) are G-protein-coupled (metabotropic) cholinergic receptors that can have either excitatory or inhibitory effects and have a longer onset latency (Gu 2002). Muscarinic AChRs are expressed both in the CNS and PNS and account for approximately 90% of all cholinergic receptors (Sofuoglu and Mooney 2009). At least five different subtypes can be distinguished, labeled M_1–M_5 (Bymaster et al. 2003), that can be divided into two classes based on their G-protein-coupling mechanism: M_1, M_3, and M_5 versus M_2 and M_4 (Caulfield and Birdsall 1998; Eglen 2006; Ryan et al. 2019). The first group, referred to as the "M_1-like" subtypes are located postsynaptically and have excitatory downstream effects, whereas the second group, referred to as the "M_2-like" subtypes, are located pre- and postsynaptically and have predominantly inhibitory effects (Jones et al. 2012; Ryan et al. 2019). In addition to a "classic" agonist binding site, muscarinic receptors also have allosteric binding sites enabling the modulation of agonist activation. Of all mAChRs, the M_1 receptor has the highest expression rate in the CNS, in particular in the cortex, hippocampus, and striatum, and is increasingly implicated in cognitive processes (Eglen 2006) and considered a potential target for treatment of cognitive symptoms in psychiatric and neurological disorders including schizophrenia.

15.3 Cholinergic System in Psychosis

The cholinergic system has been broadly related to neurodegenerative disorders characterized by cognitive decline and/or motor symptoms including Alzheimer's disease (AD) and Parkinson's disease (PD), partly because of its close relation with the dopaminergic system (McCluskey et al. 2019). Since psychotic disorders are also associated with cognitive decline, the cholinergic system became of interest for these disorders as well. Nevertheless, to date, studies examining the cholinergic system in patients with a psychotic disorder are limited, and most of the evidence is derived from preclinical and post-mortem studies.

15.3.1 Nicotinic PET/SPECT Imaging in Psychosis

15.3.1.1 Post-Mortem Studies

Most evidence for changes in nAChRs availability in psychotic patients comes from post-mortem studies. Several studies have demonstrated decreased expression of nicotinic receptors in schizophrenia (Vingerhoets et al. 2019a; Court et al. 1999; Freedman et al. 1995; Marutle et al. 2001). Freedman et al. (Freedman et al. 1995) used both [^{125}I]-α-bungarotoxin (α-BTX), an α-neurotoxin with a binding site at nicotinic α_7, α_8, and α_9 subunits (Court et al. 1999; Chen and Patrick 1997), and [^{3}H]-cytisine, a nicotinic agonist with high affinity predominantly for the $\alpha_4\beta_2$ subunits, to assess nicotinic receptor binding in schizophrenia. They report a decrease in the number of nicotinic receptors in hippocampal brain tissue of eight patients with schizophrenia compared to eight age-matched controls. In line with these results, Court et al. (1999) found reduced [^{125}I]-α-BTX binding in the thalamus of schizophrenia patients compared to controls. Contrary, the authors did not find a reduction of [^{3}H]-nicotine binding. Similarly, using [^{125}I]-α-BTX, Guan et al. (1999) found a decrease of nicotinic α_7 subunits in the frontal cortex of schizophrenia patients. Finally, the laminar distribution of nicotinic receptors were examined in 12 post-mortem brains of schizophrenia patients using [^{125}I]-α-BTX, [^{3}H]-cytisine, and [^{3}H]-epibatidine (high affinity for α_3 and α_4 subunits) (Marutle et al. 2001). Patients with schizophrenia had fewer [^{125}I]-α-BTX binding sites in the cingulate cortex compared to smoking control subjects, but not when compared to all control subjects. In the orbitofrontal and temporal cortex, results did not reach significance, although a trend for decreased [^{125}I]-α-BTX binding in the orbitofrontal cortex and increased [^{125}I]-α-BTX binding in the temporal cortex was found. Moreover, [^{3}H]-cytisine binding was increased in the cingulate cortex of schizophrenia patients compared to the total sample of controls as well as only the smoking controls. In the same region, higher [^{3}H]-cytisine binding was observed in all layers with the exception of layer 1 in schizophrenia compared to controls that smoked.

15.3.1.2 In Vivo Studies

Nicotine is considered the most addictive component of tobacco (Brody et al. 2006). NAChRs in the brain mediate nicotine's action, of which those containing $\alpha_4\beta_2$ are the most abundant in the brain, have the highest affinity for nicotine, and are

instrumental in mediating nicotine's reinforcing properties (D'Souza et al. 2012). Human post-mortem studies in "healthy" tobacco users demonstrated an increase in nicotinic binding sites (Benwell et al. 1988). In vivo, an upregulation of the nACh $\alpha_4\beta_2$ receptor subtype has been reported in healthy smokers compared to nonsmokers using 2-[^{18}F]fluoro-3-(2(*S*)azetidinylmethoxy)pyridine (2-[^{18}F]F-A-85380) positron emission tomography (PET) (Wüllner et al. 2008). The vast majority of patients with a psychotic disorder smoke tobacco (Myles et al. 2012; Lucatch et al. 2018), and most patients use tobacco excessively (Barnes et al. 2006; Vingerhoets et al. 2019b), suggesting altered nAChR binding in these patients. Indeed, thalamic 2-[^{18}F]F-A-85380 binding potential nondisplaceable (BP_{ND}) was found to be lower in tobacco using patients with paranoid schizophrenia and one tobacco using healthy control subject compared to four nonsmoking healthy controls (Brašić et al. 2012). It must be noted though that all tobacco-using participants had smoked shortly before scanning. Therefore, it is likely that many of the nAChRs were already occupied by nicotine.

The SPECT ligand [(123)I]-5-iodo-3-[2(S)-azetidinylmethoxy]pyridine) ([^{123}I]5-IA-85380) has been used for in vivo quantification of the nicotinic receptors with high affinity for β_2 subunits. Using this tracer, earlier post-mortem findings of lower β_2^*-nicotinic receptor availability in tobacco using schizophrenia patients compared to smokers without schizophrenia were confirmed in the frontal cortex, parietal cortex, and thalamus (D'Souza et al. 2012). Moreover, β_2^*-nicotinic receptor availability was inversely correlated with negative symptoms. Elaborating on these findings, β_2^*-nicotinic receptor availability was compared between tobacco and non-tobacco-using patients with schizophrenia as well as healthy controls matched for smoking, age, and sex (Esterlis et al. 2014). The total sample of schizophrenia patients displayed lower β_2^*-nicotinic receptor availability relative to the total control group, and, overall, nonsmokers had lower β_2^*-nicotinic receptor availability compared to smokers. Interestingly, there was no smoking by diagnosis interaction effect, but smoking schizophrenia patients had higher β_2^*-nicotinic receptor availability opposed to nonsmoking schizophrenia patients. Higher β_2^*-nicotinic receptor availability was associated with less negative symptoms and better executive control, and chronic use of antipsychotics did not appear to be related to β_2^*-nicotinic receptor availability.

Another nAChR subtype strongly associated with tobacco use is the α_7 receptor which consists entirely of α_7 subunits (Lucatch et al. 2018). Of all the nicotinic receptors, this subtype has been studied most frequently in relation with psychotic disorders, and like the nACh $\alpha_4\beta_2$ receptor, this subtype has been linked to excessive tobacco use in schizophrenia (Tregellas and Wylie 2019). Because of its relatively low expression rate in the human brain, it has been proven difficult to develop PET/SPECT tracers to image this receptor subtype in the brain (Marutle et al. 2001; Coughlin et al. 2019). Recently, quantification of the nicotinic α_7 receptor has been feasible using the PET tracer [^{18}F]JHU82132; 3-(1,4-diazabicyclo[3.2.2]nonan-4-yl)-6-[^{18}F]fluorodibenzo[*b*,*d*]thiophene 5,5-dioxide ([^{18}F]ASEM) (Wong et al. 2014). Using [^{18}F]ASEM PET, Wong et al. (Wong et al. 2006) found reduced binding in the cingulate cortex, frontal cortex, and hippocampus in five out of six

schizophrenia patients compared to controls (Wong et al. 2018). Moreover, a small pilot study in nonsmoking patients with recent-onset psychosis showed lower [^{18}F]ASEM binding in the hippocampus than control subjects, in particular those patients with non-affective psychosis (Coughlin et al. 2018). In addition, lower [^{18}F]ASEM binding was associated with worse verbal memory and processing speed, implying a role of het nicotinic α_7 receptor in cognitive deficits in psychotic disorders.

15.3.2 Muscarinic PET/SPECT Imaging in Psychosis

15.3.2.1 Post-Mortem Studies

Accumulating evidence suggests that altered or deficient muscarinic signaling underlies the clinical symptoms of psychosis, including cognitive deficits (Carruthers et al. 2015; Ryan et al. 2019; Vingerhoets et al. 2019a; Bakker et al. 2018). Evidence for involvement of the cholinergic muscarinic receptors in psychosis has mainly been gained from studying CNS tissue obtained post-mortem (Raedler et al. 2007). These post-mortem studies have yielded mixed results. An early study using the nonselective tracer [^{3}H](R)-3-quinuclidinylbenzilate ([^{3}H]QNB) reported reduced levels of muscarinic receptor binding in the frontal cortex of schizophrenia patients compared to control subjects (Bennett et al. 1979). In a different study also using [^{3}H]QNB, an increased number of muscarinic receptors were found in the orbitofrontal (OFC) and medial frontal cortex in medicated patients with schizophrenia compared to controls (Watanabe et al. 1983). Contrary, unmedicated patients did not differ from controls, suggesting an effect of long-term antipsychotic use. However, this discrepancy in findings could also be associated with the nonselectiveness of [^{3}H]QNB. Later studies have reported differences using more selective ligands such as [^{3}H]pirenzepine and found a significant decrease of muscarinic M_1 and M_4 receptors in the striatum (Dean et al. 1996; Crook et al. 1999), hippocampus (Crook et al. 2000), and PFC (Crook et al. 2001; Dean et al. 2002) of schizophrenia patients but not in the parietal cortex (Dean et al. 2002). In addition, these changes in M_1 receptor density appear to be characteristic for schizophrenia since no changes were found in bipolar and depressive disorders (Zavitsanou et al. 2004). However, other studies did find altered numbers of M_2 and M_3 receptors in schizophrenia (Raedler et al. 2007; Zavitsanou et al. 2004; Scarr et al. 2006).

A more recent post-mortem study using [^{3}H]pirenzepine reported a decrease of muscarinic M_1 receptors up to 74% in the dorsolateral prefrontal cortex (DLPFC) in subgroup of patients with schizophrenia comprising approximately 25% of the sample (Scarr et al. 2009). The authors labeled this subgroup "muscarinic receptor-deficit schizophrenia" (MRDS) and hypothesized that this may be a subgroup of patients displaying more severe cognitive symptoms, given the role of M_1 receptors in several cognitive functions, although data of cognitive function were not available. Interestingly, this so-called MRDS subgroup did not differ from other schizophrenia patients in terms of clinical characteristics including gender, age, duration of illness, or any particular drug treatment (Scarr et al. 2009).

15.3.2.2 In Vivo Studies

The number of in vivo studies examining changes in muscarinic receptor density in psychosis is still limited. Nevertheless, these studies support the post-mortem findings of reduced M_1 receptor density in patients with a psychotic disorder. In a [^{123}I]IQNB SPECT study by Raedler et al. (Raedler et al. 2003a), patients with schizophrenia who were medication-free at time of scanning displayed decreased muscarinic receptor availability in the cortex and basal ganglia. Muscarinic receptor occupancy was decreased up to 35% in schizophrenia patients compared to matched control subjects in this sample of 12 patients. Unfortunately, [^{123}I]IQNB binds with very high affinity to all subtypes of the muscarinic receptors (Raedler et al. 2007). Therefore, it is unknown whether this decreased availability reflects predominantly a reduction in M_1 receptors.

SPECT imaging was also used to examine the effects of antipsychotic medication on the cholinergic muscarinic system. Raedler et al. (Raedler et al. 2000) used [^{123}I]IQNB SPECT to study the effects of the antipsychotic olanzapine at a daily dose of 5 and 20 mg, respectively, on the cholinergic muscarinic receptors in the cortex, striatum, thalamus, and the pons of schizophrenia patients. At both a low and high dosage of olanzapine, [^{123}I]IQNB binding was significantly lower compared to [^{123}I]IQNB binding in medication-free subjects in all brain regions except the striatum. Moreover, in these same brain areas, [^{123}I]IQNB binding was significantly lower at a dose of 20 mg compared to 5 mg indicating that olanzapine blocks muscarinic receptors in vivo significantly, possibly explaining the low incidence of anticholinergic side effects. In a different study by Raedler et al. (Raedler et al. 2003b), and also using [^{123}I]IQNB SPECT, the impact of low to moderate dosages of the antipsychotic clozapine on muscarinic receptors in the basal ganglia, cortex, thalamus, and pons was examined. Compared to medication-free psychotic subjects, [^{123}I]IQNB binding was lower in all examined brain areas, and decreases in binding were observed with increasing dose. In a separate study, the authors compared the previously reported effects of olanzapine and clozapine directly and concluded that clozapine treatment resulted in a stronger muscarinic receptor blockade than olanzapine (Raedler 2007).

The effects of antipsychotic treatment on cholinergic muscarinic receptors were also examined with the SPECT ligand [^{123}I]-iododexetimide ([^{123}I]IDEX). This ligand predominantly binds to the M_1 subtype, although it also has relatively high affinity for the M_4 subtype, but not for $M_{2,3,5}$ receptors (Bakker et al. 2015). In this study by Lavalaye and co-workers (Lavalaye et al. 2001), [^{123}I]IDEX binding in the cortex and striatum of patients stabilized on the antipsychotics olanzapine or risperidone was compared directly as well as to healthy control subjects. Patients treated with olanzapine displayed lower binding ratios in both the cortex and striatum than patients treated with risperidone as well as control subjects, reflecting higher levels of muscarinic receptor occupancy by olanzapine. Moreover, patients treated with risperidone also showed lower binding ratios compared to controls, but this was only significant in the striatum.

In a more recent study also using [^{123}I]IDEX SPECT imaging, Bakker et al. (Bakker et al. 2018), found a link between lower M_1 receptor binding in the DLPFC and poorer performance on a verbal learning and memory task. Moreover, lower M_1

binding in the hippocampus was associated with worse delayed recognition of verbal information. In addition, higher negative symptom severity was associated with lower M_1 binding in the hippocampus. Since in this study no healthy control subjects were included, it remains unknown whether these findings are specific for patients with a psychotic disorder. Indeed, administration of a muscarinic M_1 antagonist produced cognitive impairments in subjects with a psychotic disorder (Vingerhoets et al. 2017; Veselinović et al. 2015). Figure 15.1 displays [^{123}I]IDEX binding in the brain of a patient with a psychotic disorder.

15.4 Conclusion and Future Directions

To summarize, cholinergic alterations are increasingly linked to psychosis. Both post-mortem and in vivo PET and SPECT studies provided evidence for altered nicotinic and muscarinic receptors in psychosis, suggesting that reductions of cholinergic receptors, in particular nicotinic $\alpha_4\beta_2$ and α_7 as well as muscarinic M_1 receptors, could be identifiable biomarkers for psychotic disorders. These results are supported by findings of altered brain choline concentrations in MRS studies (Kirtaş et al. 2016; Bustillo et al. 2002, 2014; Plitman et al. 2016) and pharmacological (challenge) studies reporting memory deficits after administration of anticholinergics in psychotic patients (Vingerhoets et al. 2017; Veselinović et al. 2015). Overall, this may suggest that a subgroup of psychotic patients may benefit from cholinergic pharmacological treatment. However, results of pharmacological interventions targeting the cholinergic system have been mixed. For example, AChE-Is have overall not yielded much positive results (Vingerhoets et al. 2013; Santos et al. 2018), although some studies have found improvement in speed of processing after AChE-I add-on treatment in schizophrenia (Santos et al. 2018). These limited beneficial effects of AChE-Is are likely due to the fact that AChE-Is may not affect AChR function directly. Contrary, monotherapy with xanomeline, a muscarinic M_1 agonist, has shown to improve both positive and negative as well as cognitive symptoms in patients with schizophrenia (Shekhar et al. 2008). This may suggest that selective targeting of cholinergic receptors may be a more successful strategy than increasing ACh levels per se. Nevertheless, muscarinic drugs cause a variety of PNS-related side effects (particularly related to the gastrointestinal tract), possibly because lack of selectivity for the M_1 subtype, and currently no M_1 agonists are approved for treatment of psychosis. Since PET and SPECT have the potency to identify chemical signatures, these techniques may be useful tools for identification of biomarkers and examining medication response. Moreover, PET and SPECT have the potential to become useful tools in stratification of patients in order to inform treatment decisions, if validated further (Coughlin et al. 2019). In particular patients with first-episode psychosis may benefit from methods allowing identification of personalized effective treatments. At present, finding an effective treatment can be a search which burdens affected (young) patients by unnecessary prolongation of symptoms and unwanted side effects. Moreover, this could lead to nonadherence of future treatment. Stratification of psychotic patients can guide personalized medicine which is beneficial for patients, their environment, and the broader society.

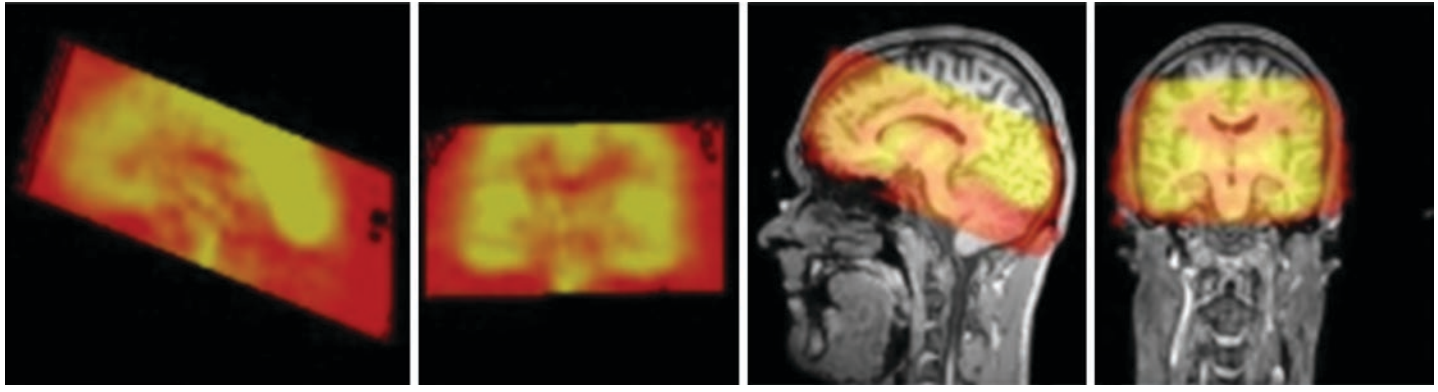

Fig. 15.1 Adapted from Bakker et al. (Bakker et al. 2018). The left panel displays [^{123}I]IDEX binding in a subject with a psychotic disorder demonstrating high cortical binding and no binding in white matter and cerebrospinal fluid. The right panel shows the same [^{123}I]IDEX SPECT scan co-registered to the subjects' own structural T1 MRI scan. Darker areas are overlay white matter tracts, ventricles, and cerebellum indicating no [^{123}I]IDEX binding in these areas

15.4.1 Cholinergic Transporter Imaging

In addition to targeting nicotinic and muscarinic cholinergic receptors, there are developments to target the vesicular acetylcholine transporter (VAChT). VAChT activity is distinct from the therapeutic site of AChE-I and has been described as a more pure indication of presynaptic cholinergic terminal density compared to other cholinergic targets (McCluskey et al. 2019; Bohnen et al. 2018). Although [^{123}I]iodobenzovesamicol ([^{123}I]IBVM) SPECT has been available for imaging VAChT for decades (Kuhl et al. 1994), no studies using this technique to examine patients with psychotic disorders have been performed. In recent years, new PET tracers have been developed to study VAChT. One of these tracers is [^{18}F]fluoroethoxybenzovesamicol ([^{18}F]FEOBV). As compared to the SPECT tracer [^{123}I]IBVM, this PET tracer offers the possibility to in vivo examine smaller brain regions (Petrou et al. 2014). Although at present, no [^{18}F]FEOBV PET studies have been performed in psychotic disorders, decreased [^{18}F]FEOBV binding has recently been demonstrated in cortical and subcortical brain areas involved in cognition functioning in disorders characterized by cognitive deficits, namely, dementia with Lewy bodies and AD (Nejad-Davarani et al. 2019; Aghourian et al. 2017). Therefore, and considering the increasing evidence of involvement of the cholinergic system in psychotic disorder and efforts of developing cholinergic treatments for these disorders, [^{18}F]FEOBV PET may be a useful tool to increase our knowledge of cholinergic abnormalities in psychosis. Potentially, it can be used to stratify patients and guide clinical decision-making in the future.

15.5 Concluding Remarks

To conclude, both post-mortem and in vivo SPECT and PET studies demonstrated cholinergic alterations in patients with psychotic disorders which may be linked to negative and cognitive symptoms. Therefore, a subgroup of patients could possibly benefit from cholinergic treatment. Cholinergic PET and SPECT imaging can potentially be used to stratify patients with cholinergic abnormalities in the future in order to guide clinical decision-making and personalized medicine and to optimize treatment outcome for psychotic patients.

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Molecular Imaging in Schizophrenia Spectrum Disorders

16

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Contents

Abstract

In this chapter, we aim to shed light on the schizophrenia spectrum disorders using molecular imaging. Schizophrenia spectrum disorders consist primarily of the disorders with full-blown psychosis in their course and are grouped in the DSM-V category of schizophrenia and other psychotic disorders. The treatment of psychosis has been very successful in the era of psychopharmacology, starting with the discovery of the "neuroleptic" drug chlorpromazine (Largactil). The notion that the so-called typical antipsychotics bind to dopamine D_2 and D_3

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receptors is one of the cornerstones of the dopamine hypothesis of schizophrenia (Davis et al., Am J Psychiatry 148:1474–1486, 1991). For more than a decade, this hypothesis has been the most influential hypothesis in schizophrenia research. It postulates that schizophrenia is a manifestation of a "hyperdopaminergic" state in some regions of the brain. The binding of antipsychotics to D_2/D_3 receptors can be directly visualized and quantified with dopamine receptor PET and SPECT ligands, such as [^{11}C]-raclopride or [^{123}I]-IBZM, respectively (Laruelle, Q J Nucl Med 42:211–221, 1998). Typical antipsychotics bind to D_2/D_3 receptors and displace these radiotracers from the postsynaptic receptors in the dopamine projection areas, such as the striatum, providing a unique way to quantify occupancy of these compounds to the D_2/D_3 receptors. In one of the first human studies with [^{11}C]-raclopride, described that an occupancy of 70–80% of the D_2/D_3 receptors was sufficient for its antipsychotic effects while parkinsonistic effects were associated with much higher occupancies. The anti-dopaminergic effects in the striatum explain the major side effect of typical antipsychotics, i.e., parkinsonism. Very efficacious second-line or "atypical" antipsychotics appear to be less dependent on D_2 blockade for clinical effect. The major example of this line of drugs is clozapine. Clozapine acts partly by its affinity for the postsynaptic $5HT_{2A}$ receptor but has "pleiotropic" effects by affecting many other neurotransmitter receptors, hormone receptors, and inflammatory mediators. However, it was found that the newer "atypical" antipsychotics marketed after clozapine still bind for a large proportion to dopamine D_2/D_3 receptors, which contributes significantly to their antipsychotic efficacy. Despite the enormous progress in the development of antipsychotics, and growth of choice for the clinician to treat schizophrenia, the effect remains limited to a suppressive effect on the positive psychotic symptoms, like delusions and hallucinations. Antipsychotics do not cure the disease and have major metabolic side effects, like weight gain, increasing the risk for diabetes enormously. Therefore, more knowledge on the working mechanism and the discovery of alternative molecular pathways of treatment are needed. It is the aim of this chapter to translate molecular imaging in experimental models of schizophrenia and patients to better understand the etiopathogenesis of the clinical syndrome of schizophrenia. The ultimate aim is to design better prevention, care, and cure for schizophrenia by pinpointing to the molecular focus of the disease process.

16.1 The Disease

In the nineteenth-century German literature on medicine of psychiatric disorders, the schizophrenia spectrum disorders are very well described. In those times, the loss of mental functions was assumed to be the primary clinical feature of the disease, and this point of view resulted in the labeling of the disease with the term "dementia praecox." In our days, these function losses are designated as "negative

symptoms." Examples of such declining functions are loss of initiative, attention deficits, cognitive and intellectual decline, and depression of mood. The "functions gained" during a psychosis such as delusions, hallucinations, and increased power of (bizarre) associations are currently designated as positive symptoms. The disease is thought to be exclusive for humans and supposed to be rising in incidence during the era of industrialization and urbanization. The early periods of urbanization in the seventeenth to eighteenth century coincided with the start of institutionalization of psychiatry. This was the era of the start and rise of asylums for the insane. The epidemiology of schizophrenia is still showing an urban peak, with other factors such as crowding, poor social integration, cannabis use, and sexual transmission of diseases adding to the risk. Experiencing influenza infections or famine conditions during the second trimester of pregnancy infers a small increase of risk for the child to acquire schizophrenia.

The lifetime prevalence of schizophrenia is 1% (Torrey 1987), with a peak incidence of new cases between 15 and 25 years of age. Possibly a second peak around 40 years of age occurs in females. The disease has features of a waxing and waning course, with psychoses at the time of waxing, and negative symptoms appearing in a subgroup of patients independent of psychoses. The disease tends to become recurrent or chronic, despite adequate use of medication and psychological treatment. Antipsychotics are usually efficacious against positive symptoms, but are notoriously inadequate if negative symptoms arise. For clozapine there is some proof for effects on the negative symptom cluster, but clozapine is a broadly acting drug with many side effects. New drugs that act like clozapine have been developed (risperidone, olanzapine, quetiapine), but the superior effect on cognition has not been proved. Some new approaches focus on other transmitters like glutamate and its receptors like the N-methyl-D aspartate (NMDA) receptor and the AMPA receptor. Some alternative strategies based on augmentation of NMDA receptor neurotransmission are currently in phase III trials (glycine inhibitors), with the promise of cognition-enhancing properties with less side effects. This promise has to our knowledge not yet been fulfilled by other drugs than clozapine.

16.2 The Hypotheses

Three major hypotheses of the biological etiology of schizophrenia are superficially addressed in this paragraph to prepare the further discussion of neuroimaging in schizophrenia: the dopamine hypothesis, the glutamate hypothesis, and the inflammation hypothesis.

As stated before, the dopamine hypothesis of schizophrenia has been the most influential. It is based on the fact that all antipsychotics bind to D_2/D_3 receptors. In addition, it has been found that increasing availability of dopamine in the synaptic cleft after administration of amphetamines can induce psychotic-like behavior, with profound paranoia and hallucinations both in healthy subjects and patients with schizophrenia. These observations fuel the dopamine hypothesis, stating either

hyperavailability of dopamine or receptor hypersensitivity as the cause of (part) of the disease. But the abovementioned observations do not explain why the effects of D_2-blocking and dopamine-releasing drugs are temporary whereas psychosis in schizophrenia has a protracted course. In addition they do not explain the lack of response of negative and cognitive symptoms to dopaminergic drugs (Davis et al. 1991).

Decades ago, a new hypothesis has been postulated that schizophrenia is associated with aberrations in the glutamatergic neurotransmission (Javitt and Zukin 1991). This is based on the observation that subjects treated with antagonists of the glutamatergic NMDA receptors (PCP or ketamine) show a clinical syndrome that is very difficult to distinguish from schizophrenia. In addition, there is some preliminary evidence that enhancement of NMDA neurotransmission is associated with beneficial effects in patients with schizophrenia, suggesting that indeed glutamatergic neurotransmission is involved in the pathophysiology of schizophrenia. Finally, the old hypothesis that schizophrenia might be caused by an inflammatory or infectious insult during brain development has experienced a revival. Major genetic studies with GWAS (genome-wide association studies) show an association between MHC (major histocompatibility complex) antigen-presenting phenotypes and schizophrenia, and specifically the complement 4 expression within the MHCIII region is involved (Sekar et al. 2016). An increased activity of resident immune cells (microglia) in the brain is possibly also associated with schizophrenia.

16.3 Human Imaging Studies

The majority of molecular imaging studies have focused on several parts of the dopamine system. In the first approach to image the dopamine system in schizophrenia, the postsynaptic D_2/D_3 receptors were the target using tracers such as [^{11}C]-NMSP, [^{11}C]-raclopride, and [^{123}I]-IBZM. Currently, more than 20 studies have been published, and pooling of the data presented in these studies has indicated that there is indeed a small increase in D_2/D_3 receptor availability in patients with schizophrenia (Howes et al. 2012). However, a key negative finding is that no postsynaptic D_2/D_3 receptor availability changes appear in *medication-naïve* patients. An increase in the postsynaptic D_2/D_3 binding potential in *medicated* patients seems to be a secondary effect of receptor upregulation by dopamine blockade. These studies focused on the striatum, as this brain region has the highest density of dopamine projections in the brain, and could therefore be reliably imaged. However, the development of high-affinity tracers, like [^{11}C]-fallypride and [^{11}C]-FLB457, enabled the visualization of extrastriatal D_2/D_3 receptors. A meta-analysis of eight studies revealed nonsignificant reductions of D_2/D_3 receptor availability in the thalamus of schizophrenic patients (Kambeitz et al. 2014), which is in contrast with the small increase in the striatum. Despite being the most abundant dopamine receptor in the brain, much less attention has been given to the D_1 receptor. This is related to the fact that the D_1 receptor is not a major target for antipsychotic drugs. However, the D_1 receptor might be related to the cognitive deficits observed in schizophrenia.

The PET tracers [^{11}C]-SCH23390 and [^{11}C]-NNC112 have been used to determine the D_1 receptor availability. The limited number of studies that have been performed in schizophrenia did not indicate a clear change in D_1 receptor availability but did suggest that antipsychotic medication decreases the availability and that the D_1 receptor is involved in psychosis (Cervenka 2019).

The D_2/D_3 receptor tracer [^{11}C]-raclopride and [^{123}I]-IBZM can also be used to probe dopamine release in vivo (Laruelle 1998). Using pharmacological, such as administration of methylphenidate or amphetamine, or psychological approaches, such as stress paradigms, the bioavailability of dopamine in the synaptic cleft can be increased. When combined with a PET or SPECT study, this increase in dopamine competes with the radiotracer resulting in a decrease of the amount of binding. It has been found that the decrease in receptor binding is linearly related to the increase in dopamine, providing a unique method to probe dopamine release in vivo. Three studies using this paradigm have been performed in patients with schizophrenia from two different groups all describing an increased amphetamine-induced dopamine release in the striatum (Abi-Dargham et al. 1998; Breier et al. 1997; Laruelle et al. 1996). In contrast, amphetamine-induced dopamine release was found to be decreased in the dorsolateral prefrontal cortex, and this decrease extended to other extrastriatal regions (Slifstein et al. 2015).

Evidence for increased presynaptic dopamine synthesis has been found from PET studies using the PET tracer [^{18}F]-DOPA. More than 15 studies have been published on [^{18}F]-DOPA uptake in patients with schizophrenia describing a consistent increase in uptake (Howes et al. 2012). Indeed, this is one of the most replicated findings in molecular imaging in schizophrenia. No difference has been found in the dopamine transporter, which has been assessed with tracers such as [^{123}I]-FP-CIT, [^{18}F]-CFT, [^{123}I]-β-CIT, and [^{99m}Tc]-TRODAT 1 (Howes et al. 2012). This indicates that the dopamine synapse is still intact in schizophrenia but the presynaptic activity and dopamine release are increased in patients suffering from this disease. One could conclude that the regulation of dopamine release in schizophrenia is deficient and not the dopamine neurons themselves. Major players in the regulation of presynaptic dopamine release are the neurotransmitters glutamate and GABA. Indeed, direct imaging of glutamatergic receptors in patients with schizophrenia may shed some light on this regulation. Unfortunately, quantification of glutamate receptors in vivo in patients with schizophrenia has been challenging, mainly due to a lack of tracers for this purpose. With PET it is currently only possible to image the metabotropic glutamate receptor type 5 (mGluR5) with tracers such as [^{11}C]-ABP688 (Ametamey et al. 2007), which is a big step forward in the in vivo characterization of glutamatergic neurotransmission in neurological and psychiatric diseases. In the first PET study with [^{11}C]-ABP688, no differences in the mGluR5 availability were found between schizophrenic patients and controls, nor any relation with symptom severity (Akkus et al. 2017). This lack of differences was confirmed in a later study by another group (Brambilla et al. 2020), which did find a relation between low mGluR5 receptor availability and negative, depressed, and cognitive symptoms, which were associated with smoking. In this context it needs to be mentioned that smoking was found to result in a decreased mGluR5 receptor availability (Akkus et al. 2013). While several

new PET tracers for the N-methyl-D-aspartate (NMDA) receptors are currently being tested in humans, a first SPECT study revealed decreased binding of the NMDA receptor tracer [^{123}I]-CNS-1261 in the left hippocampus of drug-naïve schizophrenic patients (Pilowsky et al. 2006). Interestingly, besides direct imaging of glutamate receptors, [^{11}C]-ABP688 and PET may also be used for the quantification of glutamate release after a pharmacological or cognitive challenge. Pharmacologically, this can be accomplished with administration of sub-anesthetic dosages of ketamine or with administration of N-acetylcysteine. Indeed, there is already proof of concept using the N-acetylcysteine challenge with [^{11}C]-ABP688. Applications of these tracers and techniques will open a new era in the molecular imaging of schizophrenia and hopefully shed some more light on the pathophysiology of the disease.

A very new focus of research in schizophrenia is the process of neuroinflammation. A key player in neuroinflammation is the activated microglia. Microglia, the macrophage of the brain, will be activated in all conditions associated with neuronal injury. Indeed, an increase in the numerical density of microglia has already been demonstrated in the temporal and frontal cortex of patients with chronic schizophrenia. Activated microglia can be quantified in vivo with translocator protein (TSPO) ligands, such as the first-generation ligand [^{11}C]-(R)-PK11195 and second-generation ligands [^{11}C]-PBR28, [^{18}F]-PBR111, and [^{18}F]-FEPPA. In the first two PET studies, it was found that there is indeed increased specific binding of [^{11}C]-(R)-PK11195 in patients with schizophrenia as compared with controls (Doorduin et al. 2009; van Berckel et al. 2008). Interestingly, it was found that the hippocampus is primarily involved in the inflammatory process, a site that may well be responsible for the immediate memory problems in schizophrenia (Doorduin et al. 2009). Following these two initial studies, over ten additional studies have been published, with inconsistent results showing a decrease or an increase in binding, or no changes (Marques et al. 2019). This might be related to PET methodology, as both first- and second-generation ligands were used, with the latter being sensitive for a polymorphism in the TSPO (Kreisl et al. 2013), and results were reported using different outcome measures (binding potential and volume of distribution). Moreover, a major caveat in interpretation of these newer results is patient heterogeneity, and how acutely and how severely psychotic the patients in these studies were. Milder psychotic symptoms might reflect lower microglial activation. Preliminary results (Jonker et al. 2016) from a double-blind placebo-controlled study with a high dose of the antiviral drug valaciclovir, in more severely psychotic patients, indicated a trend toward reduction in hippocampal microglia activation.

Activated microglia may play an important role in the functional handicaps associated with schizophrenia. Indeed, in a hypothetical model, any unknown trigger having an effect on the limbic brain regions including the hippocampus may cause locally activated microglia, which by itself can induce a cascade of responses limiting the functions of the limbic system, whether emotional, cognitive, or both. Given the potential role of microglia in schizophrenia, the methodological challenges of TSPO PET, and the recent suggestion that TSPO is a poor marker of microglia activation (Sneeboer et al. 2020), new PET tracers for imaging of microglia activation need to be developed.

16.4 Small-Animal Studies

Given the impact schizophrenia has on the life of patients and their environment, there is a desperate need for improved treatment strategies. Ideally these treatments should be targeted, but the poor understanding of the exact molecular mechanisms involved in schizophrenia hampers the development of targeted treatment. Studies in small animals, i.e., mice and rats, are important for the identification of molecular mechanism involved in schizophrenia and the development and evaluation of treatment, especially because it allows for manipulations and interventions that are not possible to perform in a clinical setting. Such studies would benefit from the use of small-animal PET and SPECT. With these techniques, it is possible to study the different molecular mechanisms, such as dopaminergic and glutamatergic neurotransmission, during different manipulations, such as exposure to inflammatory or infectious agents, in a single animal longitudinally and to combine imaging with behavioral analysis. Furthermore, many of the PET and SPECT tracers that are first tested in small animals can subsequently be applied in a clinical setting allowing for direct translation of the findings. Below is an overview of studies in animal models of schizophrenia that used small-animal PET or SPECT or autoradiography to measure dopamine- and glutamate-related processes and inflammation in the brain.

There are numerous animal models of schizophrenia in which mice or rats display a schizophrenic-like behavior. In this paragraph the models described in the literature are attributed to drug-induced, neurodevelopmental, infectious, and genetically induced models of schizophrenia.

Injection of antagonists of the NMDA receptor, such as ketamine, phencyclidine (PCP), or MK801, exacerbates symptoms in schizophrenic patients. Likewise, both acute and chronic administrations of these antagonists in rodents result in the display of schizophrenic-like behavior. Both dopamine and glutamate receptors were found to be affected by treatment with NMDA antagonists. A single injection with PCP was found to decrease the binding of the D_1-ligand [^{3}H]-SCH23390 in the striatum and increase the overall binding of the D_2-ligand [^{3}H]-raclopride, 4 h after injection (Dalton and Zavitsanou 2011). However, chronic treatment (1 month) of rats with MK801 was shown to decrease the binding of the D_2/D_3-ligand [^{123}I]-epidepride in the striatum and midbrain as shown by ex vivo autoradiography (Huang et al. 2012). SPECT/CT imaging with [^{123}I]-epidepride also revealed a decreased binding in the striatum and midbrain. Changes in glutamate receptors were studied after chronic treatment (14 days) with PCP. An increased binding of the NMDA ligand [^{3}H]-MK801 was found in the hippocampus, 1 and 24 h after the last treatment with PCP (Newell et al. 2007). Binding was decreased at 14 days after the last PCP treatment. In a similar study, it was shown that 14 days of PCP treatment caused a decrease in binding of the AMPA-ligand [^{3}H]-AMPA in the hippocampus, amygdala, and part of the parietal cortex (Zavitsanou et al. 2008). Acute treatment of rats with a sub-anesthetic doses of ketamine did not affect [^{11}C]-ABP688 binding to mGluR5 (Kosten et al. 2018). Treatment of rats with MK801 for 7 days resulted in an increased binding of [^{11}C]-ABP688 in the caudate putamen (Servaes et al. 2019). In contrast, 1 month of treatment of rats with MK801 was only found

to cause a small nonsignificant increase in mGluR5 availability, as measured with [^{11}C]-ABP688 PET (Kosten et al. 2016). The MK801 treatment did result in a reduced uptake of the TSPO ligand [^{18}F]-PBR11, which was in contrast with the postmortem findings of increased microglia activation.

Rat pups that were treated with the NMDA antagonist CGP40116 on a total of 8 days up until postnatal day 21 show a schizophrenic-like behavior at postnatal day 60 (Wedzony et al. 2008). This behavior was found to be accompanied by decreased binding of the D_3-ligand [^{3}H]-7-OH-DPAT in the nucleus accumbens. Binding of the D_1-ligand [^{3}H]-SCH23390 and the D_2-ligand [^{3}H]-spiperone was not affected. This finding of an intervention early in life and the development of schizophrenia at early adulthood is related to the hypothesis that schizophrenia is a neurodevelopmental disease. Perinatal events may cause a disruption of normal brain development, causing schizophrenia later in life.

One such an event is maternal immune activation. Injection of pregnant rats with the viral mimic polyinosinic/polycytidylic acid (poly I:C) or bacterial lipopolysaccharide (LPS) elicits schizophrenic-like symptoms in the offspring at adulthood. In search for dopaminergic changes in such a model, it was found that LPS injection of pregnant rats resulted in decreased binding of the D_2-ligand [^{3}H]-YM901512 in the prefrontal cortex at postnatal days 35 and 60 (Baharnoori et al. 2013). Binding in subcortical regions was not affected. Additionally, binding of the D_1-ligand [^{3}H]-SCH23390 was not affected by the LPS-induced maternal immune activation. In a study in rhesus monkeys, maternal immune activation was found to result in a higher striatal influx of [^{18}F]-FMT, a PET tracer used for imaging of presynaptic dopamine levels (Bauman et al. 2019). The maternal immune activation might additionally lead to immune activation in the offspring. An increased [^{11}C]-(R)-PK11195 uptake ratio was found in the hippocampus and prefrontal cortex in the 8-week-old offspring (Li et al. 2018).

In addition, early stressful events were found to induce schizophrenic-like symptoms in rats that become evident at adulthood. Two or more stressful events may however induce stronger symptoms and better mimic the human situation. Maternal separation and treatment with corticosterone at adulthood were found to have an impact on the dopaminergic regulation of behavior but did not affect binding of the dopamine transporter ligand [^{3}H]-GBR12935 in the striatum and nucleus accumbens (Choy and Van den Buuse 2008). The effect of combined birth complications, as an early stressful event, and stress at adulthood on dopamine receptors was additionally studied (El-Khodor and Boksa 2001). In adult rats that were born via cesarean section (C-section), an increased binding of the D_1-ligand [^{3}H]-SCH23390 was found in frontal brain regions, when compared to vaginal birth. Binding to D_2 and D_3 was not affected by birth via C-section. Exposure to stress resulted in a decrease in D_1 binding in frontal brain regions, which was most prominent in rats born via C-section and normalized the increase in D_1 binding caused by C-section alone. Binding of the D_2-ligand [^{3}H]-YM091512 in the nucleus accumbens was increased by stress, which was most prominent in the rats born via C-section. Stress also increased D_3 binding by [^{3}H]-7-OH-DPAT in the nucleus accumbens, but only in the vaginally born rats.

In order to induce neurodevelopmental deficits, neonatal lesions in brain areas that are thought to be involved in schizophrenia, such as the hippocampus and amygdala, can be experimentally caused by injection of a neurotoxic compound. Such neonatal lesions induce behavioral changes similar to those observed in schizophrenia and affect the expression of dopamine receptors. Neonatal, bilateral lesioning of the ventral hippocampus resulted in a marked reduction in binding of the D_3-ligand [^{3}H]-7-OH-DPAT in the nucleus accumbens, olfactory tubercle, and ventral striatum on postnatal days 41 and 62 (Flores et al. 1996). D_1 binding of [^{3}H]-SCH23390 was only decreased at postnatal day 62, and D_2 binding of [^{3}H]-spiperone was not affected. Neonatal lesioning of the amygdala revealed comparable results (Bouwmeester et al. 2007). Binding of the D_1-ligand [^{3}H]-SCH23390 and the D_2-ligand [^{3}H]-spiperone was reduced in rats that were lesioned at postnatal day 7, but not in those lesioned at postnatal day 21. The reduction was more prominent for D_2. Binding of the D_3-ligand [^{3}H]-7-OH-DPAT was not affected by the lesion. In order to mimic the exacerbation of symptoms in schizophrenia with PCP, rats with a neonatal, bilateral lesion of the ventral hippocampus were subjected to daily PCP injections on 14 consecutive days at adulthood (Hori et al. 2000). In these rats the effect on dopamine and NMDA receptors was studied. Binding of the D1-ligand [^{3}H]-SCH23390 was not affected by the lesion or PCP treatment alone, but was increased in the striatum of lesioned rats that were subjected to PCP treatment. PCP treatment decreased the binding of the D_2-ligand [^{3}H]-YM091512 in the striatum and nucleus accumbens of non-lesioned and in the nucleus accumbens of lesioned rats. Binding of the NMDA-ligand [^{125}I]-MK801 was affected by PCP treatment alone, but not by the lesion alone. In general, in both the non-lesioned and lesioned rats, PCP decreased binding in the frontal and cingulate cortex and increased binding in the thalamus, hippocampal regions, and the substantia nigra. Striatal [^{125}I]-MK801 binding was not affected by PCP treatment.

Besides the induction of schizophrenic-like behavior by drugs and perinatal events, there are also genetic animal models of schizophrenia. The metabotropic glutamate receptor type 5 (mGluR5) knockout (KO) mouse shows behavior that is relevant to schizophrenia endophenotypes. Similar to schizophrenic patients, these KO mice show an increased sensitivity to the NMDA antagonist MK801 (i.e., increased sensitivity to psychomimetics). Binding of the NMDA-ligand [^{3}H]-MK801 in the KO mice was not different from normal mice (Gray et al. 2009). Treatment with MK801 caused an increase in [^{3}H]-MK801 binding in hippocampal regions in the KO mice, but not in normal mice. Binding of the D_2-ligand [^{3}H]-YM09151 was not different in the KO mice and was not affected by MK801 treatment. Another genetic model for schizophrenia is the Brattleboro rat, which lacks the neuropeptide vasopressin. When compared to control rats, binding of the D_2-ligand [^{3}H]-spiperone was increased in the nucleus accumbens and the striatum (Shilling et al. 2006). Binding of the D_1-ligand [^{3}H]-SCH23390 was not different in the Brattleboro rats. Imaging studies have additionally been performed in mice with a mutant disrupted-in-schizophrenia-1 (DISC1) gene. A translocation in this gene was discovered in families with high rates of schizophrenia, and although DISC1 is not a strong and specific risk factor for schizophrenia only, modulation of this gene

in mice leads to the display of schizophrenic-like behavior. A study with [^{11}C]-raclopride showed a higher striatum-to-cerebellum ratio in the mutant DISC1 mouse, as well as an increased level of D_2/D_3 receptors in the striatum as measured with [^{3}H]-spiperone autoradiography (Jaaro-Peled et al. 2013).

Studies exploring the effects of infections on behavior in animal models of schizophrenia are based on the clinical knowledge that infections that target the limbic system may have a prodromal stage sometimes very similar to paranoid schizophrenia. Herpes simplex virus type I, the causative agent of fever blisters and herpes encephalitis, specifically targets limbic brain regions such as the hippocampus and may cause classic schizophrenia-like symptoms in the prodromal phase. A schizophrenia-like animal model was designed by applying human strain HSV-1 into the nasal cavity of rats, creating herpes encephalitis in the limbic system, which was imaged with the herpes-specific radiopharmaceutical [^{18}F]FHPG (Buursma et al. 2005). Very interestingly, treatment with antipsychotic drugs such as clozapine and risperidone, proved to be very effective immune modulators, reduces microglia activation and behavioral abnormalities and death of the animals in the herpes encephalitis model (Klein et al. 2014). Also changes in key neurotransmitter systems involved in schizophrenia were found in these experiments. Change in pre-pulse inhibition, a sensitive, but not specific, sign of information processing deficits in schizophrenia, was not mimicked in this animal model. The translation of these virus imaging experiments from the animal model to humans is in its infant stage. Preliminary results indicate that in patients with severe psychosis, the herpes-specific radiopharmaceutical [^{18}F]FHBG is trapped more prominently in temporal cortical and subcortical (limbic) brain regions. Severe psychosis was defined strictly with the PANSS interview: Patients were included only when they experienced five on one item, or four on two items of the positive subscale of the PANSS.

The abovementioned studies are only a selection of the investigations performed in animal models of schizophrenia. They are examples to show the work that has been done on dopamine and glutamate receptors, inflammation, and even infection with HSV-1, using radiolabeled molecules. In the majority of studies in the animal models of schizophrenia, changes in dopamine and glutamate receptors were found, and microglia activation was a very robust finding in these models. However, results need to be replicated in patients with schizophrenia to make a firm translational link between models of the disease and the disease itself.

In conclusion, molecular imaging has already provided much insight into the pathophysiology of schizophrenia and may give clues for development of new treatment strategies that treat all aspects of the disease. A new frontier in the direct future is the imaging of glutamate/NMDA neurotransmission in patients with schizophrenia. In addition, imaging of infection and neuroinflammation provides a very different view on the pathophysiology of schizophrenia, enabling new treatment strategies. Molecular imaging makes it also possible to monitor the effect of such treatments directly on their target in the brain and link it to the clinical outcome. This provides important information for dosing of disease-modifying agents and ultimately could be used for personalized treatment. The field is hampered, however, by the limited

availability of good and validated PET and SPECT tracers to probe in patients the several receptor systems which animal models indicate to be affected by the disease. This is an area in which academic and industrial partners should collaborate, and indeed this has already provided new tracers. Only with such a joint approach we can identify new targets that may eventually lead to a radically different way of treatment of patients with schizophrenia.

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17 Neuroimaging Findings in Patients with Hallucinations: Evidence from Neurodegenerative and Psychiatric Conditions

Stefania Pezzoli and Annalena Venneri

Contents

Abstract

Hallucinations are severe and disabling symptoms experienced in various neurodegenerative and psychiatric conditions. Over the years, neuroimaging techniques have allowed the investigation of the neural mechanisms underpinning this symptomatology. The present chapter summarises positron emission tomography and single-photon emission computed tomography studies of hallucinations in patients with neurodegenerative and psychiatric disorders. The majority of these studies focused on visual hallucinations (VH) in Lewy body disease (LBD) and auditory verbal hallucinations (AVH) in schizophrenia, given their

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clinical relevance and high prevalence in these conditions. Impairments in bottom-up and top-down mechanisms appeared to be involved. Dysfunctions in brain areas implicated in sensory processing have been found in regions consistent with the hallucination sensory modality, especially in occipito-temporal areas in LBD with VH, and in primary and associative auditory cortices in schizophrenia with AVH, as well as in language-related regions in the latter. Top-down control mechanisms may also play a role that may be linked to impaired activity in frontoparietal areas in LBD and in the anterior cingulate cortex in schizophrenia. These findings suggest that similar mechanisms may underlie different types of hallucinations across diagnoses. Top-down control mechanisms over sensory pathways might foster the genesis and emergence of these symptoms.

17.1 Introduction

Hallucinations are involuntary sensory experiences occurring in the absence of corresponding external sensory inputs that are experienced as real percepts (Allen et al. 2008; Collerton et al. 2005; Waters et al. 2012, 2014). They may occur in all sensory modalities, although visual and auditory hallucinations are the most common in neurodegenerative and psychiatric disorders. Hallucinations are generally distressing symptoms, with a significant impact on patients' quality of life (Hugdahl 2017; Onofrj et al. 2013). Along with delusions, they are referred as psychotic symptoms.

Recurrent and complex visual hallucinations (VH) are repetitive, involuntary and well-formed images, usually of people, animals and objects, perceived in the absence of real stimuli (Collerton et al. 2005). They are commonly experienced by patients with neurodegenerative conditions, especially Lewy body disease (LBD), term that refers to a spectrum of disorders characterised by the neural inclusion of α-synuclein protein aggregates called Lewy bodies (LBs) (Dickson et al. 2009; Lippa et al. 2007). VH are a strong predictor of LB pathology, experienced by roughly 60–80% of patients with dementia with Lewy bodies (DLB), 45–65% of patients with Parkinson's disease dementia (PDD) and 25–40% of patients with Parkinson's disease (PD), three forms of LBD (Aarsland et al. 2001; Emre et al. 2007; Onofrj et al. 2013; Tiraboschi et al. 2006; Williams and Lees 2005). Moreover, they are among the core features of DLB symptomatology (McKeith et al. 2017). Although less commonly, hallucinations in LBD may also be experienced in other sensory modalities (McKeith et al. 2017). Other related minor visuo-perceptual phenomena, including sensations of presence, sideway passages and visual illusions, may also be present and may be shown in conjunction with VH (Aarsland et al. 2009; McKeith et al. 2017; Onofrj et al. 2013). Patients with Alzheimer's disease (AD) may also experience hallucinations, especially visual and auditory hallucinations, although less frequently than in LBD (Bassiony and Lyketsos 2003; El Haj et al. 2017; Linszen et al. 2018). Hallucinations in the auditory modality are more frequent in psychiatric conditions,

including schizophrenia and bipolar disorder (Waters et al. 2012). The most common type of auditory hallucinations is hearing voices, although non-verbal content may also occur (Alderson-Day et al. 2016). Auditory verbal hallucinations (AVH) refer to the subjective experience of hearing voices in the absence of external sensory stimulation and are a common symptom of psychotic disorders (Hugdahl 2017; Waters et al. 2012). AVH are one of the main clinical characteristics of schizophrenia, experienced by approximately 70% of patients (Allen et al. 2007; Jardri et al. 2011; Waters et al. 2012). In 25% of cases, AVH are drug-resistant, and patients often engage in conversations with their voices (Hugdahl 2017; Jardri et al. 2011). The emotional value associated with hallucinations is usually negative, and patients often report associated anxiety and depression (Waters et al. 2012). Around 27% of patients with schizophrenia may also experience VH (Waters et al. 2014).

The rapid advancement of neuroimaging techniques over the last decades has allowed the study of different aspects of brain function and structure, both in the healthy brain and in various neuropsychiatric, neurological and neurodegenerative conditions. Neuroimaging techniques have been increasingly used in studies of these phenomena to shed light on symptom-specific neural mechanisms, including hallucinations in different sensory modalities. The aim of the present chapter was to review functional neuroimaging studies exploring the neural activity associated with hallucinations by means of positron emission tomography (PET) and single-photon emission computed tomography (SPECT). We focused on VH and AVH, the most studied types of hallucinations, mainly due to their clinical relevance and high prevalence, especially VH in LBD and AVH in schizophrenia. Firstly, studies investigating alterations in brain glucose metabolism, cerebral blood flow (CBF) and neurotransmitter dysregulations in patients with hallucinations in neurodegenerative and psychiatric conditions were reviewed. Then, PET and SPECT findings were discussed in the light of the current literature on VH and AVH, with particular reference to studies using other neuroimaging modalities.

17.2 PET and SPECT Imaging of Hallucinations in Neurodegeneration

Brain glucose metabolism and CBF have been studied in relation to the presence of hallucinations in neurodegenerative disorders, including PD, DLB and AD.

PET and SPECT studies on hallucinations in PD and DLB have focused mainly on the visual modality, since VH are a common feature of this symptomatology. Overall, studies suggested a pattern of posterior hypometabolism/perfusion across different conditions, especially in areas involved in visual processing. Most studies used a between-subject design and investigated trait-related neural correlates of VH comparing patients with and without these symptoms. Other investigations used a correlational approach to explore the association between indices of VH and glucose metabolism/CBF. In the following subsections, PET and SPECT studies on hallucinations in PD, DLB and AD are reviewed separately for each condition.

17.2.1 PET and SPECT Findings on Hallucinations in Parkinson's Disease

The majority of the studies on VH in LBD were on PD and generally reported occipital, occipito-temporal and parietal hypometabolism/perfusion, with the precuneus, lingual and fusiform gyri appearing particularly affected (Boecker et al. 2007; Gasca-Salas et al. 2016; Matsui et al. 2006b; Oishi et al. 2005; Park et al. 2013). Most studies compared the pattern of glucose metabolism/CBF between PD patients with and without VH (summarised in Table 17.1), while others investigated the relationship between brain glucose metabolism and clinical variables. Only one study, a single case report, described a patient with PDD while experiencing VH during a SPECT scan and showed increased regional CBF in the temporal lobe bilaterally and in the left inferior frontal gyrus (Kataoka et al. 2008).

In a PET study, Gasca-Salas et al. (2016) compared PD patients with mild cognitive impairment (MCI), with (n = 9) and without (n = 12) VH. The authors found regions of hypometabolism in hallucinating patients in the left lingual gyrus, right inferior temporal gyrus and in the cuneus, precuneus and middle occipital gyrus

Table 17.1 Summary of PET and SPECT studies comparing patients with and without hallucinations in PD

Study	Participants	Method	Main results associated with hallucinations
Boecker et al. (2007)	8 PD VH 13 PD NVH	FDG-PET	VH < NVH: LR inferior parietal lobule, precuneus, L supramarginal gyrus, middle frontal gyrus, middle temporal gyrus, parahippocampal gyrus, lingual gyrus, R cingulate gyrus
Gasca-Salas et al. (2016)	9 PD VH 12 PD NVH	FDG-PET	VH < NVH: R lingual gyrus, inferior temporal gyrus, precuneus, precentral gyrus, L postcentral gyrus, bilateral middle occipital gyrus
Matsui et al. (2006b)	31 PD VH 39 PD NVH	SPECT	VH < NVH: LR inferior parietal lobule, inferior temporal gyrus, precuneus gyrus, occipital cortex
Nagano-Saito et al. (2004)	8 PD VH 11 PD NVH	FDG-PET	VH > NVH: L superior frontal gyrus
Oishi et al. (2005)	24 PD VH 41 PD NVH	SPECT	VH < NVH: R fusiform gyrus
Osaki et al. (2005)	20 PD (9 VH) 10 PDD (10 VH)	SPECT	VH vs. NVH: No differences
Park et al. (2013)	7 PD VH 8 PD CI VH 13 NVH	FDG-PET	VH < NVH: LR middle and inferior temporal cortex, L lingual gyrus and L angular gyrus CI VH < NVH: Temporo-parieto-occipital cortices Hallucination score—Negative correlations: LR superior temporal gyrus, L fusiform gyrus

CI Cognitive impairment, *FDG* Fluorodeoxyglucose, *L* Left, *NVH* No visual hallucinations, *PET* Positron emission tomography, *PD*, Parkinson's disease, *PDD* Parkinson's disease dementia, *SPECT* single-photon emission computed tomography, *R* Right, *VH* Visual hallucinations

bilaterally, suggesting a role of regions involved in higher visual processing in the development of VH (Gasca-Salas et al. 2016). In this study, the two subgroups of patients were matched for age, gender, years of education, disease duration and severity (Gasca-Salas et al. 2016). Park et al. (2013) showed consistent results, although statistical significance level was not adjusted to account for multiple comparisons. In particular, they found hypometabolism in patients with complex and minor VH in the left lingual and angular gyri, left occipital areas and temporal and frontal cortices bilaterally. Similarly, in another FDG-PET study, patients with VH ($n = 8$) presented reduced regional cerebral glucose metabolism in the left lingual, parahippocampal and middle frontal and temporal gyri, inferior parietal lobule and precuneus bilaterally, in comparison with patients without VH ($n = 11$) (Boecker et al. 2007). On the other hand, Nagano-Saito et al. (2004) reported hypermetabolism in the left superior frontal gyrus in patients with VH compared with those without. Moreover, when both subgroups of patients were compared separately with healthy participants, reduced regional glucose metabolism was 24% greater in patients with VH in occipital, occipito-temporal and parietal areas (Nagano-Saito et al. 2004). Inconsistencies between studies in reporting increased or decreased frontal metabolism might be partially due to differences in the characteristics of the sample, including demographics and other clinical features, such as disease duration and global cognitive impairment. For example, patients included in the study by Boecker et al. (2007) were slightly older, with longer disease duration and lower Mini-Mental State Examination (MMSE) scores, evaluating global cognitive impairment, than those assessed by Nagano-Saito et al. (2004). In addition, in Boecker et al. (2007), hallucinating patients had more severe motor symptoms, although included as covariate of no interest in the statistical analysis, and were at a more advanced disease stage than those not hallucinating. SPECT studies also confirmed the pattern of occipito-temporal, occipital and parietal alterations described above. Matsui et al. (2006b) compared brain perfusion between 31 PD patients with VH and 39 without. Hallucinating patients presented significantly decreased hypoperfusion in the inferior parietal lobule, precuneus, inferior temporal gyrus and occipital cortex. In another whole-brain SPECT study, Oishi et al. (2005) found reduced CBF in the right fusiform gyrus, significant after correcting for multiple comparisons, and other temporal and parietal regions, using a rather liberal threshold. On the other hand, other studies found no differences in occipital perfusion between hallucinating and non-hallucinating patients with PD (Osaki et al. 2005) and DLB (Lobotesis et al. 2001) and this might be due to methodological differences between studies. In fact, the latter studies used a region of interest (ROI) approach, as opposed to whole-brain analyses performed by other investigations (Matsui et al. 2006b; Oishi et al. 2005).

In a multimodal neuroimaging study, Nishio et al. (2017) explored the relationship between clinical and cognitive variables and brain structure (structural MRI) and function (FDG-PET) using a partial least-squares correlation analyses in PD patients. Clinical variables were grouped by means of factor analysis. Minor hallucinations and illusions were grouped in one factor and visual hallucination in another one along with delusions, depression and cognitive fluctuations. Minor

hallucinations were associated with posterior cortical atrophy and hypometabolism, including temporo-occipital, occipito-parietal and primary visual cortices, while the psychosis/dysphoria factor was associated with atrophy and hypometabolism mainly in the upper brainstem and thalamus (Nishio et al. 2017). In another study, Nishio et al. (2018) investigated the relationship between brain glucose metabolism and clinical variables, among which VH, kinetopsia and object misidentification illusions in PD. All these variables were related with temporo-parietal hypometabolism, and object misidentification illusions were also associated with occipital hypometabolism (Nishio et al. 2018). In this study, however, patients with VH had lower MMSE scores (Nishio et al. 2018).

Patients with LBD may experience also hallucinations in other sensory modalities, such as auditory hallucinations, although not as frequently as VH. In a SPECT study, Matsui et al. (2006a) investigated differences in brain perfusion between PD patients with VH and AVH ($n = 11$) and with VH but no AVH ($n = 17$). They found that those with both visual and verbal hallucinations presented regions of hypoperfusion located in the prefrontal cortex bilaterally and in the right superior temporal gyrus (Matsui et al. 2006a). In another SPECT study, Matsui et al. (2007) scanned PD patients while they were experiencing AVH ($n = 4$) and compared them with 77 patients with PD without these symptoms ($n = 77$), reporting hypoperfusion in the right thalamus in the AVH group.

17.2.2 PET and SPECT Findings on Hallucinations in Dementia with Lewy Bodies

Despite the high prevalence of VH in DLB, whole-brain PET studies comparing hallucinating and non-hallucinating patients are still lacking. Different methodologies have been used to study these symptoms in this condition, and the available studies have reported contrasting results (summarised in Table 17.2). Using whole-brain voxel-wise analyses, Perneczky et al. (2008) identified regions of hypometabolism in hallucinating patients ($n = 14$) compared with non-hallucinating ones ($n = 7$) in right occipito-temporal and frontal areas. In this study, correction for multiple comparisons was not applied, but differences were expected only in regions of hypometabolism found in DLB, specifically in occipital, temporo-parietal and frontal areas (Perneczky et al. 2008). Contrasting findings were reported by an ROI PET study on DLB, showing increased regional cerebral glucose metabolic rate in temporal and parietal regions (Imamura et al. 1999). However, patients without VH presented more severe global cognitive impairment and this might have influenced the results (Imamura et al. 1999). Nicastro et al. (2018) compared patients with ($n = 9$) and without ($n = 16$) feeling of presence in DLB. Regions of hypometabolism were found in patients experiencing feeling of presence in left parietal and frontal areas, namely, in the superior parietal lobule, precuneus and middle and superior frontal gyri (Nicastro et al. 2018). SPECT studies have reported occipital hypoperfusion in patients with DLB and hallucinations (Heitz et al. 2015; Pasquier et al. 2002), although they presented some limitations. For example, Heitz et al.

Table 17.2 Summary of PET and SPECT studies comparing patients with and without hallucinations in DLB

Study	Participants	Method	Main results associated with hallucinations
Heitz et al. (2015)	36 DLB VH 30 DLB NVH	SPECT	VH < NVH: L ACC, orbitofrontal cortex, cuneus Severity of VH—Associations: LR ACC, R parahippocampal gyrus, L orbitofrontal cortex, L cuneus
Imamura et al. (1999)	16 DLB VH 6 DLB NVH	FDG-PET	VH > NVH: R posterior temporal and parietal areas
Lobotesis et al. (2001)	18 DLB VH 5 DLB NVH	SPECT	VH vs. NVH: No differences
Pasquier et al. (2002)	26 DLB VH 8 DLB NVH	SPECT	VH < NVH: R occipital region
Perneczky et al. (2008)	14 DLB VH 7 DLB NVH	FDG-PET	VH < NVH: R temporo-occipital conjunction and middle frontal gyrus

ACC Anterior cingulate cortex, *DLB* Dementia with Lewy bodies, *FDG* Fluorodeoxyglucose, *L* Left, *NVH* No visual hallucinations, *PET* Positron emission tomography, *SPECT* Single-photon emission computed tomography, *R* Right, *VH* Visual hallucinations

(2015) performed whole-brain analyses without correcting the results for multiple comparisons, and Pasquier et al. (2002) reported demographic and clinical features of DLB patients without differentiating between those with VH (n = 26) and those without ($n = 4$). Other regions of hypoperfusion included the anterior cingulate and orbitofrontal cortices (Heitz et al. 2015). Another study in DLB, using factor analyses on psychotic symptoms, showed a relationship between parietal and occipital hypoperfusion and the sense of presence and hallucinations of people, but not of animals, insects and objects (Nagahama et al. 2010).

An alternative approach to performing between-group comparisons is represented by the investigation of correlations between regional brain glucose metabolism and clinical variables. Overall, indices of VH have been mainly associated with hypometabolic posterior regions (Firbank et al. 2016; Iaccarino et al. 2018; Iizuka and Kameyama 2016; Kantarci et al. 2012), consistently with the findings described above. In DLB, occipital hypometabolism correlated with severity (Firbank et al. 2016) and frequency (Firbank et al. 2016; Kantarci et al. 2012) of VH. The metabolism of other regions has also been found to correlate negatively with VH, including the posterior cingulate, and the dorsolateral frontal cortex in DLB (Morbelli et al. 2019), temporal regions in PD (Park et al. 2013) and parietal areas in both conditions (Morbelli et al. 2019; Uchiyama et al. 2015). Morbelli et al. (2019) also found a positive relationship between VH and glucose metabolism of other regions, located in the medial temporal lobe (MTL), orbitofrontal cortex, cerebellum, brainstem and basal ganglia. The latter regions were also associated with the presence of REM sleep behaviour disorder (RBD) in the same sample of DLB patients (Morbelli et al. 2019). In a FDG-PET study investigating the differences between patients with

DLB and AD, Iizuka and Kameyama (2016) also correlated brain glucose metabolism with cognitive and clinical variables, including hallucinations, even though the sensory modality was not specified. They found that the Neuropsychiatric Inventory (NPI) hallucination score was positively associated with the cingulate island sign ratio and negatively with the standardised uptake value ratio in the precuneus/cuneus (Iizuka and Kameyama 2016). O'Brien et al. (2005) found a negative correlation between hallucination scores and changes in brain perfusion over a 1-year period, especially in the precuneus and posterior cingulate gyri using SPECT imaging in a combined group of DLB and PDD patients. Iaccarino et al. (2018) undertook metabolic correlation and connectivity analyses in DLB VH (n = 19), NVH (n = 19) and controls (n = 38) by means of FDG-PET. Right occipito-temporal hypometabolism correlated negatively with the NPI hallucination score, specifically in the right middle occipital gyrus, extending to the inferior temporal gyrus (Iaccarino et al. 2018). The occipito-temporal cluster resulting from these analyses was then used to investigate metabolic connectivity, revealing decreased connectivity with the right fusiform gyrus and hippocampus in VH patients compared with NVH (Iaccarino et al. 2018).

17.2.3 PET and SPECT Findings on Hallucinations in Alzheimer's Disease

Patients with AD may also experience hallucinations although less commonly than those with LBD. VH appear to be the most common type of hallucinations, even though they can be found in any sensory modality, especially auditory hallucinations (Bassiony and Lyketsos 2003; El Haj et al. 2017; Linszen et al. 2018). Some studies investigated psychotic symptoms in AD without differentiating between hallucinations and delusions and, overall, reported frontal atrophy and hypometabolism (Murray et al. 2014). So far, only three studies have investigated the pattern of brain glucose metabolism or brain perfusion in AD with hallucinations, and these are summarised in Table 17.3.

In a SPECT study, Kotrla et al. (1995) found parietal hypoperfusion in AD patients with hallucinations compared with those without. In this study, however, the sensory modality of the hallucinations was not specified (Kotrla et al. 1995). In another study, Lopez et al. (2001) focused on VH and used $H_2{}^{15}O$-PET to investigate relative regional CBF in a small sample of AD patients. Patients with VH (n = 2) showed reduced relative CBF in the right parietal cortex compared with patients with no psychotic symptoms (n = 5) (Lopez et al. 2001). In addition to these regions, an involvement of dorsolateral and medial temporal areas was also observed in patients with VH but also in patients with delusions, when independently compared with non-psychotic patients (Lopez et al. 2001). In another recent study, Blanc et al. (2014) used voxel-based morphometry (VBM) and FDG-PET to investigate structural and functional brain features associated with hallucinations in AD. Patients with hallucinations (n = 39) had reduced GM volume and hypometabolism in the right anterior part of the insula and frontal areas compared with those without hallucinations (n = 39). Notably, anterior insula GM volume also correlated with

Table 17.3 Summary of PET and SPECT studies comparing patients with and without hallucinations in AD

Study	Participants	Method	Main results associated with hallucinations
Blanc et al. (2014)	39 AD-H 39 AD NH	FDG-PET	AD-H < AD-NH: R inferior, middle frontal gyri and insula AD-H > AD-NH: L superior frontal gyrus, fusiform gyrus, postcentral gyrus, precuneus, supramarginal gyrus Intensity of hallucinations—Correlations: L cingulate gyrus, R precentral gyrus
Kotrla et al. (1995)	10 AD-H 16 AD NH	SPECT	AD-H < AD-NH: Parietal lobe
Lopez et al. (2001)	2 AD VH 5 AD NH	$H_2{}^{15}O$-PET	AD VH < AD NVH: R parietal, L medial temporal and L dorsolateral prefrontal cortices

AD Alzheimer's disease, *FDG* Fluorodeoxyglucose, *H* Hallucinations, *L* Left, *NH* No hallucinations, *PET* Positron emission tomography, *SPECT* Single-photon emission computed tomography, *R* Right, *VH* Visual hallucinations

hallucination intensity. The authors suggested a role of the insula in the development of hallucinations in AD, especially due to its involvement in the regulation and integration of external and internal stimuli, therefore disrupting the ability to discriminate between internally generated stimuli and external information (Blanc et al. 2014). However, in this study, the sensory modality of the hallucination was not specified, and whole-brain results were not corrected for multiple comparisons, thus increasing the likelihood of type I error.

Finally, in a single-case SPECT study, Mori et al. (2006) described a 73-year-old patient with AD and musical hallucinations and compared the pattern of CBF with nine matched AD patients without hallucinations and delusions. Increased regional CBF was detected in the hallucinating patient in left temporal and parietal regions, namely, in the superior temporal and angular gyri.

17.3 PET and SPECT Imaging of Hallucinations in Psychiatric Conditions

Alterations in brain glucose metabolism and CBF have been investigated in psychiatric disorders, focusing on AVH in schizophrenia. Different techniques have been used, including FDG-PET to study patterns of brain glucose metabolism and SPECT and $H_2{}^{15}O$-PET for CBF. Most studies investigated brain activity while patients were experiencing hallucinations during the scanning sessions. Study designs varied across investigations, comprising within and between-group comparisons, as well as correlational analyses. Overall, an altered neural activity has been found in primary and association auditory cortices, in regions involved in language processing, including Broca's and Wernicke's areas, and other regions in the frontal cortex, such as the anterior cingulate cortex (ACC) and supplementary motor area (SMA), and in the MTL.

With the aim to shed light on state-related characteristics of AVH in schizophrenia, some studies have used a within-subject design (summarised in Table 17.4).

Table 17.4 Summary of PET and SPECT studies on hallucinations using within-group and between-group study designs in schizophrenia

Study	Participants	Method	Main results associated with hallucinations
Within-group design			
McGuire et al. (1993)	12 VAH (during AVH vs. remission)	SPECT	Hallucinations: ↑ L inferior frontal gyrus (Broca's area) and trend in L ACC
Parellada et al. (2008)	9 AVH (during AVH vs. remission state and LAA task)	FDG-PET	Hallucinations: ↑ LR ACC, SMA, medial frontal areas, cerebellum, R temporal pole, inferior orbitofrontal
Silbersweig et al. (1995)	5 AVH (event-related design: AVH present or absent)	$H_2{}^{15}O$-PET	Hallucinations: ↑ LR hippocampus, parahippocampus and thalamus, R ventral striatum, anterior cingulate, L orbitofrontal
Suzuki et al. (1993)	5 AH (during AH vs. remission)	SPECT	Hallucinations: ↑ L superior temporal cortex (auditory association area)
Horacek et al. (2007)	12 AH (before and after rTMS treatment)	FDG-PET	After rTMS treatment: ↓ L superior and inferior temporal gyri and insula, ipsilateral to the coil position (L temporo-parietal areas); ↑ R temporal and occipital cortices, LR middle frontal gyrus Severity of hallucinations—Correlations Before treatment: ↑ L inferior temporal gyrus, R middle frontal gyrus After treatment: ↑ R middle temporal gyrus
Klirova et al. (2013)	15 AH (FDG-PET guided rTMS)	FDG-PET	Individualised rTMS of L temporo-parietal cortex targeted to individual parameters on FDG-PET imaging (neuronavigated rTMS) represented a better treatment for AH than standard rTMS
Between-group design			
Cleghorn et al. (1992)	12 AH during scanning 10 NAH during scanning	FDG-PET	AH < NAH: LR superior temporal gyrus Intensity of hallucinations—Correlations: ↑ ACC, LR striatum
Cleghorn et al. (1990)	9 AVH during scanning 10 NAH during scanning	FDG-PET	AVH > NAH: Correlations between Broca's area, Broca's R homologue, ACC, L superior temporal Intensity of hallucinations—Correlations: ↑ AAC
Copolov et al. (2003)	8 AVH during scanning 7 NAH	$H_2{}^{15}O$-PET	Hallucinations: ↑ R ACC, prefrontal cortex, and middle temporal gyrus, L superior temporal gyrus, comprising part of Wernicke's area, hippocampus, parahippocampus, and posterior cingulate
Horga et al. (2011)	9 AVH during scanning 7 NAH	FDG-PET	AVH > NAH: L superior middle temporal cortices, caudate nucleus, LR superior medial frontal cortex AVH < NAH: Cerebellar and parietal cortices, hippocampus, parahippocampal gyrus Severity of hallucinations—Correlations: ↑ R superior temporal cortex

Table 17.4 (continued)

Study	Participants	Method	Main results associated with hallucinations
Kim et al. (2018)	10 AH during scanning 12 NAH	FDG-PET	AH < NAH: R inferior, middle, and superior frontal gyri, LR frontal regions and cingulate gyrus AH > NAH: LR putamen, L middle and inferior temporal gyri, LR fusiform gyrus, cerebellum
Kopecek et al. (2007)	15 AVH 15 NAH	FDG-PET	AVH > NAH: R middle frontal gyrus Intensity of hallucinations—Correlations: ↑ R middle frontal gyrus
McGuire et al. (1996)	6 AVH 6 NAH	$H_2{}^{15}O$-PET	Inner speech—AVH < NAH: L superior temporal sulcus, LR lingual/fusiform gyrus, R caudate Auditory verbal imagery—AVH < NAH: L middle temporal gyrus, SMA, and other cerebellar and occipito-temporal areas. AVH > NAH: R superior temporal gyrus and parietal operculum
Musalek et al. (1988)	17 AH 28 healthy controls	SPECT	AH < controls: LR frontal and medial temporal lobe areas and basal ganglia
Musalek et al. (1989)	17 AH 11 tactile hallucinations 28 healthy controls	SPECT	AH < controls: Frontal areas Tactile hallucinations < controls: LR inferior temporal regions
Stephane et al. (2006)	8 AVH 10 NAH	$H_2{}^{15}O$-PET	Reading words—Hallucinations: Reversed laterality of SMA

ACC Anterior cingulate cortex, *AH* Auditory hallucinations, *AVH* Auditory verbal hallucinations, *CBF* Cerebral blood flow, *FDG* Fluorodeoxyglucose, *L* Left, *LAA* Linguistic auditory activation, *NH* No hallucinations, *PET* Positron emission tomography, *R* Right, *rTMS* Repetitive transcranial magnetic stimulation, *ROI* Region of interest, *SMA* Supplementary motor area, *SPECT* Single-photon emission computed tomography, ↓ Decrease, ↑ Increase

Generally, these studies had a scanning session during the hallucinatory state and an additional control condition scan during remission. By means of SPECT imaging, McGuire et al. (1993) explored the pattern of regional CBF during AVH in 12 patients with schizophrenia and compared it with a control condition scan when hallucinations had resolved. ROIs were placed in regions involved in language processing, including Wernicke and Broca's areas for speech comprehension and production, respectively, as well as temporal areas, including the primary auditory cortex (McGuire et al. 1993). The authors found significantly greater rCBF in Broca's area during the hallucinatory state, suggesting a role of regions involved in speech production, also related to inner speech (McGuire et al. 1993). Consistently, results reported by Parellada et al. (2008) are in line with the inner speech hypothesis according to which schizophrenic patients with AVH would present difficulties in monitoring the generation of inner thoughts, perceived as external stimuli. The authors investigated cerebral glucose metabolism across three different conditions in a group of patients with schizophrenia and AVH. Three FDG-PET scans were acquired for each patient (n = 9), specifically during the hallucinatory state, after

medication-induced remission and while performing a linguistic auditory activation (LAA) task after remission (Parellada et al. 2008). The LAA consisted in simulating content and emotional value of the hallucinations, as previously reported from the patients themselves. During LAA, increased metabolism was detected in the superior and middle temporal cortices bilaterally and in the left hippocampus and parahippocampus. During hallucinations, instead, activation was mainly observed in frontal regions, anterior cingulate cortex and cerebellum bilaterally, and in the right superior temporal pole, suggesting a prominent role of regions involved in speech production, rather than primary auditory areas (Parellada et al. 2008). Although no differences were found in Broca's areas, the authors found increased activity of the SMA, involved in speech articulation (Parellada et al. 2008). On the other hand, Suzuki et al. (1993) found an involvement of the auditory association cortex. In this study, the pattern of regional CBF was explored by means of ^{123}I-IMP SPECT in five patients with schizophrenia and auditory hallucinations (AH) before and after neuroleptic treatment. At baseline, when patients had persistent AH, increased ^{123}I-IMP uptake was detected in the left superior temporal cortex, corresponding to the auditory association cortex, that disappeared at follow-up, after clinical improvement (Suzuki et al. 1993). In another study, Silbersweig et al. (1995) used an event-related design to capture the brain activity associated with AVH in five patients with schizophrenia using $H_2{}^{15}O$-PET. Patients were asked to press a button during AVH. Significant activity was detected in the hippocampus, parahippocampus and thalamus bilaterally, right ventral striatum, anterior cingulate and left orbitofrontal cortex (Silbersweig et al. 1995).

Two studies investigated the effect of repetitive transcranial magnetic stimulation (rTMS) on areas involved in auditory-linguistic processes (i.e. left temporo-parietal cortex) in the treatment of auditory hallucinations in schizophrenia (Horacek et al. 2007; Klirova et al. 2013). Horacek et al. (2007) included 12 patients with medication-resistant auditory hallucinations and investigated the effect of 2-week treatment with rTMS on brain metabolism measured with FDG-PET. Whether patients were hallucinating or not during the scanning sessions, however, was not specified (Horacek et al. 2007). Before treatment, severity of auditory hallucinations, assessed with the auditory hallucination rating scale (AHRS), positively correlated with glucose metabolism in the left inferior temporal gyrus and right middle frontal gyrus. After treatment and clinical improvement, instead, hallucination scores positively correlated with the right middle temporal gyrus (Horacek et al. 2007). Moreover, after treatment, decreased glucose metabolism was detected in the left superior and inferior temporal gyri and insula, ipsilateral to the coil position (left temporo-parietal areas), as well as decreases in hallucination scores. Increased metabolism was also detected in the right temporal and occipital cortices and in the middle frontal gyrus bilaterally (Horacek et al. 2007). In another study, Klirova et al. (2013) found that individualised rTMS of the left temporo-parietal cortex targeted to individual parameters on FDG-PET imaging (neuronavigated rTMS) represented a better treatment for auditory hallucinations than standard rTMS in a group of 15 patients with paranoid schizophrenia.

Other studies used a between-group design, mainly investigating differences in neural activity between patients during the hallucinatory state and patients without hallucinations. Cleghorn et al. (1990) compared the brain activity of nine patients with chronic schizophrenia experiencing AVH during FDG-PET scanning with ten patients who had recovered from auditory hallucinations and a group of control participants (n = 10). The authors hypothesised an involvement of regions associated with speech and language processing, including frontal and temporal areas. Although no significant differences were found between groups, hallucination scores were positively associated with anterior cingulate metabolism (Cleghorn et al. 1990). Moreover, hallucinating patients had significantly higher correlations of glucose metabolism than the non-hallucinating group between language-related regions, including Broca's area and its right hemisphere homologue, anterior cingulate and left superior temporal gyrus (Cleghorn et al. 1990). In another FDG-PET study undertaken by the same group, patients who hallucinated during scanning (n = 12) showed regions of hypometabolism located in the superior temporal lobe, comprising Wernicke's areas and auditory cortex, in comparison with non-hallucinating patients (n = 10) (Cleghorn et al. 1992). Moreover, relative metabolism in the anterior cingulate cortex and in the striatum positively correlated with hallucinations scores. In this study, however, patients with hallucinations were younger at disease onset, were less educated and had more severe cognitive impairment and this might have had an impact on the results (Cleghorn et al. 1992). To note, in these studies, non-hallucinating patients had experienced hallucinations at some point during the course of their illness (Cleghorn et al. 1992, 1990). More recently, Horga et al. (2011) explored the pattern of glucose metabolism associated with AVH in unmedicated patients with first-episode schizophrenia, already included in a previous study (Parellada et al. 2008), by means of whole-brain FDG-PET and correlational analyses. Importantly, comparisons in glucose metabolism were performed with a group of patients who had never reported hallucinatory behaviour. Regions of increased relative glucose metabolic rate in hallucinating patients (n = 9) were found in the left superior and middle temporal cortices, including the primary auditory cortex and caudate nucleus, and bilaterally in the superior medial frontal cortex compared with those without AVH (n = 7) (Horga et al. 2011). Glucose metabolism in the right superior temporal cortex positively correlated with severity of hallucinations, assessed with the psychotic symptom rating scale (PSYRATS). Moreover, relative hypoactivity was also detected in cerebellar and parietal cortices, hippocampus and parahippocampal gyrus (Horga et al. 2011). In another FDG-PET study, Kim et al. (2018) included 10 patients with schizophrenia and persistent auditory hallucinations, experienced during the scans, and compared them with 12 patients with no auditory hallucinations for at least 3 months before the study, with those who had never experienced auditory hallucinations in the course of the disease. ROI analyses revealed regions of hypometabolism in hallucinating patients located in the right inferior, middle and superior frontal gyri and hypermetabolism in the putamen bilaterally (Kim et al. 2018). Using a voxel-based approach, additional regions of increased metabolism were detected in the left middle and inferior temporal gyri, fusiform gyrus bilaterally,

and cerebellum, and lower metabolism in frontal regions, and in the cingulate gyrus bilaterally. The latter results, however, were no longer significant when correcting for multiple comparisons and potential confounding variables, such as age and depression (Kim et al. 2018). Moreover, hallucinating patients were significantly more depressed and had greater memory impairment, variables that might have had an impact on the results (Kim et al. 2018). Inconsistent findings have been reported by Kopecek et al. (2007), who found increased ^{18}FDG uptake in patients with AVH (n = 15) compared with those without (n = 15) in the right dorsolateral prefrontal cortex, namely, in the middle frontal gyrus that was positively associated with the intensity of hallucinations, measured with the Positive and Negative Symptoms Scale (PANSS). The results, however, were reported using a threshold uncorrected for multiple comparisons, and it was not clear whether patients were hallucinating during the scanning session (Kopecek et al. 2007). In another study, Copolov et al. (2003) included eight patients that experienced AVH during $H_2{}^{15}O$-PET scanning and seven patients who had never reported the presence of AVH during the course of the disease. The latter were scanned while hearing human voices as auditory stimuli. Perception of human speech was associated with activity in the superior temporal gyrus bilaterally, comprising primary and association auditory cortices. Hallucinations, instead, were associated with activity in the anterior cingulate and prefrontal cortices, and middle temporal gyrus in the right hemisphere, as well as left-lateralised activity in the superior temporal gyrus, comprising part of Wernicke's area, hippocampus, parahippocampus and posterior cingulate (Copolov et al. 2003). The authors interpreted the presence of hallucinations as internally generated memories of speech, reaching awareness and subject to distorted post-retrieval confirmation (Copolov et al. 2003). Previous SPECT studies showed increased rCBF in medial temporal lobe structures, including the hippocampus, parahippocampus and amygdala, and basal ganglia, as well as reduced frontal CBF in hallucinating patients compared with healthy control participants (Musalek et al. 1988, 1989). In addition, Musalek et al. (1989) found reduced CBF in inferior temporal regions in patients with tactile hallucinations.

Inconsistencies between studies in the direction of frontal and temporal metabolism/CBF might be due to differences in methodology, experimental conditions and demographic and clinical characteristics of the sample. In the majority of the studies, patients were hallucinating during the scanning session, suggesting that the results may be attributed to features related to the hallucinatory state, rather than symptom-related traits. However, the way patients are defined as hallucinating or non-hallucinating (state vs. trait) poses interpretative issues (Allen et al. 2012). For example, in some studies the clinical control group included patients who had presented hallucinations during the course of the disease, but were not hallucinating during the scanning session (Cleghorn et al. 1992, 1990), while others included only patients who had never experienced hallucinations (Copolov et al. 2003; Horga et al. 2011). In this context, stating well-defined inclusion and exclusion criteria for each patient group, as well as clear research questions, is crucial to aid the understanding of trait/state-related neurobiological mechanisms underpinning the symptomatology.

With the aim to investigate trait and cognitive features associated with hallucinations in schizophrenia, other studies used $H_2{}^{15}O$-PET imaging during cognitive tasks (McGuire et al. 1996; Stephane et al. 2006). McGuire et al. (1996) included six patients with AVH and six without, who performed three different tasks involving the silent reading of words. In the baseline condition, participants had to read the words silently, in the inner speech task, they were asked to imagine speaking sentences based on the words, and in the auditory verbal imagery task, the imagined sentences had to be spoken by another person's voice. During the inner speech condition, hallucinating patients presented lower rCBF than non-hallucinating patients in the left superior temporal sulcus, lingual/fusiform gyrus bilaterally and right caudate (McGuire et al. 1996). During auditory verbal imagery, reduced rCBF was found in patients with AVH in the left middle temporal gyrus (BA 21), supplementary motor area (BA 6) and other cerebellar and occipito-temporal areas. On the other hand, increased activation was detected in the right superior temporal gyrus (BA 42) and right parietal operculum in comparison with non-hallucinating patients. The authors suggested that hallucinations were linked to dysfunctions in brain areas involved in the monitoring of inner speech. In particular, the decreased activation of the supplementary motor areas was interpreted as reflecting a less accurate attribution of the inner speech source (McGuire et al. 1996). Similarly, Stephane et al. (2006) compared brain activity of patients with AVH ($n = 8$) and patients who had never experienced this symptom during the course of the disease ($n = 10$) by means of $H_2{}^{15}O$-PET. In the experimental condition, participants were asked to read aloud single words, while the control condition consisted in looking at the displayed words without reading them. AVH patients showed reversed laterality of the supplementary motor area, that was more pronounced in the right hemisphere in comparison with NVH patients and a group of healthy volunteers ($n = 12$). The authors interpreted the laterality of the supplementary area activation in hallucinating patients as difficulties in attributing to themselves a self-generated action. In this context, hallucinations would be experienced following aberrant self-attribution of inner speech (Stephane et al. 2006). A summary of studies using a between-group design in the investigation of the neural features related to hallucinations in schizophrenia can be found in Table 17.4.

Other studies used a correlational approach to investigate functional brain features associated with hallucinations in schizophrenia. Gordon et al. (1994) reported early evidence of functional brain abnormalities in patients with schizophrenia with recent history of auditory hallucinations, especially reflecting an atypical right temporal lobe dominance, measured by means of SPECT imaging. Consistently, in a PET study, Gur et al. (1995) found that hypometabolism of the superior temporal lobe was significantly associated with more severe hallucinations. Sabri et al. (1997) investigated the pattern of regional CBF using PET in relation to different positive and negative symptoms in a sample of unmedicated patients with acute schizophrenia ($n = 24$). The authors found that measures of hallucinations were negatively associated with regional CBF in the left thalamus. On the other hand, negative correlations were detected between delusions and rCBF in the anterior cingulate, frontal and medial temporal cortices. Correlations between CBF and positive symptoms

were no longer significant after neuroleptic treatment (Sabri et al. 1997). In a $H_2{}^{15}O$-PET study, Lahti et al. (2006) performed correlational analyses in two separate cohorts of unmedicated patients with schizophrenia (cohort 1, $n = 32$; cohort 2, $n = 23$) to investigate patterns of CBF associated with positive symptoms (hallucinations/delusions and disorganisation) and negative symptoms. In cohort 1, hallucinations/delusions scores were negatively associated with rCBF in the left hippocampus and parahippocampus, while a positive correlation was detected in cohort 2 with the anterior cingulate and inferior frontal cortices (Lahti et al. 2006). In the latter study, however, no separate analyses were carried out to differentiate between hallucinations and delusions, and thus it is difficult to infer symptom-specific mechanisms related to the presence of hallucinations only (Lahti et al. 2006).

Finally, an early single-case SPECT study described a 41-year-old patient with schizophrenia before and after pharmacological treatment (Notardonato et al. 1989). Increased activity in the right temporal lobe and basal ganglia was detected in relation to AH. After treatment and clinical improvement, the pattern of activity appeared more distributed and symmetrical (Notardonato et al. 1989).

17.4 Neurotransmitter Imaging of Hallucinations

PET and SPECT imaging has also been used to investigate the levels of striatal dopamine transporter (DAT) in LBD (Jaakkola et al. 2017; Roselli et al. 2009) and schizophrenia (Artiges et al. 2017; Cassidy et al. 2018).

Nigrostriatal dopaminergic depletion and the presence of LBs are the main neuropathological features of PD, as well as DLB (Dickson et al. 2009; Jellinger 2012). Historically, VH in PD were considered as drug-induced symptoms, especially following treatment with levodopa, the precursor of dopamine and the gold standard treatment for PD (ffytche et al. 2017; Onofrj et al. 2013). Subsequent studies, however, have shown that these symptoms also occur in unmedicated patients and that antiparkinsonian medications do not increase the risk of developing VH, suggesting that these symptoms represent an intrinsic feature of the disease (ffytche et al. 2017, Onofrj et al. 2013). Only a few PET/SPECT studies have investigated dopaminergic dysfunctions in relation to VH in LBD. Kiferle et al. (2014) used ^{123}I-FP-CIT SPECT to assess striatal DAT availability in PD patients who subsequently developed VH ($n = 18$) in comparison with patients without VH ($n = 18$). Patients with VH at follow-up had significantly lower ^{123}I-FP-CIT uptake at baseline in the right caudate, but not in the left caudate, and putamen bilaterally. Similarly, Jaakkola et al. (2017) found lower DAT binding in the ventral striatum bilaterally, and in the right putamen in patients that subsequently developed VH ($n = 22$), compared with those that did not ($n = 48$). The authors suggested an involvement of fronto-striatal circuits, typical of PD, in the development of VH (Jaakkola et al. 2017). Consistently, in a sample of patients with DLB, negative correlations were found between striatal ^{123}I-FP-CIT uptake and severity/frequency of hallucinations, as well as depression, apathy and delusions (Roselli et al. 2009). Another PET study, instead, investigated serotonin 2A receptor binding in PD with

and without VH (Ballanger et al. 2010). Results indicated an increased binding in hallucinating patients in regions part of the ventral visual pathway (occipito-temporal), involved in object perception and recognition, and prefrontal and insular areas (Ballanger et al. 2010).

Hyperactivity of the dopaminergic system, reflecting increased striatal dopamine synthesis, has been repeatedly found in schizophrenia and has been linked to psychotic symptoms (Fusar-Poli and Meyer-Lindenberg 2013; Howes et al. 2009). However, imaging studies investigating dopamine uptake in patients with schizophrenia and hallucinations are still lacking. Artiges et al. (2017) investigated striatal and extra-striatal DAT availability in patients with schizophrenia by means of [^{11}C]PE2I, a selective DAT radioligand for PET imaging. Compared with controls ($n = 30$), patients with schizophrenia ($n = 21$) showed higher DAT availability in the striatum, substantia nigra/ventral tegmental area, nucleus accumbens, amygdala, thalamus, hippocampus and orbitofrontal gyrus. Positive correlations were found between hallucination scores and DAT availability in the left amygdala and hippocampus (Artiges et al. 2017). Cassidy et al. (2018) used an auditory task inducing auditory illusions under different levels of uncertainty and measured striatal dopamine using PET in patients with schizophrenia with and without hallucinations and healthy controls. Their hypothesis was based on a model of Bayesian inference and hallucinations, proposing that hallucinations arise from perceptual biases based on top-down context-dependent predictions, underlined by dopamine dysregulations. The authors found that patients with schizophrenia and hallucinations were characterised by a perceptual bias reflecting an overweight of prior expectations leading to imprecise predictions, especially in conditions of contextual uncertainty. Severity of hallucinations correlated with higher release of dopamine in the striatum and stronger perceptual bias (Cassidy et al. 2018).

Overall, the abovementioned findings suggest that alterations in the striatal dopaminergic system might play a role in the development of hallucinations, despite differences observed across different diagnoses (i.e. hypoactivity in PD and hyperactivity in schizophrenia).

17.5 Discussion

The aim of the present chapter was to provide an up-to-date review of PET and SPECT neuroimaging studies that have investigated the functional neural correlates of hallucinations in neurodegenerative and psychiatric conditions. A limited amount of studies was available using these imaging techniques and generally included small sample sizes. The most studied types of hallucinations were those experienced in the visual sensory modality in neurodegenerative conditions, mainly LBD, and auditory hallucinations in schizophrenia. The studies of hallucination in AD were only a small number and with small sample sizes, and do not warrant any firm conclusion. Overall, evidence regarding both neurodegenerative and psychiatric disorders suggests an involvement of sensory-related bottom-up processes, consistent with the hallucination sensory modality, and top-down control mechanisms. In

the following subsections, the results described in the present chapter are discussed separately for VH in neurodegenerative disorders and auditory hallucinations in schizophrenia. Finally, common and distinct mechanisms for hallucinations in different sensory modalities are proposed.

17.5.1 Visual Hallucinations in Lewy Body Disease

The majority of the studies including a sample of hallucinating patients with neurodegenerative conditions explored the trait-related neural activity associated with VH in LBD, comparing the pattern of cerebral metabolism/blood flow in patients without hallucinations among the clinical features. The most consistent finding is represented by occipital and occipito-temporal hypometabolism/perfusion in patients with VH, both in PD (Boecker et al. 2007; Gasca-Salas et al. 2016; Matsui et al. 2006b; Oishi et al. 2005; Park et al. 2013) and DLB (Heitz et al. 2015; Imamura et al. 2008; Pasquier et al. 2002; Perneczky et al. 2008). Occipital/occipito-temporal hypometabolism has also been found to correlate with the severity of VH, as shown by FDG-PET investigations in DLB (Firbank et al. 2016; Iaccarino et al. 2018; Kantarci et al. 2012). These findings suggest a contribution of dysfunctional ventral visual pathways, involved in the formation of object visual representation (Kravitz et al. 2013), in the development of VH in LBD. This is in line with the multifactorial model of VH proposed by Collerton et al. (2005). The authors suggested that recurrent, complex VH may be the result of combined deficits in visual attention and visual perception (object recognition), the latter supported by impaired activity within the ventral visual stream (Collerton et al. 2005). Neuropsychological studies have also confirmed an impairment in visual perception in patients with LBD and VH, in both LB dementia (Mori et al. 2000; Mosimann et al. 2004) and cognitively unimpaired PD (Barnes et al. 2003; Ibarretxe-Bilbao et al. 2010; Koerts et al. 2010; Ramirez-Ruiz et al. 2006, 2007a). On the other hand, no evidence of neuropathological alterations, namely, LBs accumulations, has so far been reported in the occipital lobe in relation to VH (Kalaitzakis et al. 2009), suggesting that the above-mentioned alterations do not reflect underlying neuropathological events directly, but might be the result of altered functional brain networks. Occipito-temporal alterations have been found in relation to VH in LBD also using other imaging modalities (Pezzoli et al. 2017). For example, decreased occipital and temporal activity has been found in response to visual stimuli in PD patients with VH compared with those without, detected by means of fMRI (Holroyd and Wooten 2006; Lefebvre et al. 2016; Stebbins et al. 2004). Furthermore, evidence of altered structural connectivity has been reported in the inferior longitudinal fasciculus in DLB patients with VH (Kantarci et al. 2010), a bundle of associative fibres connecting occipital and temporal areas that has been associated with visual memory and perception (Catani and Thiebaut De Schotten 2008). Other studies also showed occipito-temporal grey matter loss in hallucinating PD patients compared with those without VH (Bejr-Kasem et al. 2019; Goldman et al. 2014; Ramirez-Ruiz et al. 2007b; Watanabe et al. 2013).

In addition to visual processing impairments, Collerton et al. (2005) proposed a contribution of visual attention deficits in the development of VH. The top-down control of spatial attention has been shown to rely on a frontoparietal network of regions (Gazzaley and Nobre 2012; Nobre and Mesulam 2014) that, if disrupted, may constitute a vulnerability to VH in LBD. Studies have shown frontal (Boecker et al. 2007; Heitz et al. 2015; Perneczky et al. 2008) and parietal (Boecker et al. 2007; Gasca-Salas et al. 2016; Matsui et al. 2006b; Park et al. 2013) hypometabolism/perfusion in hallucinating LBD patients compared with non-hallucinating ones. However, inconsistencies have also been reported, including frontal and parietal hypermetabolism (Imamura et al. 1999; Nagano-Saito et al. 2004). Frontal grey matter loss has been shown in LBD patients with VH, especially in those with dementia, that has been associated with visual attention deficits (Sanchez-Castaneda et al. 2010; Pezzoli et al. 2019). These findings are in line with the more severe attention and executive deficits observed in patients with VH (Cagnin et al. 2013; Grossi et al. 2005; Hepp et al. 2013; Santangelo et al. 2007). There is a close relationship between cognitive impairment and VH that tend to be more severe, complex and common in patients with DLB and PDD (Onofrj et al. 2002). In addition, more severe progressive cognitive decline has been detected in patients with VH in comparison with those without (Ibarretxe-Bilbao et al. 2010; Ramirez-Ruiz et al. 2007a). Nevertheless, due to the limited amount of studies available, it is difficult to infer disease-specific neural mechanisms associated with VH across the LBD spectrum and how they are related to the presence of dementia, suggesting the need for further investigation.

Neuropathological studies have shown high proportion of LBs mainly in frontal and medial temporal areas (Gallagher et al. 2011; Harding et al. 2002a, b; Kalaitzakis et al. 2009; Papapetropoulos et al. 2006). In this context, functional and macrostructural alterations in frontal regions, and underlying neuropathological features, may represent hallmarks of impaired large-scale attention networks that may appear more pronounced in patients with dementia (Pezzoli et al. 2019). Studies have also associated executive dysfunction to VH, especially in PD (Barnes and Boubert 2008; Grossi et al. 2005; Ozer et al. 2007; Santangelo et al. 2007). Dopaminergic dysfunction due to disrupted fronto-striatal circuits reflecting nigrostriatal dopaminergic depletion is thought to underlie, at least in part, executive impairments in PD (Kehagia et al. 2010; Lewis et al. 2003). Within this framework, altered frontal activity (Boecker et al. 2007, Heitz et al. 2015, Perneczky et al. 2008), along with lower DAT availability (Jaakkola et al. 2017; Kiferle et al. 2014), might also be contributing factors to VH.

Complex behaviour has been increasingly conceptualised as resulting from the coordinated activity of distinct brain areas, often spatially remote, but interconnected (Nobre and Mesulam 2014; Rosazza et al. 2012). The functional connectivity of brain regions relies on the temporal coherence of their neural activity (Rosazza et al. 2012; Sporns 2013) and has been widely studied by means of resting-state fMRI. This approach allows the investigation of the brain intrinsic functional organisation and over the years has led to the identification of independent brain networks (Damoiseaux et al. 2006; Kalcher et al. 2012; Raichle 2015; Rosazza and Minati

2011). Among these, one of the most studied is the default mode network (DMN), a resting-state network activated during rest and deactivated during goal-related activities. The DMN includes regions such as the posterior cingulate, precuneus, inferior parietal lobule, medial prefrontal cortex and temporal areas (Buckner et al. 2008; Greicius et al. 2003; Raichle et al. 2001; Rosazza and Minati 2011; Utevsky et al. 2014). Even though it has been proposed that VH generate from a disrupted organisation of functional brain networks (Shine et al. 2014a, 2011), there is still insufficient evidence fully corroborating this hypothesis. In a recent model, Shine et al. (2011) suggested that hallucinations arise from a disrupted engagement of brain networks regulating attention, specifically the dorsal and ventral attention networks and the DMN (see Fig. 17.1). According to this model, false images would originate from the emergence of previously recorded percepts in the DMN, along with altered top-down and bottom-up attention processes (Shine et al. 2011). The most consistent findings among resting-state fMRI studies is represented by increased connectivity of DMN-related regions in hallucinating patients with PD, especially frontal and parietal areas (Franciotti et al. 2015; Yao et al. 2014). Interestingly, in these studies, patients with and without VH had reduced connectivity when compared with control subjects (Franciotti et al. 2015, Yao et al. 2014), suggesting that increased functional connectivity observed in VH patients, compared with non-hallucinating ones, may reflect dysfunctional compensatory mechanisms that, in turn, may foster the development of VH. DMN-related dysfunctions were also reported by a recent resting-state fMRI study on minor hallucination in PD (Bejr-Kasem et al. 2019). The authors focused on the posterior cingulate, a central hub of the DMN, showing increased connectivity between this region and temporal and parietal areas (Bejr-Kasem et al. 2019).

17.5.2 Auditory Hallucinations in Schizophrenia

The majority of the studies on psychiatric conditions investigated the neural activity associated with AVH in schizophrenia and scanned patients while they were experiencing the symptoms. Allen et al. (2008) proposed a model for AVH suggesting a role of brain networks involved in top-down and bottom-up processes. Specifically, AVH would arise from hyperactivity of sensory areas, as well as altered top-down modulation of areas involved in speech production (inferior frontal gyrus) and comprehension (Wernicke's area), and monitoring areas (ACC, prefrontal areas) (Allen et al. 2008). Findings are in line with this view. Among PET and SPECT studies, one of the most consistent results is represented by alterations in sensory areas, comprising primary and association auditory cortices, and other language-related regions, including Wernicke and Broca's areas. Overall, these studies showed hyperactivity in superior and middle temporal and frontal areas in patients during the hallucinatory state, specifically increased cerebral glucose metabolism/CBF (Copolov et al. 2003; McGuire et al. 1993; Horga et al. 2011; Suzuki et al. 1993). Consistently, the severity of the hallucinations was found to correlate with glucose metabolism in superior temporal lobe areas (Gur et al. 1995; Horga et al. 2011). Structural neuroimaging studies have also shown abnormalities in these structures,

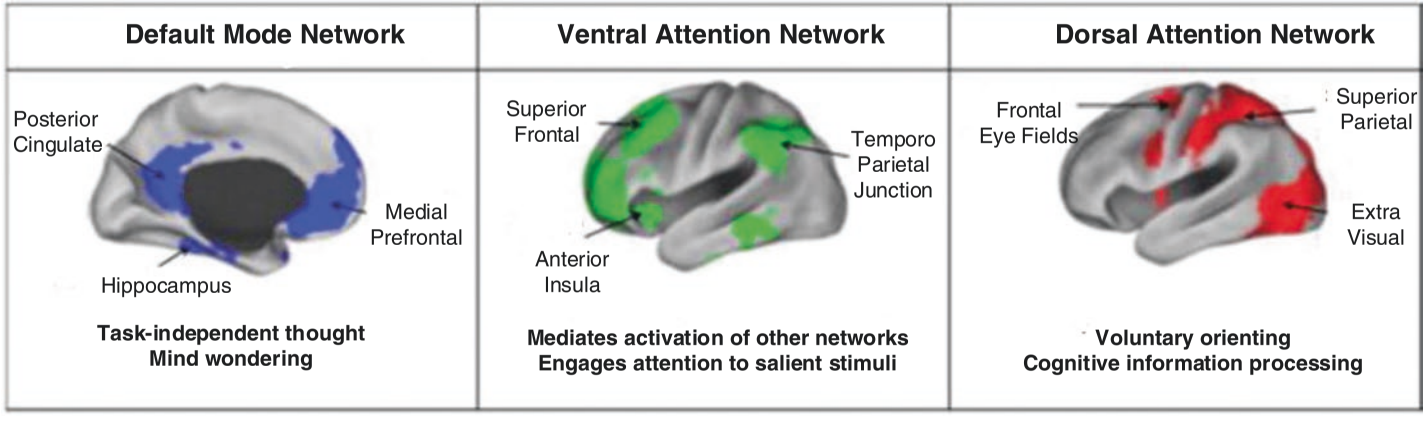

Fig. 17.1 Attentional control networks and their associated areas and function. Reproduced with permission from Table 1 in Shine et al. (2014b)

especially grey matter loss in the superior and middle temporal gyri, involved in auditory and language processing (Allen et al. 2012). A meta-analysis of VBM studies has also reported an association between severity of AVH and reduced grey matter in the superior temporal gyrus, especially in the left hemisphere (Modinos et al. 2013). The contribution to AVH of superior/middle temporal regions has also been supported by fMRI studies (Allen et al. 2008, 2012). A meta-analysis of functional neuroimaging of AVH, including both FDG-PET and fMRI studies, reported an involvement of these regions, along with other areas including Broca's area, insula, parietal and medial temporal lobe structures (Jardri et al. 2011). These findings, together, support the hypothesis that AVH may arise from aberrant functioning at different levels of language processing, especially in the auditory cortices and other superior temporal areas involved in speech perception, as well as frontal areas involved in speech production. Other findings are in line with models suggesting that AVH arise from aberrant monitoring of inner speech, whereby self-generated verbal thoughts would be erroneously attributed to an external source (Allen et al. 2007). PET studies suggested a contribution of the SMA in the defective attribution of the inner speech source (McGuire et al. 1996; Stephane et al. 2006). Other findings are consistent with this view and reported dysfunctions in regions involved in self-monitoring of inner speech, including the SMA, prefrontal, temporal, parahippocampal, hippocampal and cerebellar areas (Allen et al. 2007; Parellada et al. 2008; Shergill et al. 2003, 2000).

Impaired structural and functional connectivity in hallucinating patients with schizophrenia has been found in frontotemporal tracts/regions, in line with the abovementioned results (Allen et al. 2012; Mechelli et al. 2007; Tracy and Shergill 2013). Indeed, one of the most consistent findings of resting-state fMRI studies of AVH in schizophrenia is represented by disrupted functional connectivity in auditory and language-related areas, especially frontotemporal regions (Alderson-Day et al. 2016; Tracy and Shergill 2013). Altered functional connectivity of other networks has also been reported, including the DMN, salience and central executive networks, suggesting a contribution to AVH of other cognitive dysfunctions, such as cognitive control and attention (Alderson-Day et al. 2016). The salience network is involved in generating appropriate behaviour to salient stimuli by detecting and integrating internal and external events, and in switching attention between the DMN and the central executive network, and includes the ACC, insula and ventral striatum (Alderson-Day et al. 2016; Menon 2011; Menon and Uddin 2010). Hubs of the central executive network include the dorsolateral prefrontal, lateral parietal and supragenual anterior cingulate cortices (Alderson-Day et al. 2016). PET and SPECT findings on AVH in schizophrenia provide evidence of impaired activity in the ACC and striatum, as well as other frontal areas (Copolov et al. 2003; Horga et al. 2011; Kopecek et al. 2007; Parellada et al. 2008; Silbersweig et al. 1995). Moreover, the severity of the hallucinations correlated with metabolism in the ACC, in the striatum (Cleghorn et al. 1992, 1990) and in dorsolateral prefrontal cortex (Kopecek et al. 2007). It has been proposed that AVH may arise from aberrant interactions between the DMN, salience and executive control networks, along with altered connectivity in auditory and language-related networks, as shown in Fig. 17.2 (Alderson-Day

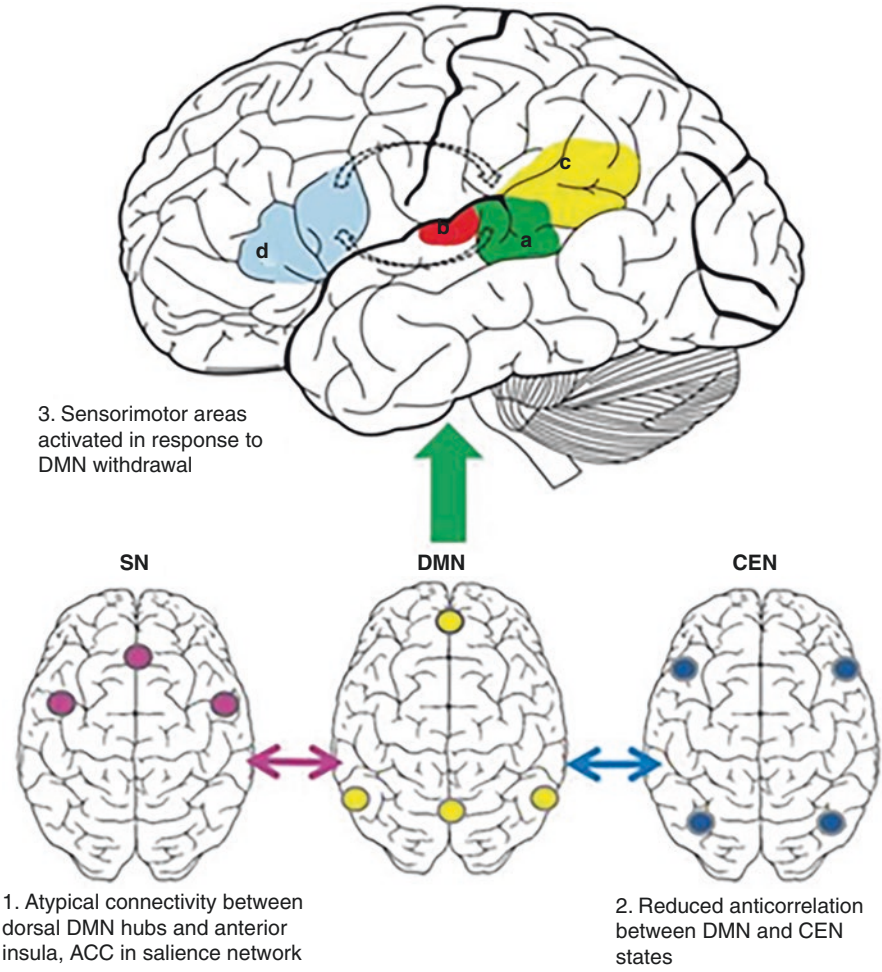

Fig. 17.2 Initial AH studies focused on resting connectivity in auditory and language regions (upper figure), primarily identifying atypical connectivity of left posterior STG (a), PAC (b) and the TPJ area (c). Findings of atypical resting connectivity between left IFG (d) and STG are inconsistent, although both areas are often implicated during AH. More recent findings implicate atypical interaction of the DMN, SN and CEN in those prone to AH (lower figures). The combination of atypical DMN interaction with SN (1) and CEN (2) and altered resting connectivity in sensory areas could prompt the collapse of internally focused states into activation of auditory cortex (3), that is then reverberated along a frontotemporal loop. The IFG, STG and surrounding areas are often implicated in symptom-capture studies (Jardri et al. 2011). Abbreviations: *ACC* Anterior cingulate cortex, *AH* Auditory hallucination, *CEN* Central executive network, *DMN* Default mode network, *IFG* Inferior frontal gyrus, *PAC* Primary auditory cortex, *SN* Salience network, *STG* Superior temporal gyrus, *TPJ* Temporo-parietal junction. Reproduced from Alderson-Day et al. (2016) and used under the Creative Commons Attribution License

et al. 2016). Due to the limited amount of findings, however, this hypothesis needs to be investigated further in order to clarify the role of these networks in the genesis of AVH in schizophrenia.

17.5.3 Common and Distinct Mechanisms of Hallucinations across Diagnoses and Sensory Modalities

The findings described in this chapter suggest the presence of common neural mechanisms underlying hallucinations across diagnosis, especially impaired regions involved in sensory processing, consistent with the sensory modality of the hallucinations, and other differential top-down neurocognitive mechanisms.

Patients with LBD presented reduced metabolism/CBF in regions sustaining the formation of object visual representations, reflecting dysfunction of a ventral visual pathway comprising primary and associative visual cortices, occipito-temporal and inferior temporal areas (Dicarlo et al. 2012; Kravitz et al. 2013). Patients with schizophrenia and AVH, instead, presented overactivity of primary and associative auditory cortices, and other regions involved in language processing, related to both speech comprehension and production (i.e. superior temporal and inferior frontal). Discrepancies in the direction of such alterations, namely, reduced activity in LBD with VH and increased activity in schizophrenia with AVH, may be explained by methodological differences between studies. No study on VH in LBD scanned patients while experiencing hallucinations, and, therefore, these findings may reflect trait-related features of the symptomatology. On the other hand, the majority of the studies on schizophrenia investigated the neural activity associated with the hallucinatory state and assessed the patients while experiencing AVH during the scanning session.

Other studies suggest the contribution to hallucinations of sensory regions, for example, those including patients with Charles Bonnet syndrome, a condition characterised by prominent peripheral visual impairment and recurrent complex VH in the absence of other major psychopathological symptoms (Collerton et al. 2005). In these patients, altered activation of occipital and occipito-temporal areas has been reported (Ffytche et al. 1998; Kazui et al. 2009). Accordingly, lesions studies point in the same direction. It has been shown that patients with post-lesion hallucinations in different sensory modalities (visual, auditory or somatic) presented alterations in brain regions consistent with the sensory modality of the hallucinations that may lead to compensatory activations of areas within the corresponding sensory pathway (Braun et al. 2003).

Despite methodological differences across studies, the findings described above, together, suggest the involvement of dysfunction in sensory regions in the development of hallucinations. These alterations extended to areas involved in further information processing, including those sustaining the formation of visual representation, associated with VH in LBD, and language processing, related to AVH in schizophrenia. In the light of the evidence so far reported in the literature, we can speculate that such dysfunctional information processing mechanisms may represent

necessary contributors to the hallucinatory phenomenon. In order to be actually experienced, however, hallucinations seem to require the involvement of other altered top-down neurocognitive mechanisms. In LBD, frontal alterations might be hallmarks of impaired top-down attention control mechanisms that in turn may constitute a vulnerability to VH. It has been suggested that VH may generate from impaired regulation of attention networks and the DMN (Shine et al. 2011, 2014b). Similarly, in schizophrenia, dysfunctions in the DMN, salience and executive networks have been proposed to underlie AVH, suggesting a contribution of other high cognitive functions, including cognitive control of attention (Alderson-Day et al. 2016). Within this framework, the altered activity reported in the ACC and ventral striatum might play a role. Nevertheless, there is still insufficient evidence to corroborate this view, in both LBD and schizophrenia, highlighting the need for further research exploring large-scale functional brain networks by means of connectivity analyses.

17.5.4 Conclusions

The present chapter provides an overview of PET and SPECT studies on hallucinations in patients with neurodegenerative and psychiatric conditions. Overall, the findings suggest a complex combination of neural dysfunctions associated with these symptoms. Impairments in both bottom-up and top-down mechanisms appear to play a significant role. Dysfunctional sensory processing was found in brain regions consistent with the sensory modality of the hallucinations, especially in occipito-temporal areas in LBD patients with VH, and in primary and associative auditory cortices and other regions involved in language processing in schizophrenia with AVH. The role of specific top-down control functions might be slightly different across conditions and appeared to involve mainly frontoparietal areas in LBD and the ACC and ventral striatum in schizophrenia. Within this process, dysfunctional top-down control mechanisms over sensory pathways might foster the generation and emergence of hallucinations. Resting-state fMRI and metabolic connectivity studies might be particularly helpful to shed light on hallucination-related functional organisation of brain regions in large-scale functional networks that, if impaired, might contribute to the development of these symptoms across different diagnoses and sensory modalities.

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TSPO Imaging in Psychiatric Disorders

18

Simon Cervenka and Romina Mizrahi

Contents

Abstract

In recent years there has been an increased interest in the immune system as a target for treatment across several psychiatric disorders. To aid this development, methods for patient stratification and treatment monitoring are needed. Positron Emission Tomography (PET) targeting the 18-kD translocator protein (TSPO) is to date the most established method to study brain immune function. In psychosis and schizophrenia, early reports in small samples found evidence for an increase in TSPO, whereas more recent work using radioligands with higher-specific to non-specific binding ratio has indicated lower levels in patients. In contrast, a series of studies have found higher levels of TSPO in patients with major depressive disorder. Reports of alterations of TSPO in alcohol use disorder, cannabis use, and

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obsessive-compulsive disorder warrant further research. Methodological limitations such as low signal-to-noise ratio for first-generation radioligands and lack of arterial input function limit the evidential value of some studies. Moreover, the lack of cell-type and functional specificity of TSPO means this biomarker has to be validated for each condition separately.

18.1 Introduction

A causative role for the immune system in the manifestation of psychiatric symptoms has been discussed for several decades. Early observations include psychotic symptoms in patients with autoimmune or infectious diseases engaging the brain (Oommen et al. 1982; Felgenhauer 1990) and depressive-like symptoms (also termed "sickness behavior") in response to experimentally induced immune activation (Reichenberg et al. 2001; Dantzer et al. 2008). Research in psychiatric populations has revealed evidence of genetic (Ripke et al. 2014; Odell et al. 2005; Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium 2015) and epidemiological (Blomström et al. 2016; Benros et al. 2013) nature in favor of the immune hypothesis, and studies in blood and cerebrospinal fluid (CSF) have shown increases in pro-inflammatory markers across several psychiatric diagnoses (Miller et al. 2011; Mitchell and Goldstein 2014; Dowlati et al. 2010; Enache et al. 2019). Similarly, immune mechanisms have been implicated in experimental studies on alcohol as well as psychostimulants and cannabis (Qin et al. 2008; Thomas et al. 2004; Crews and Vetreno 2016; Mecha et al. 2016). With regard to treatment, initial trials using anti-inflammatory medication in schizophrenia and depression have shown improvement in some cases (Sommer et al. 2012; Husain et al. 2017). However, in order to confirm an engagement of the brain immune system and thus pave the way for causative treatment, more direct methods to quantify the brain immune system are needed.

The 18-kD translocator protein (TSPO), previously known as the peripheral benzodiazepine receptor, is present in mitochondria of mostly glial cells in the brain as well as immune cells in the periphery (Braestrup et al. 1977; Canat et al. 1993). TSPO is expressed in normal conditions and has been shown to be involved in cholesterol transport, but the exact physiological role of the protein is not fully understood. Based on experimental data showing increases in TSPO expression in response to inflammatory stimuli (Venneti et al. 2013), TSPO has been viewed as a marker for immune activation; and therefore Positron Emission Tomography (PET) studies targeting this protein have been the most established method thus far to study brain immune function.

Initial TSPO PET studies were performed using the first-generation TSPO radioligand [^{11}C]PK11195, which was developed in the 1990s. Due to the low signal-to-noise ratio of this tracer, much effort has been invested into the development of second-generation radioligands, with higher brain uptake and specific to nonspecific binding ratios (Imaizumi et al. 2008; Wilson et al. 2008). In early studies using second-generation TSPO radioligands, it was observed that a small

PET studies comparing TSPO binding in psychiatric patients to that of healthy control subjects

Publication	Population	Sample size (P/C)	Medication	Radioligand	Outcome measure	Kinetic model	TSPO genotyped	Statistically significant group differences	Comment (may remove this)
van Berckel et al. (2008a, b)	Schizophrenia	10/10	Medicated	[^{11}C] PK11195	BP_P	2TCM	No	Total GM ↑	
Doorduin et al. (2009a, b)	Schizophrenia	10/7	Medicated	[^{11}C] PK11195	BP_{ND}	2TCM	No	Hippocampus ↑	
Takano et al. (2010)	Schizophrenia	14/14	Medicated	[^{11}C] DAA1106	BP_{ND}	2TCM	No	n.d.	
Kenk et al. (2014)	Schizophrenia	27/16	Medicated	[^{18}F]FEPPA	VT	2TCM	Yes	n.d.	
Bloomfield et al. (2016)	Schizophrenia	14/14	Medicated	[^{11}C]PBR28	DVR[a]/VT	2TCM-1	Yes	GM, FC, TC ↑/n.d.[b]	No difference in VT
	Ultra high risk	14/14	DN	[^{11}C]PBR28	DVR[a]/VT	2TCM-1	Yes	GM, FC, TC ↑/n.d.	
Coughlin et al. (2016)	Schizophrenia	12/14	Medicated	[^{11}C] DPA713	VT	2TCM	Yes	n.d.	
Hafizi et al. (2017a, b)	First episode psychosis	19/20	14 DN, 5 DF	[^{18}F]FEPPA	VT	2TCM	Yes	n.d.	
Holmes et al. (2016a, b)	Schizophrenia	16/16	8 medicated, 6 DN, 2 DF	[^{11}C] PK11195	BP_{ND}	SRTM (CER)	No	n.d.	Increases in medicated patients
Van der Doef et al. (2016)	Psychotic disorder	19/17	Medicated	[^{11}C] PK11195	BP_{ND}	SRTM (SVCA4)	No	n.d.	
Collste et al. (2017a, b)	First episode psychosis	14/14	DN	[^{11}C]PBR28	VT	2TCM	Yes	GM, FC, TC, hip ↓	

(continued)

Publication	Population	Sample size (P/C)	Medication	Radioligand	Outcome measure	Kinetic model	TSPO genotyped	Statistically significant group differences	Comment (may remove this)
Di Biase et al. (2017)	Schizophrenia	33/27	Medicated	[^{11}C] PK11195	BP_{ND}	SRTM (CER)	No	n.d.	
	Ultra high risk	10/27	DN	[^{11}C] PK11195	BP_{ND}	SRTM (CER)	No	n.d.	
Hafizi et al. (2017a, b)	Clinical high risk	24/23	22 DN 2 DF	[^{18}F]FEPPA	VT	2TCM	Yes	n.d.	
Ottoy et al. (2018)	Schizophrenia	11/17	Medicated	[^{11}C] PBR111	VT	2TCM-1 k	Yes	n.d.	Interaction effect between age and patient status
Hannestad et al. (2013)	Major depression	10/10	8 medicated 2 DF	[^{11}C]PBR28	VT	2TCM	Yes	n.d.	CRP > 3 was exclusion criterion
Su et al. (2016)	Late-life depression	5/13	No data	[^{11}C] PK11195	BP_{ND}	SRTM (CER)	No	L subgenual ACC, R parahippocampus ↑[c]	No corrections for multiple comparisons
Holmes et al. (2018)	Major depression	14/13	DF	[^{11}C] PK11195	BP_{ND}	SRTM (CER)	No	ACC ↑	
Setiawan et al. (2015, 2018)	Major depression	50/30[d]	11 DN 19 DF?	[^{18}F]FEPPA	VT	2TCM	Yes	PFC, ACC, insula ↑	
Richards et al. (2018)	Major depression	28/20	16 medicated 12 DF	[^{11}C]PBR28	VT/fP	2TCM	Yes	n.d.	Increases in DF
Li et al. (2018a, b)	Major depression	50/30[e]	DN	[^{18}F]FEPPA	VT	2TCM	Yes	GM, WM, FC, TC, Hipp ↑	
Sekine et al. (2008)	Methamphetamine users	12/12	N/A	[^{11}C] PK11195	BP_{ND}	SRTM[f]	No	N/A[f]	Method and results not valid

Narendran et al. (2014)	Cocaine users	15/17	N/A	[^{11}C]PBR28	VT	T2CM	Yes	n.d.	
Kalk et al. (2017)	Alcohol dependence	9/20	N/A	[^{11}C]PBR28	VT	T2CM	Yes	Hippocampus ↓	
Hillmer et al. (2017)	Alcohol dependence	15/15	N/A	[^{11}C]PBR28	VT	T2CM	Yes	Cerebellum, FC, striatum, hippocampus ↓	
Da Silva et al. (2019)	Cannabis users	24/27	N/A	[^{18}F]FEPPA	0	T2CM	Yes	PFC, TC, ACC, cerebellum ↑	
Suzuki et al. (2013)	Autism	20/20	N/A	[^{11}C] PK11195	BP_{ND}	SRTM[d]	No	N/A[f]	Method and results not valid
Haarman et al. (2014)	Bipolar disorder	14/11	13 medicated 1 DF	[^{11}C] PK11195	BP_{ND}	2TCM	No	R Hippocampus ↑	
Attwells et al. (2017)	OCD	20/20	DF	[^{18}F]FEPPA	VT	2TCM	Yes	Striatum, OFC, thalamus, ACC ↑	

HC healthy control subjects, *OCD* obsessive-compulsive disorder, *DN* drug naïve, *DF* drug free, *VT* total distribution volume, *BPND* binding potential (specific over non-displaceable binding), *BPP* binding potential specific binding over total plasma, *2TCM* two tissue compartment model, *2TCM-1 k* 2TCM with additional irreversible compartment, *PFC* prefrontal cortex, *CER* using cerebellum as pseudoreference region, *SVCA4* using supervised cluster analysis with four kinetic classes as pseudoreference region, *n.d.* no statistically significant difference, *GM* gray matter, *FC* frontal cortex, *TC* temporal cortex, *Hip* hippocampus, *PFC* prefrontal cortex, *ACC* anterior cingulate cortex, *WM* white matter, *OFC* orbitofrontal cortex

[a]DVR calculated using marginal means from an ANCOVA model, using whole brain VT as covariate

[b]Brain VT showed trend level decrease in patients ($p = 0.051$)

[c]No correction for multiple comparisons were performed

[d]20 patients and 25 HC from Setiawan et al. 2015 were included in 2018 publication

[e]40 patients and 20 HC from Li et al. 2018a were included in 2018b

[f]Reference input derived from control subjects and results therefore not deemed valid

proportion of the population did not show specific binding, which was attributed to different polymorphisms of the TSPO gene (Owen et al. 2012). Based on these different genotypes, the population can be classified as high-affinity binders (HABs), mixed-affinity binders (MABs), and low-affinity binders (LABs). Although effects of TSPO genotype had been shown also for [^{11}C]PK11195 in peripheral tissue (Kreisl et al. 2010), the increased sensitivity of second-generation radioligands means that this factor has to be taken into account in the analysis, and also that LAB individuals, corresponding to around 9% of the (western) population, have to be excluded due to insufficient affinity for quantification for most radioligands (Owen et al. 2012).

To date, around 25 studies have been performed where TSPO levels have been directly compared between psychiatric patients and healthy control subjects, the results of which will be summarized in this chapter.

18.2 Psychotic Disorders

Schizophrenia and psychotic disorders are the psychiatric patient group that have been most extensively studied using TSPO PET, with in total 13 studies encompassing almost 250 patients or individuals at high risk for psychosis. In the first TSPO schizophrenia study by van Berckel et al. in 2008, [^{11}C]PK11195 was used in a sample of ten medicated patients and ten control subjects (van Berckel et al. 2008a). Quantification was performed using a two-tissue compartment (2TCM) model with arterial input function and using the resulting microparameters to calculate binding potential in relation to plasma (BP_P) (Innis et al. 2007a). An increase was observed in total gray matter, which was the only region studied. In a subsequent study in a similarly small sample of recent-onset schizophrenia, the same methodology was used, yielding binding potential in relation to non-displaceable binding (PB_{ND}). Increased binding was observed in hippocampus, although this effect became evident only after normalizing to total gray matter (Doorduin et al. 2009a).

In the first psychosis study employing a second-generation TSPO radioligand, 14 chronic schizophrenia patients and a corresponding number of control subjects were examined using [^{11}C]DAA1106 (Takano et al. 2010). BP_{ND} as quantified using 2TCM showed no difference between groups. However, in this study the TSPO genotype was not known, significantly limiting the interpretability of the results. In another study, the second-generation TSPO radioligand [^{18}F]FEPPA was used in a large group of 18 chronic schizophrenia patients compared to 27 volunteers. Using total distribution volume (V_T) derived using 2TCM as outcome, corresponding to total binding in brain in relation to plasma, no difference was found compared to control subjects (Kenk et al. 2014). A subsequent study in high-risk individuals and chronic patients showed increased levels of binding in cortical gray matter regions compared to control subjects (Bloomfield et al. 2016). Here, the authors calculated binding as marginal means derived from a statistical model controlling for binding in whole brain, a relative approach that has been questioned (Narendran and Frankle

2016; Matheson et al. 2017). Notably, V_T values in gray matter were numerically lower in both groups compared to control subjects, thus contradicting the conclusions drawn. This was the case both when using 2TCM and 2TCM-1k, a model which proposes to take an irreversible binding component into account.

Since antipsychotic compounds have been known to affect immune function (Drzyzga et al. 2006; Danovich et al. 2008), medication is a potential confounder in all the studies mentioned thus far. Addressing this shortcoming, a study with a combination of 5 untreated and 14 drug-naïve first episode psychosis patients was examined using [^{18}F]FEPPA, finding no difference in V_T (Hafizi et al. 2017a). In a following study in 14 antipsychotic-naïve patients using [^{11}C]PBR28, significantly lower levels of V_T in patients were observed (Collste et al. 2017a). Additional studies using both [^{11}C]PK11195 and second-generation radioligands in different disease stages also failed to show increases in patients compared to control subjects (Coughlin et al. 2016; Van Der Doef et al. 2016; Holmes et al. 2016a; Di Biase et al. 2017; Ottoy et al. 2018), although one [^{11}C]PK11195 study found elevated binding in a small subgroup of medicated patients (Holmes et al. 2016a). A study in a large group of high-risk individuals, using the second-generation TSPO radioligand [^{18}F]FEPPA, found no differences in binding (Hafizi et al. 2017b), aligning to the results of Bloomfield et al. when using non-normalized binding measures (Bloomfield et al. 2016).

A common problem in PET research is the use of small sample sizes, yielding limited power to detect true differences, as well as increasing the risk for false positives. To address this limitation, individual participant TSPO data was combined from five studies using second-generation TSPO radioligands in schizophrenia or first episode psychosis patients. Strong evidence was obtained for a decrease in TSPO in gray matter regions, with effect sizes ranging from −0.47 to −0.63 (Plavén-Sigray et al. 2018a). No effect of antipsychotic medication on V_T was observed. An additional meta-analysis using summary statistics found evidence of increases in binding in [^{11}C]PK11195 studies and no difference in second-generation TSPO radioligand studies (Marques et al. 2019). However, due to methodological caveats of [^{11}C]PK11195 discussed below, the evidential value of the [^{11}C]PK11195 studies is limited (Plavén-Sigray and Cervenka 2019).

Taken together, the overall evidence is in favor of lower TSPO binding in psychosis patients. Although the underlying biology is unclear, this suggests altered function of brain glial cells in psychosis. It has been hypothesized that the causative role of immune factors in schizophrenia may be related to microglia-mediated excessive synaptic pruning, which may explain the cortical thinning and synaptic loss observed in MR and postmortem studies (Sekar et al. 2016; Cannon 2015; Sellgren et al. 2019; Glausier and Lewis 2013). Thus far, two studies have investigated the relationship between TSPO and brain structure in psychosis spectrum patients. Selvaraj et al. showed a relationship between TSPO binding and total cortical GM volume; however this was using the relative measure of TSPO binding which means that the interpretation of the findings is unclear (Selvaraj et al. 2018). In a much larger cohort of in total 90 clinical high-risk individuals, first episode

psychosis patients and control subjects, associations were observed between TSPO binding and outward and inward morphological alterations in hippocampus, representing the first association between a brain immune marker and structural morphology (Hafizi et al. 2018).

18.3 Depression

During recent years, TSPO PET has been applied increasingly also in patients with major depressive disorder (MDD). In the first report published, Hannestad et al. used [^{11}C]PBR28 to examine ten MDD patients and ten control subjects (Hannestad et al. 2013). No group difference was observed, either when using a one-tissue compartment (1TCM), 2TCM or the multilinear analysis MA1 to derive V_T, or after correcting for free fraction. Apart from the limitation of a small sample size, in this study elevated C-reactive protein was used as an exclusion criterion, which may have influenced the results. Moreover, patients showed only mild-to-moderate symptom severity at time of scanning, which represented a reduction from screening. Subsequently, Setiawan et al. used [^{18}F]FEPPA to study 20 medication-free patients with major depression (MD), compared to 20 control subjects (Setiawan et al. 2015). Increases in TCM-derived V_T were shown in prefrontal cortex, anterior cingulate (ACC), and insula. Symptom scores were positively correlated to TSPO V_T in the ACC, after correcting for genotype. The results of elevated TSPO were later confirmed when adding additional 30 patients and 5 controls to the same sample (Setiawan et al. 2018). In a study using [^{11}C]PK11195 in 14 patients with depression and 13 controls, BP_{ND} was quantified using cerebellum as reference region in a simplified reference tissue model (Holmes et al. 2018). Significantly higher binding was found in ACC in patients, although the absolute difference in binding was low. Using similar methodology, increases in [^{11}C]PK11195 was observed in five individuals with late-life depression, although the very small sample size as well as a lack of control for multiple comparisons limits the interpretability (Su et al. 2016). In an additional study using [^{11}C]PBR28, in 28 patients and 20 controls, no significant difference between groups, using plasma fraction-corrected V_T as outcome measure. However, a post hoc analysis revealed increased V_T in a subgroup of 16 patients with ongoing antidepressant medication (Richards et al. 2018). Finally, in 2 publications based on overlapping samples, in cluding a total of 50 MDD patients and 30 HC were examined using [^{18}F]FEPPA. Increases were observed in GM, WM, frontal and temporal cortices, as well as hippocampus (Li et al. 2018a, b).

Recently, results from TSPO PET studies in depression were analyzed in a summary statistics meta-analysis, showing increases in TSPO density in ACC, TC, FC, insula, and hippocampus with a standardized effect size of 0.71 (Enache et al. 2019). Interestingly, it was suggested that TSPO increases in depression may reflect increased recruitment of peripheral monocytes, which is in line with experimental data showing alterations in blood-brain barrier integrity in chronic social stress (Menard et al. 2017).

18.4 Substance Use Disorders

Based on animal studies showing an involvement of microglia in the neurotoxic effects of alcohol and psychostimulants, efforts have been made to investigate TSPO levels in individuals with substance use disorders. An initial study used [^{11}C]PK11195 to examine 12 methamphetamine users and 12 healthy control subjects (Sekine et al. 2008). BP_{ND} was calculated using SRTM, with averaged TACs from cortical regions from the control group as reference input. BP_{ND} increases in patients ranged from 3- to 15-fold. Importantly, the unorthodox choice of reference region means that differences in delivery of radioligand to brain as well as nonspecific binding cannot be controlled for, severely limiting the interpretability of the results. In a subsequent study using [^{11}C]PBR28, Narendran et al. investigated 15 chronic cocaine abusers in comparison with 17 control subjects (Narendran et al. 2014). V_T was calculated using 2TCM, showing no difference between groups.

[^{11}C]PBR28 has been used in two recent studies on alcohol dependence. Kalk et al. examined 9 patients within 1 month of withdrawal and 20 control subjects, showing significantly lower V_T in hippocampus in patients (Kalk et al. 2017). In a similar study, 15 patients were examined within 1–4 days ($n = 14$) or 24 days ($n = 1$) after their last drink and compared to 15 control subjects (Hillmer et al. 2017). Again, contrary to the initial hypothesis, decreases in V_T in patients were observed in hippocampus, striatum, frontal cortex, and cerebellum. In the latter study, PET data was paralleled by reduced cytokine expression in cultured monocytes after stimulation with lipopolysaccharide, in a subgroup of subjects.

Finally, following experimental data showing that the cannabinoid system can modulate immune responses, [^{18}F]FEPPA and PET were very recently used to examine 24 chronic cannabis users and 27 controls (Da Silva et al. 2019). V_T was higher across all regions examined a priori, with more prominent effects for individuals who met criteria for cannabis use disorder. TSPO levels were positively correlated with increased blood CRP levels as well as subjective measures of stress and anxiety.

18.5 Other Disorders

To date, one study investigated TSPO in developmental disorders. Suzuki et al. used [^{11}C]PK11195 to examine 20 individuals with autism spectrum disorders and 20 matched controls. BP_{ND} was quantified using SRTM, with averaged cerebellar TACs from the control group as input function for both patients and control subjects. Increases in BP_{ND} were reported in all brain regions examined. As commented above, no clear conclusions can be drawn due to the use of this reference region approach.

Using the same radioligand, Haarman et al. examined 14 bipolar type I patients compared to 11 healthy controls (Haarman et al. 2014). All patients except one were euthymic, and 13 were taking mood stabilizers. BP_{ND} was quantified using 2TCM with an arterial input function, estimated as k3/k4. Binding in whole brain gray

matter was used as a covariate to reduce variability. Hippocampus was selected as the main ROI and showed increases on the right side in patients. No other brain region reached statistical significance.

Finally, a recent study examined TSPO in a group of 20 patients with obsessive-compulsive disorder and 20 control subjects, using [^{18}F]FEPPA (Attwells et al. 2017). None of the patients were on medication. V_T as quantified using 2TCM was higher in striatum, orbitofrontal cortex, thalamus, as well as ACC. A correlation was observed between symptom severity and TSPO levels in orbitofrontal cortex, although this was not corrected for multiple comparisons.

18.6 Methodological Considerations

When interpreting the results from TSPO PET imaging, there are some methodological aspects to consider. In the field of psychosis and schizophrenia, apparent different results have been obtained using [^{11}C]PK11195 compared to that of second-generation TSPO radioligands, necessitating a closer inspection of the differences in characteristics between these tracers. By performing PET experiments where the specific binding is blocked using a cold compound, the ratio between specific and non-displaceable (background) binding, referred to as non-displaceable binding potential (BP_{ND}) (Innis et al. 2007b), can be estimated. For [^{11}C]PK11195, this approach has yielded BP_{ND} values in the range of 0.7–0.8 in healthy control subjects, suggesting that the background signal is proportionally larger than target signal (Kobayashi et al. 2017). This ratio is significantly lower than has been reported for the second-generation TSPO radioligands [^{11}C]PBR28 (Plavén-Sigray et al. 2019; Owen et al. 2014), [^{11}C]DPA713 (Kobayashi et al. 2017), and the more recently developed [^{11}C]ER176 (Ikawa et al. 2017). Importantly, a consequence of lower signal-to-noise ratio means lower accuracy and reliability of the measurement.

A second caveat when interpreting TSPO PET results relates to the difference in quantification methods between studies. An important premise for TSPO quantification is that there is no reference region devoid of TSPO in the brain (Doble et al. 1987). This means that arterial blood sampling is necessary to establish the delivery of radioligand to brain, permitting kinetic modeling of the time activity curve data. Using this method, the gold standard outcome is considered to be the total distribution volume (V_T), which is an estimate of radioligand binding in relation to plasma. Since arterial sampling can be cumbersome and technically difficult, attempts have been made to find simplified methods of analysis. For the majority of [^{11}C]PK11195 studies in psychiatric disorders, reference tissue approaches have been used, either using the cerebellum as "pseudoreference" region (Di Biase et al. 2017; Holmes et al. 2016b, 2018; Su et al. 2016) or deriving an input function using cluster analysis (Van Der Doef et al. 2016; Di Biase et al. 2017). Using a test-retest dataset in healthy control subjects, these approaches showed intraclass correlation coefficient values in the range of 0.3–0.5

(Plavén-Sigray et al. 2018b), suggesting that at least half of the variability in BP_{ND} is due to measurement error. Moreover, there was a lack of correlation between BP_{ND} and BP calculated using microparameters, as employed in studies in psychosis and bipolar disorder (Haarman et al. 2014; van Berckel et al. 2008b; Doorduin et al. 2009b), and V_T. Thus, in absence of clear increases in TSPO, the combination of low specific binding and suboptimal methods of quantification, we suggest that results from [^{11}C]PK11195 studies should be interpreted with caution. As mentioned above, two [^{11}C]PK11195 studies also used TACs from the control group as input function for the whole sample, creating further problems for interpretation (Sekine et al. 2008; Suzuki et al. 2013).

In studies using second-generation TSPO radioligands such as [^{11}C]PBR28, one approach to reduce variability in the data has been to calculate ratios between binding in target region and reference region, using standardized uptake values (SUVR) or V_T (DVR) (Lyoo et al. 2015). A drawback of this relative approach is that the resulting values are sensitive to changes in the normalizing region (Narendran and Frankle 2016). Moreover, a study in healthy controls suggested that in absence of clear increases, the high intercorrelation between binding in target and "normalizing" regions means that much of the biological signal is lost, leading to low reliability and low correlation to the gold standard V_T measurement (Matheson et al. 2017). In one study in psychosis and ultra-high-risk individuals, yet another approach was used whereby V_T in the normalizing region was entered as a covariate in the statistical model, and DVR was extracted as predicted values (Bloomfield et al. 2016). When the target region is included in the normalizing region, the regional intercorrelation is likely to increase, further reducing signal-to-noise.

One potential caveat that has been discussed when using arterial blood as input function for quantification is that peripheral inflammation may lead to biased results. Based on in vitro studies showing binding of [^{11}C]PK11195 to acute phase proteins (Lockhart et al. 2003), it has been hypothesized that inflammation may lead to increased protein binding, such that the true input function is overestimated, leading to false low values of binding in brain. However, there is to date no study showing a clear effect of free fraction on V_T. Instead, in a study by Sandiego and co-workers using the pro-inflammatory agent lipopolysaccharide (LPS) (Sandiego et al. 2015), there was no increase in radioligand binding to plasma proteins, despite a clear peripheral pro-inflammatory activation. The arterial input function was decreased, which is expected due to the increase in peripheral binding, whereas brain V_T was increased. Similarly, at least three of the clinical studies reviewed above showed decreases in brain V_T in patients in absence of changes in radioligand protein binding, despite previous research showing peripheral increases in pro-inflammatory markers in these populations (Kalk et al. 2017; Hillmer et al. 2017; Collste et al. 2017b). Further investigations into the effect of peripheral immune activation on central TSPO binding are warranted.

Considering the sometimes surprising findings of reduction in TSPO in clinical studies, additional work has been directed towards understanding the underlying biology. First, it has become clear that TSPO is not specific for microglial

activation. The protein is expressed in astrocytes (Toth et al. 2016; Lavisse et al. 2012; Notter et al. 2018a) as well as in vascular cells (Veronese et al. 2017) and to some extent in neurons (Notter et al. 2018b). Second, animal and in vitro human data has challenged the view of TSPO as a specific pro-inflammatory marker. In a mouse model of low-grade immune activation, TSPO was found to be decreased, despite elevated levels of classical pro-inflammatory markers such as IL-1b and IL-6 (Notter et al. 2018a). In vitro assays of human cells have shown that TSPO may not increase upon stimulation with LPS (Narayan et al. 2017) and might even show decreased levels (Owen et al. 2017). Finally, the physiological role of TSPO may present yet another confounder. Recently, a large multicenter study of [^{11}C]PBR28 in healthy control subjects (Tuisku et al. 2019) found that radioligand binding was associated to increasing age, confirming findings that were evident in some, but not all previous studies (Paul et al. 2019; Suridjan et al. 2014). Moreover, relationships were found also for BMI and sex results that may reflect the suggested role of TSPO in hormone production.

18.7 Conclusions

The increasing application of TSPO PET in psychiatric populations during recent years has led to the emergence of some patterns that appear to vary between disorders. The evidence is in favor of an increase in TSPO in depression, whereas psychosis patients and potentially also subjects with alcohol use disorder show decreases. Additional understanding of the underlying biology is now needed to fully interpret these findings. It is likely that new cell and activation-specific PET markers need to be developed in order to robustly assess pro-inflammatory brain immune activation.

The large interindividual variability in TSPO in combination with the small samples usually employed in PET research means that power is often lacking. For instance, for studies employing second-generation TSPO tracers to study psychosis patients, the power to detect a medium-size effect was 23–34% (Plavén-Sigray et al. 2018a). This may lead to the failure to detect clinically meaningful effects but equally increase the risk of false positives that are not replicated in subsequent studies (Button et al. 2013). Since larger samples may be unattainable for individual research centers, one important way forward is to further develop multicenter collaborations where data is pooled at the individual participant level. Apart from increasing power, this would also open up for investigations into subgroups of patients, also across diagnostic boundaries, possibly stratifying patients into different etiopathologies.

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Neuroimaging in Delirium

19

Anita Nitchingham and Gideon Caplan

Contents

Abstract

Delirium is commonly diagnosed and associated with multiple poor outcomes, yet to date there are no licensed treatments for use on hospital wards. The pathophysiology of delirium is incompletely understood presenting a barrier to therapeutic innovation. When clinically indicated, neuroimaging is used to identify or exclude precipitating brain pathology in delirium. Neuroimaging also offers a noninvasive means of advancing our understanding of the neural mechanisms leading to delirium and identifying potentially modifiable pathways. However, delirium is a transient and heterogeneous disorder posing major methodological challenges in research. Nonetheless, there are several noteworthy published studies using a variety of imaging techniques including SPECT and PET but also structural and functional magnetic resonance imaging that offer valuable insights into delirium pathophysiology.

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19.1 Introduction

Delirium is a serious neuropsychiatric disorder precipitated by acute illness affecting up to 50% of older hospitalized patients (Inouye et al. 2014). Delirium could be described as "decompensated brain failure," when an external insult overwhelms cerebral reserves leading to impaired brain function heralded by altered cognition and consciousness. According to the *Diagnostic and Statistical Manual of Mental Disorders* (fifth edition, DSM-V), delirium is defined as acute and fluctuating disturbances in cognition, particularly attention and awareness, precipitated by an underlying medical cause (American Psychiatric Association 2013). Psychotic features and behavioral changes may also feature. Disturbed circadian rhythm is common, with maximal cognitive disturbance often occurring in the evening or overnight. Three main subtypes exist: hyperactive, hypoactive, and mixed delirium where patients fluctuate between hyper- and hypoactive forms.

Although advancing age and underlying dementia are two of the strongest risk factors, delirium commonly occurs in other settings including palliative care, postoperatively, and in particular the intensive care unit where the incidence has been found to be as high as 82% (Inouye et al. 2014). Regardless of the population, the sequelae of delirium are multiple and significant. Acutely, delirium is associated with increased mortality, falls, pressure areas, and lengthier hospital stay (O'Keeffe and Lavan 1997). Beyond this, delirium leads to new cognitive impairment, accelerated dementia, post-traumatic stress disorder, reduced functional independence, admission to nursing home, and death (Witlox et al. 2010; McCusker et al. 2003; Brück et al. 2018). The economic costs attributable to delirium are substantial, with annual costs estimated to be $8.8 billion in Australia and up to $152 billion in the United States (Pezzullo et al. 2019; Leslie 2008).

Studies suggest that up to 40% of delirium is preventable with multimodal nonpharmacological intervention aimed at identifying and mitigating established risk factors including visual and hearing impairment, immobilization, psychoactive drug use, sleep disturbance, social isolation, and dehydration (Hshieh et al. 2015). To date, there are no licensed pharmaceutical agents for the prevention or treatment of delirium. Low doses of antipsychotics are traditionally prescribed when nonpharmacological interventions have failed to control distressing symptoms or when safety is compromised; however, there is a lack of evidence to support this practice (Neufeld et al. 2016). In fact, one study found worsening symptoms following prescription of antipsychotics (Agar et al. 2017). The development of efficacious treatments for this distressing condition must become a priority.

Despite growing interest, the pathophysiology of delirium remains unknown thus impeding therapeutic development. Leading hypotheses include neuroinflammation (Cerejeira et al. 2010), neurotransmitter dysregulation (Hshieh et al. 2008), neural functional dysconnectivity (Choi et al. 2012), and impaired cerebral perfusion and metabolism (Haggstrom et al. 2017a). Modern neuroimaging modalities have been essential in advancing our understanding of the neural mechanisms underlying delirium.

19.2 Neuroimaging in Clinical Practice

Delirium is a clinical diagnosis, and at present there are no biomarkers or neuroimaging modalities that can diagnose delirium. Therefore, in clinical practice the role of neuroimaging is to identify possible causes. Routine structural imaging, including computed tomography (CT) or magnetic resonance imaging (MRI), of delirious patients presenting to hospital is often unnecessary. However, there are a subgroup of higher-risk patients in whom neuroimaging may be warranted; if history is suggestive of fall or head injury, anticoagulation therapy, focal neurological deficit, or where no other cause for delirium is identified. Studies report 2–14% of scans yield pathological findings that could explain the delirium and lead to a change in management (Hufschmidt and Shabarin 2008; Theisen-Toupal et al. 2014). These findings may include ischemic and hemorrhagic stroke or space occupying lesions. The absence of focal signs is the best predictor of a normal brain scan, and when combined with intercurrent fever or dehydration, the likelihood of having normal CT or MRI has been shown to be 96% (Hufschmidt and Shabarin 2008). Currently, functional neuroimaging techniques are used for research purposes only.

19.3 Neuroimaging and the Pathophysiology of Delirium

Neuroimaging modalities provide a noninvasive means of assessing structural and functional predictors, correlates, and consequences of delirium. In recent years there has been a blossoming of neuroimaging research in delirium across a variety of populations although there is still much to be explored. Thus far, studies have adopted a number of techniques including CT, structural and functional MRI, single-photon emission-computed tomography (SPECT), and positron emission tomography (PET). Transcranial Doppler and near-infrared spectroscopy have also been used to assess cerebral perfusion, oxygenation, and autoregulation (Nitchingham et al. 2018); although these modalities measure important physiological outcomes, they do not provide neuroanatomical information and were considered beyond the scope of this chapter.

19.3.1 CT/MRI: Structural Neuroimaging

Most structural neuroimaging studies are set in the preoperative setting and assess the association between baseline neurodegenerative and neurovascular disease and the risk of developing delirium. Only two studies have assessed the effects of delirium longitudinally.

Baseline cerebral atrophy and lower brain volumes do not show a consistent association with the development of delirium (Kant et al. 2017). Only one study has assessed brain volumes following an episode of delirium (Gunther et al. 2012). Forty-seven survivors of critical illness (average age 58 years) underwent MRI on

discharge from hospital and at 3 months follow-up. Longer duration of delirium was associated with smaller brain volume; this persisted for 3 months post-discharge. In addition, small brain volumes predicted cognitive impairment at 12 months follow-up (Gunther et al. 2012). This may suggest that delirium causes cerebral atrophy and cognitive impairment; however, it is difficult to establish causality as no baseline neuroimaging studies or cognitive assessments were performed.

There appears to be some association between white matter changes and delirium development (Kant et al. 2017). Most published studies suggest that delirium is associated with higher baseline and postoperative white matter hyperintensity burden (Nitchingham et al. 2018).

Recent studies have assessed white matter microintegrity using diffusion tensor imaging (DTI).

Cavallari et al. explored the relationship between white matter microintegrity and delirium incidence and severity in 136 patients (mean age 76 years) undergoing a variety of elective surgical procedures (Cavallari et al. 2016). Cognition was assessed preoperatively, and patients with dementia or recent delirium were excluded. DTI-MRI was performed median 7 days prior to surgery. White matter tract abnormalities in the cerebellum, cingulum, corpus callosum, internal capsule, thalamus, basal forebrain, occipital, parietal, and temporal lobes were associated with increased incidence and severity of postoperative delirium (Cavallari et al. 2016). Interestingly, in the same cohort, white matter hyperintensity volume did not predict delirium; a possible explanation for this is that DTI-MRI has greater sensitivity for detecting subtle structural abnormalities (Cavallari et al. 2015). Repeat DTI imaging 1 year postoperatively demonstrated longitudinal changes in periventricular, frontal, parietal, and temporal white matter microintegrity, with the right hemisphere being affected more than the left (Cavallari et al. 2017). This important finding suggests that delirium itself may contribute to the development of the observed microstructural abnormalities post-surgery which could explain the new cognitive impairment and accelerated dementia which can occur following an episode of delirium. Although, given the long duration between scans, it is possible that the observed degenerative changes could have occurred independently of the episode of delirium, particularly given the significant abnormalities noted preoperatively (Cavallari et al. 2017).

Important elements of these results have been replicated in other cohorts. Baseline white matter tract abnormalities particularly in the corpus callosum, fronto-thalamic, and limbic systems predicted postoperative delirium (Shioiri et al. 2010; Rolandi et al. 2018). Survivors of intensive care delirium demonstrated white matter tract abnormalities in the corpus callosum persisting for 3 months post-discharge (Morandi et al. 2012).

Compared to several studies assessing white matter disease, grey matter is underrepresented in published literature. In the largest study, Shioiri et al. assessed grey matter volume in 116 patients post-cardiothoracic surgery (Shioiri et al. 2016). Delirious patients demonstrated a reduction in grey matter fraction in the temporal and limbic lobes.

19.3.2 Functional MRI

Functional MRI studies demonstrate resting network disintegration. A particular area of focus has been the default mode network (DMN) which is highly active during periods of restful wakefulness and less active during goal-orientated tasks. The major functional hubs of the DMN include the posterior cingulate cortex (PCC), precuneus, and medial prefrontal cortex. As core clinical features of delirium include altered arousal and inattention, it is hypothesized that abnormal DMN connectivity may be responsible (Choi et al. 2012).

In a prospective case-control study, Choi et al. recruited 22 older inpatients with delirium secondary to a variety of medical causes and conducted resting state fMRI during delirium; 13 patients underwent repeat fMRI following resolution of delirium (mean 5.8 days) (Choi et al. 2012). Age- and sex-matched non-delirious controls with various illnesses were recruited from a pre-existing databank. Delirium was associated with increased functional connectivity in the dorsolateral prefrontal cortex and posterior cingulate cortex; the inverse was observed in control patients. Increased connectivity in the precuneus and PCC was also noted in delirious patients. In addition, the connectivity between intralaminar thalamic and caudate nuclei with subcortical regions was decreased during delirium but improved following recovery (Choi et al. 2012). Further analysis of the same cohort of patients demonstrated that more profound network disintegration is correlated with longer duration of delirium (van Montfort et al. 2018).

The findings of increased DMN and reduced subcortical connectivity have also been noted in postoperative delirium, specifically two hip fracture populations (Rolandi et al. 2018; Oh et al. 2019).

One study used proton magnetic resonance spectroscopy (^{1}H-MRS) to quantify regional cerebral metabolites during delirium (Yager et al. 2011). Thirteen patients (five delirious) underwent ^{1}H-MRS in the centrum semiovale a median of 15 days post-bone marrow transplant for hematological malignancies. Measured metabolites included *N*-acetyl aspartate (NAA), a marker of myelin synthesis and neuronal integrity, and choline (tCho), reflecting phospholipid membrane turnover and demyelination with elevated levels linked to inflammatory processes (Nitchingham et al. 2018; Yager et al. 2011). The delirium group demonstrated lower NAA and higher tCho suggesting diminished neuronal integrity or a catabolic process with possible inflammation.

Hshieh et al. assessed cerebral perfusion with arterial spin labeling MRI (ASL-MRI) in 146 older patients undergoing a range of elective surgical procedures. ASL-MRI was performed preoperatively (<14 days). Thirty-two patients (22%) developed postoperative delirium. No association between preoperative global or regional cerebral blood flow and postoperative delirium incidence or severity was found. The authors hypothesized that this may be because ASL-MRI measures of cerebral blood flow may lack sensitivity or that other factors, such as white matter integrity, may predispose patients to developing delirium. It should be noted that assessment of cerebral blood flow during delirium using other imaging modalities, such as

transcranial Doppler and near-infrared spectroscopy, suggest reduced cerebral perfusion and oxygenation (Nitchingham et al. 2018). Thus, while reduced CBF may not be a predictor of delirium, it is likely a feature of active delirium.

19.3.3 SPECT

Although there are a number of SPECT studies reporting on cerebral blood flow during delirium, most are case reports or case series (Alsop et al. 2006). Within these studies there is diversity of clinical presentations and delirium etiologies, radioactive isotopes, and scan processing and reporting methods (Alsop et al. 2006). Most studies suggest delirium is associated with reduced blood flow; however, as SPECT does not provide an absolute measurement of blood flow, it cannot be determined whether these changes are global or regional (Alsop et al. 2006).

In one prospective cohort study, 22 older patients with varying etiologies of delirium underwent ^{99m}Tc HPAO SPECT during delirium, 6 of whom underwent repeat scanning following resolution of delirium. On visual analysis, 11 patients demonstrated frontal or parietal hypoperfusion. Semiquantitative analysis identified reduced blood flow in the left inferior front, right temporal, right occipital, and pontine regions ($p < 0.01$). There was evidence of improved perfusion in three of the six patients who underwent repeat scanning suggesting reversible regional perfusion abnormalities occur during delirium (Fong et al. 2006).

19.3.4 PET

Use of PET scanning in delirium is relatively novel, and beyond case reports there are only three published studies of varying quality and small sample sizes. Two studies have assessed cerebral glucose metabolism during delirium using fluorodeoxyglucose (FDG).

Haggstrom et al. recruited 13 patients admitted to the geriatric ward with a variety of medical conditions to undergo FDG-PET CT in the resting state. Six patients underwent repeat scanning following resolution of delirium (median 80 days) (Haggstrom et al. 2017b). Visual analysis found widespread cortical hypometabolism with relative sparing of the sensorimotor cortex. Repeat scans demonstrated improved, but not normalized, metabolism throughout the cerebral cortex (Fig. 19.1). On semiquantitative analysis, whole brain metabolism was 1.4% higher following resolution of delirium. The study also focused on the posterior cingulate cortices (PCC) which are the central hub of the DMN. Reversible hypometabolism of the PCCs was found. Of note, greater metabolism in both PCCs correlated with better performance on neuropsychological tests of attention and shorter duration of delirium, consistent with the important role of the DMN in attention (Haggstrom et al. 2017b). Of note, there was no control group in this study, so it is possible that the observed reversible hypometabolism resulted from acute illness.

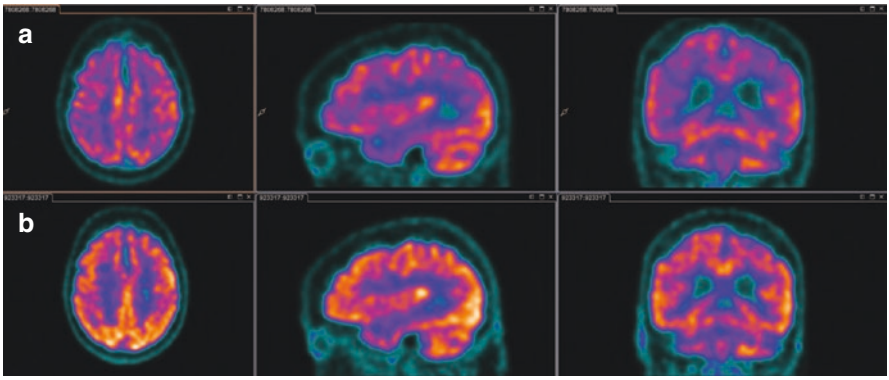

Fig. 19.1 Fluorodeoxyglucose positron emission tomography performed in an older patient during and after delirium. The top row (**a**) is during delirium, while the bottom row (**b**) is taken after delirium. Darker colors indicate hypometabolism. The top row illustrates global hypometabolism during delirium. The bottom row illustrates an overall improvement, but not normalization, in metabolism. (Reprinted from Haggstrom et al. (2017b), with permission. Copyright @ 2017 SAGE)

In the other FDG-PET study, Ma et al. recruited patients with postoperative delirium admitted to the intensive care unit (Ma et al. 2017). Thirteen patients with hyperactive delirium and 13 matched controls underwent FDG-PET. Scanning was conducted during delirium or acute illness for controls. Delirium was associated with hypometabolism throughout the entire cortex. A significant limitation of this study was that dementia was a possible confounder, as there was no baseline cognitive testing reported. In addition, although the study was published in 2017, patient recruitment occurred in 2011, and therefore the study was conducted on an older PET CT scanner with much lower resolution than currently available PET CT prohibiting more detailed assessment of the anatomical and subcortical regions.

One pilot study used PET to investigate the relationship between amyloid burden and the development of delirium (Rolandi et al. 2018). Sixteen patients post-hip fracture repair (mean age 79 years) with no history of dementia, underwent ^{18}F-flutemetamol PET, five of which had delirium. All patients with postoperative delirium were amyloid negative, while 45% of the non-delirious patients were amyloid positive. As delirium results from pre-existing brain vulnerabilities and exposure to acute stressors, patients with dementia are at higher risk of developing delirium. However, neuropathological investigations in the oldest-old demonstrate no relationship between classical neuropathological hallmarks of dementia and history of delirium (Davis et al. 2017). Other studies have found no association between higher pre-surgery cerebrospinal fluid (CSF) beta amyloid level and postoperative delirium; in fact one study found lower CSF amyloid to tau ratio predicted postoperative delirium (Rolandi et al. 2018; Xie et al. 2014a, b). Although the sample size is small, the results of this study are consistent with previous and intriguingly suggest that amyloid may be protective against delirium.

19.4 Methodological Considerations and Recommendations for Future Investigations

There have been many gains over the past decade: more prospective studies, improved clinical assessment of delirium, greater consideration for confounders, and increasing use of validated methods of assessing radiological outcomes (Nitchingham et al. 2018; Soiza et al. 2008). Yet imaging delirious patients present methodological challenges leading to small sample sizes and restricted generalizability.

Delirious patients may not tolerate scanning procedures, and as a result neuroimaging studies often have a bias toward patients with hypoactive delirium. Furthermore, it is difficult to rationalize the use of psychotropics or sedatives to aid in obtaining scans as these drugs may lead to worsening delirium and also interfere with functional neuroimaging results. The widespread use of medications that act on the central nervous system may also impact patient recruitment for functional studies. Another barrier is that duration of delirium is highly variable; some patients may recover within 1 day, while others may take weeks or less commonly months (Cole et al. 2008). Therefore, functional imaging studies may miss the window of opportunity to scan patients during delirium, and longitudinal studies must consider variable lengths of delirium recovery. This tends to bias imaging studies against short duration delirium, although the implications of this bias are not clear. Additionally, delirium is a highly heterogeneous condition; delirious patients have varying age and baseline vulnerabilities, this influences the generalizability of findings, particularly age-related neuropathology such as white matter disease.

As a result of these challenges, there is a preponderance of structural neuroimaging studies that focus on predictors of delirium. There is still much to be gained from structural neuroimaging studies, particularly longitudinal studies which assess the impact of delirium on brain structures. This would advance our understanding of the interface between delirium and dementia, a relatively unexplored field of critical importance.

Although functional neuroimaging is in its relative infancy and presents greater obstacles, these studies may provide the greatest insights into delirium pathophysiology and in the future may identify pathways amenable to therapeutic intervention (Haggstrom et al. 2017a). Further ^{1}H-MRS studies would allow greater assessment of brain metabolites. Dynamic contrast-enhanced MRI could be utilized to assess blood-brain barrier permeability, abnormalities of which have previously been implied in studies of the serum and cerebrospinal fluid of delirious patients (Hov et al. 2016; Hughes et al. 2016).

In theory, there are a variety of PET radioligands in existence which would offer insights into delirium pathophysiology; neuroinflammation could also be assessed using PET imaging with the use of translocator protein (TSPO) radioligands, where TSPO uptake reflects microglial activation (Politis 2012); dopamine synthesis and transport can be also be assessed to further understand neurotransmitter activity during delirium (Elsinga et al. 2006); acetylcholinesterase activity can also be evaluated using PET (Kikuchi et al. 2013). In reality, however, many newer radioligands

require specialist facilities including access to a cyclotron, and therefore applying such techniques to acutely delirious patients is currently impractical.

There is a need to replicate published neuroimaging studies in a variety of affected populations to allow firmer conclusions to be drawn. Ideally, future studies should conduct imaging at more than one time point to distinguish abnormalities related to delirium rather than baseline neuropathology. Appropriate control subjects must also be recruited, not only should they be aged and sex matched, but consideration should also be given to acute and chronic physiological burden of illness and baseline cognitive function. Efforts to improve the tolerability of imaging procedures should also be considered; relaxation techniques or involving carers to escort patients during imaging may be beneficial (Alsop et al. 2006).

19.5 Conclusion

Neuroimaging has great potential to advance our understanding of the pathophysiology of delirium. Although performing imaging studies on delirious patients poses challenges, with careful planning and consideration, many of these barriers can be overcome. Studies suggest white matter hyperintensity burden and white matter tract abnormalities predict delirium. Functional neuroimaging techniques demonstrate abnormalities in default mode network connectivity and reduced cerebral perfusion and metabolism during delirium. More focus on the long-term sequelae of delirium is needed. Opportunities for future research are vast and pose the potential to identify therapeutic targets for this common and serious condition.

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Part V

Impulse Control and Related Disorders

PET and SPECT in Personality Disorders

20

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Contents

Abstract

Over the past two decades, there has been an emerging interest in the neurobiology of personality disorders. Specific neurocircuitry alterations have been identified as the biological underpinnings of the dimensional traits that underlie personality disorders. In this chapter we review the most significant neuroimaging findings using PET and SPECT in relation to personality disorders and dimensions.

20.1 Introduction

The focus of research into the neurobiology of psychiatric disorders has increasingly shifted from categories to dimensions of psychopathology and their neurocircuitry underpinnings (as exemplified by the Research Domain Criteria (RDoC)

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initiative of the National Institute of Mental health (NIMH)) (Insel et al. 2010). There is an emerging neurobiology of personality disorders that focuses on exploring the altered neurocircuitry associated with dimensions such as affective dysregulation (affective instability and negative affectivity), disinhibited aggression, anxiety/avoidance, cognitive/perceptual dysregulation, and social detachment/isolation. The prototypic personality disorders are characterized by the extremes of these traits. For example, borderline personality disorder (BPD) is composed of high affective instability, disinhibition/aggression, and social cognitive/interpersonal impairment. Antisocial personality disorder (ASPD) is characterized by disinhibition/impulsive aggression. Schizotypal personality disorder (SPD) is characterized by social isolation/detachment and cognitive/perceptual disorganization. Avoidant personality disorder (AVPD) is characterized by detachment and negative affectivity. Obsessive-compulsive personality disorder (OCPD) is characterized by negative affectivity and conscientiousness. The relation between the affective instability and disinhibition of BPD and limbic structures such as the amygdala as regulated by prefrontal regions including the orbital frontal cortex (OFC) is an example of a neural circuit implicated in a personality dimension.

BPD (New et al. 2008), ASPD (Patrick et al. 2009), and SPD (Siever and Davis 2004) have been the most studied among personality disorders (PDs) and have the largest empirical evidence of clinical utility and validity (Skodol et al. 2011). Since the neurobiological underpinnings of other DSM-5 personality disorders are less well understood and there are very few studies using PET and SPECT on these disorders, they are not reviewed in detail in this chapter.

Of note, there are some important limitations of the reviewed studies including limited sample sizes, differences in comorbidity and clinical heterogeneity of the patients included, differences in the characteristics of the control subjects, differences in the subject's handedness across studies, gender differences and differences in medications, and ongoing psychotherapeutic interventions. All of these factors may confound the results by affecting regional cerebral metabolism.

20.2 Borderline Personality Disorder (BPD)

BPD is characterized by a pervasive pattern of instability of interpersonal relationships, self-image, and affects and marked impulsivity beginning by early adulthood and presents in a variety of contexts, as indicated by at least five of nine DSM-5 criteria (APA 2013). Core dimensions of BPD include affective instability, disinhibition/impulsive aggression, and social cognitive/interpersonal impairment.

There are a number of comprehensive reviews of the neurobiological abnormalities in BPD. They support a model of reduced medial prefrontal modulation of limbic structures (especially the amygdala), which appear to be hyperactive in BPD, causing dysregulation of emotions and aggression (Bohus et al. 2004; Mauchnik and Schmahl 2010).

Multiple studies have found altered activation of frontal and prefrontal areas involved in emotion regulation in BPD (see Table 20.1 for a summary of all studies

Table 20.1 PET and SPECT studies in BPD

	Study	Method	Sample size (patients – controls)	Subjects state	Main results
1.	Bøen et al. (2019)	FDG PET	22 BPD – 22 BIP-II – 21 HC	Resting state (association with current mood state also examined)	– Both BPD and BIP-II groups showed hypometabolism of glucose compared to HC in the insula, brainstem, and frontal white matter – BPD also showed hypometabolism in the hypothalamus, midbrain, and striatum, linked potentially to endocrinological disturbances involving the HPA axis, oxytocin, and testosterone – Potentially shared pathophysiological mechanisms between both BPD and BIP-II disorders – Uncorrected analyses showed difference between the disorders regarding correlation with clinical variables and should be considered with caution – No association was seen between current mood state, as determined by Montgomery-Asberg Depression Rating Scale and metabolism in BPD
2.	Charles et al. (2013)	FDG PET	14 BPD	Medication-free (likely resting state)	– Significant negative correlation between glucose metabolism in frontal lobe and scores on BDHI – Small correlation seen between brain metabolic changes in posterior regions of the brain and diagnostic behavioral rating scale scores (ZAN-BPD) – Statistical relationship between BDHI scores to brain regions was much more robust than those of ZAN-BPD – Supports findings of negative relationship between frontal lobe metabolism and aggression in personality disorders

(continued)

Table 20.1 (continued)

	Study	Method	Sample size (patients – controls)	Subjects state	Main results
3.	Davis et al. (2018)	[^{18}F]FPEB PET	20 MDD (9 BPD) – 20 HC	Not mentioned (likely resting state)	– Significantly higher mGluR5 VT in individuals with comorbid BPD compared to only MDD and HC participants across brain regions (32% higher in the amygdala, $p < 0.001$; 24% higher in the dorsolateral PFC, $p = 0.015$; 29% higher in the orbital frontal cortex) – In BPD group only, higher mGluR5 VT across regions of interest was also associated with history of suicide attempt (28–33% higher, $p = 0.022$–0.046) – Findings suggest mGluR5 may be a critical treatment target for BPD and suicidal behavior in this patient group
4.	De la Fuente et al. (1994)	FDG PET	10 BPD – 15 HC	Resting state	– No metabolic asymmetry or hypometabolism compared to HC in specific ROIs in the temporal lobe
5.	De la Fuente et al. (1997)	FDG PET	10 BPD – 15 HC	Auditory cortical activation task vs resting state	– Hypometabolism in the premotor area, PFC, ACC, thalamus, caudate, and lenticular nuclei
6.	Frankle et al. (2005)	SERT radiotracer [^{11}C]McN 5652 PET	10 (7 BPD + IED, 3 IED) – 10 HC	Resting state	– Reduced SERT availability in the ACC
7.	Goethals et al. (2005)	^{99m}Tc-ECD brain perfusion SPECT	37 BPD and/or ASPD – 34 HC	Resting state	– Hypoperfusion in temporal cortex and PFC
8.	Goyer et al. (1994)	FDG PET	17 (6 BPD) – 43 HC	Auditory cortical activation task vs resting state	– Hypometabolism in frontal cortex; inverse correlation between frontal cortex metabolism and lifetime history of impulsive aggression

9.	Holtedahl et al. (2012)	FDG PET	22 BIP-II – 22 BPD	According to standard procedures	– Significantly higher glucose metabolism bilaterally in the cerebellum, left gyrus inferior temporalis, and right gyrus postcentralis in BIP-II compared to BPD – Higher glucose metabolism observed in BPD group bilaterally in the pedunculus cerebellaris
10.	Holtedahl et al. (2014)	FDG PET	22 BPD – 22 BIP-II – 21 HC	Not mentioned (likely resting state)	– BPD patients exhibited significantly lower glucose metabolism compared to HC in both cerebellar hemispheres – There was also lower cerebellar glucose metabolism bilaterally in the cerebellum in BPD compared to BIP-II
11.	Juengling et al. (2003)	FDG PET	12 BPD – 12 HC	Resting state	– Frontal and prefrontal hypermetabolism in BPD compared to HC and hypometabolism in the hippocampus and cuneus
12.	Koch et al. (2007)	SERT-specific ligand [^{123}I] ADAM SPECT	8 BPD – 9 HC	Resting state	– Higher SERT binding in BPD compared to HC in target regions of brainstem and hypothalamus; SERT binding correlated with impulsivity
13.	Kolla et al. (2012a)	[^{11}C] harmine PET	10 MDD + BPD – 10 HC	In MDD + BPD group, 7 medication-free, 3 taking SSRI; HC were medication-free. All participants nonsmoking and no illicit drug use	– In MDD + BPD MAO-A VT in PFC was on average 16% greater than the HC ($p < 0.05$) – No difference in MAO-A VT in PFC of MDD + BPD patients taking SSRI or not taking SSRI – Other brain regions showed similar MAO-A VT elevations in the MDD + BPD group

(continued)

Table 20.1 (continued)

	Study	Method	Sample size (patients – controls)	Subjects state	Main results
14.	Kolla et al. (2012b)	[^{11}C] harmine PET	19 BPD – 12 HC (age and sex-matched)	Smoking and illicit substance free (likely resting state)	– MAO-A VT was elevated in BPD compared to HC by 27% in the prefrontal and by 19% in the anterior cingulate cortices ($p < 0.001$) – Within the BPD subjects, MAO-VT was elevated by 45% in prefrontal and 37% in anterior cingulate cortex regions among severely dysphoric patients compared to mildly dysphoric patients ($p = 0.01$)
15.	Kolla et al. (2013)	[^{11}C] harmine PET	22 BPD – 14 HC	Nonsmoker and free of illicit substance use (no specific state mentioned; likely resting state)	– MAO-A VT was found to be elevated in BPD compared to HC in PFC (by 36%) and ACC (by 32%) – PFC and ACC MAO-A VT levels were found to be higher by 52% and 48% in BPD patients with severe dysphoria compared to healthy controls
16.	Lai et al. (2007)	SPECT	5 BPD – 5 HC	(1) Pretreatment basal resting state SPECT; (2) pretreatment psychological stress condition SPECT; (3) posttreatment psychological stress condition SPECT post 16 weeks of psychodynamic psychotherapy	(1) Pretreatment basal SPECT: hyperperfusion in frontal and limbic areas in BPD compared to HC; (2) Pretreatment psychological stress SPECT: Hyperperfusion of temporal, parietal, occipital, and limbic areas. (3) Posttreatment psychological stress SPECT: hyperperfusion in frontal and limbic areas (in only 2 treated BPD patients), similar to basal SPECT
17.	Lange et al. (2005)	FDG PET	17 BPD – 9 HC	Resting state	– Hypometabolism in temporal pole/anterior fusiform gyrus, precuneus, and posterior cingulate cortex; impaired memory performance correlated with metabolism in ventromedial and lateral temporal cortices

18.	Leyton et al. (2001)	Trapping of 5-HT precursor analog alpha-[^{11}C] MTrp (an index of 5-HT synthesis capacity) PET	13 BPD – 11 HC	Resting state	– Lower α-[^{11}C]MTrp trapping in corticostriatal pathways, including superior temporal gyrus and ACC, negatively correlated with impulsivity scores
19.	New et al. (2002)	FDG PET	13 IED (8 BPD) – 13 HC	Resting state (placebo) vs m-CPP	– Unlike normal subjects, patients with impulsive aggression did not show activation in the left anteromedial orbital cortex in response to m-CPP – The ACC, normally activated by m-CPP, was deactivated in patients – The posterior cingulate gyrus was activated in patients and deactivated in HC
20.	New et al. (2004)	FDG PET	10 BPD + IED	Resting state (1) At baseline; (2) After 12 weeks of fluoxetine	– Increased metabolism in OFC and medial temporal cortex after treatment with fluoxetine
21.	New et al. (2007)	FDG PET	26 IED + BPD – 24 HC	Resting state (placebo) vs m-CPP	– No differences in amygdala metabolism between BPD patients and HC – The tight coupling of metabolic activity between the right OFC and ventral amygdala seen in HC with dorsoventral differences in amygdala circuitry was not present in IED + BPD patients

(continued)

Table 20.1 (continued)

	Study	Method	Sample size (patients – controls)	Subjects state	Main results
22.	New et al. (2009)	FDG PET	38 IED + BPD – 36 HC	Aggression provocation task (PSAP), 2 conditions: (1) Provocation; (2) Non-provocation	– BPD + IED patients increased metabolism in the OFC and amygdala when provoked, while HCs decreased metabolism in these areas – HCs increased metabolism in anterior, medial, and dorsolateral prefrontal regions during provocation more than BPD + IED patients
23.	Oquendo et al. (2005)	FDG PET	11 BPD + MDD – 8 MDD without Cluster B PD	Resting state vs fenfluramine	– BPD + MDD patients had greater metabolism in parietotemporal cortical regions before and after fenfluramine compared to those without BPD; they had less metabolism in the ACC at baseline compared to those without BPD and fenfluramine abolished this difference – Impulsivity was positively correlated with metabolism in superior and middle frontal cortex – Hostility was positively correlated with metabolism in temporal cortex
24.	Perez-Rodriguez et al. (2012)	FDG PET	38 IED + BPD – 36 HC	Aggression provocation task (PSAP), 2 conditions: (1) Provocation; (2) Non-provocation	– Male IED + BPD patients had significantly lower striatal metabolism than all other groups during both conditions
25.	Prossin (2014)	Mu-opioid receptor selective radiotracer [^{11}C] carfentanil PET	10 BPD	Mood induction	– Plasma IL-18 was associated with baseline central endogenous opioid tone and sadness-induced endogenous opioid release, unilaterally within the right ventral palladium ($p < 0.001$)

26.	Prossin et al. (2010)	Mu-opioid receptor radiotracer [^{11}C] carfentanil PET	18 BPD – 14 HC	Neutral and sustained sadness states	– BPD patients showed higher mu-opioid nondisplaceable binding potential than HC at baseline (neutral state) in the OFC, caudate, nucleus accumbens, and amygdala, but lower binding potential in the posterior thalamus – Sadness induction was associated with greater reductions in binding potential (endogenous opioid system activation) in BPD patients in the pregenual ACC, OFC, ventral pallidum, amygdala, and inferior temporal cortex, and with endogenous opioid system deactivation in the nucleus accumbens, hypothalamus, and hippocampus/parahippocampus
27.	Salavert et al. (2011)	FDG PET	8 BPD – 8 HC	Resting state	– BPD patients showed hypometabolism in frontal lobe and hypermetabolism in motor cortex (paracentral lobules and postcentral cortex), medial and anterior cingulate, occipital lobe, temporal pole, left superior parietal gyrus, and right superior frontal gyrus
28.	Siever et al. (1999)	FDG PET	6 IED (4 BPD) – 5 HC	Resting state (placebo) vs fenfluramine	– Compared with HC, patients showed significantly blunted metabolic responses to fenfluramine in the OFC, adjacent ventral medial, and cingulate cortex

(continued)

Table 20.1 (continued)

	Study	Method	Sample size (patients – controls)	Subjects state	Main results
29.	Schlesinger et al. (2013)	FDG PET	14 BPD	Subjects were on 8 weeks of olanzapine during the second scan	– Baseline metabolic activity in cortical areas including the posterior cingulate, thalamus, and parietal areas correlates with the degree of improvement in response to olanzapine treatment – Mean scores on all clinical measures improved from week 0 to 8 of taking olanzapine – ZAN-BPD scores were positively correlated with higher metabolism in the posterior cingulate and parietal cortex bilaterally and negatively correlated with higher thalamic metabolism – Decreased impulsivity was also correlated with higher activity in posterior cingulate and precuneus, while higher baseline activity in the thalamus and caudate was correlated with lower levels of improvement – Decreased hostility was associated with higher metabolism in left temporal and parietal lobes – Improvement in depression associated with elevated activity in the left posterior cingulate and inferior parietal lobe but negatively correlated with activity in rostral and subgenual anterior cingulate
30.	Schmahl et al. (2003)	[^{15}O]H2O PET	10 BPD + sexual/physical abuse – 10 sexual/physical abuse without BPD	Listening to neutral script vs abandonment script	– Listening to abandonment scripts was associated with larger increases in perfusion in the dorsolateral PFC and cuneus and with larger decreases in perfusion in ACC, temporal cortex, and visual association cortex in women with BPD compared to women without BPD

31.	Schmahl et al. (2004)	[^{15}O]H2O PET	10 BPD + sexual/physical abuse – 10 sexual/physical abuse without BPD	Listening to neutral script vs traumatic abuse script	– Women with BPD failed to activate ACC and OFC compared to women without BPD after listening to traumatic abuse scripts
32.	Soloff et al. (2014)	[^{18}F] altanserin PET; MRI	33 BPD – 27 HC	Not mentioned (likely resting state)	– Among BPD group, aggression, Cluster B comorbidity, ASPD, and childhood abuse were each related to altenserin binding – Increased aggression and impulsivity negatively correlated with BP_{ND} – BP_{ND} values predicted impulsivity and aggression in females but not males in BPD and in males but not females in HC – Altenserin binding was greater in females than males in all contrasts but did not differentiate suicide attempters from non-attempters – Region-specific differences in serotonin-2A receptor binding related to diagnosis and gender predicted clinical expression of aggression and impulsivity
33.	Soloff et al. (2000)	FDG PET	5 BPD – 8 HC	Resting state (placebo) vs fenfluramine	– In response to placebo, metabolism was greater in HC than BPD patients in the PFC including medial and orbital regions, superior temporal gyrus, and insular cortex – In response to fenfluramine, metabolism (relative to placebo) was greater in HC compared to BPD patients in medial and orbital PFC, middle and superior temporal gyri, parietal lobe, and caudate

(continued)

Table 20.1 (continued)

	Study	Method	Sample size (patients – controls)	Subjects state	Main results
34.	Soloff et al. (2003)	FDG PET	13 BPD – 9 HC	Resting state	– Significant reductions in metabolism in BPD subjects relative to HC were found in medial OFC; these differences became insignificant after covarying for impulsivity or impulsive aggression
35.	Soloff et al. (2005)	FDG PET	22 BPD – 24 HC	Resting state (placebo) vs fenfluramine	– In response to placebo, female, but not male, HC had increased metabolism in PFC compared with BPD patients, especially in medial OFC – Male, but not female, BPD subjects, showed hypermetabolism compared with HC in parietal and occipital cortex – In response to fenfluramine (relative to placebo), significant decreases in metabolism were found in male, but not female, BPD subjects, in the left temporal lobe – Female, but not male, HC showed decreased metabolism in frontal and temporal cortex – Covarying for impulsive aggression rendered the gender differences non-significant

Abbreviations: *[^{11}C]McN 5652* [^{11}C](+)-6β-(4-methylthiophenyl)-1,2,3,5,6α,10β-hexahydropyrrolo [2,1-a]isoquinoline, *FDG* 2-deoxy-2-[^{18}F]fluoro-D-glucose, *alpha-[^{11}C]MTrp* alpha-[^{11}C]methyl-L-tryptophan, *ACC* Anterior Cyngulate Cortex, *ASPD* Antisocial Personality Disorder, BP_{ND} Binding Potentials, *BIP-II* Bipolar II Disorder, *BPD* Borderline Personality Disorder, *BDHI* Buss-Durkee Hostility Index, *[^{123}I] ADAM* [^{123}I] (2-([2-([dimethylamino]methyl)phenyl]thio)), *ECD* Ethylcysteinate dimer, *HC* Healthy Controls, *IED* Intermittent Explosive Disorder, *MRI* Magnetic Resonance Imaging, *MDD* Major Depressive Disorder, *MAO-A* Monoamine oxidase-A, *m-CPP* meta-chlorophenylpiperazine, *OFC* Orbital frontal cortex, *PSAP* Point Subtraction Aggression Paradigm, *PET* Positron emission tomography, *PFC* prefrontal cortex, *ROI* Region of interest, *5-HT* Serotonin, *SSRI* serotonin selective reuptake inhibitor, *SERT* Serotonin transporter, *SPECT* Single photon emission computed tomography, *VT* Total Volume of distribution, *ZAN-BPD* Zanarini Rating Scale for Borderline Personality Disorder

reviewed) (Charles et al. 2013; Goethals et al. 2005; Goyer et al. 1994; Soloff et al. 2003). Most, but not all (Juengling et al. 2003), PET and SPECT imaging studies have found that OFC and/or the anterior cingulate cortex (ACC) is less active in BPD than controls (De La Fuente et al. 1997; Goyer et al. 1994; Leyton et al. 2001; New et al. 2002; Oquendo et al. 2005; Salavert et al. 2011; Siever et al. 1999; Soloff et al. 2000, 2003), and this hypometabolism is correlated with impulsive aggression (Charles et al. 2013; Schlesinger et al. 2013; Soloff et al. 2003, 2014). Using script-driven imagery during PET, Schmahl et al. (Schmahl et al. 2003, 2004) found that women with BPD failed to activate the ACC and OFC compared to women without BPD after listening to traumatic abuse scripts (Schmahl et al. 2004). In the same sample, the authors also showed that listening to abandonment scripts was associated with larger increases in perfusion in the dorsolateral prefrontal cortex and cuneus, and with larger decreases in perfusion in the ACC, temporal cortex, and visual association cortex in women with BPD compared to women without BPD (Schmahl et al. 2003).

The amygdala, a key area for emotion regulation and encoding, is another region of interest for the study of affective dysregulation in BPD. Although earlier neuroimaging studies suggested amygdala hyperactivity in BPD, a recent meta-analysis of functional magnetic resonance imaging (fMRI) studies found less activation in the amygdala in BPD compared to control subjects under conditions of negative emotionality (Ruocco et al. 2013). Several, but not all (de la Fuente et al. 1994; Salavert et al. 2011), PET and SPECT studies also point to abnormalities in the amygdala and surrounding temporal lobe areas in BPD patients (Davis et al. 2018; Goethals et al. 2005; Holtedahl et al. 2012; Juengling et al. 2003; New et al. 2009; Schlesinger et al. 2013). In a PET study of laboratory-induced aggression using the Point Subtraction Aggression Paradigm (PSAP), we showed that BPD patients with impulsive aggression responded aggressively to provocation and showed increased relative glucose metabolic rate in the OFC and amygdala, but not in more dorsal brain regions associated with top-down cognitive control of aggression (New et al. 2009). In contrast, during aggression provocation, healthy controls showed increased metabolism in dorsal regions of the prefrontal cortex, which are involved in top-down cognitive control of aggression and emotion (New et al. 2009). We have also reported poor connectivity in BPD patients between the OFC and amygdala associated with aggression in a PET study. The tight coupling of metabolic activity between the right OFC and ventral amygdala seen in healthy subjects was lacking in subjects with BPD and comorbid intermittent explosive disorder (IED) (New et al. 2007).

A pilot study using SPECT on a very small sample ($n = 5$) showed that BPD patients had hyperperfusion at rest in the frontal and limbic areas compared to controls. During a pretreatment psychological stress condition, BPD patients showed hyperperfusion of temporal, parietal, occipital, and limbic areas compared to the control group, which was interpreted as higher emotional reactivity to stress condition. According to the authors, the lack of frontal activation under stress condition (as opposed to the basal condition) could represent the absence of frontal modulation of the emotional response under stress condition. After 16 months of

psychodynamic psychotherapy, the posttreatment neural pattern in two treated BPD patients under stress condition was different from their pretreatment pattern, and it was similar to their pattern in basal condition. According to the authors, this suggested a lower perceived psychological stress. Moreover, the posttreatment neural pattern included a strong frontal activation, absent in pretreatment SPECT under stress condition. The authors interpreted this as a more efficacious cortical top-down control on subcortical areas after treatment (Lai et al. 2007).

*In summary, it seems that in BPD patients, prefrontal brain regions that normally control expressions of aggression and emotion (*e.g.*, the OFC and ACC) may fail to become activated in response to emotional stress, while several areas of the limbic system appear to hyper-respond to emotional probes.*

Several studies have found metabolic abnormalities in BPD in other areas. Lange et al., using ^{18}FDG-PET, showed hypometabolism in temporal and medial parietal cortical regions in BPD patients compared to healthy controls. These areas are involved in episodic memory consolidation and retrieval and are believed to be part of a network of tonically active brain regions that gather information about the world around and within us (Lange et al. 2005). Bøen et al. compared BPD and bipolar II disorder patients and found glucose hypometabolism in both groups compared to healthy controls in the brainstem and frontal regions. BPD showed additional hypometabolism in the hypothalamus, midbrain, and striatal regions, which could be linked to potential endocrinological disturbances involving oxytocin and testosterone (Bøen et al. 2019). Holtedahl et al. conducted a similar comparison, where they found reduced glucose metabolism in both cerebellar hemispheres of BPD compared to healthy controls and lower metabolism bilaterally in the cerebellum in BPD compared to bipolar II patients (Holtedahl et al. 2014). Using ^{18}FDG-PET, we found that male BPD patients with comorbid IED had significantly lower striatal metabolism than female BPD patients with IED and healthy controls in response to aggression-provoking and non-provoking versions of the PSAP. These sex differences suggest differential involvement of frontal-striatal circuits, involved in motivated behaviors and processing of rewarding stimuli, in BPD-IED (Perez-Rodriguez et al. 2012). Other studies have also reported sex differences in the distribution of brain hyper- and hypometabolism measured with PET in patients with BPD and controls. It has been hypothesized that sex differences in serotonergic function may mediate differences in brain metabolism and impulsive aggression in subjects with BPD (Soloff et al. 2005, 2014).

However, it is important to note that most of the circuits implicated in BPD (including a model of decreased ACC/OFC response with an associated amygdala hyper-reactivity) seem to be involved in other psychiatric disorders, including MDD (Davidson et al. 2003), bipolar disorder (Blumberg et al. 2003), and PTSD (Shin et al. 1999), questioning the specificity of the findings presented above.

Searching for more specific neurobiological findings in BPD, a number of studies have investigated the role of serotonin. Impaired serotonergic function may underlie the hypothesized imbalance between prefrontal top-down control and limbic hyper-responsivity described above. Since early cerebrospinal fluid (CSF) studies found low CSF serotonin metabolites in individuals with a history of suicide

attempts (Asberg and Traskman 1981; Asberg et al. 1976) or impulsive aggression (Coccaro 1989), numerous studies have investigated the role of serotonin in BPD. Studies using diverse methodologies have replicated decreases in serotonergic responsiveness in BPD (Coccaro et al. 1989; Dougherty et al. 1999; O'Keane et al. 1992), including neuroimaging using pharmacologic probes of serotonin (Leyton et al. 2001; New et al. 2002, 2004; Siever et al. 1999; Soloff et al. 2000). A PET study using the ligand [^{11}C]McN 5652 showed that patients with personality disorders and impulsive aggression had significantly reduced serotonin transporter (SERT) availability in the ACC compared with healthy subjects. In other regions, serotonin transporter density was nonsignificantly lower in personality disordered patients than in healthy subjects (Frankle et al. 2005). Using SPECT and a new highly selective SERT ligand ([^{123}I] ADAM (2-([2-([dimethylamino]methyl)phenyl]thio)-5-^{123}I-iodophenylamine), Koch et al. found significantly higher SERT binding, which was associated with higher impulsivity scores, in the brainstem and hypothalamus in patients with BPD compared with healthy controls. This could either reflect a higher number of serotonin transporters with an increased capacity of presynaptic serotonin reuptake or an increased number of available binding sites, due to lower endogenous serotonin levels (Koch et al. 2007). Additionally, a study by Soloff et al. found a negative association between binding potential at the serotonin-2A receptor and impulsivity and aggression, where they found that binding potentials predicted female impulsivity and aggression in the BPD group and male impulsivity and aggression in the healthy control individuals (Soloff et al. 2014). Three studies by Kolla et al. also found elevated levels of monoamine oxidase-A (MAO-A), which is an oxidative enzyme that catalyzes the degradation of serotonin, norepinephrine, and dopamine in the prefrontal (Kolla et al. 2012a, b, 2013) and the anterior cingulate cortices of patients with BPD (Kolla et al. 2012b, 2013) or BPD and comorbid major depressive disorder (Kolla et al. 2012a) compared to healthy controls. Both prefrontal cortex hypometabolism found in BPD as described above and impulsive aggression scores have been shown to improve after treatment with fluoxetine (New et al. 2004) or administration of the serotonin-releasing agent fenfluramine (Oquendo et al. 2005), in some—but not all (Siever et al. 1999; Soloff et al. 2000)—studies.

Taken together, these data suggest a model in which impaired serotonergic facilitation of "top-down" control may underlie the hypothesized imbalance between prefrontal regulatory areas and limbic hyper-responsivity. However, it should be noted that the specificity of this finding to BPD has yet to be tested.

Recently there has been growing theoretical interest in neuropeptides in BPD, such as opioids, oxytocin, and vasopressin. However, only two recent imaging studies have focused on the opioid system in BPD. Prossin and colleagues used PET, with the μ-opiate ligand, [^{11}C] carfentanil, to examine μ-opioid receptor binding in the brains of patients with BPD during induction of neutral and sad emotional states. They found greater baseline μ-opioid receptor availability in BPD, which could be interpreted as a deficit in endogenous opioids (Prossin et al. 2010). They also found that sad mood inductions increased endogenous opioid release, unilaterally within the right ventral pallidum (Prossin 2014). This is consistent with lower levels of

endogenous opioids in self-injurers (Stanley et al. 2009). One theory about self-cutting in BPD is that it is a method of releasing endogenous opioids, to compensate for an opioid deficit. According to this model, patients learn to cut themselves to release opiates, which reward their behavior (New and Stanley 2010; Stanley and Siever 2010). A new neuropeptide model of BPD hypothesizes that an opiate-deficit might also explain the interpersonal difficulties characteristic of BPD. In animals, opioids are involved in regulation of emotional and stress responses, attachment behavior, and anxiety-like responses, and they mediate the soothing and comforting that infants receive from maternal grooming and touching (Panksepp et al. 1980). In humans, opiates are involved in emotion regulation (Kennedy et al. 2006). This is a very theoretically attractive model, and current research is underway to provide more robust empirical evidence for it.

20.3 Schizotypal Personality Disorder (SPD)

Schizotypal personality disorder (SPD) belongs to the schizophrenia spectrum, characterized by the presence of attenuated schizophrenia symptoms. Research on SPD offers a potential window into the pathophysiological mechanisms underlying schizophrenia, in a less impaired and less heavily medicated population. Table 20.2 provides an overview of all PET and SPECT studies in this area.

SPD is characterized according to the DSM-5 as "a pattern of acute discomfort in close relationships, cognitive or perceptual distortions, and eccentricities of behavior" (APA 2013). Psychoticism, cognitive deficits, and interpersonal dysfunction are the core dimensions of SPD.

Psychotic-like symptoms are a key feature of SPD patients. In fact, the term "schizotype" was used to describe individuals who showed attenuated psychotic symptoms that were phenotypically similar to those in schizophrenia, without experiencing extreme psychosis (Chan et al. 2019). Like in schizophrenia, increased dopaminergic neurotransmission is associated with more prominent psychotic symptoms in SPD, and the dimension of psychotic-like symptoms has been correlated with measures of dopaminergic activity. Studies using dopaminergic probes have shown evidence of increased dopaminergic transmission in the striatum in SPD. Using SPECT, Abi-Dargham et al. observed increased amphetamine-induced dopamine release in the striatum in SPD patients compared to controls, which was similar to that found in remitted schizophrenic patients. The authors hypothesized that the dopaminergic dysregulation seen in schizophrenia spectrum disorders might have a trait component, present in remitted schizophrenic patients and in SPD, and a state component, associated with psychotic exacerbations but not SPD (Abi-Dargham et al. 2004). In healthy volunteers, the availability of striatal dopamine $D_{2/3}$ receptors measured with PET is associated with schizotypal features, specifically the Schizotypal Personality Questionnaire disorganized subscale scores (Chen et al. 2012). Recently, Howes et al. showed that, compared to healthy controls, SPD patients have increased dopamine synthesis capacity, measured with [^{18}F]6-fluoro-L-dopa PET, in the whole striatum and its associative and sensorimotor subdivisions

Table 20.2 PET and SPECT studies in SPD

	Study	Method	Sample size (patients–controls)	Subjects state	Main results
1.	Abi-Dargham et al. (2004)	DA $D_{2/3}$ radiotracer IBZM SPECT	13 SPD – 13 HC	Baseline and after amphetamine administration	– No baseline differences in striatal specific DA D2/3 receptor availability between SPD and HC – Amphetamine induced a larger decrease in striatal specific DA D2/3 receptor availability (IBZM binding) in SPD patients
2.	Buchsbaum et al. (1997)	^{99m} Tc-HMPAO SPECT	10 SPD – 9 HC	Activation tasks: (1) WCST; (2) SMT (control task)	– HC showed greater activation in the precentral gyrus during the WCST, while SPD patients showed greater activation in the middle frontal gyrus – Relative flow in the PFC was correlated with better WCST performance in HC, but not in SPD; SPD patients showed correlations of good and bad performance with metabolism in the middle and inferior frontal gyrus, respectively
3.	Buchsbaum et al. (2002)	FDG PET	27 SCZ – 13 SPD – 32 HC	Verbal learning task	– SPD patients did not differ from HC in most lateral frontal regions, but they had values intermediate between those of HC and SCZ patients in lateral temporal areas – SPD patients showed higher metabolic rates than HC in medial frontal and medial temporal areas
4.	Chen et al. (2012)	DA $D_{2/3}$ radiotracer IBZM SPECT	55 HC	Resting state	– SPQ total scores were not correlated with the availability of striatal DA D2/3 receptors – The SPQ disorganized subscale scores were positively correlated with the availability of right striatal DA D2/3 receptors

(continued)

Table 20.2 (continued)

	Study	Method	Sample size (patients–controls)	Subjects state	Main results
5.	Hazlett et al. (1999)	FDG PET	27 SCZ – 13 SPD – 32 HC	Verbal learning task	– SPD patients did not differ from HC in thalamic metabolism
6.	Haznedar et al. (2004)	FDG PET	27 SCZ – 13 SPD – 32 HC	Verbal learning task	– SPD patients had higher metabolism in the posterior cingulate than HC
7.	Howes et al. (2011)	[^{18}F]6-fluoro-L-dopa PET (to measure DA synthesis capacity)	6 SPD – 29 HC	Resting state	– DA synthesis capacity was elevated in SPD compared to HC in the striatum
8.	Jensen et al. (2014)	^{99m}Tc-HMPAO SPECT, MRI, CT	34 Schizophrenia spectrum disorder (21 in forensic unit, 13 without any violent history in an open ward)	Not mentioned Resting?	– Neither CT nor MRI revealed pathological findings – SPECT showed areas of changed perfusion in 25 of 34 patients (18 of violent patients and 7 of non-violent group, $p = 0.040$) – Hypoperfusion mainly seen in temporal lobe and amygdalae but also in parietal and occipital lobes – Chronic substance use documented in 59%, with 71% in violent and 38% in non-violent group – 18 patients in violence group scored higher than 20 on HCR-20 risk assessment scheme
9.	Shihabuddin et al. (2001)	FDG PET	16 SPD – 27 SCZ – 32 HC	Verbal learning task	– SPD patients showed increased metabolism in the ventral putamen
10.	Soliman et al. (2008)	DA tracer [^{11}C] raclopride PET	16 SPD – 10 HC	Psychological stress task and sensory-motor control	– Only SPD patients with negative schizotypy, but not other SPD patients or HC, showed increased dopamine release in the stress condition, in an area including ventral striatum, putamen, and caudate

11.	Thompson et al. (2020)	[^{11}C]raclopride PET	16 SPD – 16 HC	First scan at baseline, second scan after receiving amphetamine challenge Both scans were taken on the same day	– SPD was not associated with increased striatal dopamine release – There were no significant differences between the two participant groups in terms of dopamine D_2-receptor availability (binding potential, BP_{ND}) or percent change post-amphetamine (ΔBP_{ND}) in any striatal subregion or whole striatum – In SPD, positive symptoms were associated with ΔBP_{ND} in the ventral striatum and increased dopamine release, while disorganized symptoms were significantly negatively associated with ΔBP_{ND} in several striatal subregions and lower dopamine release – There were also positive correlations between working memory performance and striatal ΔBP_{ND}
12.	Thompson et al. (2014)	[^{11}C]NNC112 PET	18 SPD (unmedicated) – 21 HC	Not mentioned PET was taken on a different day than the cognitive assessments, so potential differences in state function may have been present	– No significant differences in PFC binding potential at the D1-receptor between the two groups; SPD not associated with alterations in D1-receptor in PFC – BP_F ($p = 0.22$) and BP_P ($p = 0.47$) in the medial PFC found to be significantly negatively correlated to PASAT performance – BP was not significantly correlated to performance on the 2-back test – Higher D1-receptor availability in PFC associated with lower WM performance on PASAT in SPD

Abbreviations: *BP, BP_F, BP_{ND}, BP_P* Binding-potential Measures, *IBZM* [^{123}I]iodobenzamide, *FDG* 2-deoxy-2-[^{18}F]fluoro-D-glucose, *DA* Dopamine, *SPD* Schizotypal Personality Disorder, *PASAT* Paced Auditory Serial Addition Test, *PET* Positron emission tomography, *PFC* prefrontal cortex, *SCZ* Schizophrenic, *SPQ* Schizotypal Personality Questionnaire, *SPECT* Single photon emission computed tomography, *^{99m}Tc-HMPAO* Technetium-99m-d,l-hexamethylpropylene amine oxime, *SMT* Symbol Matching Test, *WCST* Wisconsin Card Sort Test, *WM* Working Memory

(Howes et al. 2011). Using PET and [^{11}C]raclopride, Soliman et al. reported that patients with negative symptoms of schizotypy show greater striatal dopamine release than healthy controls in response to stress (Soliman et al. 2008). On the other hand, a recent study by Thompson et al. found no significant difference between SPD individuals and healthy controls in terms of D_2-receptor availability (binding potential, BP_{ND}) or percent change post-amphetamine activation (ΔBP_{ND}) in any striatal subregion or whole striatum. They did however find a moderate association between severe positive symptoms in SPD and increased dopamine release in the ventral striatum, and a slight negative association between severe disorganized symptoms and lower striatal dopamine release (Thompson et al. 2020).

It has been suggested that dopaminergic activity can be relatively increased or decreased, depending on the predominance of psychosis-like (hypervigilance and stereotypic cognitions/behaviors) or deficit-like (deficits in working memory, cognitive processing, and hedonic tone) symptoms, respectively (Siever and Davis 2004).

Of note, SPD patients have less prominent psychotic symptoms than patients with schizophrenia (Chan et al. 2019). This is hypothesized to be due to better buffered subcortical dopaminergic activity (Kirrane and Siever 2000; Siever and Davis 2004; Siever and Weinstein 2009). This may result in lower reactivity to stress by subcortical dopaminergic systems, which may protect against psychosis (Mitropoulou et al. 2004; Siever and Davis 2004; Siever and Weinstein 2009).

In summary, SPD patients share some of the dopaminergic abnormalities underlying psychotic-like symptoms found in schizophrenia, including increased dopaminergic neurotransmission, but in a milder form, possibly due to better buffered subcortical dopaminergic activity.

Patients with SPD also suffer cognitive impairment similar to that found in patients with schizophrenia, likely associated with structural brain abnormalities, especially in temporal areas. However, SPD patients have less impaired executive function than schizophrenic patients, maybe due to higher prefrontal function reserves (Siever and Davis 2004; Siever and Weinstein 2009).

Decreased dopaminergic and noradrenergic activity in the prefrontal cortex may underlie the cognitive impairment in SPD. This is supported by functional studies showing abnormal frontal activation during executive functioning and working memory tasks in SPD. For example, Buchsbaum et al. found abnormal patterns of prefrontal activation with SPECT in SPD patients compared to healthy controls using the Wisconsin Card Sorting Test (WCST). Moreover, different subregions of the prefrontal cortex correlated with good performance on the WCST in SPD patients and controls, respectively (Buchsbaum et al. 1997). Unlike schizophrenic patients and healthy controls, SPD patients seem to activate other compensatory regions during executive function tasks (Buchsbaum et al. 1997, 2002; Koenigsberg et al. 2005). Buchsbaum et al. found that in SPD patients the WCST activated the middle frontal gyrus, while in healthy controls it activated the precentral gyrus (Buchsbaum et al. 1997). Thompson et al. on the other hand found no significant difference between unmedicated SPD patients and healthy controls in binding potential in the prefrontal cortex in D_1-receptors; however, higher D_1-receptor availability in the prefrontal cortex was associated with lower working memory

performance as measured by the PASAT in SPD individuals (Thompson et al. 2014). In another study, they observed that SPD patients had abnormally high metabolic rates in both medial frontal and medial temporal areas and in the frontal Brodmann area 10 (Buchsbaum et al. 2002). Of note, this "hyperactivation" on medial frontal areas could be interpreted instead as a failure of task-related "deactivation" of one of the default mode network regions, all of which are highly active at rest and which have been shown to deactivate during performance of cognitive tasks in healthy controls but not in schizophrenic patients (Whitfield-Gabrieli and Ford 2012). Jensen et al., using SPECT, found hypoperfusion mainly in the temporal lobe and amygdala areas but also parietal and occipital lobes of patients with schizophrenia spectrum disorder. However, 59% of patients also had a history of substance abuse, and therefore whether this association was related to substance use or mental illness in this patient group remains unclear (Jensen et al. 2014). Haznedar et al. found that SPD patients had higher PET metabolic rates in the left posterior cingulate gyrus than healthy controls during a verbal working memory task (Haznedar et al. 2004). Shihabuddin et al. observed that patients with SPD showed elevated PET relative glucose metabolic rate in the putamen compared with both schizophrenic patients and healthy controls (Shihabuddin et al. 2001). In contrast, in other brain areas such as the thalamus, there were no differences in metabolic activity measured with PET between SPD patients and healthy volunteers, although there were differences in thalamus shapes between SPD patients and controls (Hazlett et al. 1999).

In summary, SPD subjects show cognitive impairments that seem to be related to reduced prefrontal dopaminergic function and that can be partially compensated by activation in brain areas that are not otherwise activated in healthy controls.

20.4 Antisocial Personality Disorder (ASPD)

ASPD is characterized in the DSM-5 by a pervasive pattern of disregard for and violation of the rights of others that has been occurring since the age of 15 years, as indicated by at least three of seven criteria, namely, a failure to conform to social norms, deceitfulness, impulsivity or failure to plan ahead, irritability and aggressiveness, recklessness, irresponsibility, and indifference to the welfare of others (APA 2013).

It is important to distinguish between ASPD and psychopathy. Psychopathy is a construct characterized by severe deficits in emotional processing (reduced guilt, empathy, and attachment to significant others; callous and unemotional traits) and increased risk for antisocial behavior (Cleckley 1941; Hare 2003). These emotional detachments tend to be much more pronounced in psychopaths compared to individuals with ASPD (Oldham et al. 2014). Despite its overlap with ASPD, psychopathy is a distinct disorder: while most individuals who are diagnosed with psychopathy will also meet criteria for ASPD, only about 10% of those with ASPD meet criteria for psychopathy (NCCM 2010). Different types of aggression are characteristic of ASPD and psychopathy, respectively. While impulsive or reactive aggression is a core dimension of ASPD, instrumental aggression has been uniquely linked to

psychopathy (Blair 2010; Dolan 2010; Dolan and Park 2002; Ostrov and Houston 2008). Reactive aggression is associated with a lack of impulse control (e.g., as in ASPD, intermittent explosive disorder, and BPD) and includes aggressive behavior that is retaliatory/impulsive (i.e., road rage), occurs in response to a perceived threat, and is associated with negative affect (i.e., hostility or anger). In contrast, instrumental aggression is controlled/planned and serves an instrumental, goal-directed end (i.e., a planned robbery to obtain the victim's money) (Dolan 2010; Ostrov and Houston 2008).

Based on animal models, reactive aggression is part of a progressive response to threat mediated by a threat system that involves the amygdala, the hypothalamus, and the periaqueductal gray: distant threats cause freezing, closer threats induce flight, and very close threats where escape is impossible cause reactive aggression. This system is regulated by the medial, orbital, and inferior frontal cortices (Blair 2007, 2010). According to this model, individuals with high reactive aggression should show increased amygdala responses to emotional provocation and reduced frontal emotional regulatory activity (Blair 2010).

In support of this model, multiple studies have reported decreased activity in the frontal lobes in individuals with antisocial and violent behavior, particularly in the OFC, ACC, and dorsolateral prefrontal cortex (Bassarath 2001; Brower and Price 2001; Hoptman 2003; Pridmore et al. 2005; Wahlund and Kristiansson 2009; Yang et al. 2008; Yang and Raine 2009). Table 20.3 summarizes all PET and SPECT studies that have been performed in ASPD. Raine et al. (1998) observed that impulsive murderers had lower left and right prefrontal metabolism with PET, higher right hemisphere subcortical metabolism, and lower right hemisphere prefrontal/subcortical ratios. In contrast, murderers with instrumental aggression had prefrontal metabolism more similar to healthy controls. Using SPECT, Kuruoglu et al. (1996) observed hypoperfusion in the frontal lobes of alcoholics, which was more pronounced among those diagnosed with ASPD. In a sample of opioid addicts, Gerra et al. found that ASPD was associated with low perfusion in the right frontal lobe (Gerra et al. 1998). Goethals et al. showed that patients with BPD or ASPD who had impulsive behavior had low perfusion in the right prefrontal and temporal cortex, but they found no differences in brain perfusion between BPD and ASPD patients (Goethals et al. 2005). Patients with frontotemporal dementia, who have anterior frontal or temporal hypoperfusion on SPECT, have higher rates of antisocial behaviors than patients with Alzheimer's dementia, who have posterior temporal-parietal hypoperfusion (Miller et al. 1997). Moreover, antisocial symptoms in patients with frontotemporal dementia are correlated with reduction of perfusion in the OFC (Mychack et al. 2001; Nakano et al. 2006). The data also suggest decreased serotonergic responsiveness in ASPD compared to healthy volunteers in the OFC, adjacent ventral medial frontal cortex, and cingulate cortex (Siever et al. 1999).

In recent years, Kolla et al. have investigated the role of monoamine oxidase-A (MAO-A) in influencing impulsivity and violent behavior in individuals with ASPD (Kolla et al. 2014a, b, 2015b). MAO-A is a pro-apoptotic oxidative enzyme that is

Table 20.3 PET and SPECT studies in ASPD

	Study	Method	Sample size (patients–controls)	Subjects state	Main results
1.	Gerra et al. (1998)	^{99m}Tc-HMPAO SPECT	27 detoxed opiate addicts (9 ASPD) – 9 HC	Resting state	– A decrease in metabolism in the frontal lobe was found in detoxed opiate addicts with ASPD compared to HC
2.	Goethals et al. (2005)	^{99m}Tc-ECD brain perfusion SPECT	37 (BPD and/or ASPD) – 34 HC	Resting state	– Hypoperfusion in temporal cortex and PFC in patients with BPD and/or ASPD compared to HC
3.	Kolla et al. (2015a)	[^{11}C] harmine PET; fMRI	19 ASPD (impulsive)	Resting state	– There was functional coupling of the VSs with bilateral dorsomedial prefrontal cortex that was correlated with VS MAO-A VT levels ($p = 0.04$) – There was also functional coupling of the VSi with right hippocampus that was anti-correlated with VS MAO-A VT levels ($p = 0.01$) – VSs dorsomedial prefrontal cortex FC was negatively correlated with NEO Personality Inventory-Revised impulsivity ($p = 0.03$), and VSi-hippocampus FC was negatively correlated with Barratt Impulsiveness Scale-11 motor impulsiveness ($p = 0.03$) – Association of VS MAO-A level with FC in striatal regions linked to impulsive behavior in the ASPD population group

(continued)

Table 20.3 (continued)

	Study	Method	Sample size (patients–controls)	Subjects state	Main results
4.	Kolla et al. (2014a)	[^{11}C] harmine PET (HRRT PET camera); Logan model with arterial sampling; MRI for ROI analysis	18 ASPD – 18 control	Medication, smoking and illicit substance use free No other mention of state (likely resting state)	– MAO-A VT was significantly reduced in ASPD compared to controls on average by 19.3% in VS and 18.8% in OFC ($p = 0.003$) – There was also a significant reduction in all the analyzed regions of the brain ($p = 0.022$) – Lower VS MAO-A VT was associated with more risky and impulsive decision-making with negative correlation with self-reported impulsivity on the NEO-PI-R scale as well ($p = 0.034$) – Participants with most impulsivity on PCL-R scale had the lowest VS MAO-A VT ($p = 0.013$) – There was no significant correlation between OFC MAO-A VT and impulsivity
5.	Kolla et al. (2015b)	[^{11}C] harmine PET	18 ASPD – 18 age- and sex-matched controls	Not mentioned (likely resting state)	OFC and VS MAO-A VT were lower by 19% in ASPD compared to the control group ($p = 0.003$) – Similar effects were observed in the prefrontal cortex, anterior cingulate cortex, dorsal putamen, thalamus, hippocampus, and the midbrain ($p = 0.029$) – In ASPD, VS MAO-A VT was negatively correlated with self-report and behavioral measures of impulsivity ($p < 0.05$)

6.	Kolla et al. (2014b)	[^{11}C] harmine PET	15 ASPD – 15 HC	Participants were medication-free, nonsmoking, and free of illicit substance use Participants were matched on current alcohol dependence No history of mood or psychotic disorders	– MAO-A VT levels in the PFC (17.8%, $p = 0.001$) and other brain regions ($p = 0.002$–0.013) except for the midbrain were significantly lower in ASPD compared to HC ($p = 0.001$)
7.	Kuruoglu et al. (1996)	^{99m}Tc-ECD brain perfusion SPECT	40 alcohol dependence (15 ASPD) – 10 HC	Resting state	– More marked frontal hypoperfusion in patients with ASPD compared to HC
8.	Miller et al. (1997)	^{133}X and ^{99m}Tc brain perfusion HMPAO SPECT	22 FTD – 22 AD	Resting state	– Higher rate of antisocial behaviors in subjects with anterior frontotemporal hypoperfusion than in those with posterior temporal-parietal hypoperfusion
9.	Mychack et al. (2001)	^{133}X and ^{99m}Tc brain perfusion HMPAO SPECT	12 FTD with right-sided frontotemporal hypoperfusion – 19 FTD with left-sided frontotemporal hypoperfusion	Resting state	– Higher rate of undesirable social behaviors in subjects with right-sided frontotemporal hypoperfusion than in those with left-sided frontotemporal hypoperfusion
10.	Nakano et al. (2006)	^{99m}Tc-ECD brain perfusion SPECT	22 FTD – 76 HC	Resting state	– Antisocial behavioral symptoms were correlated with perfusion in the OFC, inferior frontal gyri, cingulated gyrus, caudate, and insula

FDG 2-deoxy-2-[^{18}F]fluoro-D-glucose, *AD* Alzheimer's disease, *ASPD* Antisocial Personality Disorder, *ECD* Ethylcysteinate dimer, *FTD* Fronto-temporal dementia, *FC* Functional Connectivity, *fMRI* Functional Magnetic Resonance Imaging, *HMPAO* Hexamethyl-propyl-eneamine-oxime, *MAO-A* Monoamine oxidase-A, *MRI* Magnetic Resonance Imaging, *NEO-PI-R* Revised NEO Personality Inventory, *PCL-R* Psychopathy Checklist-Revised, *OFC* Orbital frontal cortex, *PET* Positron emission tomography, *ROI* Region of Interest, *SPECT* Single photon emission computed tomography, *VT* Total Volume of distribution, *VS* Ventral Striatum, *VSi* Ventral Striatum Inferior, *VSs* Ventral Striatum Superior

known to metabolize serotonin, norepinephrine, and dopamine, which are neurotransmitters that have been related to aggression and impulsivity. While studies have found associations between low levels of MAO-A and increased impulsivity and aggression in animal models, Kolla et al. investigated this phenomenon in humans (Kolla et al. 2014a, b, 2015b). Kolla et al. found significantly lower levels of MAO-A in the prefrontal cortex, orbital frontal cortex, and ventral striatum of ASPD compared to healthy control individuals (Kolla et al. 2014a, b, 2015b). A similar reduction in MAO-A levels was seen in other brain regions (Kolla et al. 2014b), including the prefrontal cortex, anterior cingulate cortex, dorsal putamen, thalamus, and the hippocampus (Kolla et al. 2015b). While Kolla et al. (2015b) observed lowered MAO-A levels in the midbrain region of ASPD compared to healthy controls, such differences were not seen among patients in another study (Kolla et al. 2014b). Additionally, Kolla et al. found that decreased MAO-A levels in the ventral striatum (Kolla et al. 2015a, b) were associated with increased levels of aggression, impulsivity, and risky decision-making, while such associations were not observed between MAO-A levels in the orbital frontal cortex and impulsivity (Kolla et al. 2014a).

Kolla et al. also considered the relationship between the superior (VS_s) and inferior (VS_i) ventral striatum seeds, impulsivity, and MAO-A levels in patients with ASPD. They found functional coupling between the VS_s and the bilateral prefrontal cortex, which was correlated with MAO-A levels in the ventral striatum, as well as between the VS_i region and the right hippocampus which was negatively correlated with MAO-A ventral striatum levels. Both of these functional connectivities were found to be negatively correlated with impulsivity, as measured by the NEO Personality Inventory and the Barratt Impulsiveness scales. In summary, this study identified potential associations between MAO-A levels in the ventral striatum and functional connectivity in striatal regions with impulsivity in ASPD individuals (Kolla et al. 2015a).

Of note, the heterogeneity of the ASPD diagnosis itself and of the samples and control groups analyzed (e.g., different demographic groups, psychiatric comorbidities, etc.) likely accounts for the fact that the neuroimaging abnormalities in ASPD are less consistent than those found in psychopathy (Nordstrom et al. 2011; Yang and Raine 2009). The majority of the studies and meta-analyses focus on broadly defined antisocial constructs, including individuals with ASPD with or without psychopathy, psychopathy with or without ASPD; antisocial behavior, conduct disorder, oppositional defiant disorder, disruptive behavior disorder, criminals, violent offenders, or aggressive individuals (Yang and Raine 2009). Very few studies focus on ASPD specifically, and even less studies have attempted to tease apart the specific neuroimaging abnormalities that may distinguish ASPD from psychopathy (Boccardi et al. 2010; Gregory et al. 2012; Tiihonen et al. 2008).

In summary, research suggests that impulsive aggression, a core dimension of antisocial spectrum disorders, is associated with abnormal activity in areas of the frontal lobes related to regulation of aggression, particularly the OFC, ACC, and dorsolateral prefrontal cortex.

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Abnormalities of Neurotransmission in Drug Addiction

21

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Abstract

Substance use disorders are prevalent and severe conditions associated with numerous health, social, and economic harms. While the neurobiological mechanisms are still not fully understood, adaptations in multiple neurotransmitter systems have been implicated in the development and maintenance of substance use disorders. The advent of molecular imaging techniques has provided a unique opportunity to better understand abnormalities of neurotransmission in humans with substance use disorders, and this insight may ultimately lead to improved treatment options in the future. This chapter provides a summary of positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies in humans with alcohol, tobacco, cannabis, opioid, and stimulant use disorders. Studies to date provide consistent evidence that the dopaminergic system is disrupted in populations with substance use disorders, although there has been little research in other neurotransmitter systems and findings of existing studies have been mixed. Many PET and SPECT studies investigating abnormalities of neurotransmission in substance use disorder are limited by small sample sizes and over-reliance on male samples without comorbid conditions. In addition, the use of cross-sectional study designs does not make it possible to draw conclusions about causality.

21.1 Introduction

Substance use disorders are chronic relapsing conditions characterized by compulsive drug use and loss of control over drug taking. Alcohol, tobacco, cannabis, opioid, and stimulant are among the most common substance use disorders in the United States (NIDA 2017). Current diagnostic criteria (DSM-5) for each of these requires the presence of at least 2 out of 11 symptoms in the past 12 months (including hazardous use; the need to use larger amounts; physical, psychological, and social problems; neglecting responsibilities at home, school, or work; craving; and withdrawal), with severity classified as mild, moderate, or severe as the number of symptoms increase (APA 2013). According to a 2014 national survey, more than 20 million adults in the United States had a substance use disorder in the past year (Lipari and Van Horn 2017). Substance use disorders are associated with significant disease burden; for example, mortality risk is approximately 15, 6, and 5 times higher compared to the general population for opioid, amphetamine, and alcohol use disorders, respectively (Chesney et al. 2014), and tobacco use is estimated to kill more than eight million people each year (WHO 2019). In addition, substance use disorders impose a huge economic burden; the cost associated with alcohol, tobacco, and illicit drug abuse (e.g., related to crime, lost productivity at work, and health care) is estimated to be $740 billion annually in the United States alone (NIDA 2017).

While the pathogenesis of substance use disorders is still not fully understood, the reinforcing effects of acute exposure to most drugs of abuse is thought to be mediated by increased dopamine transmission in brain reward pathways, and

adaptations in the function of multiple neurotransmitter systems have been implicated in the transition to addiction. Better understanding abnormalities in these neurotransmitter systems in chronic drug users could help to explain the pathophysiology of substance use disorders and ultimately to identify biomarkers and potential targets for future treatments for this serious public health problem. The advent of molecular imaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) has allowed researchers to begin characterizing alterations in neurotransmission in vivo in humans with substance use disorders.

PET and SPECT are high-resolution imaging techniques that can be used to assess neurochemical activity in the brain by labelling target molecules with radioactive tracers. The radiotracer can then be detected by virtue of its radioactive signal, allowing activity at specific sites of interest to be quantified. Radiotracers are available for various neurotransmitter precursors, receptors, transporters, and metabolizing enzymes although it is not possible to study all aspects of each neurotransmitter system as suitable tracers are yet to be developed for some targets of interest. Commonly used outcome measures in PET studies are distribution volume and binding potential which are used variously as indicators of receptor density, neurotransmitter levels, or receptor occupancy. Interpretation of these PET outcome measures is complex and depends on the context of the study. For a thorough review of PET methodology, experimental design, and interpretation of PET data in the context of addiction, see (Morris et al. 2014).

In addition to measuring activity in specific neurotransmitter system targets, PET and SPECT imaging can also be utilized to assess cerebral blood flow and brain glucose metabolism using the SPECT and PET tracers technetium-99m (^{99m}Tc) and ^{18}F-fluorodeoxyglucose (FDG-PET). Studies comparing chronic drug users with healthy controls using ^{99m}Tc and PET-FDG have consistently shown global reductions in cerebral blood flow and glucose metabolism in individuals with various substance use disorders (e.g., Amen et al. 2017; Botelho et al. 2006; Holman et al. 1991; London et al. 1990; Melgaard et al. 1990; Moreno-Lopez et al. 2012; Parkar et al. 2010). Associations between reduced blood flow or glucose metabolism with clinical variables such as severity of drug dependence, drug consumption, and cognitive impairments have also been observed. While such studies do not provide a direct or specific assessment of the function of specific neurotransmitter systems, cerebral blood flow has been shown to reflect the brain-wide metabolic demands of several neurotransmitter systems in humans (Dukart et al. 2018). These findings are therefore highly suggestive of abnormalities in multiple neurotransmitter systems in chronic drug users.

This chapter presents the findings of human PET and SPECT studies that have directly assessed changes in specific neurotransmitter systems in substance use disorders focusing in turn on alcohol-, tobacco-, cannabis-, opioid-, and stimulant-dependent populations, compared with healthy controls. Table 21.1 lists the radiotracers used in the studies reviewed in this chapter. Literature relating to acute drug effects on neurotransmission is outside the scope of this review. Likewise, relevant preclinical and other human work related to abnormalities of

Table 21.1 PET and SPECT radiotracers used in studies investigating neurotransmission in substance use disorders[a]

	Alcohol	Tobacco	Cannabis	Opioids	Stimulants
Dopaminergic system	*PET* [^{11}C]raclopride [^{18}F]fallypride [^{18}F]FDOPA [^{11}C]-(+)-PHNO [^{123}I]PE2I [^{11}C]DTBZ [^{11}C]d-threo methylphenidate [^{11}C]-harmine *SPECT* [^{123}I]β-CIT [^{99m}Tc]TRODAT-1 [^{123}I]epidepride	*PET* [^{11}C]raclopride [^{18}F]fallypride [^{18}F]FDOPA [^{11}C]-(+)-PHNO [^{123}I]PE2I 2-FA [^{11}C]-SCH-23390 [^{11}C]-FLB-457 [^{11}C]clorgyline [^{11}C]L-deprenyl-D2 [^{11}C]befloxatone [^{11}C]-harmine *SPECT* [^{123}I]β-CIT [^{99m}Tc]TRODAT-1 [^{123}I]5-IA	*PET* [^{11}C]raclopride [^{18}F]FDOPA [^{11}C]-(+)-PHNO [^{123}I]PE2I	*PET* [^{11}C]raclopride [^{18}F]-FECNT *SPECT* [^{123}I]β-CIT [^{99m}Tc]TRODAT-1 [^{123}I]FP-CIT [^{123}I]IBZM	*PET* [^{11}C]raclopride [^{18}F]fallypride [^{18}F]FDOPA [^{11}C]-(+)-PHNO [^{11}C]DTBZ [^{11}C]NPA [^{11}C]NNC [^{18}F]methylspiroperidol [^{11}C]β-CFT [^{11}C]cocaine *SPECT* [^{123}I]β-CIT [^{99m}Tc]TRODAT-1
Serotonergic system	*PET* [^{11}C]DASB [^{11}C]McN5652 [^{11}C]-methyl-*l*-tryptophan [^{11}C]P943 [^{11}C]WAY100635 [^{11}C]-harmine *SPECT* [^{123}-I]β-CIT [^{123}-I]I-ADAM	*PET* [^{11}C]DASB [^{11}C]clorgyline [^{11}C]befloxatone [^{11}C]-harmine *SPECT* [^{123}-I]β-CIT [^{123}-I]I-ADAM		*SPECT* [^{123}-I]β-CIT [^{123}-I]I-ADAM	*PET* [^{11}C]P943 *SPECT* [^{123}I]β-CIT

(continued)

Table 21.1 (continued)

	Alcohol	Tobacco	Cannabis	Opioids	Stimulants
GABAergic system	*PET* [^{11}C]Ro15 4513 [^{11}C]flumazenil *SPECT* [^{123}I] iomazenil	*PET* [^{11}C]Ro15-4513 *SPECT* [^{123}I]iomazenil		*PET* [^{11}C]Ro15-4513	
Opioidergic system	*PET* [^{11}C]carfentanil [^{11}C]diprenorphine [^{11}C]methylnaltrindole [^{11}C]-LY2795050	*PET* [^{11}C]carfentanil		*PET* [^{11}C]carfentanil [^{11}C] diprenorphine [^{18}F]cyclofoxy	*PET* [^{11}C]GR103545
Glutamatergic system	*PET* [^{11}C]ABP68814 [^{18}F]FPEB				*PET* [^{11}C]ABP688
Endocannabinoid system	*PET* [^{11}C]COMAR [^{18}F]FMPEP-d_2 [^{18}F]MK-9470		*PET* [^{11}C]OMAR [^{18}F]FMPEP-d_2 [^{18}F]MK-9470 [^{11}C]CURB		
Cholinergic system	*SPECT* [^{123}I]5-I-A-85380		*PET* 2-[^{18}F]FA		

[a]Based upon radiotracers used in studies reviewed in this chapter. This table illustrates that the majority of work has focused on the dopaminergic system and that alcohol, tobacco, and stimulant use disorders have received the most attention to date

neurotransmission but that do not involve PET or SPECT imaging (e.g., post-mortem studies, or studies of associations with functional imaging or behavioral tasks) are presented to provide context where appropriate; however this chapter does not provide a comprehensive review of these studies.

21.2 Alcohol

21.2.1 Dopaminergic System

Chronic alcohol exposure is thought to result in downregulated dopaminergic activity in the mesocorticolimbic reward system, leading to craving and relapse to drinking. In rodents decreased dopaminergic activity has been observed following prolonged periods of alcohol consumption, including decreased dopamine (DA) receptor gene expression, decreased DA output, and blunted dopaminergic response to an alcohol challenge (Barak et al. 2011; Feltmann et al. 2016; Jonsson et al. 2014). Human PET and SPECT studies have investigated alterations in multiple aspects of the dopaminergic system including DA synthesis, DA release, the DA transporter (DAT), and availability of DA receptors in individuals with alcohol use disorder (AUD).

21.2.1.1 Dopamine Synthesis and Presynaptic Function

Radiotracers used in neuroimaging studies of presynaptic DA function in alcohol dependence include 6-[^{18}F]-fluorodopa (FDOPA), the uptake of which estimates presynaptic DA synthesis capacity, and (+)[^{11}C]dihydrotetrabenazine ([^{11}C]DTBZ) which binds to the type 2 vesicular monoamine transporter (VMAT2) to investigate presynaptic monoaminergic terminals. Studies using these radiotracers to explore presynaptic DA function in individuals with AUD compared to healthy controls have produced mixed results. Using FDOPA Tiihonen and colleagues found increased DA synthesis capacity in the striatum of ten alcoholics with varying duration of abstinence (from 3 days to 42 months) (Tiihonen et al. 1998), while Heinz et al. (2005b) observed no difference between those with AUD (n = 12; detoxified ~36 days) versus healthy controls, and in the latter study DA synthesis capacity was negatively correlated with craving (Heinz et al. 2005b). In another study using the tracer [^{11}C]DTBZ, VMAT2 was lower in the putamen (i.e., dorsal striatum) of seven males with severe chronic alcoholism compared to healthy controls (Gilman et al. 1998), suggesting decreased presynaptic dopaminergic stores (while VMAT2 is not exclusively involved in the transport of DA, in the DA-rich striatum it is most likely to provide an index of DA stores). It seems unlikely that the discrepant findings of these studies are due to the different radiotracers used given that two studies using the same radiotracer produced divergent results (Heinz et al. 2005b; Tiihonen et al. 1998); however all three studies had small sample sizes, and there was some variability in the duration of abstinence which may explain the lack of consistent findings. Therefore the relationship between chronic alcohol use and presynaptic DA function is currently unclear.

21.2.1.2 Dopamine Transporter

Imaging studies exploring availability of DAT in AUD have employed a range of radiotracers including [^{99m}Tc]TRODAT-1, [^{11}C]d-threo methylphenidate, [^{123}I]PE2I, and [^{123}-iodium]-2-β-carbomethoxy-3-β-(4-iodophenyl-tropane) ([^{123}-I]β-CIT). These radiotracers bind to DAT which serves as a marker for presynaptic DA neurotransmission. Research examining DAT availability in AUD has produced inconsistent results. One study found reduced DAT availability during acute withdrawal (~48 h) in 26 male alcoholics, which was associated with neurocognitive deficits (Yen et al. 2015). Another study compared DAT levels in 27 alcohol-dependent individuals to healthy controls during acute withdrawal and after 4 weeks of abstinence (Laine et al. 1999). In this study, those with AUD showed lower DAT during acute withdrawal but not after prolonged abstinence, suggesting chronic alcohol abuse induced downregulation of DAT that may be restored upon alcohol abstinence. However, two SPECT studies using [^{123}I]PE21 (n = 9) and [^{123}-I]β-CIT (n = 29) also support the finding of decreased DAT availability during prolonged (several weeks) abstinence (Repo et al. 1999; Tiihonen et al. 1995). Other SPECT studies have failed to show any differences in DAT availability in AUD at all using the tracers [^{123}-I]β-CIT (n = 14) and [^{11}C]d-threo methylphenidate (n = 5) (Heinz et al. 2000a; Volkow et al. 1996). The latter studies focused on individuals with late-onset or "type I" alcoholism. Thus, while there is some evidence to support lower DAT availability in chronic alcohol users, more research is required to understand the time course of alcohol-related DAT regulation and the impact that sample characteristics may have on such effects.

21.2.1.3 Dopamine D2/D3 Receptors

The majority of imaging research examining the role of DA receptors in AUD has focused on the D2 and, more recently, the D3 receptors. This is primarily due to the increased availability of radiotracers that bind to the D2 receptors (e.g., PET, [^{18}F]fallypride, [^{11}C]raclopride, [^{18}F]desmethoxyfallypride; SPECT, [^{123}I]epidepride). Recently, the development of a D3-preferring radiotracer, [^{11}C]-(+)-PHNO, has enabled the assessment of D3 receptors in AUD. No investigations to date have explored the regulation of other DA receptor subtypes (i.e., D1, D4, and D5).

Dopamine D2 Receptors. Most research examining D2 receptors in AUD has used the radiotracers [^{11}C]raclopride or [^{18}F]fallypride and shows decreased striatal D2 availability in recently detoxified individuals with AUD compared to healthy controls (AUD sample sizes ranged from n = 9 to n = 15), with studies suggesting the magnitude of decrease is between 10 and 20% (Heinz et al. 2004; Hietala et al. 1994; Martinez et al. 2005; Volkow et al. 1996, 2002). However a PET study using [^{11}C]raclopride (n = 17 AUD) and SPECT studies using [^{123}I]IBZM (n = 9 AUD) and [^{123}I]epidepride (n = 21 AUD) failed to observe significant differences in D2 density (Guardia et al. 2000; Repo et al. 1999; Rominger et al. 2012). Postmortem studies support a decrease in human D2 levels, showing ~20% to 30% lower D2 receptor binding in the dorsal striatum and nucleus accumbens (NAc) of alcohol-dependent individuals compared to

controls, e.g., (Tupala et al. 2003). Preclinical studies have also found reduced D2 receptor levels in alcohol-preferring rats (McBride et al. 1993; Stefanini et al. 1992; Strother et al. 2003) providing further support for the notion that chronic alcohol abuse appears to be associated with lower D2 availability in humans. Reduced D2 availability has also been shown to correlate with increased craving (Heinz et al. 2004) and increased alcohol intake (Martinez et al. 2005) suggesting a functional relationship between decreased D2 levels and clinical aspects of AUD.

While AUD appears to be associated with lower D2 availability, it is unclear if this is a consequence of AUD or if it represents a predisposing risk factor. Recovery of D2 availability with increasing durations of abstinence might suggest the former. However PET studies using [^{11}C]raclopride at different stages of abstinence has failed to show a difference in receptor levels between early and late stage abstinence (Volkow et al. 2002) or an association of D2 levels with time since last alcohol use (Hietala et al. 1994; Volkow et al. 1996). On the other hand, another study showed that a subset of four individuals with AUD who achieved prolonged abstinence saw a 30% increase in striatal and thalamic D2 (Rominger et al. 2012). Therefore, it is currently unclear whether there is recovery of D2 receptors following alcohol abstinence. Several PET studies have examined whether lower D2 levels are a predisposing factor for AUD by comparing D2 levels of healthy individuals at higher risk of developing AUD (by virtue of family history of AUD) to healthy controls with no family history of AUD. The studies conducted to date have all used the radiotracer [^{11}C]raclopride. Two of these studies showed significantly higher D2 levels in the caudate and ventral striatum of individuals with a family history of AUD compared to those without a family history (Alvanzo et al. 2017; Volkow et al. 2006). The authors suggest that these findings may indicate a protective effect of increased D2 availability against the development of alcohol abuse. However, one study failed to find a difference in D2 levels between individuals with and without a family history of AUD (Munro et al. 2006). Therefore, while there is some evidence to support the idea that higher D2 levels may confer protection against AUD, more research is required to confirm this.

Dopamine D3 Receptors. With the advent of [^{11}C]-(+)-PHNO, a D3-preferring radiotracer with 20-fold increased affinity for D3 over D2 receptors (Searle et al. 2010), the scientific community has a new tool to assess the contribution of D3 in AUD. The sole study investigating D3 using [^{11}C]-(+)-PHNO found no difference between 16 males with AUD and 13 healthy controls in striatal areas but did see higher D3 in the hypothalamus of those with alcohol dependence (Erritzoe et al. 2014). This is consistent with [^{11}C]-(+)-PHNO PET studies in other substance use disorders which have also seen higher D3 in non-striatal areas of drug users compared to healthy controls (Boileau et al. 2012; Matuskey et al. 2014b). Therefore, early data suggests that D3 regulation in non-striatal areas may be involved in substance use disorders, but more research is needed to validate this in AUD specifically. Given convergent preclinical data supporting D3 involvement in AUD, we can expect more studies investigating this in the future.

21.2.1.4 Dopamine Release

Studies comparing [^{11}C]raclopride PET scans before and after a pharmacological challenge (i.e., administration of a psychostimulant) to provide an indirect measure of DA release suggest that DA release is disrupted in individuals with AUD. For example, approximately 2 weeks after detoxification, blunted amphetamine-induced DA release was observed in the limbic (but not associate or sensorimotor) striatum of 15 alcohol-dependent individuals compared to controls (Martinez et al. 2005). In another study, methylphenidate-induced DA release was approximately 50–70% lower in the putamen and ventral striatum of 20 male alcoholics, abstinent for a minimum of 30 days, compared to controls (Volkow et al. 2007). In the latter study, resting metabolic activity in prefrontal brain regions was correlated with methylphenidate-induced changes in DA release in controls but not in alcohol-dependent participants. This suggests that decreased dopaminergic activity in AUD may be due to disrupted prefrontal regulation of DA mesolimbic pathways. This is consistent with preclinical work showing that the influence of the prefrontal cortex on behavior regulation is decreased following chronic drug exposure and that this may contribute to loss of control over drug taking (Homayoun and Moghaddam 2006).

21.2.1.5 Monoamine Oxidase

The enzyme monoamine oxidase is involved in the degradation of neurotransmitters. Monoamine oxidase A (MAOA) is involved in the metabolism of DA, serotonin, and noradrenaline, whereas monoamine oxidase B (MAOB) is primarily involved in metabolism of DA. Pharmacological inhibition of monoamine oxidase leads to increased neurotransmitter levels, a mechanism that has been targeted for the treatment of conditions such as Parkinson's disease and depression. Monoamine oxidase may be increased in AUD due to oxidative stress caused by alcohol consumption (Das and Vasudevan 2007). However results of biosampling and postmortem studies in humans have proved inconclusive, although these studies largely failed to control for important confounding variables such as tobacco smoking. A single PET study has compared MAOA levels in 16 non-smoking alcohol-dependent participants with 16 healthy controls using the radiotracer [^{11}C]-harmine. MAOA was an average of 32% greater in multiple brain regions including the prefrontal cortex in alcoholics compared to controls. In addition, increased MAOA was correlated with greater duration of heavy drinking (Matthews et al. 2014).

21.2.2 Serotonergic System

Preclinical studies have demonstrated an association between low serotonin (5-HT) function and increased alcohol preference, and in humans alcoholism has been linked with loss of serotonergic neurons in postmortem studies (e.g., Chen et al. 1991; Halliday et al. 1993; Little et al. 1998) and a reduction in 5-HT metabolites in vivo (Fils-Aime et al. 1996). Furthermore, increasing 5-HT via administration of tryptophan or selective 5-HT reuptake inhibitors (SSRIs) has been shown to

modestly reduce alcohol consumption. Therefore, several strands of evidence suggest that AUD is associated with low serotonergic activity. A number of radiotracers are available for use in human imaging studies of the serotonergic system, and to date such studies have investigated availability of the 5-HT transporter (SERT), 5-HT_{1A} and 5-HT_{1B} receptors, and 5-HT synthesis in AUD. In addition, studies combining PET imaging with a pharmacological challenge have provided information about 5-HT signaling in alcoholics.

21.2.2.1 Serotonin Transporter

The majority of PET or SPECT studies investigating the serotonergic system in AUD have focused on the SERT, although findings of these studies have been inconsistent. Using the SPECT tracer [^{123}-I]β-CIT, Heinz et al. (1998) found a reduction in SERT availability of approximately 30% in the brainstem (raphe nuclei) of 22 alcoholics compared to healthy controls, after approximately 1 month of abstinence (Heinz et al. 1998). However, two follow-up studies by the same group, also using the tracer [^{123}-I]B-CIT, found similar reductions in the raphe area only in male alcoholics (Heinz et al. 2002) and a subgroup of alcoholic patients with a genetic variation (*ll*-homozygotes) of the SERT gene promoter region (5-HTTLPR) (Heinz et al. 2000b). Outside of the brainstem, one study investigated SERT availability in the basal ganglia and limbic system of 15 recovering alcoholics (abstinent for an average of 17 years) using the PET tracer [^{11}C]McN5652. Compared to controls this study found reductions in SERT in the midbrain, thalamus, amygdala, pons, anterior and posterior cingulate cortices, orbitofrontal cortex, and cerebellum of individuals with a past history of alcoholism (Szabo et al. 2004). This is consistent with autoradiographic studies showing decreased SERT binding in the amygdala, anterior cingulate cortex, and striatum of alcoholics postmortem (Storvik et al. 2006, 2007). However, in contrast, a later study using the SPECT tracer [^{123}-I]I-ADAM found reduced SERT, during intoxication or withdrawal, in the midbrain of a subgroup of nine alcoholics without comorbid anxiety or depression, but no differences compared to controls in the striatum or thalamus (Ho et al. 2011). Finally, two PET studies (n = 14 and n = 32; alcoholic-dependent participants) using the selective SERT radiotracer [^{11}C]DASB found no difference between alcoholics in early abstinence (~2 weeks) and healthy controls in multiple regions of interest including brainstem, midbrain, and cortical regions (Brown et al. 2007; Martinez et al. 2009a). Probes for measuring SERT have different characteristics. For example, a comparative evaluation of the PET tracers [^{11}C]McN5652 and [^{11}C]DASB suggests that while both radiotracers bind preferentially in brain regions known to have high SERT density, [^{11}C]DASB may be a more suitable index of SERT due to lower nonspecific binding, higher plasma free-fraction, and faster kinetics (Frankle et al. 2004; Szabo et al. 2002). The mixed findings of PET studies investigating SERT to date could therefore reflect methodological heterogeneity including the use of different radiotracers and inconsistencies in data analysis or varied sample characteristics including differences in duration of abstinence. Further work is needed to explore SERT changes in AUD.

21.2.2.2 5-HT$_{1A}$ and 5-HT$_{1B}$ Receptors

Two PET studies of the 5-HT receptors have been undertaken to date. The first found a significant increase in 5-HT$_{1B}$ receptors in the ventral striatum of 12 alcoholics in early abstinence (~4 weeks) compared to controls, using the selective 5-HT$_{1B}$ antagonist tracer [^{11}C]P943 (Hu et al. 2010). This is consistent with a study showing that elevated expression of 5-HT$_{1B}$ receptors in the ventral striatum of rats was associated with increased alcohol consumption and preference for higher concentrations of alcohol (Hoplight et al. 2006), although in humans 5-HT$_{1B}$ receptor densities in postmortem alcoholic brains were not different compared to controls (Storvik et al. 2012). The second study compared 13 alcoholics, after at least 2 weeks of abstinence, with controls using the tracer [^{11}C]WAY100635 and found no difference in 5-HT$_{1A}$ receptors in multiple areas of interest including brainstem, midbrain, and cortical regions (Martinez et al. 2009a). A recent autoradiographic study showed that AUD was associated with increased 5-HT$_{1A}$ binding postmortem in the prefrontal and anterior cingulate cortices, but only in a subgroup who died by suicide. Thus, due to the limited number of studies currently available, it is unclear how 5-HT receptor availability is altered in humans with AUD. Future research should explore the possibility that AUD-associated changes in 5-HT receptor availability may depend on the presence of comorbid depressive disorder.

21.2.2.3 Serotonin Synthesis

One small study assessed the rate of 5-HT synthesis in eight non-depressed alcoholics within 1 week of entry into treatment. The PET tracer [^{11}C]-methyl-*l*-tryptophan was used, which provides regional estimates of the conversion of tryptophan to 5-HT. Compared to controls the rate of 5-HT synthesis was lower in alcoholics in the medial prefrontal cortex and dorsal anterior cingulate gyrus but higher in the superior temporal gyrus and occipital lobe (Nishikawa et al. 2009). Additionally, lower 5-HT synthesis in the gyrus rectus, medial frontal area, and amygdala was negatively correlated with a quantity-frequency measure of alcohol consumption. This study was conducted very early in abstinence, and participants had been actively drinking in the week prior to inclusion; therefore it remains to be confirmed if the observed effects would persist into later abstinence.

21.2.2.4 Serotonergic Challenge

Administration of a pharmacological agent to induce or mimic the effect of 5-HT release (i.e., a 5-HT challenge) can be used in combination with molecular imaging to investigate region-specific metabolic responses to 5-HT release, indicating activity of the serotonergic system. In one such study, the partial 5-HT$_{2C}$ agonist m-chlorophenylpiperazine (mCPP), or placebo, was administered prior to a FDG-PET scan, and regional cerebral metabolism of glucose in 18 abstinent male alcoholics was compared to that of healthy controls. A blunted response to mCPP was found in alcoholics in the orbitofrontal cortex, head of caudate, and middle frontal gyrus (Hommer et al. 1997). In another study fenfluramine was used to stimulate 5-HT release/inhibit reuptake prior to FDG-PET imaging in depressed patients with (n = 8) and without (n = 18) comorbid AUD. Patients with comorbid AUD, who had

been abstinent for ~2 months, showed reduced metabolic activity in the anterior medial prefrontal cortex, which was restored following fenfluramine challenge (Sher et al. 2007). The results of these studies are consistent with disrupted 5-HT transmission in alcoholics compared to controls; however they should be interpreted with caution since they provide only an indirect measure of 5-HT function.

21.2.3 GABAergic System

Chronic exposure to alcohol is thought to lead to compensatory changes in GABAergic function, particularly within the γ-aminobutyric acid A ($GABA_A$) receptor, that contribute to tolerance, dependence, and symptoms of withdrawal. Human gene association studies and several strands of preclinical work (including altered expression of GABAergic genes in animals bred for high alcohol consumption, gene association studies, and gene deletion studies) provide evidence of GABAergic involvement in alcohol dependence (for a review see Stephens et al. (2017)). To date molecular imaging studies of the GABAergic system in humans with AUD have investigated availability of the $GABA_A$ receptor using the non-selective radiotracers [^{11}C]flumazenil and [^{123}I] iomazenil, as well as the tracer [^{11}C]Ro15 4513 which is selective for the α5 receptor subtype. In addition, studies combining PET imaging with a pharmacological challenge have allowed indirect assessment of GABAergic signaling.

21.2.3.1 GABA Receptors

$GABA_A$ Receptors. The majority of human imaging studies using the non-selective $GABA_A$ receptor radiotracers [^{123}I]iomazenil and [^{11}C]flumazenil appear to support a decrease in $GABA_A$ receptor availability. Three small (n = 9, 11 and 12 AUD) SPECT studies using [^{123}I]iomazenil reported binding reductions of up to 20% in cortical areas including frontal, anterior cingulate, parietal, occipital, and cerebellar cortices, in male and female alcoholics after 3–30 months of abstinence (Abi-Dargham et al. 1998; Lingford-Hughes et al. 1998, 2000). A further two PET studies using [^{11}C]flumazenil also found decreased receptor availability: first in the medial frontal lobes (including superior frontal gyrus and cingulate gyrus) of 17 males with severe chronic alcoholism after 30 days abstinence (Gilman et al. 1996), and second small decreases (6–8%) in the orbitofrontal cortex and anterior cingulate cortex of 10 males abstinent for an average of 7 months (Lingford-Hughes et al. 2005). However, there have been some conflicting findings. For example, Staley et al. (2005) reported increased [^{123}I]iomazenil binding in multiple cortical areas in a subgroup of eight non-smoking alcoholic males after 1 week of abstinence, although there was no significant difference between alcoholics and controls when scans were repeated after 4 weeks (Staley et al. 2005). Similarly, Cosgrove et al. (2014a) found increased [^{123}I]iomazenil binding in ten non-smoking alcoholics at 3, 10, and 30 days into withdrawal, with small and regionally specific effects at 3 days, large widespread increases of up to 38% after 10 days, and a return to baseline levels again at 30 days. Interestingly, in alcohol-dependent smokers (n = 17), large

global increases in [^{123}I]iomazenil binding were observed at all three scans, suggesting that alcohol dependence and tobacco use may have interactive effects on the GABAergic system (Cosgrove et al. 2014a). In addition, two small studies using [^{11}C]flumazenil reported increased $GABA_A$ receptor availability in the cortex, cerebellum, and basal ganglia of six abstinent alcoholics with chronic hepatic encephalopathy and alcohol-related cirrhosis (Jalan et al. 2000) and no difference in frontal, temporal, occipital, and cerebellar cortical regions of interest in five chronic alcohol users compared to five controls (Litton et al. 1993), although the latter study also reported large intra-individual variability which may have masked group differences. The studies of Staley et al. and Cosgrove et al. were conducted much earlier in abstinence than other studies that showed decreases in $GABA_A$ receptor availability, and so it is possible that the discrepant findings could reveal something about the time course of changes in receptor availability in AUD. The mixed findings presented here could also be explained by variations in sample characteristics (including severity of AUD) and methodological details such as small sample sizes and failure to correct for alcohol-related brain atrophy, disulfiram treatment (which reduces [^{11}C]flumazenil binding), or comorbid anxiety (which can impact on GABAergic neurotransmission independent of alcoholism).

$GABA_A$ α5 Subtype Receptors. The α5 subtype of the $GABA_A$ receptor (GABRA5) has been particularly implicated in the reinforcing effects of alcohol. For example, preclinical studies show that self-administration of alcohol is reduced in α5 knockout mice and in wild types treated with an α5 inverse agonist. A single PET study in human alcoholics has been conducted using the tracer [^{11}C]Ro15 4513 which is selective for GABRA5. Lower binding was observed in the NAc, parahippocampal gyri, right hippocampus, and right amygdala of eight male alcoholics, abstinent for an average of 33 months, compared to controls (Lingford-Hughes et al. 2012). This reduction in GABRA5 availability is consistent with several studies using non-specific $GABA_A$ receptor radiotracers and also with preclinical work. Preclinical and human postmortem studies indicate that chronic alcohol exposure results in differential, regionally specific alterations in $GABA_A$ receptor subunits (for a review see Enoch (2008)); therefore this study provides an important first step in characterizing specific $GABA_A$ receptor subtypes in AUD.

21.2.3.2 GABAergic Challenge

Two early PET studies assessed sensitivity to lorazepam, a benzodiazepine agonist that enhances GABAergic signaling, in alcoholics compared to controls. These studies showed reduced regional brain glucose metabolism in the thalamus, basal ganglia, and orbitofrontal cortex of ten male alcoholics compared to controls, both during early abstinence and after protracted withdrawal (Volkow et al. 1997a, 1993b). The blunted response to lorazepam in these studies indirectly indicates reduced GABA receptor function in a corticostriatal loop in alcoholics. In a later study, Lingford-Hughes et al. (2005) found a blunted physiological response to the benzodiazepine agonist midazolam (specifically, a 50% reduction in sleep time) in ten alcohol-dependent males who had been abstinent for an average of 7 months, despite having the same level of receptor occupancy as controls (Lingford-Hughes

et al. 2005). The findings of these studies are consistent with reduced sensitivity of the GABA-benzodiazepine receptor in alcoholism. Further, a study comparing non-alcoholics with and without a family history of alcoholism showed an attenuated decrease in glucose metabolism in the cerebellum following lorazepam challenge among those with a family history, suggesting that blunted sensitivity to GABAergic stimulation might represent a risk factor for AUD (Volkow et al. 1995).

21.2.4 Opioidergic System

The reinforcing effects of alcohol are partly mediated by endogenous opioids that bind to various opioid receptors. Opioid receptor types include the mu(μ)-opioid receptor (MOR), delta(δ)-opioid receptor (DOR), and kappa(κ)-opioid receptor (KOR). Preclinical and clinical research has implicated these receptor subtypes in various aspects of alcohol use (Nutt 2014). PET studies have utilized [^{11}C]carfentanil to measure MOR, [^{11}C]methylnaltrindole to measure DOR, [^{11}C]-LY2795050 to measure KOR, and [^{11}C]diprenorphine to non-selectively measure all three receptor types.

μ-*opioid Receptors.* The majority of research exploring opiate receptors in AUD has focused on the MOR. These studies have compared receptor levels between individuals with AUD and healthy controls but produced mixed results. One of the earliest studies showed a decrease in MOR following detoxification in the right dorsal lateral prefrontal cortex, right anterior frontal, and right parietal cortex of eight males with AUD (Bencherif et al. 2004). In contrast, other research has found no differences in cortical MOR levels but significantly increased striatal MOR in 25 individuals with AUD immediately after detoxification and again after 5 weeks abstinence (Heinz et al. 2005a) and increased non-cortical (i.e., amygdala, caudate, globus pallidus, insula, putamen, and thalamus) MOR in 25 alcoholics compared to controls after 5 days abstinence (Weerts et al. 2011). The findings of increased MOR levels are consistent with a study that reported a global, but non-significant, increase in opioid receptors using the non-selective radiotracer [^{11}C]diprenorphine in 11 alcohol-dependent individuals (Williams et al. 2009). However, PET studies of MOR in AUD are difficult to interpret in light of the fact that [^{11}C]carfentanil and [^{11}C]diprenorphine binding are sensitive to competition with endogenous opioids, such that increased binding of these radiotracers may reflect either increased receptor levels *or* decreased synaptic opioid peptide concentrations (i.e., reduced release of endogenous opioids in the absence of changes in receptor levels). A recent study addressed this by examining [^{11}C]carfentanil binding in a postmortem alcohol-dependent population (therefore devoid of active neurotransmission) and found significantly reduced [^{11}C]carfentanil binding in striatal areas (Hermann et al. 2017). This suggests MOR levels are decreased in the striatum of individuals with AUD, leading the authors to conclude that previous studies showing increased radiotracer binding to MOR reflected decreased opioid peptide competition as opposed to increased receptor availability. They also suggest that reduced MOR contributes to increased tolerance to the rewarding effects of alcohol.

δ-*opioid Receptors.* A single human imaging study using the selective PET tracer [^{11}C]methylnaltrindole has been conducted to compare DOR levels in 20 alcohol-dependent individuals versus 18 healthy controls after ~5 days abstinence (Weerts et al. 2011). Results showed an increase in DOR levels in those with AUD, although this did not reach statistical significance. Interestingly, this study also found a positive correlation between increased DOR and recency of alcohol drinking in individuals with AUD.

κ-*opioid Receptors.* To date only one study has explored KOR levels in AUD using a selective PET radiotracer. This study showed significantly lower KOR availability in 36 individuals with AUD compared to 28 healthy controls in a number of brain regions (amygdala, caudate and putamen, frontal cortex, insula, pallidum, and parietal and temporal cortex) (Vijay et al. 2018). Correlations between receptor levels and behavioral measures were not investigated in this study so the clinical implications of this finding remain to be confirmed in future research.

21.2.5 Glutamatergic System

Preclinical work suggests that chronic excessive alcohol use interferes with glutamatergic neurotransmission by homeostatic upregulation of glutamate receptors, especially in mesocorticolimbic and extended amygdala reward circuits, and this is thought to be involved in the development of tolerance to alcohol and symptoms of alcohol withdrawal (such as craving) (Rao et al. 2015). However, to date only two PET studies have investigated the glutamatergic system in humans with alcohol dependence. Akkus et al. (2018) assessed availability of the metabotropic glutamate receptor mGluR5, using the selective radiotracer [^{11}C]ABP68814, in 14 non-smoking patients with AUD after at least 25 days abstinence compared with 14 healthy controls. Alcoholic patients had increased mGluR5 availability in several regions of interest within the temporal lobe, with the largest effect seen in the amygdala (Akkus et al. 2018). This is consistent with preclinical evidence showing mGluR5 involvement in binge-like alcohol drinking, increased mGluR5 following prolonged alcohol intake, and decreased alcohol intake following administration of negative allosteric modulators (Cozzoli et al. 2012; Mihov and Hasler 2016; Obara et al. 2009). Conversely, using another mGluR5-selective radiotracer, [^{18}F]FPEB, Leurquin-Sterk et al. (2018) found reductions in mGluR5 availability of between 14 and 36%, mainly in limbic and cortical regions (with the largest difference observed in the caudate nucleus), in 16 recently abstinent alcohol-dependent patients compared to 32 controls (Leurquin-Sterk et al. 2018). The conflicting findings of these two studies may be due to differences in study design, including the use of different tracers. Another notable difference between the studies was the smoking status of the participants; since reductions in mGluR5 have been observed previously in smokers and ex-smokers, this could represent a potential confounding variable in the study by Leurquin-Sterk et al. in which the majority of the alcohol-dependent group were also tobacco smokers (Akkus et al. 2013). Further research is needed to clarify the role of metabotropic receptors, such as mGluR5, in alcohol dependence and abstinence. In addition, while preclinical work suggests

a role for the ionotropic glutamate receptors in AUD (particularly the NMDA receptor), it has not been possible to confirm this in human PET studies due to the lack of a suitable radiotracer.

21.2.6 Endocannabinoid System

Preclinically, chronic alcohol exposure is associated with alterations in the endocannabinoid system, in particular the cannabinoid CB1 receptor. For example, increased CB1 receptor signaling has been shown to increase alcohol intake, and CB1 receptor blockade decreases alcohol intake (for a review see (Henderson-Redmond et al. 2016)). In humans, a postmortem study showed reduced CB1 and reduced activity of the fatty acid amide hydrolase enzyme (FAAH; responsible for metabolizing the endogenous endocannabinoid anandamide) in the ventral striatum of alcoholics compared to controls (Vinod et al. 2010). To date human imaging work investigating availability of CB1 is limited to three PET studies, each using a different radiotracer. In the smallest of the studies, [^{11}C]COMAR was used to estimate CB1 density in eight males with alcohol dependence in early abstinence (2–4 weeks after last drink). Compared to controls there was an approximately 20% increase in CB1 in multiple regions, including the amygdala, hippocampus, putamen, insula, anterior and posterior cingulate, and orbitofrontal cortex (Neumeister et al. 2012). In contrast, another study of 18 male alcoholics, using the PET tracer [^{18}F]FMPEP-d_2, showed a 21–35% reduction in CB1 (with the largest effect observed in white matter) in alcoholics compared to controls during immediate abstinence (3–7 days) and at 2–4 weeks abstinence (Hirvonen et al. 2013). Similarly, the third study measured CB1 availability during immediate abstinence (an average of 5 days from last drink) and again in early abstinence (1 month) using the PET tracer [^{18}F]MK-9470 in 26 alcohol-dependent males. Compared to controls there was an average global reduction in CB1 availability of 16% in alcoholics during immediate abstinence, which did not recover when scans were repeated during early abstinence (Ceccarini et al. 2014). The latter two studies are consistent with reduced CB1 receptors in postmortem tissue of alcoholics, and the persistent reductions in CB1 could be explained by a neuroadaptive downregulation, although this remains to be confirmed. Future studies should also confirm whether the findings extend to females.

21.2.7 Cholinergic System

Human imaging studies of the cholinergic system in AUD are limited. A single small SPECT study investigated the availability of β_2 subunit containing nicotinic acetylcholine receptors (β_2*-nAChR) in 11 heavy drinkers (>70 standard drinks per month) compared to controls. Scans were performed using the [^{123}I]5-I-A-85380 SPECT tracer, on average 2 days after the last alcoholic drink. The study failed to find the hypothesized decrease in β_2*-nAChR availability (i.e., there was no difference between heavy drinkers compared to controls) in several regions of interest including thalamus, striatum, cerebellum and parietal, frontal, anterior cingulate,

temporal, and occipital cortices (Esterlis et al. 2010). It is unclear if these findings will replicate in patients with a diagnosis of AUD, although a previous postmortem tissue study found no difference in [^{3}H]nicotine binding in the thalamus or frontal cortex of alcoholics compared to controls (Hellstrom-Lindahl et al. 1993).

21.2.8 Conclusion

While there have been several PET and SPECT imaging studies investigating neurotransmitter abnormalities in AUD, no single neurotransmitter system has been studied in depth, and there are limitations of the existing work. The majority of relevant studies to date have focused on the dopaminergic system and to a lesser extent on the serotoninergic, GABAergic, and opioidergic systems. There is consistent evidence that AUD is associated with decreased D2 receptor availability and D3 receptor function is beginning to be explored following the development of a D3-preferring radiotracer. Findings relating to other aspects of the dopaminergic system (e.g., DA synthesis, DAT) are less clear. There is some evidence of reduced activity in the serotonergic system in AUD, although findings of studies investigating SERT are mixed (most likely as a result of methodological differences between studies), and there has been limited consideration of other 5-HT receptors. Studies of the GABAergic system have been somewhat mixed but on balance so far are consistent with a decrease in receptor availability and blunted GABAergic signaling, although the specific roles of individual receptor subtypes remain to be delineated. Evidence of opioidergic involvement in AUD is sparse, although there is some evidence of a decrease in MOR availability and to a lesser extent also in KOR. Too few studies evaluating function in other neurotransmitter systems, such as the glutamate or endocannabinoid systems, are available to be able to draw conclusions, and findings within these systems are inconsistent. A major limitation of the existing studies in all neurotransmitter systems is that samples have largely been restricted to males and it is unclear whether findings will be consistent in other subpopulations (e.g., alcoholics with comorbid tobacco use disorder). In addition, many existing studies are limited by small sample sizes. Finally, in common with molecular imaging studies in other substance use disorders, it is unclear from comparisons of dependent populations with healthy controls whether observed alterations in neurotransmitter systems arise as a consequence of chronic alcohol exposure or if they represent a vulnerability to AUD.

21.3 Tobacco

21.3.1 Cholinergic System

Imaging studies investigating neurotransmission in smokers have predominantly focused on nicotinic acetylcholine receptors (nAChRs). PET studies have used the radiotracer 2-[^{18}F]fluoro-3-(2(S)azetidinylmethoxy pyridine (2-FA) to measure

nAChRs as it has high specificity for the $\alpha 4\beta_2$* subunit (α4β2*; the asterisk indicates the potential presence of other subunits) (Gallezot et al. 2005). Two small studies demonstrated higher levels of nAChRs in current smokers ($n = 6$ and $n = 7$) compared to nonsmokers, with the brainstem and cerebellum showing the greatest difference (Mukhin et al. 2008; Wüllner et al. 2008). Moreover, there seems to be a difference between menthol cigarette smokers ($n = 22$) and non-menthol smokers ($n = 41$), whereby those who smoked menthols had higher α4β2* density in the brainstem, cerebellum, and corpus callosum. However, consistent with the previous studies, smokers (both menthol and non-menthol smokers) had significantly higher α4β2* density than nonsmokers (Brody et al. 2013a). Furthermore, rates of nicotine metabolism in smokers affect nAChR availability. Slow metabolizers were found to have lower α4β2* nAChR availability in the thalamus than normal metabolizers (Dubroff et al. 2015). Research has investigated the effect of treatment for tobacco dependence on nAChR density. Smokers ($n = 48$) were scanned before and after 11 weeks treatment with cognitive behavioral therapy, bupropion, or placebo. It was found that after treatment, smokers had decreased α4β2* nAChR density in the prefrontal cortex, brainstem, and cerebellum. This study also showed that α4β2* nAChR density was correlated with the number of cigarettes smoked per day (Brody et al. 2013b). In addition, smokers with lower upregulation of α4β2* nAChRs have a better chance of quitting smoking after treatment than smokers with greater upregulation of α4β2* nAChRs (Brody et al. 2014). As expected, the amount smoked plays a role in nAChR occupancy, and smoking to satiety nearly saturates α4β2* nAChRs (i.e., 95% occupancy) (Brody et al. 2006a). Although nicotine is the primary constituent in cigarettes that affects nAChRs, smoking a denicotinized cigarette resulted in higher α4β2* receptor occupancy in the thalamus, brainstem, and cerebellum than not smoking, thus suggesting that there are other components in tobacco that bind to α4β2* nAChRs. However, smoking a low-nicotine cigarette increased binding to 79% as compared to 26% for the denicotinized cigarette, thereby confirming that nicotine is the major factor in nAChR occupancy (Brody et al. 2009a).

Research using SPECT has focused on the β2*-nAChR. The radiotracer [^{123}I]5-IA-85380 ([^{123}I]5-IA) is a nicotinic agonist that binds to β2*-nAChRs (Mukhin et al. 2000). One study demonstrated that 16 smokers had higher β2*-nAChR availability than nonsmokers in the striatum, cerebellum, and cortex in early abstinence (i.e., 4–9 days) (Staley et al. 2006). However, it was later shown that this difference was only present in males; female smokers did not have any significant differences in β2*-nAChR availability compared to female nonsmokers in any brain region (Cosgrove et al. 2012). Research has also investigated β2*-nAChRs at different stages of abstinence. Mamede et al. (2007) found that after quitting smoking for 4 h, β2*-nAChR availability decreased in smokers ($n = 16$) by 33.5% but increased by 25.7% after 10 days of abstinence and by 21 days of abstinence had decreased again to the same level as nonsmokers. Another study showed that β2*-nAChR availability in smokers ($n = 19$) compared to nonsmokers in the striatum, cerebellum, and cortex was not different after 1 day of abstinence, higher at 1 week of abstinence, and not different at 4 weeks or 6–12 weeks of abstinence (Cosgrove

et al. 2009). This is consistent with the study of Mamede et al. and demonstrates that normalization of β2*-nAChR availability persists to at least 12 weeks. The fact that there was a decrease in availability after 4 h and no difference after 1 day of abstinence may have been due to the fact that nicotine and its metabolites had not yet cleared from the brain, thus interfering with radiotracer binding.

21.3.2 Dopaminergic System

Nicotine leads to DA release in several known ways: it directly stimulates dopaminergic neurons in the ventral tegmental area (VTA) which release DA in the NAc; it activates nAChRs on dopaminergic terminals; and it increases DA release (Di Chiara and Imperato 1988; McGranahan et al. 2011). Dopaminergic activation by smoking is centered in the mesolimbic and mesocortical systems. DA binds to D1, D2, and D3 receptors, with binding in the dorsal striatum primarily to D2, binding in substantia nigra primarily to D3, and mixed binding in the globus pallidus (approximately 65% binding to D3) (Tziortzi et al. 2011). Previous studies have showed evidence that DA mediates the rewarding effect of nicotine (Brody et al. 2004; Corrigall et al. 1992; Le Foll et al. 2014) as well as withdrawal effects (Rada et al. 2001; Rahman et al. 2004). Changes in the DA reward pathway and related circuits are hypothesized to underlie the inability to refrain from smoking (Dani 2003). In the last few decades, many SPECT and PET studies have investigated aspects of the dopaminergic system in smokers including DA release, DA receptor availability, DAT availability, and DA synthesis. The most common radiotracer used in such studies is [^{11}C]raclopride, a D2/D3 receptor antagonist (Chukwueke and Le Foll 2019). All studies reviewed in this section are PET studies which used [^{11}C]raclopride, unless noted otherwise.

21.3.2.1 Dopamine Release

PET studies in smokers have evaluated DA release by measuring changes in binding potential after an acute challenge with either nicotine or another stimulant, such as amphetamine. By evaluating binding potential before and after treatment, changes in DA release can also give us insights into the mechanisms of pharmacological treatments for smoking cessation.

Striatal DA Release. Brody et al. demonstrated increased DA release in the ventral striatum of ten nicotine-dependent participants after smoking a cigarette (Brody et al. 2004), a finding which was confirmed in a double-blind randomized control trial which used nicotine gum (Takahashi et al. 2008). Another study in 13 regular smokers demonstrated an increase in DA in the dorsal striatum after smoking a cigarette during smoking cessation treatment (Weinstein et al. 2016). However, other studies have not shown any nicotine-induced DA release in regular smokers after smoking a cigarette ($n = 10$) (Barrett et al. 2004) or after administration of a nicotine nasal spray ($n = 10$) (Montgomery et al. 2007). By using denicotinized cigarettes, one may explore the impact of smoking cues on DA release. A small number of studies demonstrated that nicotine induces DA secretion in the ventral striatal but

denicotinized cigarettes do not (Brody et al. 2009b; Scott et al. 2007). Interestingly one study showed that while nicotinic cigarettes led to DA release from the whole striatum, denicotinized cigarettes led to a release only from the right dorsal striatum (Domino et al. 2013).

[^{11}C]-(+)-PHNO-is a D2/D3 agonist with a preference for D3 and is a sensitive probe for changes in DA preclinically and in humans (Girgis et al. 2011; Tziortzi et al. 2011). In cigarette smokers elevated DA release has been observed in the whole striatum, mostly in the limbic (i.e., ventral) striatum and the ventral pallidum—a region rich in D3 receptors (Di Ciano et al. 2018; Le Foll et al. 2014). In addition, 11 smokers treated with varenicline (a nicotinic partial agonist used for the treatment of tobacco use disorder) for 7 weeks had reduced binding in the dorsal caudate and reduced craving, suggesting varenicline-induced increase in DA release (Di Ciano et al. 2016).

Several studies have demonstrated correlations between ventral striatal DA release with reduced craving, improvement in withdrawal symptoms, improved mood (Brody et al. 2004, 2009b; Le Foll et al. 2014; Takahashi et al. 2008), and subjective measures of nicotine dependence severity (Scott et al. 2007; Takahashi et al. 2008). This suggests there may be a functional relationship between striatal DA release and clinical aspects of tobacco use disorder.

Extra-striatal DA Release. Cortical DA release has been assessed using [^{11}C]-FLB-457, a high-affinity D2/D3 receptor ligand with greatest sensitivity to changes in extra-striatal regions with low DA receptor density (Narendran et al. 2009). A study that examined cortical DA transmission among ten dependent tobacco smokers demonstrated increased release of DA in the cortex, primarily in the cingulate cortex (Wing et al. 2015). In addition, chronic guanfacine treatment (a noradrenergic α2a agonist that can be used for nicotine smoking cessation) reduced binding potential in the amygdala of 12 tobacco smokers, suggesting guanfacine-induced DA release. Reduced binding was correlated with clinical outcomes, specifically longer latency to smoke and fewer cigarettes smoked during a self-administration period (Sandiego et al. 2018).

Previous research has investigated several individual differences that may be associated with DA release in both striatal and non-striatal areas in smokers. Studies suggest there may be sex-specific alterations in DA release in smokers. For example, Cosgrove et al. reported that male smokers had rapid DA release in the ventral striatum, whereas women responded faster in a discrete subregion of the dorsal putamen (Cosgrove et al. 2014b). Another study which used the radiotracer [^{11}C]-FLB-57 reported that female smokers had significantly less amphetamine-induced DA release in the dorsolateral prefrontal cortex compared to both male smokers and female nonsmokers (Zakiniaeiz et al. 2019). These sex differences may reflect different incentives for smoking: men may smoke for the reinforcing drug effect, whereas women may smoke for mood regulation or due to cue reactivity. It also suggests that future treatments for smoking cessation could be tailored according to sex (Cosgrove et al. 2014b; Zakiniaeiz et al. 2019). There is also some evidence that genetic polymorphisms may influence DA release in smokers. For example, individuals who carry the minor G allele of the MOR (nine-repeat allele

of the DAT, Val/Val genotype of the catechol-*O*-methyltransferase enzyme, and seven-repeat allele of the D4 receptor), genotypes associated with low resting DA tone, have greater smoking-induced DA release (Brody et al. 2006b; Domino et al. 2013). Finally, while the prevalence of smoking is higher among individuals with a mental health disorder (John et al. 2004), it is unclear if this is associated with DA release. For example, in one study 10 smokers with a history of depression had greater DA release compared to 46 smokers with no history of depression (Brody et al. 2009c). On the other hand, another study showed that depressed smokers ($n = 8$) had blunted response to an amphetamine challenge compared to nonsmokers with ($n = 10$) and without ($n = 11$) depression (Busto et al. 2009). The conflicting findings may stem from methodological differences; therefore the impact of psychiatric comorbidities on DA release in smokers remains to be confirmed.

21.3.2.2 Dopamine Receptors

Dopamine D1 Receptors. Two studies using [^{11}C]-SCH-23390, a D1 receptor ligand, have reported reduced availability of D1 receptors in the striatum, most prominently the ventral striatum, in smokers ($n = 11$ and $n = 12$ smokers) (Dagher et al. 2001; Yasuno et al. 2007). One of the studies also reported restoration of D1 receptors among male ex-smokers following 6 months of abstinence and a negative correlation with both cue-induced craving and regional cerebral blood flow (Yasuno et al. 2007).

Dopamine D2/D3 Receptors. Studies of D2/D3 receptor availability have shown mixed results. Two earlier small studies ($n = 6$ smokers in each case) did not demonstrate any changes in DA receptor availability among smokers (e.g., Scott et al. 2007; Takahashi et al. 2008), and a meta-analysis reported no overall significant difference in D2/D3 receptor availability in smokers compared to nonsmokers (Ashok et al. 2019). However, recent studies have demonstrated different results. For example, 21 smokers had lower D2/D3 availability in the dorsal caudate and putamen compared to 26 nonsmokers (Albrecht et al. 2013a); 17 heavy smokers showed reduced D2/D3 availability in the dorsal striatum compared to 21 nonsmokers in a study using the radiotracer [^{18}F]-fallypride (Fehr et al. 2008); and smokers ($n = 8$) had lower D2/D3 availability in the dorsal striatum compared to nonsmokers ($n = 18$) and ex-smokers ($n = 10$) (Wiers et al. 2017). Interestingly, in the latter study, current smokers had reduced D2/D3 availability in the ventral striatum compared to nonsmokers but not ex-smokers, suggesting restoration of receptor availability in this region among ex-smokers.

The findings of studies investigating associations between D2/D3 receptor availability with variables related to tobacco consumption and severity of dependence have been inconsistent. In one study, lower striatal D2/D3 receptor availability was correlated with greater severity of nicotine dependence (Okita et al. 2016b), while another study showed no such correlation (Fehr et al. 2008), where sample sizes were similar ($n = 20$ and $n = 17$ smokers, respectively) and [^{18}F]fallypride was used as the PET radiotracer in both studies. Additionally, while low receptor availability was correlated with higher cigarette use and dependence severity in one of these studies (Okita et al. 2016b), in the other nicotine craving while smoking as usual

was positively correlated with D2/D3 receptor availability in the ventral striatum and orbitofrontal cortex and negatively correlated with D2/D3 receptor availability in the anterior cingulate and inferior temporal cortex (Fehr et al. 2008).

Individual differences associated with changes in receptor availability in smokers have been investigated. Using [^{11}C]-(+)-PHNO, Di Ciano et al. reported that during abstinence slow nicotine metabolizers had lower receptor availability in regions of the associative striatum and sensorimotor striatum (Di Ciano et al. 2018). Several studies have also reported sex differences. Brown et al. replicated the finding that male but not female smokers have significantly lower striatal D2/D3 receptor availability (Brown et al. 2012). In another study using [^{11}C]-FLB-457 as a radiotracer, Zakiniaeiz et al. reported significantly lower dorsolateral prefrontal cortex D2 availability in smokers compared to nonsmokers. This decrease was driven by lower availability in male smokers compared to male nonsmokers, while there was no significant difference between female smokers and female nonsmokers (Zakiniaeiz et al. 2019). Finally, in a study using [^{18}F]fallypride, Okita et al. demonstrated that female smokers have greater midbrain D2/D3 binding but male smokers do not. In addition, midbrain D2/D3 binding was negatively correlated with severity of dependence in female but not male smokers (Okita et al. 2016b). The decrease in striatal DA receptor availability in men but not in women might suggest that in men, due to increased striatal DA tone, there is downregulation of dopaminergic receptors. Conversely, in women there was a decrease in availability of D2/D3 in the midbrain, without any significant downregulation of D2/D3 availability in the striatum. The authors suggest that higher midbrain availability may mitigate against striatal downregulation (Okita et al. 2016b).

21.3.2.3 Dopamine Transporter

The DAT regulates synaptic DA levels (Cosgrove et al. 2010). An initial study which used [^{123}I]β-CIT to evaluate changes in DAT in smokers found no difference between 21 smokers and 21 nonsmokers in striatal DAT availability (Staley et al. 2001). However, more recent studies that used [^{99m}Tc]TRODAT found lower striatal DAT availability in 8 smokers compared to controls (Newberg et al. 2007) and decreased DAT availability in the caudate and putamen of 11 smokers compared to 11 controls (Yang et al. 2008). In the latter study, decreased DAT availability was correlated with nicotine dependence severity. Another PET study using [^{11}C]PE2I, a selective DAT radioligand, reported lower DAT availability in the ventral striatum, midbrain, middle cingulate, and thalamus of 14 tobacco smokers (Leroy et al. 2012). A recent meta-analysis concluded that studies to date are consistent with striatal DAT downregulation in smokers (Ashok et al. 2019).

21.3.2.4 Dopamine Synthesis

DA synthesis capacity can be assessed using[^{18}F]-fluoro-L-DOPA. One study reported significantly higher presynaptic DA activity in the dorsal striatum of 9 male smokers (Salokangas et al. 2000), while another study found no difference in the whole striatum of 15 smokers compared to controls (Bloomfield et al. 2014b). In a more recent study, it was found that DA synthesis capacity was lower in the

caudate nuclei (part of the dorsal striatum) of smokers (n = 30); however capacity was increased after 3 months in those who were able to abstain (n = 15), suggesting recovery of DA synthesis capacity following a period of abstinence (Rademacher et al. 2016).

21.3.2.5 Monoamine Oxidase

Preclinical and non-imaging studies in humans (e.g., measurement of monoamine oxidase in platelets or cerebrospinal fluid) suggest that monoamine oxidase is decreased in tobacco smokers (Berlin and Anthenelli 2001). Two early PET studies investigating monoamine oxidase in smokers found reduced MAOA (an average reduction of 28%) in the cortical areas, cingulate gyrus, thalamus, basal ganglia, and cerebellum of 15 current smokers compared to 16 nonsmokers using the radiotracer [^{11}C]clorgyline and reduced MAOB in current smokers (n = 8) compared to both nonsmokers (n = 8) and former smokers (n = 4) using the radiotracer [^{11}C]L-deprenyl-D2 (Fowler et al. 1996, 1998). Similarly, a later study using the radiotracer [^{11}C]befloxatone found MAOA was reduced by 60% in the cingulate gyrus, prefrontal cortex, occipital cortex, and cerebellum and by 40% in the caudate nucleus and putamen of seven current smokers compared to six nonsmokers (Leroy et al. 2009). Most recently, Bacher et al. (2011) used the PET tracer [^{11}C]harmine to measure MAOA in heavy smokers during acute withdrawal. In contrast to the previous studies in which participants were permitted to smoke as normal immediately prior to the PET scans, smokers in this study were required to abstain for 8 h prior to the scan. Compared to controls MAOA was increased by ~25% in the prefrontal and anterior cingulate cortex in smokers during acute withdrawal (Bacher et al. 2011). This suggests that inhibition of MAOA by tobacco smoking may be reversed relatively rapidly. In addition, since MAOA metabolizes 5-HT as well as DA, the increase in MAOA during acute withdrawal may provide an explanation for the low mood frequently observed following withdrawal from tobacco smoking.

21.3.3 GABAergic System

To our knowledge, only one PET study investigating $GABA_A$ receptor availability in smokers compared to nonsmokers has been conducted. Volunteers with a history of smoking (either current smokers or individuals who previously smoked five cigarettes per day for at least 6 months; n = 8) and nonsmokers (n = 12) were subjected to [^{11}C]Ro15-4513 PET scans. Those with a history of smoking had increased total $GABA_A$ receptor availability compared to nonsmokers. Significant increases were found in the presubgenual cingulate and parahippocampal gyrus, and non-significant trends were found in the insula, NAc, and subgenual cingulate. In addition, ex-smokers (smokers who had not smoked in the past 6 months) compared to nonsmokers were found to have higher total $GABA_A$ availability in the insula, parahippocampal gyrus, presubgenual cingulate, amygdala, NAc, hippocampus, subgenual cingulate, and anterior cingulate. This suggests altered receptor availability persists even after quitting smoking or that it may be a marker for smoking

predisposition. When investigating by receptor subtypes, availability of the α1 subtype was significantly lower in ex-smokers compared to nonsmokers in the NAc and presubgenual cingulate, whereas availability of the α5 subtype was significantly higher in the amygdala, anterior cingulate gyrus, NAc, and presubgenual cingulate (Stokes et al. 2013). Therefore, although total $GABA_A$ receptor availability appeared to be increased in smokers, there may be important differences between receptor subtypes which require further clarification in future studies.

Two SPECT studies using [^{123}I]iomazenil found no difference in $GABA_A$ receptor availability between smokers ($n = 15$ and $n = 26$) and nonsmokers, nor in smokers after smoking abstinence (Esterlis et al. 2009, 2013). There may be several reasons for the discrepancy between these findings and the previous PET study. For instance, the PET study of Stokes et al. looked at limbic $GABA_A$ availability and included only male participants, whereas the SPECT studies by Esterlis and colleagues looked at cortical $GABA_A$ availability and included both men and women. Furthermore, the difference in resolution between PET and SPECT, as well as the differences in receptor affinity between the two tracers, could play a role in the conflicting findings.

21.3.4 Serotonergic System

The SERT has been investigated in smokers using PET and SPECT imaging. In one study the SERT radiotracer [^{11} C]DASB was given to 116 participants (52 smokers and 64 nonsmokers) along with a PET scan. No difference was found in SERT availability in the midbrain between smokers and nonsmokers (Smolka et al. 2019). Similarly, a study using [^{123}I]ADAM and SPECT found no difference in SERT availability in the midbrain, basal ganglia, or thalamus between smokers ($n = 16$ males) and nonsmokers ($n = 32$ males) (Zhao et al. 2016). In accordance with the previous studies, one study using [^{123}I]β-CIT, a SPECT radiotracer for both DAT and SERT, found no difference between smokers ($n = 21$) and nonsmokers ($n = 21$) in SERT availability in the diencephalon (Staley et al. 2001). Although this area has not been widely studied, the findings to date suggest that SERT is not altered in smokers.

21.3.5 Opioidergic System

Studies in smokers with regard to the opioidergic system have focused on MOR. PET studies have used the radiotracer [^{11}C]-carfentanil, a MOR agonist. Researchers found that smokers ($n = 6$ males) had significantly lower binding potential of MOR in the rostral anterior cingulate, thalamus, amygdala, and NAc compared to nonsmokers ($n = 6$ males). Although there were significant differences in all of these regions, the percent reduction varied between regions, with the lowest reduction in the rostral anterior cingulate (13% reduction) and highest in the thalamus (42% reduction) (Scott et al. 2007). Subsequently, the same group of researchers reported

similar findings in a larger sample (Nuechterlein et al. 2016). Smokers (n = 24 males) after an overnight abstinence were shown to have significantly lower binding potential than nonsmokers (n = 22 male) in the right basal ganglia (there was a trend toward significance in the left basal ganglia) and thalamus. In addition, binding potential in the left and right basal ganglia was negatively correlated with FTND scores in smokers (Nuechterlein et al. 2016). On the other hand, some studies have found no differences in MOR binding between smokers (n = 10 and n = 22) and nonsmokers (Kuwabara et al. 2014; Ray et al. 2011). The discrepancy may be due to major differences in the study designs. For instance, Ray et al. and Kuwabara et al. included male and female participants, whereas Scott et al. and Nuechterlein et al. only included males. This could be important since under resting conditions, males and females have been shown to have variable MOR binding potentials (Zubieta et al. 1999). Also, the baseline measure in the studies of Ray et al. and Kuwabara et al. may have been confounded by the use of an intervention using a denicotinized cigarette, although they did find that in the bilateral superior temporal cortices, MOR availability was negatively correlated with FTND scores.

21.3.6 Conclusion

In conclusion, research on abnormalities of neurotransmission in smokers has mainly pertained to nicotinic acetylcholine receptors and to the dopaminergic system. There is evidence supporting increased DA release in smokers, accompanied by downregulation of DA receptors and transporters. There are some inconsistencies in findings among studies of the dopaminergic system, although these may be attributable to methodological differences such as the severity of tobacco use disorder and time between acute challenge (i.e., nicotine exposure) and scan acquisition. Alterations in the dopaminergic system in females and smokers with psychiatric comorbidities remain to be confirmed. There seems to be consensus that nAChRs are upregulated in smokers. Although research is limited on the serotonergic system, smokers seem to be no different than nonsmokers with regard to SERT availability. However, evidence to date on abnormalities in $GABA_A$ receptors and MOR availability in smokers is mixed. The majority of studies investigating alterations in neurotransmitter systems in chronic tobacco users have a number of limitations such as small sample sizes, increased focus on male participants, and variability in study procedures; thus there is a need for further research.

21.4 Cannabis

21.4.1 Dopaminergic System

Cannabinoid stimulation of the CB1 receptor affects multiple neurotransmitter systems including the dopaminergic system, and acute administration of delta-9-tetrahydrocannabidiol (THC; the main psychoactive ingredient of cannabis) leads to

firing of mesolimbic DA neurons and increased striatal DA. Conversely, chronic exposure to cannabis has been associated with decreased dopaminergic activity in preclinical studies. For example, in rodents early life and adolescent exposure to THC has been shown to result in blunted dopaminergic response to natural reinforcers and CB1 receptor agonists in adulthood (Bloomfield et al. 2016; Scherma et al. 2016). To date human molecular imaging studies of the dopaminergic system in chronic cannabis users have investigated availability of striatal D2/3 receptors and availability of the DAT and DA synthesis. In addition, changes in DA signaling have been investigated in studies combining PET imaging with a pharmacological or stress challenge.

21.4.1.1 Dopamine D2/D3 Receptors

Several PET studies have investigated the availability of striatal D2/D3 receptors in chronic cannabis users compared to controls using the radiotracer [^{11}C]raclopride. One small study found no difference in striatal D2/D3 receptor availability in six young male chronic cannabis users after 12 weeks of abstinence compared to controls (Sevy et al. 2008). This was confirmed in 2 later studies, the first showing no difference in D2/D3 receptor availability in the caudate, putamen, or ventral striatum of 16 mild to moderately cannabis-dependent individuals after a few weeks of abstinence (Urban et al. 2012), and the second showing no alteration in D2/D3 receptor availability in any striatal subdivision in 10 individuals with a history of cannabis use with an average duration of abstinence of 17 months (Stokes et al. 2012). The latter study also found no correlation between lifetime frequency of cannabis use and D2/D3 receptor availability. Studies of chronic cannabis users (n = 18 and n = 24) during active use have also failed to demonstrate changes in D2/D3 receptor availability compared to controls (Albrecht et al. 2013b; Volkow et al. 2014), although one of these studies did report an inverse relationship between cannabis consumption and striatal D2/D3 availability among cannabis users (Albrecht et al. 2013b). These findings are consistent with a [^{11}C]raclopride PET study in nonhuman primates that showed no difference in D2/D3 availability between rhesus monkeys chronically exposed to THC versus drug-naïve animals (John et al. 2018). Thus, studies consistently show that chronic cannabis use is not associated with alterations in D2/D3 receptor availability during abstinence. D2/D3 receptor availability also appears to be unaltered during active use, suggesting that the lack of effect in abstinent samples is not due to normalization of DA function after cessation of cannabis use. However, the majority of samples included in the studies conducted to date are limited to male cannabis users with only mild dependence, and it is unclear whether alterations in receptor availability may be observed in females or in cannabis users with more severe dependence.

21.4.1.2 Dopamine Transporter

A single human PET study has investigated availability of the DAT in striatal and extra-striatal regions in individuals with cannabis addiction. This study compared 11 healthy nonsmokers with 14 tobacco-dependent and 13 tobacco- and cannabis-dependent individuals using the selective DAT radiotracer [^{11}C]PE2I. DAT

availability was 20% lower in the dorsal striatum and 15% to 30% lower in ventral striatum, midbrain, middle cingulate, and thalamus of current drug users compared to controls. In addition, DAT availability was modestly lower (although this effect did not reach significance) in all regions of interest in the tobacco- and cannabis-dependent group compared to the tobacco-dependent only group (Leroy et al. 2012). A major limitation of this study is that since all drug users were tobacco dependent, it is not possible to isolate the effects of cannabis dependence, and it is unclear to what extent the observed effects reflect tobacco dependence. Further work is therefore needed to elucidate the effect of cannabis dependence on DAT availability.

21.4.1.3 Dopamine Synthesis

The PET tracer 3,4-dihydroxy-6-[(18)F]-fluoro-L-phenylalanine ([^{18}F]-DOPA) has been used to investigate presynaptic DA function in recent cannabis users (average time since last use ~14 h). Reduced DA synthesis capacity was observed in the whole striatum, and in the associative and limbic striatal subdivisions, of 19 cannabis users compared to controls with the largest effect observed in the right putamen. Additionally, DA synthesis capacity was negatively associated with cannabis use and positively associated with age of onset of cannabis use (Bloomfield et al. 2014a). While this study appears to provide support for a reduction in DA synthesis capacity, particularly among the heaviest cannabis users, it is possible that comorbid tobacco and other substance use could explain the findings. Furthermore although DA synthesis capacity was not associated with cannabis-induced psychotic symptoms, since the sample consisted of cannabis users who experienced psychotic-like symptoms when they consumed cannabis, it is also unclear if the findings will extend to those who do not experience psychotic symptoms. Research is also needed to confirm if these findings will persist later into abstinence.

21.4.1.4 Dopamine Release

Molecular imaging techniques combined with a pharmacological or stress challenge (to increase DA release) have been used to assess sensitivity to dopaminergic stimulation in cannabis users, although findings have been mixed. One study conducted in early abstinence using the D3 receptor preferring radiotracer [^{11}C]-(+)-PHNO found no difference in stress-induced DA release in 13 cannabis-dependent individuals compared to controls (Mizrahi et al. 2013). Of two studies using an amphetamine challenge in recently abstinent cannabis users, the first found no difference in striatal DA release in any region of interest including the ventral striatum in 16 cannabis users with mild to moderate dependence compared to matched controls, using the PET tracer [^{11}C]raclopride. However, younger age of cannabis use onset was associated with decreased DA release (Urban et al. 2012). In contrast the second study found reduced DA release in the whole striatum, associative and sensorimotor striatal subdivisions, and the pallidus using the PET tracer [^{11}C]-(+)-PHNO in 11 severely dependent cannabis users. Lower DA release in the associative striatum was correlated with attentional impulsivity and negative symptoms related to schizophrenia (van de Giessen et al. 2017). Finally, a further study using methylphenidate challenge and [^{11}C]raclopride PET scans found blunted dopaminergic response in 24 chronic cannabis users, including attenuated physiological responses

and subjective drug effects, as well as decreases in distribution volumes of [^{11}C]raclopride in the striatum. This study also reported an inverse correlation between DA responses in the ventral striatum with severity of cannabis dependence and craving (Volkow et al. 2014). Thus, there is some evidence of attenuated responses to dopaminergic stimulation in cannabis users. Decreased brain reactivity to DA stimulation might contribute to negative emotionality and addictive behaviors. However, these studies provide only indirect evidence of altered dopaminergic function in cannabis users and since findings are mixed should be interpreted with caution.

21.4.2 Endocannabinoid System

21.4.2.1 CB1 Receptors

Preclinical studies show that chronic administration of THC or CB1 receptor agonists leads to decreased CB1 receptor availability (e.g., for a review see Tanda and Goldberg (2003)). It is thought that downregulation of CB1 may explain the development of tolerance to cannabis and desensitization to its rewarding effects. Downregulation of CB1 in humans has been demonstrated in a small postmortem study that found decreased CB1 in the mesencephalon, basal ganglia, and hippocampus of long-term cannabis users compared to controls (Villares 2007). In addition, impairments in motor learning have been observed in chronic cannabis users, similar to deficits observed in mice strains lacking the CB1 receptor, indirectly suggesting that chronic cannabis use may downregulate CB1 (Skosnik et al. 2008).

To date three human PET studies have been conducted to directly investigate availability of CB1 in chronic cannabis users. One study using the PET tracer [^{18}F]MK-9470 found global decreases in CB1 availability in ten chronic cannabis users after a few days of abstinence. Reductions of approximately 11–13% compared to controls were reported in regions of interest including the temporal lobe, anterior and posterior cingulate cortex, and NAc (Ceccarini et al. 2015). In another study [^{18}F]FMPEP-d2 was used to estimate CB1 receptor density before and after abstinence in 30 chronic cannabis users compared to controls. This study showed initially decreased CB1 availability in cortical regions in cannabis users, with a return to normal levels after 4 weeks of continuously monitored abstinence. There was also an inverse association between CB1 receptor density and years of cannabis smoking (Hirvonen et al. 2012). Rapid normalization of CB1 availability was also observed by D'Souza et al. (2016) using the tracer [^{11}C]OMAR. Cannabis-dependent males (n = 11) underwent PET scans before abstinence and again after 2 days and 28 days of monitored abstinence. Reductions in CB1 availability were observed before abstinence in multiple brain regions in cannabis users compared to controls, with an average 15% global reduction. However, no reductions in CB1 availability were observed after 2 days or 28 days of abstinence, and CB1 availability was negatively associated with withdrawal symptoms (D'Souza et al. 2016). The findings of these studies are consistent with downregulation of brain CB1 receptors as a result of cannabis exposure in cannabis use disorder (CUD). Correlations between decreased CB1 receptor availability with greater cannabis use and more severe withdrawal symptoms suggest that downregulation of CB1 receptors may represent

a mechanism by which cannabis dependence is promoted. In addition, rapid normalization of CB1 availability following abstinence suggests that the effect of chronic cannabis exposure on CB1 is reversible.

21.4.2.2 Fatty Acid Amide Hydrolase

The endogenous cannabinoid anandamide has been shown to be downregulated in rodents following repeated THC administration (e.g., Di Marzo et al. (2000)), and in humans lower levels of anandamide have been observed in the cerebrospinal fluid of regular cannabis users (Morgan et al. 2013). Anandamide is metabolized by the fatty acid amide hydrolase (FAAH) enzyme, and since the recent development of the selective [^{11}C]CURB PET tracer, it is possible to directly assess in vivo levels of FAAH in humans. In a PET study that compared ten chronic, frequent cannabis users after overnight abstinence with healthy controls, global FAAH binding was 14–20% lower in cannabis users. Low FAAH binding was also correlated with increased blood and urine THC metabolites and with higher trait impulsiveness (Boileau et al. 2016). Since previous work suggests anandamide levels are lower in cannabis users, Boileau and colleagues hypothesized that compensatory increases in FAAH activity might be expected in this group, and so the study findings did not support this hypothesis. It is possible that chronic cannabis exposure may suppress anandamide synthesis which would also result in decreased FAAH, although the findings remain to be confirmed and the mechanism linking reduced anandamide with changes in FAAH activity is unclear.

21.4.3 Cholinergic System

Preclinical studies suggest that the cholinergic system plays an important role in cannabis-related impairments in cognitive function including attention, memory, and executive function that may not be fully reversible and may interfere with successful CUD treatment. To date no molecular imaging studies have specifically addressed cholinergic function in CUD, although a single PET study has investigated the availability of α4β2* subunit containing nicotinic acetylcholine receptors (nAChRs) in male smokers with heavy cannabis use, using the radiotracer 2-FA (Brody et al. 2016). This study showed that 18 smokers who were also heavy cannabis users had higher α4β2* nAChR availability in the brainstem and prefrontal cortex compared to smokers who did not use cannabis. While the findings of this study hint at elevated cholinergic activity in cannabis users, the increase in nAChRs may be explained by increased tobacco smoking in the group who were also cannabis users. Further work is needed to investigate alterations in cholinergic activity in chronic cannabis users.

21.4.4 Conclusion

The majority of PET and SPECT imaging studies investigating neurotransmitter abnormalities in CUD have focused on the dopaminergic and endocannabinoid

systems. There is little evidence of alteration in dopaminergic activity in chronic cannabis users, in contrast to other substance addictions, such as alcohol, cocaine, and heroin, in which neuroadaptive reductions in DA function are consistently reported. In particular studies suggest that D2/D3 receptor, and possibly DAT, availability is unaltered in CUD. It is unclear if there is a decrease in DA synthesis in CUD due to the potential confounding effect of other substance dependence in the single study conducted to date. Furthermore studies of DA signaling have provided mixed results, and interpretation of these studies is additionally limited by methodological heterogeneity. Further work is required to determine if blunting of the dopaminergic system is not a feature of CUD or if characteristics of the studies conducted to date may explain the observed lack of effect. Studies to date suggest that CUD is more likely to be mediated by changes in the endocannabinoid system, with converging preclinical, postmortem, and human imaging evidence showing decreases in CB1 receptor availability. Further work is required to confirm the role of endogenous cannabinoid signaling in CUD. In common with PET imaging studies in other substance use disorders, major limitations of studies in the dopaminergic and endocannabinoid systems in CUD are that they have largely been restricted to males and many have small sample sizes.

21.5 Opioids

21.5.1 Dopaminergic System

21.5.1.1 Dopamine D2/D3 Receptors

Lower D2/D3 receptor availability in opiate dependence compared to healthy controls has been found in PET studies with the radiotracer [^{11}C]raclopride (Martinez et al. 2012; Wang et al. 1997b) and in a SPECT study with the radiotracer [^{123}I]IBZM (Zijlstra et al. 2008). For instance, Martinez and colleagues found reduced [^{11}C]raclopride binding in the limbic striatum, the anterior and posterior caudate, as well as the anterior and posterior putamen of 16 recently abstinent (~2 weeks) heroin-dependent participants compared to 16 healthy controls (Martinez et al. 2012). Studies investigating D2/D3 availability have also assessed the impact of acute drug challenge on receptor availability with the difference in binding between pre- and post-drug challenge indicating drug-induced DA release. There is consensus that opiate use disorder (OUD) is associated with reduced DA release in response to acute opioid challenge. For instance, striatal [^{11}C]raclopride binding in opioid-dependent individuals (n = 14 and n = 10) was unaffected by intravenous diamorphine or subcutaneous hydromorphone, despite marked subjective increases in ratings of "intoxication," "rush," and "high" (Daglish et al. 2008; Watson et al. 2014). Moreover, there were no significant correlations between subjective ratings of "high" and radiotracer binding in the striatum, and the expectation of diamorphine administration also failed to elicit an increase in DA release (Watson et al. 2014). This hypodopaminergic response to acute drug challenge is not restricted to opioids; Martinez and colleagues assessed change in [^{11}C]raclopride binding following acute challenge to the stimulant methylphenidate and found reduced DA

release following stimulant administration in individuals with heroin dependence compared to healthy controls (Martinez et al. 2012).

Overall, findings that OUD is associated with both reduced D2/D3 availability and lower DA release is consistent with the DA hypothesis of addiction (Melis et al. 2005) that implicates a long-lasting hypodopaminergic state throughout the addiction cycle. However, hyperdopaminergic states in the presence of drug cues are thought to drive further drug taking (Leyton and Vezina 2014). In line with this, the SPECT study by Zijlstra and colleagues found changes in radiotracer binding indicative of increased DA release in the right putamen following drug cue exposure in an abstinent opiate-dependent group but not in age-matched healthy controls (Zijlstra et al. 2008). Differences in DA release following cue but not drug exposure supports the idea that drug cues are powerful modulators of neural and behavioral responses in OUD (L. Yang et al. 2019; Yang et al. 2009) and that these responses do not desensitize with extended use, unlike responses to drug exposure itself that may drive dose escalation.

21.5.1.2 Dopamine Transporter

Most studies assessing DAT availability in OUD have used the SPECT radiotracer [^{99m}Tc]TRODAT-1. These studies have found significant striatal reductions in DAT availability in individuals with opiate dependence compared to healthy controls (Hou et al. 2011; Liang et al. 2016, 2017; Liu et al. 2013; Xu et al. 2015; Yeh et al. 2012; Yuan et al. 2017). For example, one of the largest studies found more than 30% reduction in DAT availability in the left and right striatum of 64 heroin users undergoing long-term abstinence treatment compared to 20 healthy controls (Xu et al. 2015). PET studies have also confirmed a reduction in DAT availability in heroin dependence. For instance, one study found a 15.7–17.6% reduction in striatal DAT availability in 20 heroin-dependent participants (after ~2 weeks abstinence) compared to 10 healthy controls using [^{18}F]-FECNT as the radiotracer (Xu et al. 2017). However, not all studies have found significant reductions. One SPECT study using [^{123}I]β-CIT found similar striatal DAT availability in eight currently using heroin users and eight healthy controls (Cosgrove et al. 2010). In another SPECT study using [^{123}I]FP-CIT, a non-significant reduction in striatal DAT availability was found in ten heroin users (abstinent for ~2 weeks) compared to controls, although this difference did become significant once those with positive urine screens for opioids and cocaine were removed from the analysis (Zaaijer et al. 2015). DAT reduction in OUD appears to be a long-lasting abnormality but with some evidence of recovery in DAT availability with protracted abstinence. For instance, one PET study comparing heroin users with prolonged abstinence, methadone-maintained heroin users, and healthy controls showed that both heroin users with prolonged abstinence and those receiving substitution therapy had reduced DAT uptake function in the caudate compared to healthy controls. However, methadone maintenance was also associated with lower DAT uptake function in the putamen compared to both healthy controls and those with prolonged abstinence (Shi et al. 2008). Longitudinal SPECT studies have somewhat confirmed a delayed recovery interpretation. DAT availability remained low in former heroin users with

6 and 12 months of abstinence compared to healthy controls (Liu et al. 2013; Xu et al. 2015). However, at 12 months of abstinence, there was an upregulation of DAT, albeit not back to the level of healthy controls, suggesting that normalization of DAT may occur with extended abstinence (Xu et al. 2015).

Genetic, structural, and functional imaging studies provide evidence that indirectly supports the molecular imaging studies reported here showing a reduction of DAT in OUD. For instance, the degree of functional connectivity between frontal, parietal, and striatal networks varies as a function of DAT genotype (Gordon et al. 2012). Specifically, Gordon and colleagues found that 10/10 homozygotes for the variable number of tandem repeats in the 3′-untranslated region of the DAT1 gene show greater functional connectivity than 9/10 heterozygotes, during a working memory task. Importantly, ten-repeat alleles are associated with greater striatal DAT expression in vivo compared to nine-repeat alleles (Fuke et al. 2001). This suggests that reduced DAT, as seen in OUD, may be related to dysfunctional frontostriatal connectivity. Interestingly, long-term prescription opioid use has been shown to be associated with both structural and functional abnormalities in frontostriatal circuitry that may contribute to the severity of prescription opioid misuse (McConnell et al. 2019).

21.5.2 Opioidergic System

Studies that have assessed opioidergic receptor availability in OUD compared to healthy controls have used either non-selective radiotracers or those that label MOR. In one PET study with a non-selective radiotracer, [^{11}C]diprenorphine, eight opioid-dependent participants stable on methadone substitution therapy and eight healthy controls were compared. This study found no significant group differences in [^{11}C]diprenorphine binding and no relationship between methadone dose and MOR occupancy (Melichar et al. 2005). However, a further PET study with a non-selective MOR and KOR radiotracer, [^{18}F]cyclofoxy, in 14 former heroin users stable on methadone substitution therapy and 14 healthy controls did find group- and dose-related associations with [^{18}F]cyclofoxy binding (Kling et al. 2000). Specifically, Kling and colleagues found that [^{18}F]cyclofoxy binding was lower by 19–32% in the amygdala, anterior cingulate cortex, putamen, and thalamus of former heroin users 22 h after their last dose of methadone compared to healthy controls. Further, the degree to which binding was lower in the caudate and putamen of the former user group was related to plasma levels of methadone, suggesting that lower binding in the former users was driven by receptor occupancy of their substitution therapy rather than an innate group difference in receptor availability. In another PET study, binding of the MOR-selective radiotracer, [^{11}C]carfentanil, in three heroin-dependent participants while maintained on two different doses of buprenorphine (2 and 16 mg) and on placebo following detoxification was compared to healthy matched controls. In this study, buprenorphine dose-dependently reduced MOR availability relative to placebo. In addition, heroin users in the placebo condition (i.e., during withdrawal) had greater MOR binding potential in the

inferofrontal and anterior cingulate cortices compared to healthy controls (Zubieta et al. 2000). Increased MOR binding potential in heroin users compared to healthy controls is concordant with the finding that opioid receptor availability positively correlates with reward dependence in healthy males, suggesting opioid receptor density is associated with personality traits related to addiction vulnerability (Schreckenberger et al. 2008).

Alterations in KOR still warrant evaluation in vivo in human opioid users compared to controls. To our knowledge no studies with a KOR-selective tracer have been conducted to date, despite KOR involvement in addictive processes (Karkhanis et al. 2017) and initial preclinical success in the development of a radiotracer (Poisnel et al. 2008).

21.5.3 Serotonergic System

SPECT studies have assessed the availability of SERT in OUD. One study in eight currently using heroin-dependent participants and eight healthy controls using [^{123}I]β-CIT, a radiotracer containing a cocaine derivative that binds with high affinity to SERT in the diencephalon and brainstem as well as to striatal DAT, found a non-significant reduction in SERT availability in heroin users (Cosgrove et al. 2010). However, significantly lower SERT availability was found in a much larger SPECT study, using [^{123}I]ADAM to assess midbrain SERT, in 32 opioid-dependent users (either undergoing methadone-free abstinence or very low-dose methadone) compared to 32 healthy controls (Yeh et al. 2012). However, in this study, SERT availability tended to be higher in methadone-free versus low-dose methadone users. The finding of lower SERT availability in opioid users is corroborated by a meta-analysis of genetic evidence finding that the S allele of the common SERT gene polymorphism (5-HTTLPR; rs25531), conferring a reduced SERT transcription rate and resulting in less efficient 5-HT reuptake and decreased expression of SERT, is associated with heroin dependence (Lin and Wu 2016).

Future research into the serotonergic system in vivo in human opioid users compared to controls could explore the involvement of 5-HT receptors. For example, preclinical SPECT evidence suggests that canine cerebral 5-HT$_{2A}$ receptors are reduced with prolonged morphine exposure (Adriaens et al. 2014). Human research is needed given that these receptors may regulate impulsive action (Fink et al. 2015; Winstanley et al. 2004) and that impulsivity is associated with misuse of prescription opioids (Marino et al. 2013; Vest et al. 2016).

21.5.4 GABAergic System

A single PET study using [^{11}C]Ro15-4513 has investigated differences in 12 males with OUD using opiate maintenance therapy compared with 13 healthy, matched controls (Lingford-Hughes et al. 2016). This radiotracer contains the atypical benzodiazepine derivative, Ro15-4513, thought to have greatest affinity for GABRA5

(Momosaki et al. 2010). Indeed, [^{11}C]Ro15-4513 binding in this PET study was significantly reduced in the NAc in OUD, with spectral analysis indicating that the reduction in binding was associated with reduced GABRA5 and not those receptors containing α1 subunits (Lingford-Hughes et al. 2016). While the relative contribution of $GABA_A$ receptor subunits to addiction is still being uncovered, $GABA_A$ receptors have been implicated in addiction because of the role they play in motivational learning and striatal inhibition (Stephens et al. 2017). Further research is required to elucidate the relevance of GABRA5 to opioid addiction. However, studies with ligands selective for GABRA5 suggest these receptors may have a role in drug self-administration but that this effect may be independent of drug reinforcement (Ruedi-Bettschen et al. 2013; Stephens et al. 2005). Furthermore, they may also have a role in the expression of stress-induced behaviors (Piantadosi et al. 2016) although their role, if any, in stress-induced self-administration and relapse remains to be determined.

In the future, development of specific radiotracers and molecular imaging of alternative $GABA_A$ receptor subunits is required, given the potential roles that these have in addiction (Stephens et al. 2017). In addition, $GABA_B$ receptors also have important roles in the control of neurotransmitter release, reward processes, and addiction (Tyacke et al. 2010; Vlachou and Markou 2010), but molecular imaging studies are currently lacking in OUD.

21.5.5 Conclusion

There have been few molecular imaging studies assessing neurotransmitter abnormalities in OUD. Nevertheless, there have been some consistent findings, most notably in the dopaminergic system. Studies find reductions in the DAT and in D2/D3 availability as well as a hypodopaminergic response to drug exposure which supports the DA hypothesis of addiction (Melis et al. 2005). While it is clear that OUD is a complex disorder involving abnormalities in multiple components of several neurotransmitter systems, further work is required before consensus can be reached regarding the specifics of these abnormalities. In addition, there are still neurotransmitter systems that have yet to be probed with PET or SPECT in OUD. For example, a magnetic resonance spectroscopy study found elevated glutamate levels in the NAc of prescription opioid addicts relative to healthy controls (Liu et al. 2017), but to our knowledge, no PET or SPECT studies have assessed the glutamatergic system in OUD. There is also evidence of an interaction between the opioidergic and endocannabinoid system in reward processing and addiction (Befort 2015), and the advent of the first PET tracer for imaging FAAH (Wilson et al. 2011), an important enzyme regulating endocannabinoid tone, will allow studies of this neurotransmitter system to be conducted in OUD.

There are several limitations of the PET and SPECT studies assessing neurotransmitter abnormalities in OUD. There is a high degree of heterogeneity between study populations with regard to drug-taking history and current treatment (nevertheless this review highlights some consistent findings). In addition, studies

are limited by small sample sizes meaning that they are not adequately powered to allow for meaningful evaluation of factors that may influence radiotracer binding such as age, gender, duration of opioid use or abstinence, polysubstance use, or psychiatric comorbidity. For instance, age and gender influence binding of [^{11}C]carfentanil to MOR (Zubieta et al. 1999) and age may affect uptake of the DAT radiotracer [^{11}C]CFT (Kawamura et al. 2003). This is an important consideration given age differences between cases and controls in a study assessing DAT uptake function (Shi et al. 2008). Another limitation is the over-representation of male participants. This may be problematic in terms of generalization of findings. While males are more likely to die from prescription overdoses than females, females have a higher prevalence of prescription opioid use, and longitudinal data suggests that opioid overdoses have increased more in females compared to males (Serdarevic et al. 2017; Unick et al. 2013). Finally, molecular imaging findings in OUD are correlational and so cannot provide evidence as to whether abnormalities found in neurotransmitter systems are a cause or a consequence of OUD. Nevertheless, an increased understanding of such abnormalities offers the prospect of developing evidence based biomarkers and therapeutics targeting these systems.

21.6 Stimulants

21.6.1 Dopaminergic System

The vast majority of imaging studies of psychostimulants have focused on the DA system. This is not surprising given the early predominance of DA theories of reward (Wise 1978) that colored research in the addictions for decades. Further, the dependence-producing properties of psychostimulants such as cocaine and methamphetamine are believed to be due to their ability to increase DA levels in key terminal regions such as the NAc (Di Chiara et al. 1991). Cocaine, amphetamine, and methamphetamine all block DAT, thereby increasing DA levels, while amphetamines also promote an increase in DA release in these areas (for a review see dela Pena et al. (2015)).

The effects of repeated psychostimulants on the brain have been studied within a framework of either sensitized changes in DA or tolerance to effects of drugs over time. Evidence from the preclinical literature provides strong support for the development of a sensitized response of the DA system to psychostimulants over time (Robinson and Berridge 1993). To achieve sensitization, psychostimulants are generally administered to animals on an intermittent schedule followed by a period of withdrawal, when the sensitized response, typically locomotion, is evidenced following a challenge with the psychostimulant. By comparison, long-term, chronic, and repeated administration over many days seems to lead to tolerance of DA (Robinson and Becker 1986). Thus, the pattern of use and duration of withdrawal is important in determining whether, at least in animals, tolerance or sensitization is observed. In this regard, studies of the long-term effects of psychostimulants in humans generally

recruit participants who meet DSM criteria for dependence. Thus, their pattern of use is more likely to be consistent with the development of tolerance. A recent meta-analysis revealed that DAT availability was higher in cocaine addicts but lower in amphetamine addicts. This suggests that, in cocaine users, levels of DA are reduced, consistent with tolerance (Proebstl et al. 2019). On the surface, this latter finding seems to point to an increase in DA levels in methamphetamine users; however, it should be considered that chronic use of amphetamines has been shown to lead to neurotoxic changes in levels of DAT. In the same meta-analysis, Proebstl et al. also concluded that the D2 receptor was decreased in people dependent on either cocaine or amphetamine. Important questions still remain about changes in neurotransmitter systems with repeated use of psychostimulants. First, most studies to date (reviewed below) tested participants at about 2 weeks of withdrawal, and it is unclear if changes in the transporter and the DA system in general are persistent for many months or if they appear early in withdrawal. Theories about tri-phasic changes (Gawin and Kleber 1986) in abstinence symptoms influenced early studies, and it remains to be determined whether changes in brain neurotransmitters follow this pattern. Further, although Proebstl et al. (2019) found consistent decreases in D2 receptors in cocaine and (meth)amphetamine dependence, comparisons with D3 receptors, critical to substance use disorders (Le Foll et al. 2000), were not conducted.

21.6.1.1 Dopamine D2/D3 Receptors

Two PET studies using [^{18}F]fallypride found evidence for decreased levels of D2 receptors in the caudate (Ballard et al. 2015), putamen, and NAc (Lee et al. 2009) of methamphetamine users during early abstinence from stimulants (less than 10 days). When tested at about 2 weeks of abstinence, studies of changes in DA receptors have unequivocally established that D2 receptors are downregulated at this time. For example, in cocaine-dependent individuals, D2 receptors were lower in the striatum and putamen, as well as the caudate and ventral striatum in studies using the radiotracers [^{11}C]raclopride (Martinez et al. 2004, 2007, 2011; Narendran et al. 2011) and [^{11}C]-(+)-PHNO (Worhunsky et al. 2017). These changes seem to be limited to certain brain areas, as 1 study of D2 receptors using the radiotracer [^{18}F]fallypride in 23 methamphetamine-dependent participants found no differences compared to healthy controls in the cingulate and insula (Okita et al. 2016a). Similarly, these decreases seem to be restricted to the D2 receptor because, at 2 weeks of abstinence, D1 receptor levels were not different between 25 cocaine-dependent participants and 23 healthy controls in a study using [^{11}C]NNC. There were, however, correlations between D1 receptor levels and years of cocaine use, and those with the lowest D1 receptor levels in the ventral striatum were more likely to self-administer a dose of cocaine in a laboratory setting (Martinez et al. 2009b). Decreases in D2 receptors appear to be long lasting, as persistent decreases in these receptors were found in a [^{18}F]*N*-methylspiroperidol PET study at 3–4 months of abstinence in 20 cocaine-dependent participants (Volkow et al. 1993a). Decreased D2 receptors also appear to be associated with decreased metabolic activity in the frontal cortices; 1 study of 20 cocaine users with the tracer [^{11}C]raclopride showed

those with higher D2 receptors had increases in metabolism when challenged with methylphenidate (Volkow et al. 1999).

Interesting differences between the regulation of D2 and D3 receptors have emerged. Using [^{11}C]-(+)-PHNO, an agonist radiotracer for which binding to D2 or D3 receptors is region-specific, has revealed that D3 receptors are upregulated in psychostimulant dependence. For example, in methamphetamine dependence, increased binding of [^{11}C]-(+)-PHNO to D3-rich areas such as the substantia nigra was associated with severity of use and predicted motivation to use methamphetamine. In the same study, binding of [^{11}C]-(+)-PHNO to the D2-rich areas of the dorsal striatum and sensorimotor striatum was decreased and associated with severity of use in 16 methamphetamine users (Boileau et al. 2012). These findings of increased D3 receptors have been replicated in studies of cocaine dependence using the radiotracer [^{11}C]-(+)-PHNO (Matuskey et al. 2014b; Payer et al. 2014; Worhunsky et al. 2017) (n = 10, 15 and 26, respectively). Since all the studies cited here assessed participants within about 2 weeks of abstinence, it is not known whether the upregulation of D3 receptors is long lasting or reversible over time.

Longitudinal Studies. Longitudinal studies can provide insight into time-dependent changes in the brain by comparing various time points to each other and/or to healthy controls. In an early study, it was demonstrated that metabolic activity was decreased in many brain areas of 21 cocaine users, mostly the frontal cortex, at 1–6 weeks of abstinence (Volkow et al. 1992). This persisted and changes were even more pronounced at 3 months of withdrawal. Similarly, uptake of FDOPA was lower in 11 cocaine users at 11–30 days of abstinence, as compared to time points of less than 10 days (Wu et al. 1997). These studies are consistent with the idea that changes in the brain are enduring, are progressive, and can affect the DA system. Consistent with studies reviewed above, D2 receptors in the striatum were found to be decreased at 1 week or less of abstinence in ten cocaine-dependent individuals in a study using the radiotracer [^{18}F]*N*-methylspiroperidol (Volkow et al. 1990); however, in this early study, changes in D2 receptors were found to be recovered by 1 month of abstinence. In a subsequent study by some of the same authors (Volkow et al. 2001) that used [^{11}C]raclopride, D2 receptors were found to be decreased in 15 methamphetamine-dependent participants, and this persisted for 35 months. Thus, taken as a whole, it appears that most studies support the tenet that D2 receptors are decreased in stimulant dependence and that this is a long-term change.

21.6.1.2 Dopamine Transporter

A number of SPECT studies using [^{123}I]βCIT and [^{99m}Tc]TRODAT-1 have found evidence for an increase in the number of DAT in early abstinence, suggesting a decrease in DA levels in the striatum (Jacobsen et al. 2000; Malison et al. 1998), caudate, and putamen (Crits-Christoph et al. 2008). In one study, there was a significant association between days since use and DAT occupancy but no relationship of DAT to duration of cocaine use, amount of cocaine use, or craving (Crits-Christoph et al. 2008). In contrast to early abstinence, DAT were found to be downregulated following prolonged abstinence from psychostimulant use. After about 3 years of

withdrawal, lower levels of DAT were found in the caudate and putamen of six methamphetamine-dependent participants using the (–)-2-β-Carbomethoxy-3-β-(4-fluorophenyl)tropane (β-CFT) radioligand (McCann et al. 1998) compared to healthy controls, and DAT levels were not different from a control group of patients with Parkinson's disease. In a related study, it was also found that DAT were not different from a control group of Parkinson's patients and there was a negative correlation between the duration of methamphetamine use and DAT levels (McCann et al. 2008; Sekine et al. 2001). These findings perhaps point to a neurotoxic change in the brain of methamphetamine users. However, in a longitudinal study, DAT levels were measured using [^{11}C]cocaine at 9 months of abstinence in 16 methamphetamine-dependent patients and found to be recovered, compared to early withdrawal, in those that remained abstinent (Volkow et al. 2015). Thus, it is possible that DAT may recover in those who are able to abstain for prolonged periods of time. The association between recovery of DAT and treatment success is an area for future research, as are important questions about whether these changes in DAT are also apparent in cocaine dependence.

Longitudinal Studies. Longitudinal studies of DAT have found inconsistent results in terms of the longevity of changes in transporter levels. In one study, there were no differences across time points in DAT when 19 cocaine users were scanned with [^{123}I]βCIT at 4 days, 2 weeks, and then again at 4 weeks after cocaine use. All participants were chronic, heavy users (Bowers Jr. et al. 1998). It should be noted that there were no comparisons to healthy controls. Similarly, another study using [^{11}C]cocaine also found no differences in DAT between 20 cocaine users and controls at 5 days or 42 of abstinence (Wang et al. 1997a). By contrast, some studies have demonstrated decreased DAT levels. In one study, participants were scanned using [^{99m}Tc]TRODAT-1 at 24–48 h, 2 or 4 weeks after abstinence (Yuan et al. 2014); lower DAT levels were found in 25 methamphetamine users at all time points relative to controls. In another investigation using [^{11}C]cocaine, DAT was also decreased at about 2 weeks of abstinence in 16 heavy, chronic, cocaine users, but these changes were reversed by 9 months of abstinence (Volkow et al. 2015). The authors note that this recovery may not be evident in those who did not remain abstinent; thus there may be loss of DAT in a subpopulation. By comparison, another small study (n = 6 intermittent methamphetamine users) using the radiotracer [^{99m}Tc]TRODAT-1 found that DAT levels recovered after a 2-week abstinence (Chou et al. 2007). Differences between the findings of recovery in this study at 2 weeks and the other studies which found decreased DAT at 2 weeks may be explained by the different exposures to stimulants. As pointed out by Yuan et al., the former study investigated participants with a chronic, heavy use, and the latter study by Chou et al. studied those that had undergone intermittent exposure. Thus, recovery of DAT may be more rapid with prior intermittent use.

21.6.1.3 Dopamine Synthesis

Evidence from the preclinical literature suggests that repeated, chronic exposure to psychostimulants, similar to the exposure that may be expected in dependent

humans, may lead to tolerance to the effects of psychostimulants on the ability to increase DA levels. All studies investigating DA synthesis have used the radiotracer [^{11}C]raclopride. Seminal studies by Martinez and colleagues have demonstrated that, at about 2 weeks of abstinence, following a challenge with amphetamine, the increase in DA levels in the ventral striatum, caudate, and putamen was blunted in 24 cocaine-dependent participants compared to controls (Martinez et al. 2007). Similar blunted responses to methylphenidate were observed in a further 25 cocaine-dependent individuals in the striatum and putamen (Martinez et al. 2011). These changes appear to be long lasting, because when tested at 3–6 weeks of abstinence, 23 cocaine-dependent individuals showed a blunted response of DA in the striatum following a challenge with methylphenidate as compared to healthy controls (Volkow et al. 1997b). In the thalamus, changes in DA were greater (not blunted) in cocaine-dependent people and were associated with ratings of cocaine craving. These increases in the thalamus were also associated with activation of the medial orbital prefrontal cortex (Volkow et al. 2005). In this vein, 16 methamphetamine users who relapsed had lower DA transmission and lower D2 availability in caudate compared to controls (Wang et al. 2012). Thus, changes in D2 receptors and DA transmission may have clinical significance.

Blunted increases in DA in response to a stimulant challenge are somewhat difficult to reconcile with two studies on the effects of repeated stimulants on VMAT2. VMAT2 transports monoamines (DA, norepinephrine and 5-HT) from the cytoplasm to storage vesicles. Therefore, increases in VMAT2 would be consistent with a decrease in the availability of DA. One study using the radiotracer [^{11}C]DTBZ at about 2 weeks of abstinence, in 16 methamphetamine-dependent participants, found that VMAT2 was upregulated in the dorsal caudate, dorsal putamen, and ventral striatum relative to controls (n = 14; patients with Parkinson's disease) (Boileau et al. 2008). By contrast, a study with 16 cocaine-dependent individuals also using [^{11}C]DTBZ found that VMAT2 was downregulated compared to healthy controls (Narendran et al. 2012). Differences in the findings of these two studies may reflect the drug of dependence (cocaine versus methamphetamine) or the control comparisons (healthy controls vs Parkinson's patients) or the duration of abstinence (about 2 weeks). Indeed, at 3 months of withdrawal, VMAT2 was found to be about 10–11% lower in the caudate, putamen, and striatum of 16 methamphetamine users (Johanson et al. 2006). Further studies are warranted.

21.6.1.4 Sensitization

All of the studies reviewed above involved the testing of participants who are dependent on stimulants and thus would likely have experienced stimulants in a repeated, chronic fashion. In one important study (Boileau et al. 2006), ten non-dependent participants who had not used stimulants more than five times in their lives were given a few amphetamine administrations separated by a couple of days. PET scans using the tracer [^{11}C]raclopride were administered before treatment with amphetamine, at the first dose of amphetamine and again at the final dose of amphetamine. The final dose of amphetamine was 2 weeks after the last injection. Thus, the

treatment regimen mimicked that employed in animal studies, in which stimulants are administered intermittently and sensitization is tested after a period of abstinence. Upon testing, some subjective measures of sensitization were observed. Most compelling are the findings that DA levels were increased in the striatum, as compared to baseline, at the final test. When retested a year later, DA levels remained elevated, pointing to a persistent change in brain neurochemistry. Thus, some evidence for sensitization of the DA system exists from in vivo PET studies in humans.

21.6.2 Other Neurotransmitter Systems

The few studies that have investigated neurotransmitter systems other than DA have found few differences between controls and those with cocaine use disorder. For example, one study found that, after 7–8 days of abstinence, there were no differences between controls and individuals with cocaine use disorder in KOR, as measured with [^{11}C]GR103545 (Martinez et al. 2019). Similarly, at a minimum of 14 days of abstinence, there were no differences between groups in a marker of microglia activation, as measured with [^{11}C]PBR28 (Narendran et al. 2014).

Cocaine is known to also inhibit the reuptake of 5-HT, and thus it is not surprising that markers of the serotonergic system were altered in cocaine dependence. For example, similarly to DAT, SERT, as measured by [^{123}I]βCIT, was upregulated in 15 individuals with cocaine use disorder at about 4 days of withdrawal (Jacobsen et al. 2000). In another study with 14 cocaine users, at about 3 months of abstinence, the 5-HT$_{1B}$ receptor was downregulated in the anterior cingulate, hypothalamus, and frontal cortex, measured using the [^{11}C]P943 PET tracer (Matuskey et al. 2014a).

Mesolimbic DA is known to be mediated by glutamatergic projections from frontal and limbic areas; thus investigation of changes in the glutamatergic system in cocaine dependence is of great interest. In this regard, one PET study with the tracer [^{11}C]ABP688 at about 2–14 days of abstinence found that mGluR5 was downregulated in the striatum, amygdala, and insula of nine people with cocaine dependence; the longer the period of abstinence, the lower the levels of glutamate receptors (Milella et al. 2014).

21.6.3 Conclusion

In sum, there are some general consistencies in findings from studies of the effects of chronic, repeated exposure to stimulants on the DA system. It can be concluded from the vast majority of studies that D2 receptors are downregulated after exposure to stimulants. D3 receptors are upregulated, but it is not known at this time if this change is long lasting. Some studies have found that DAT are upregulated in early withdrawal and some longitudinal studies have found no change in transporters at various time points. Some studies have found decreases in the levels of DAT that

seem to recover over time. It is not clear if recovery is related to the type of previous exposure to stimulants or to treatment success. The notion that those who can abstain may have different recovery of brain DA is also supported by the findings that those who relapse to stimulant use have lower levels of D2 receptors and more blunted increases in DA in response to a challenge with stimulants. To date little work has investigated the role of other neurotransmitter systems in stimulant dependence, although preliminary work supports the involvement of the serotonergic and glutamatergic systems.

21.7 Chapter Summary

- Neuroadaptations in multiple neurotransmitter systems have been implicated in addiction. With the development of PET and SPECT imaging techniques, it has become possible to assess neurotransmitter synthesis, receptor availability, and neurotransmission in vivo in humans with substance use disorders, although it has not been possible to investigate all targets of interest due to lack of suitable radiotracers. Table 21.2 presents an overview of the findings of studies reviewed in this chapter.
- Unsurprisingly, the dopaminergic system has received the most attention in studies investigating neurotransmission in substance use disorders to date. There is consistent evidence of abnormalities in the dopaminergic system; specifically the D2 receptor, and to a lesser extent DAT, appears to be downregulated in individuals with most substance use disorders (with the exception of cannabis dependence). It is currently unclear if this alteration is reversible. With the development of selective radiotracers, the role of the D3 receptor is beginning to be investigated.
- There is little human imaging research investigating abnormalities in the serotonergic, GABAergic, and opioidergic systems in the majority of substance use disorders. Findings of studies that do exist are generally mixed (which may be due to heterogeneity in study design), and several targets of interest within each of these neurotransmitter systems remain to be explored.
- Specific abnormalities have been implicated in some substance use disorders: nAChRs appear to be upregulated in chronic tobacco use, and the endocannabinoid system (specifically decreases in CB1 receptor availability) is particularly implicated in cannabis dependence.
- Many PET and SPECT studies conducted to date are limited by small sample sizes and cross-sectional study design (meaning that it is not possible to determine whether abnormalities in neurotransmitter function are a consequence of chronic drug exposure or if they reflect a predisposing risk factor for substance use disorders). The majority of existing studies have recruited only male participants, and it is unclear to what extent findings will generalize to females. Studies in populations with other psychiatric comorbidities are also lacking.

Table 21.2 Summary of human PET and SPECT findings[a]

System	Target	ALCOHOL	TOBACCO	CANNABIS	OPIOIDS	STIMULANTS
Dopaminergic	Synthesis/presynaptic function	+/−	+/−			+/−
	DA release	↓	↑↑	+/−	↓	↓
	DAT	+/−	↓↓		↓↓	+/−
	D1 receptors		↓			
	D2/D3 receptors	↓↓	↓	=	↓↓	↓↓
	D3 receptors	+/−				↑
	Monoamine oxidase	↑	↓			
Serotonergic	SERT	+/−	=		↓	↑
	5-HT_{1A}/5-HT_{1B} receptors	+/−				↓
	Synthesis	↓				
GABAergic	$GABA_A$ receptors	↓	+/−		↓	
Opioidergic	μ, δ and κ receptors	+/−	+/−		↓	=
Glutamatergic	MGluR5 receptors	+/−				↓
Endocannabinoid	CB1 receptors	+/−		↓		
	FAAH			↓		
Cholinergic	nAChR receptors		↑↑			

Abbreviations: ↑↑ majority of evidence supports increase; ↑ some evidence of increase; ↓↓ = majority of evidence supports decrease; ↓ some evidence of decrease; = no change; +/− evidence mixed; blank cells indicate limited/no evidence available, or inconclusive findings (e.g., due to confounding)

[a]Based upon studies reviewed in this chapter

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Molecular Imaging Studies in Stimulant Addiction: A Cross-Species Perspective

22

Jolyon A. Jones, Bruce Russell, and Jeffrey W. Dalley

Contents

Abstract

Drug addiction is a complex and highly debilitating disorder affecting the motivational and cognitive control systems of the brain. This chapter reviews the astonishing advances made in the field of drug addiction research by the noninvasive neuroimaging techniques, positron emission tomography (PET), and

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single-photon emission computerised tomography (SPECT). Based on the seminal discovery of intracranial self-stimulation (ICSS) by Olds and Milner, the great majority of PET and SPECT studies have targeted biomarkers linked to dopamine transmission in the brain. We review evidence that diminished dopamine $D_{2/3}$ receptor availability, whether pre-existing or acquired, is a risk marker for relapse to drug seeking, using examples of successful vertical translation from experimental animals to humans. We discuss the role of antecedent personality traits (e.g. novelty/sensation seeking, impulsivity) and the impact of brain disorders such as attention deficit hyperactivity disorder (ADHD) on the emergence of compulsive drug seeking. Finally, we consider future directions of PET and SPECT research and prospects for the development of novel radiotracers.

22.1 Introduction

Drug addiction is a chronic relapsing brain disorder that places a serious burden on society. The aetiological basis of addiction is complex and multifaceted and involves a widely acknowledged but poorly understood interplay between genetic and environmental variables (Kreek et al. 2005; Schumann et al. 2010; Uhl 2010; Walker and Nestler 2018). Despite intensive research we still do not understand why individuals become dependent on drugs nor are there effective treatments. However, over the last two decades, there has been extraordinary progress in the discovery of biomarkers associated with addiction (Volkow et al. 2001a; Matochik et al. 2003; Ersche et al. 2012; Casey et al. 2014; Moeller and Paulus 2018). Unquestionably, the main catalyst for this progress has been the remarkable methodological advances in magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission computerised tomography (SPECT), together with increasingly sophisticated imaging studies in individuals at risk for the disorder (e.g. Moreno-López et al. 2012; Nord et al. 2019) and parallel advances in neuroimaging techniques and behavioural assessment in experimental animals (Nader et al. 2006; Gould et al. 2014; Virdee et al. 2012). This chapter surveys the current state of progress in molecular neuroimaging of drug addiction, both from clinical and preclinical standpoints.

In historical terms, the discovery by Olds and Milner (1954) of intracranial self-stimulation (ICSS) marked a major turning point in research into the neural mechanisms of addiction. Unsurprisingly, given the persuasive evidence that dopamine (DA) and various DA-innervated structures, in particular the nucleus accumbens (NAcb) and prefrontal cortex (PFC), are effective substrates for ICSS (Nakahara et al. 2000), there has been an overwhelming focus on DA mechanisms in addiction, not least because many drugs of abuse exert their primary effects on the mesolimbic DA system (Imperato et al. 1992; Wise and Hoffman 1992; Koob and Le Moal 2005). This concerted research effort has resulted in a number of seminal discoveries that we review below; these have gradually paved the way for neuroimaging studies of other neurotransmitter systems, including serotonin (5-HT), noradrenaline (NA),

γ-aminobutyric acid (GABA), opioid, endogenous cannabinoids, and glutamate that may underpin the loss of control and persistence of drug intake in vulnerable individuals (Cumming et al. 2003; Virdee et al. 2012).

Additionally, there is an ever-increasing recognition of the critical importance of antecedent personality traits and brain disorders in shaping an individual's trajectory to addiction. For example, personality traits encompassing impulsivity and novelty/sensation seeking are strongly associated with drug use and vulnerability to dependence (Chakroun et al. 2004; Kreek et al. 2005; Nigg et al. 2006; Verdejo-García et al. 2008; Ersche et al. 2010, 2012; García-Marchena et al. 2018). Moreover, the balance of research findings indicates that impulsivity, in particular, may be a pre-existing vulnerability marker for addiction (Verdejo-García et al. 2008; Dalley and Ersche 2019). Clinically, impulsivity is a diagnostic feature of attention deficit hyperactivity disorder (ADHD) and is co-morbid with alcohol and other drug dependencies (depicted in Fig. 22.1). In more than 50% of cases, ADHD persists into adulthood (Kieling and Rohde 2010), and although the neural substrates for the high co-morbidity of adult ADHD with drug dependence and other disorders are unclear, they are presumably dependent on shared neurobiological mechanisms (Wilens and Morrison 2011). In the following sections, we review the evidence of shared neural mechanisms between ADHD and addiction and interrelate these findings in addicts and experimental animals.

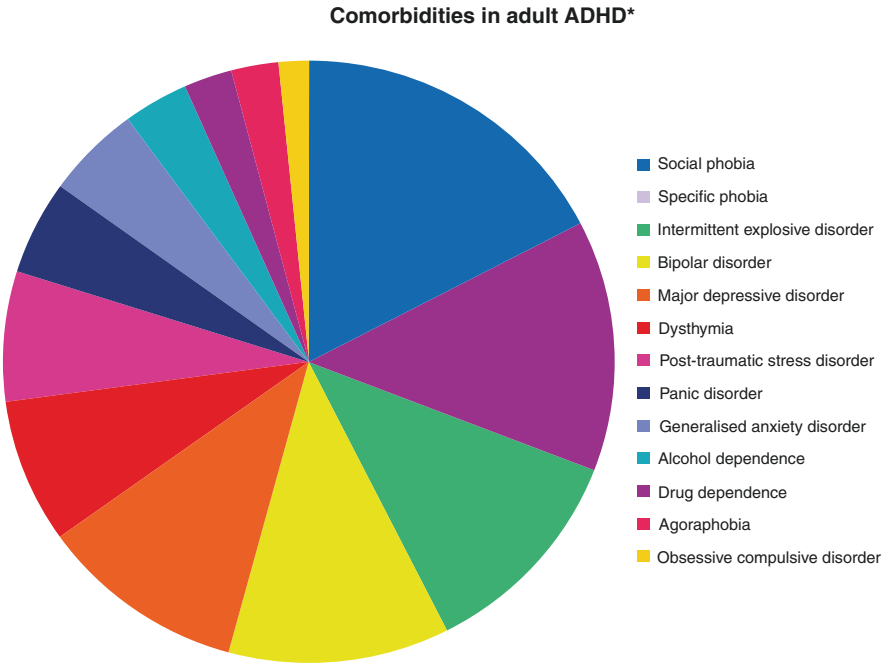

Fig. 22.1 Schematic illustration showing the major co-morbidities associated with adult attention deficit hyperactivity disorder, including alcohol and drug dependence. (From Kessler et al. 2006)

22.2 SPECT/PET Studies in Addiction

22.2.1 Studies in Animals

In general, animal models of psychiatric disorders simulate specific components of broad behavioural syndromes where clear evidence of neuropathology and altered brain metabolism is often lacking. However, modelling drug addiction is particularly challenging due to (1) the wide variability of clinical presentations, comorbidities, and symptoms which make it difficult to discern whether there is only a single illness; (2) difficulties in controlling environmental variables that putatively affect disease expression; (3) difficulties in establishing genetic linkages; and (4) controlling for age of onset, gender and ethnicity effects, and polydrug abuse. However, over the last decade, several promising animal models have been developed that capture key transitional stages of the addiction pathway, in particular, neurobehavioural vulnerability markers which carry high face validity and are not confounded by neural plasticity mechanisms associated with repeated cycles of drug bingeing and withdrawal.

However, a stark consequence of the historical underpinnings of addiction research is that the majority of molecular imaging studies have focused on markers of DA transmission in the fronto-striatal networks. Most, if not all, drugs with abuse potential increase DA release in the striatum, including the NAcb (Di Chiara and Imperato 1988; Carboni et al. 1989), and can as a result displace radioligands selective for DA receptors. The benzamide [^{11}C]-raclopride and the SPECT tracer [^{123}I]-IBZM are commonly used for this purpose given their vulnerability to competition from endogenous DA (Innis et al. 1992; Dewey et al. 1993). Stimulant drugs such as methamphetamine, cocaine, methylphenidate, and to a lesser extent even nicotine decrease the binding of [^{11}C]-raclopride and [^{18}F]-fluoroclebopride in the striatum (Mach et al. 1993; Cumming et al. 2003; Cox et al. 2009; Marenco et al. 2004), an effect also evident in mice treated with amphetamine and quantified with [^{18}F]-fallypride–PET (Rominger et al. 2010). The close relationship between radioligand displacement and stimulant-evoked DA release is corroborated by animal studies employing in vivo microdialysis in conjunction with [^{123}I]-IBZM–SPECT (Laruelle et al. 1998) and [^{11}C]-raclopride–PET (Endres et al. 1997; Lippert et al. 2019). This is also supported by an influential study of non-human primates showing that behavioural sensitisation (a putative marker of addiction) is linked to the enhanced displacement of [^{123}I]-IBZM by amphetamine (Castner et al. 2000). However, direct microdialysis measurements have not supported a sensitised DA response in rhesus monkeys exposed to high cumulative doses of cocaine (Bradberry 2011). The reason for this discrepancy is unclear but may relate to procedural and/or species differences.

Preclinical PET studies further demonstrate that $D_{2/3}$ receptor availability is profoundly diminished in the striatum by chronic exposure to psychostimulant drugs, for example, as shown in both cynomolgus monkeys and rats treated with amphetamine (Ginovart et al. 1999; Dalley et al. 2009) and methamphetamine (Thanos et al. 2017). Moreover, $D_{2/3}$ receptor availability is diminished in both primates and

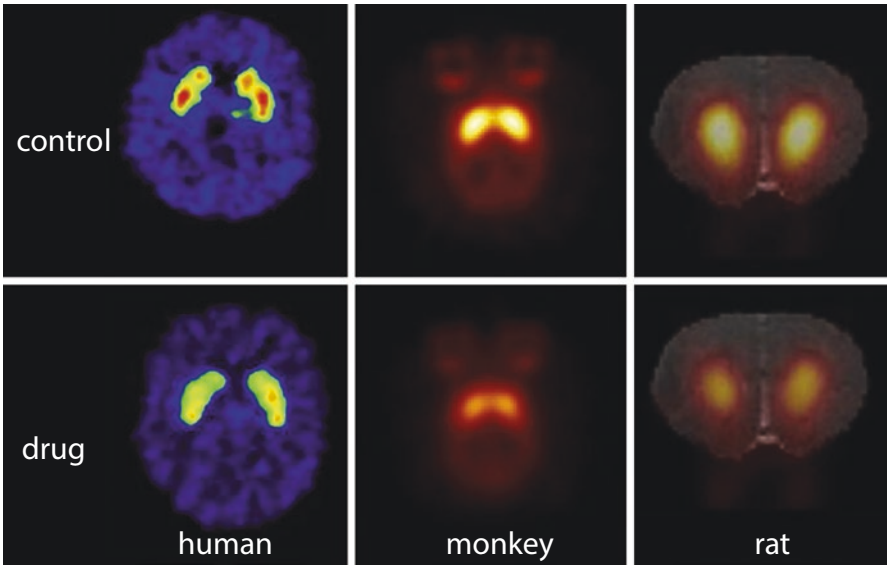

Fig. 22.2 Positron emission tomography scans showing reduced $D_{2/3}$ receptor availability in the striatum of a recently abstinent cocaine addict (Volkow et al. 2002), a rhesus macaque monkey exposed to 3-month intravenous cocaine self-administration (Nader et al. 2006), and a Lister-hooded rat exposed to prior intravenous amphetamine self-administration (Dalley et al. 2009). (From Dalley et al. (2011). Reprinted with permission from Cell Press)

adolescent rats treated with methylphenidate (Birn et al. 2019; Thanos et al. 2007). This effect is remarkably consistent across species including humans (as shown in Fig. 22.2), and based on research in animals, this may result, in part, from chronic drug exposure (Nader et al. 2006; Groman et al. 2012). However, dysfunction of $D_{2/3}$ receptors is also present prior to drug exposure in both experimental animals (Dalley et al. 2007; Caprioli et al. 2015) and humans (Buckholtz et al. 2010) which express high levels of impulsive behaviour. Thus, impaired $D_{2/3}$ receptor signalling may underlie impulsive behaviour and be a susceptibility marker that is further compromised by chronic drug abuse.

Cannella et al. 2017 evaluated the change in glucose metabolism using [^{18}F]-FDG–PET imaging in animals phenotyped as addict-like (3-crit) or non-addict-like (0-crit) in the preclinical three-criteria model of addiction (Deroche-Gamonet et al. 2004). No global changes in glucose metabolism were observed in animals phenotyped as 0-crit vs. 3-crit. However, regional changes in the medial prefrontal cortex bilaterally and the right caudate putamen were observed. Zero-crit animals showed higher standardised uptake values of glucose, unlike 3-crit animals, when compared to drug-naïve controls. These results align with human studies supporting the notion of reduced glucose metabolism in prefrontal cortical regions in cocaine-addicted patients (Volkow et al. 1992). Similarly, using [^{18}F]-FDG–PET, Nicolas and co-workers evaluated glucose metabolism longitudinally during several withdrawal phases in animals with a history of cocaine escalation. Using the

short-access vs. long-access model of escalation, animals given long-access exposure to cocaine showed a reduced level of glucose uptake in the insula cortex after 1 and 4 weeks of abstinence. After 1 week of abstinence, glucose metabolism was also reduced in the infralimbic cortex of long-access animals. Using the same long-access model, Calipari and co-workers reported reduced rates of glucose utilisation in the medial prefrontal cortex when compared to drug-naïve controls (Calipari et al. 2013). These results indicate that stimulant drugs decrease prefrontal cortical metabolism and dysregulate top–down cognitive control mechanisms, comparable to conclusions drawn from research in humans (Volkow et al. 2012).

Compelling evidence indicates that personality traits that encompass novelty/sensation seeking and impulsivity can predispose to drug use and have a detrimental impact, speeding the development of drug addiction (Chakroun et al. 2004; Koob and Le Moal 2005; Nigg et al. 2006; Belin et al. 2008, 2011; Verdejo-García et al. 2008). However, there is a paucity of preclinical PET/SPECT studies that have explicitly investigated novelty-/sensation-seeking traits. In one study the behavioural response to novelty of Gottingen minipigs was investigated using [^{11}C]-raclopride–PET (Lind et al. 2005). The core findings of this study show that the duration of contact with novel objects correlated with the amphetamine-induced decline in [^{11}C]-raclopride binding potential. Thus, novelty-preferring animals evidently show enhanced DA release in the striatum just like the addiction-prone, novelty-reactive high-responder rat described by Piazza et al. (1989). Possibly consistent with these findings, it was recently shown in rats that biased decision-making under uncertainty was influenced by $D_{2/3}$ receptor expression in the striatum (Cocker et al. 2012).

A recent study in male cynomolgus monkeys showed that social dominance predicted low novelty reactivity, measured by the latency to touch a novel object, a trait associated with resilience to addiction (Czoty et al. 2010). In this study a significant positive correlation was observed between caudate $D_{2/3}$ receptors, assessed using [^{18}F]-fluoroclebopride–PET, and latencies to touch the novel object. This intriguing research resonates with findings in humans showing higher social status to predict higher baseline [^{11}C]-raclopride binding in healthy volunteers (Martinez et al. 2010). It is also consistent with a now classic study showing the transition from single-housing to group-housing results in increased binding of [^{18}F]-fluoroclebopride to striatal $D_{2/3}$ receptors in the socially dominant cynomolgus monkey, the same subgroup which self-administered significantly less cocaine than their less dominant cage mates (Morgan et al. 2002). More recently, it was reported that social dominance in rats modulates cocaine self-administration and is associated with elevated $D_{2/3}$ receptor binding in the shell region of the nucleus accumbens (Jupp et al. 2016).

Work over a number of years has shown that impulsivity in rats predicts intravenous cocaine and nicotine self-administration (Perry et al. 2005; Dalley et al. 2007; Diergaarde et al. 2008), as well as an increased propensity to develop compulsive cocaine self-administration (Belin et al. 2008), and to relapse after a period of abstinence (Economidou et al. 2009). In our laboratory, impulsive rats were selected from an outbred Lister-hooded strain, measured by their increased propensity to ‘jump the

gun' and respond before the presentation of a discriminative visual cue using a five-choice serial reaction time task, a computerised operant test of sustained visual attention and impulsivity (Robbins 2002). The impulsive phenotype was present in a small but stable proportion of tested rats (8–14%). In a previous microPET study, impulsive rats showed significantly reduced [^{18}F]-fallypride uptake in the ventral striatum (including the NAcb), but not the caudate putamen (Dalley et al. 2007), in the absence of any prior exposure to stimulant drugs (see Fig. 22.3). Thus, low pre-existing $D_{2/3}$ receptor availability in the ventral striatum may contribute to the risk for drug escalation and relapse to drug seeking. Based on a recent ex vivo autoradiography study, the locus of this deficiency in $D_{2/3}$ receptors in high-impulsive rats appears to be the NAcb shell (Jupp et al. 2013; Barlow et al. 2018), a region acknowledged to mediate primary drug reinforcement (Everitt and Robbins 2005).

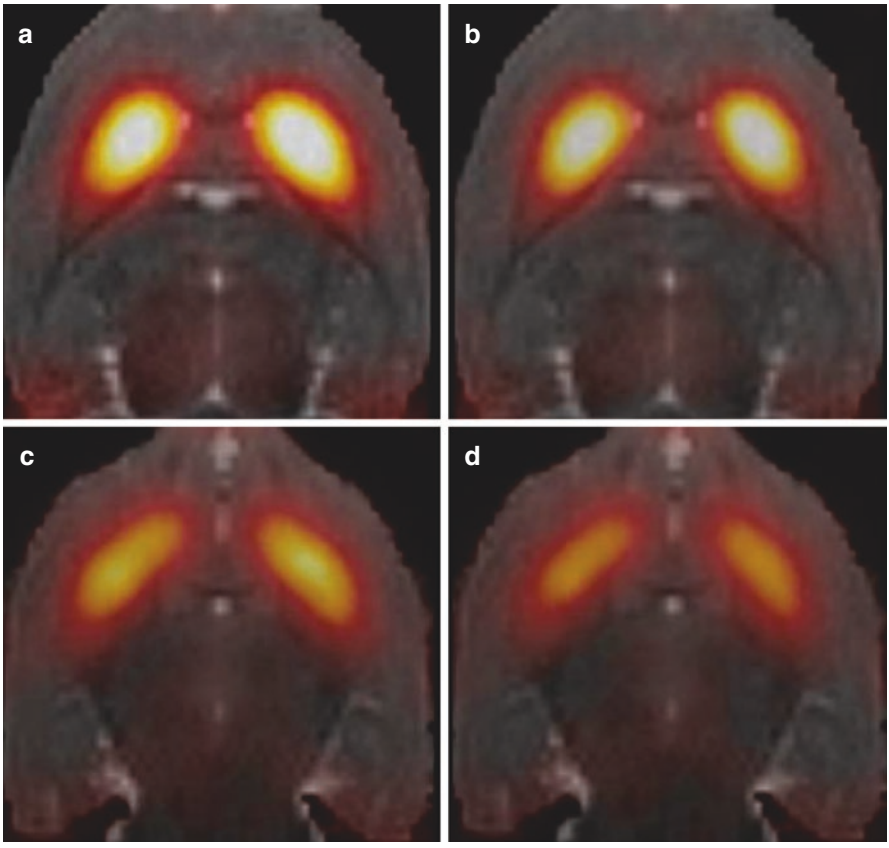

Fig. 22.3 Horizontal MR-co-registered PET scans showing reduced uptake of the high-affinity $D_{2/3}$ receptor antagonist [^{18}F]-fallypride in the ventral, but not dorsal, striatum of high-impulsive rats. The scans show, respectively, $D_{2/3}$ receptor binding in the dorsal and ventral striatum of low (**a**, **c**) and high (**b**, **d**) impulsive rats. (From Dalley et al. (2007). Reprinted with permission from AAAS)

22.2.2 Studies in Humans

In broad terms PET and SPECT studies in addiction have centred on (1) molecular correlates associated with the acute subjective experience of alcohol and other abused drugs and (2) residual and persistent markers of dysfunction in abstinent drug addicts. Subjects who self-report a 'high' following systemic administration of methylphenidate also show a significant displacement of [^{11}C]-cocaine (Volkow et al. 1999) and [^{11}C]-methylphenidate (Volkow et al. 2006) binding in the striatum, indicative of increased competition from endogenous DA. Analogous PET findings are reported for amphetamine-induced euphoria in normal healthy volunteers (Drevets et al. 2001; Smith et al. 2016) and for habitual smokers (Le Foll et al. 2014); however, one study did show that this effect was only in those that reported a positive subjective experience (Montgomery et al. 2007). These PET studies thus substantiated the view that pharmacological treatments increasing DA release, especially in the NAcb, should evoke a positive hedonic experience.

However, this view belies the complexity of contributory mechanisms to the dopaminergic response of stimulant drugs measured by PET and SPECT. For example, there is convincing evidence to suggest that brain DA is not closely associated with the state of euphoria produced by abused substances (Leyton et al. 2007) but rather 'drug wanting' and the personality trait of novelty-seeking–exploratory excitability (Leyton et al. 2002). Moreover, higher levels of trait impulsivity were predicted by diminished midbrain $D_{2/3}$ receptor binding and greater amphetamine-induced DA release in the striatum, which in turn was associated with stimulant craving (Buckholtz et al. 2010). Another study showed that lower levels of presynaptic dopamine function were negatively correlated to impulsivity (Petzold et al. 2019), while Hammes and colleagues using [^{18}F]-DOPA–PET imaging showed a decrease of dopamine synthesis capacity in the NAcb in subjects with high levels of impulsive–compulsive behaviours (Hammes et al. 2019). In addition, high psychosocial stress, which reduces dopamine synthesis capacity in the striatum (Bloomfield et al. 2019), predicted greater effects of amphetamine on striatal [^{11}C]-raclopride binding (Wand et al. 2007), whereas trait impulsivity and a history of life stresses had complex effects on the effects of an amphetamine challenge in humans (Oswald et al. 2007). Furthermore, environmental cues in healthy subjects with previous exposure to amphetamine immediately prior to scanning were sufficient to reduce [^{11}C]-raclopride binding (Boileau et al. 2007), similar to the effects of discrete visual cues conditioned with cocaine use (Wong et al. 2006). In addition, the subjective rating of pleasure produced by a bolus injection of methylphenidate in normal healthy volunteers depended inversely on baseline $D_{2/3}$ receptor availability in the caudate putamen (Volkow et al. 2006). Such effects may also be explained by reward expectancy. For example, it was recently shown that methylphenidate-induced dopamine release, as indexed by [^{11}C]-raclopride displacement, was blunted in individuals with cocaine use disorder (i.e. the drug reward was less than expected) but elevated following placebo (Wang et al. 2019). Elucidating the myriad of factors that predict individual differences in baseline and evoked changes in DA activity remains an important area of research in this field.

As the primary molecular target of cocaine and other stimulant drugs, the DA transporter (DAT) is a key biomarker for PET and SPECT research. Cocaine-abstinent addicts show increased DAT levels in the caudate putamen compared with healthy controls, measured by [^{99m}Tc]-TRODAT-1 SPECT (Crits-Christoph et al. 2008). This abnormality was found to be reversible in so far as [^{99m}Tc-TRODAT-1] uptake negatively correlated with the duration of time since the last exposure to cocaine. In an earlier study by Malison and colleagues, using [^{123}I]-β-CIT SPECT, striatal DAT levels increased by approximately 20% in cocaine addicts that were abstinent for less than 96 h (Malison et al. 1998). However, these findings conflict with studies of human methamphetamine (MA) abusers. For example, Volkow and colleagues investigated the density of DAT in abstinent MA abusers using PET and [^{11}C]-D-threo-methylphenidate and observed lower levels in the caudate and putamen (Volkow et al. 2001a, b).

Similar findings were reported in an earlier study using [^{11}C]-WIN-35,428, following an abstinence period of more than 3 years on average (McCann et al. 1998) which upheld findings showing reduced DAT in the NAcb, anterior PFC, orbitofrontal cortex (OFC), dorsolateral PFC, and amygdala of abstinent MA abusers (Sekine et al. 2001, 2003). In contrast, a longitudinal PET study using [^{11}C]-D-threo-methylphenidate during both short-term (<6 months) and long-term (12–17 months) periods of MA abstinence reported increases in DAT in the caudate and putamen (Volkow et al. 2001a). The extent of DAT recovery was associated with the severity of abuse and the duration of abstinence. Similar results were reported in a more recent study showing increased DAT levels after protracted drug abstinence (Volkow et al. 2015). Finally, the reinforcing effects of DAT blockade by cocaine have been assessed using [^{11}C]-cocaine–PET (Volkow et al. 1997a, b). Here, it was shown that intravenous administration of cocaine at doses typically used by humans (i.e. 0.3–0.6 mg/kg) blocked 60–77% of DAT binding sites. The magnitude of the self-reported 'high' positively correlated with the degree of DAT occupancy; at least 47% DAT blockade was needed for subjects to perceive the euphoric effects of cocaine.

A striking consequence of withdrawal from many drugs of abuse in humans, including stimulant- and opiate-based substances, is a diminished supply of $D_{2/3}$ receptors in the caudate and putamen (Wang et al. 1993; Volkow et al. 2001a, b; Trifilieff et al. 2017). While questions are sometimes raised about the causal basis of this effect and its generalisability to generically unrelated drugs, it is a finding that is remarkably consistent in the preclinical literature (Nader and Czoty 2005; Dalley et al. 2009; Groman et al. 2012) and thus represents a putative biomarker of prior chronic drug exposure. Not only do drug addicts show a reduction in $D_{2/3}$ receptors in the caudate and putamen, they also show a general blunting of DA release in these regions, measured by the attenuation of psychostimulant-induced changes in [^{11}C]-raclopride binding (Volkow et al. 1997a, b; Martinez et al. 2009). Those addicted to cocaine also show a reduced 'high' relative to control subjects in response to intravenous methylphenidate (Volkow et al. 1997a, b). Collectively, these findings indicate that the brain reward system is rendered profoundly hypoactive in drug addicts, an outcome caused most parsimoniously by chronic exposure to addictive substances.

A fundamental research question is the extent to which abnormalities of $D_{2/3}$ receptor binding in abstinent addicts are reversible and therefore recoverable after a protracted withdrawal period. Previous PET studies indicate that this abnormality can persist for many months following drug withdrawal (Sonsalla et al. 1989; Sharma et al. 2007; Yuan et al. 2010; Boileau et al. 2012; Ashok et al. 2017). In a recent longitudinal study using [^{11}C]-raclopride–PET, DA release was measured in the caudate putamen of MA abusers following a 60 mg oral dose of methylphenidate or placebo (Wang et al. 2012). The subjects were initially scanned within 6 months of the last MA exposure and again after 9 months. During early withdrawal MA abusers exhibited a lower availability of $D_{2/3}$ receptors in the caudate compared with control subjects. As expected, following a methylphenidate challenge, there was a decrease in striatal (caudate, putamen, ventral striatum) $D_{2/3}$ receptor availability in both MA abusers and controls. However, this decrease was attenuated in the left putamen of MA abusers, which may reflect a decrease in DA release in this region. Interestingly, the MA abusers with lower baseline $D_{2/3}$ receptor levels than control subjects within the dorsal striatum (caudate and putamen) experienced no $D_{2/3}$ receptor alterations following methylphenidate challenge and relapsed during the 9-month follow-up period. Correspondingly, MA abusers who experienced an increase in methylphenidate-evoked DA release, comparable with control subjects, did not relapse and successfully completed a 9-month abstinence period. The authors concluded that abstinent MA abusers with low striatal DA function have a greater likelihood for relapse (Wang et al. 2012). Similar conclusions have been drawn for cocaine dependence where blunted DA responsiveness appears to play a critical role in influencing choice preference for cocaine and thereby a putatively enhanced risk for relapse (Martinez et al. 2007). A more recent study evaluated the choice of pleasant vs. drug-related imagery in MA users. Choice for drug-related imagery correlated positively with baseline levels of craving and negatively with D_2-type receptor availability in the orbitofrontal cortex (Moeller et al. 2018).

As discussed above MA abuse is linked to reduced levels of $D_{2/3}$ receptors and DA release (Volkow et al. 2001a, b), which supports the proposal by some that MA addiction could potentially be treated with drugs that increase DA transmission (Kish 2008; Le Foll et al. 2014). Not only do MA addicts show reduced $D_{2/3}$ receptor densities, they also show higher levels of impulsivity than healthy control subjects, as determined using the Barratt Impulsiveness Scale (Lee et al. 2009). The underlying neural basis of increased impulsivity is only partly understood (see Dalley et al. (2011)) but may be influenced by an upregulation of D_3 receptors noted previously in abstinent stimulant addicts and rats (Mash 1997; Segal et al. 1997; Neisewander et al. 2004). Researchers have investigated the hypothesis that D_3 receptor availability is elevated in MA abusers using [^{11}C]-(+)-propyl-hexahydro-naphtho-oxazin–PET ([^{11}C]-(+)-PHNO), a selective D_3 ligand. The main findings of this research showed that ([^{11}C]-(+)-PHNO) binding was increased in the substantia nigra compared with healthy control subjects but was decreased in the D_2-rich caudate putamen and that ([^{11}C]-(+)-PHNO) binding in the substantia nigra was related to self-reported ‘drug wanting’ (Boileau et al. 2012; Payer et al. 2014). The authors

concluded that D_3 receptors are upregulated in the brain of MA abusers. Although this was the first study to specifically examine D_3 receptor density in MA addiction, all subjects were polydrug users having reported the use of cocaine, MDMA, benzodiazepines, opiates, THC, and ketamine (Boileau et al. 2012). Indeed, increased D_3 receptor binding was also apparent in cocaine-dependent subjects compared with healthy controls and was associated with increased impulsivity (Payer et al. 2014). Thus, D_3 receptor antagonism may be a viable strategy to reduce the risk of relapse by curbing impulsive behaviour (London 2020). However, while [^{11}C]-(+)-PHNO is a useful radioligand for the investigation of D_3 receptors, it lacks absolute specificity; consequently the significance of this data must be interpreted with caution.

The quantification of regional glucose metabolism by PET has been widely utilised for the investigation of brain function in addiction. Volkow and colleagues undertook a [^{18}F]-FDG–PET study of MA abusers and found a global *increase* in metabolism compared with control subjects (Volkow et al. 2001a). However, this outcome was unexpected, given past evidence of hypometabolism in abstinent cocaine addicts (Volkow et al. 1992). The authors hypothesised that the increased metabolism in MA abusers might reflect gliosis or inflammatory processes (Volkow et al. 2001a). In contrast, London and colleagues investigated metabolism in recently abstinent (4–7 days) MA abusers and reported a decrease in glucose metabolism in the anterior cingulate cortex and insula (London et al. 2004). However, they also reported hypermetabolism in the lateral OFC, middle and posterior cingulate, amygdala, ventral striatum, and cerebellar vermis which they hypothesised might reflect a short abstinence period because these regions are also thought to play a role in drug craving (Everitt and Robbins 2005).

Using [^{18}F]-FDG–PET, Berman and colleagues compared glucose metabolism in the brain of MA abusers after less than 1 week of abstinence and again after short-term periods (average of 3 months) in comparison to healthy control subjects (Berman et al. 2008). During the first month of abstinence, a critical period when relapse frequently occurs, there were no detectable metabolic changes in subcortical regions but a widespread increase in cortical glucose metabolism combined with a marked increase was observed in the parietal cortex (Berman et al. 2008). Following their first year of abstinence, MA abusers continued to show metabolic deficits in the striatum while their thalamic metabolic response normalised (Wang et al. 2004). In summary, FDG–PET studies in MA addicts have yielded a complex array of findings with some discrepancies between different studies. These inconsistencies may be due to a number of factors such as differing routes of administration (e.g. nasal inhalation vs. smoking or intravenous injection), the duration of abstinence, and also secondary exposure to other drugs of abuse.

The vesicular monoamine transporter (VMAT-2) redistributes monoamines such as DA from synaptic vesicles to the cytosol and is often targeted as a marker of DA neuron terminal integrity. Using [^{11}C]-dihydrotetrabenazine (DTBZ)–PET, Narendran and co-workers found that VMAT-2 availability was decreased in the striatum of subjects dependent on cocaine (Narendran et al. 2012), similar to findings in abstinent methamphetamine-dependent individuals (Boileau et al. 2016).

However, this effect was transient with VMAT-2 availability normalising after protracted abstinence (Boileau et al. 2016). An earlier study by Johanson using the same ligand found that VMAT-2 density was decreased in abstinent MA abusers compared with control subjects (Johanson et al. 2006). In contrast to the previously mentioned study (Boileau et al. 2016), there was no correlation between VMAT-2 levels and the duration of abstinence. This might have been due to the continued use of other drugs during this period including alcohol, cocaine, opiates, and marijuana (Johanson et al. 2006; see Boileau et al. 2008).

The density of the 5-HT transporter (5-HTT) has also been investigated in abstinent stimulant abusers. Binding of the selective 5-HTT ligand [^{11}C]-(+)-McN-5652 was reduced in the anterior cingulate cortex, OFC, dorsolateral PFC, temporal regions, thalamus, caudate, putamen, and the cerebellum of abstinent MA abusers (Sekine et al. 2006). In this study, decreased 5-HTT density in the OFC, anterior cingulate cortex, and temporal regions was associated with higher levels of aggression (Sekine et al. 2006). Diminished 5-HTT availability was also evident in abusers of 3,4-methylenedioxymethamphetamine (MDMA), the principal component of ecstasy, most notably in the cerebral cortex (Kish et al. 2010; Erritzoe et al. 2011; Urban et al. 2012). A recent meta-analysis assessed the effect of MDMA on the 5-HT system. They found that SERT density was significantly decreased across a number of different studies and within different brain regions. However, the authors found no relationship between lifetime episodes of MDMA use and reductions in SERT density, although a relationship between time of abstinence and SERT density was found (Müller et al. 2019). In contrast, Erritzoe et al. (2011) found that the number of lifetime MDMA exposures correlated negatively with both cortical and striatal SERT binding potential (Erritzoe et al. 2011).

22.3 PET/SPECT Studies in ADHD

22.3.1 Studies in Animals

To date there have been very few neuroimaging studies in animal models of ADHD, and clues to the aetiology of this disorder have mainly come from PET and SPECT studies in humans. The efficacy of psychostimulants used to treat ADHD is thought to be mediated by blockade of DAT and NET (Fone and Nutt 2005), thus restoring a presumed underlying deficiency in catecholamine transmission. Our own work has focused on an innate form of impulsivity in rats associated with an increased propensity to anticipate the onset of a visual target cue using a five-choice serial reaction time task (Dalley et al. 2007). Using [^{18}F]-fallypride–microPET, we found that $D_{2/3}$ receptor availability was significantly reduced in the ventral striatum (including the NAcb) but not the dorsal striatum. Interestingly, impulsive rats exposed to, and subsequently withdrawn from, intravenous cocaine self-administration exhibited a selective restoration of deficit $D_{2/3}$ receptors in the ventral striatum, measured by [^{18}F]-fallypride–microPET that was accompanied by a profound decrease in impulsivity (Caprioli et al. 2013). These findings tentatively

suggest that stimulant drugs may exert their clinical effects in ADHD by modulating $D_{2/3}$ receptor signalling in the striatum and such effects may be related to the baseline levels of these receptors (Caprioli et al. 2015).

A recent study in non-human primates evaluating the effect of methylphenidate on impulsive choice and DAT binding reported that low-dose methylphenidate administration primarily reduced impulsive choice action by its effect on DAT binding in the ventral striatum (Martinez et al. 2020). Using [^{11}C]-PE2I, a putative marker of DAT, the authors reported reduced binding potential in the anterior ventral striatum and ventral putamen after low-dose methylphenidate administration. The ventral striatum was subsequently determined to be necessary and sufficient for the observed behavioural effects of methylphenidate.

Other PET investigations in animals include studies of the neurofibromatosis-1 mutant (Nf+/−) mouse, which exhibits a reduced expression of the Nf1 gene (Brown et al. 2010). Children with the neurofibromatosis-1 (NF1)-inherited cancer syndrome develop benign and malignant tumours (Gutmann et al. 1997) and exhibit ADHD-like symptoms (Hyman et al. 2005). A recent [^{11}C]-raclopride–microPET study of Nf1 mutant mice demonstrated that the non-selective attention deficit arises from presynaptic defects in striatal DA homeostasis (Brown et al. 2011). Pharmacological correction of the non-selective attention abnormality was achieved by administering methylphenidate or L-deprenyl, both of which increase striatal DA levels. This murine model may thus represent a useful preclinical platform for microPET imaging studies and the development of therapeutic strategies for NF1-related attention disorder.

22.3.2 Studies in Humans

As the primary target of methylphenidate and other stimulant drugs, DAT has been widely investigated in the context of ADHD (Fone and Nutt 2005; Chu et al. 2018). The first DAT neuroimaging study was conducted in a small group of adults with ADHD using [^{123}I]-altropane–SPECT and showed that DAT levels in non-medicated patients were approximately 70% higher than those in control subjects (Dougherty et al. 1999). However, subsequent research found far smaller increases with some even failing to reach significance (Dresel et al. 2000; van Dyck et al. 2002; Larisch et al. 2006). Dresel and colleagues investigated DAT binding in 17 treatment drug-naïve adults with ADHD and compared this with 10 age- and gender-matched control subjects, measured using ^{99m}Tc-TRODAT-1 SPECT (Dresel et al. 2000). Those with a diagnosis of ADHD exhibited a 17% increase in DAT binding in the striatum compared with control subjects. DAT availability has also been shown to be lower in parents with ADHD offspring when compared to age-matched controls (Tai et al. 2019), potentially highlighting DAT as a neural endophenotype of ADHD. DAT density was also compared in nine treatment-naïve children with ADHD and six without ADHD using [^{123}I]-IPT SPECT; the main findings showed a mean increase in DAT binding in the basal ganglia of ~45% compared to control subjects (Cheon et al. 2003). A more recent study in treatment-naïve adults with ADHD found

decreased $D_{2/3}$ receptor binding in several limbic regions, a finding related to the thickness of the cerebral cortex (Cherkasova et al. 2017). Using [^{11}C]-altropane–PET, Spencer and co-workers found that overall DAT binding was increased by 28% in adults with ADHD relative to control subjects (Spencer et al. 2005). However, an earlier [^{123}I]-β-CIT SPECT study failed to show a difference in striatal DAT density between adult patients with ADHD and control subjects (van Dyck et al. 2002). Furthermore, using [^{123}I]-FP-CIT SPECT, Hesse et al. found that the striatal DAT binding ratio (specific to non-displaceable binding) was reduced in treatment-naïve adults with ADHD (Hesse et al. 2009). These conflicting results may be due to the wide spectrum of symptoms present in those with ADHD as opposed to differences in imaging techniques or the differing profile of receptor specificity of different radioligands.

At clinically effective doses, methylphenidate occupies 50% of the [^{11}C]-cocaine binding sites in the caudate and putamen of healthy volunteers (Volkow et al. 1998) and substantially increases competition with DA at [^{11}C]-raclopride binding sites (Volkow et al. 2002). It has also been shown that methylphenidate lowers DAT availability in both normal subjects and patients with ADHD. Using [^{123}I]-FP-CIT SPECT, Vles et al. investigated the effects of methylphenidate treatment on DAT binding in six patients with ADHD (aged 6–10 years). Following 3-month treatment, striatal DAT binding was reduced by 28–76% (Vles et al. 2003). A poor response to methylphenidate occurs in approximately 30% of patients with ADHD, which may be caused by lower baseline DAT availability than others with ADHD. Krause et al. investigated the relationship between DAT availability and treatment outcome using [^{99m}Tc]-TRODAT-1 SPECT and demonstrated that patients who exhibited a poor response to methylphenidate had reduced DAT availability. In contrast, those with high DAT availability responded well to treatment with methylphenidate (Krause et al. 2005; la Fougère et al. 2006). Using [^{99m}Tc]-TRODAT-1 SPECT, Akay and co-workers investigated the effect of an extended release formulation of methylphenidate over the course of 2 months in adolescents with ADHD. Participants exhibiting the most robust treatment response also showed the greatest reduction of DAT availability in the putamen (Akay et al. 2018).

22.4 Conclusions and Future Perspectives

The research findings reviewed in this chapter demonstrate the extraordinary progress in the discovery of addiction-related biomarkers made possible by translational molecular neuroimaging. After two decades of clinical and basic research, a consensus has emerged that the transition to compulsive stimulant drug seeking must entail pre-existing individual neurobiological risk factors, modified and exacerbated by both drug exposure and contextual variables, including stress. The cascade of molecular mechanisms driving the shift from initial drug use to habitual and ultimately compulsive drug seeking are largely unknown but are, without doubt, critically influenced by predisposing neural and behavioural endophenotypes (e.g. low $D_{2/3}$ receptor availability, impulsivity, novelty/sensation seeking) and by

neuroplasticity mechanisms induced by repeated bouts of drug bingeing and withdrawal (Nader et al. 2008). The great majority of PET studies in this field have been motivated by the indisputable contributions of the brain DA systems to (1) reward (Wise and Hoffman 1992; Everitt and Robbins 2005) (2) the mediation of initial pharmacological effects of virtually all abused drugs (Di Chiara and Imperato 1988), and (3) behavioural traits such as impulsivity and novelty/sensation seeking (Piazza et al. 1989; Dalley et al. 2007; Buckholtz et al. 2010). Additionally, comorbid brain disorders such as ADHD, which critically appear to influence disease progression (Verdejo-García et al. 2008), show remarkable overlaps with addiction with respect to brain DA dysfunction, as reviewed herein. An important question, therefore, is whether the treatment of juveniles with ADHD would curb or even prevent the future development of addiction in adults. A recent PET study in juvenile non-human primates found that early exposure to methylphenidate did not have an impact on the vulnerability to cocaine abuse in older animals nor did this compound influence the regulation of DAT and $D_{2/3}$ receptors in the striatum (Gill et al. 2012; Manni et al. 2019; Jordan et al. 2016). This important study suggests that methylphenidate treatment per se is not a risk factor for addiction. Furthermore, Manni and co-workers evaluated the efficacy of methylphenidate and/or atomoxetine treatment retrospectively on patients who were diagnosed with ADHD and cocaine use disorder. After treatment participants showed an improvement in negative rankings on the Cocaine Problem Severity Index questionnaire (Manni et al. 2019).

Yet, despite these seminal discoveries, there have been surprisingly few therapies developed for stimulant addiction based on the pharmacological modulation of DA transmission (Pierce et al. 2012; Kampman 2019). In hindsight, this provocative failure in rational drug design was perhaps not surprising given current conceptualisations of addiction as a progressive disorder characterised by pervasive and long-lasting disturbances in a complex myriad of neurotransmitter systems which also includes glutamate, GABA, 5-HT, and endogenous opioid systems (Kalivas and Volkow 2011). Remarkably, some of the earliest insights to this notion came from PET studies of non-human primates (Letchworth et al. 2001; Porrino et al. 2002), which exploited a key advantage of molecular neuroimaging, namely, longitudinal assessment of the same subjects.

In turning to the future, it is clear that a more complete understanding of addiction requires the noninvasive imaging of neurotransmitter systems other than the biogenic amines. Corresponding methods for ionotropic glutamatergic receptors are still an area of research under intense development (Fu et al. 2019). Moreover, promising PET ligands have been developed for mGluR1 and mGluR5 receptors (Hostetler et al. 2011; Siméon et al. 2012; Xu and Li 2019), which might eventually emerge as key agents for studies of drug-induced adaptation and the synaptic plasticity underlying addiction (Jones and Bonci 2005; Kauer and Malenka 2007). Using [^{18}F]-FPEB, a putative marker of mGluR5 binding, de Laat and co-workers showed decreased binding bilaterally in the hippocampus during drug exposure and during relapse in an animal model of cocaine use disorder. Moreover, decreased binding was also observed in the prefrontal cortex including the cingulate cortex

after drug exposure (de Laat et al. 2018). Recent reports show novel tracers are being developed with selectivity to specific subunits of the GABA receptor complex (Lin et al. 2017). However, more research is needed to exploit established and novel tracers for GABA receptor imaging (Moran et al. 2012; Andersson et al. 2019), given the evidence of increased $GABA_A$ receptor availability in smokers (Stokes et al. 2013) and GABA dysfunction both in humans with rash impulsivity (Boy et al. 2011) and experimental animals with trait-like impulsivity (Caprioli et al. 2014; Sawiak et al. 2016). Research to develop PET ligands for the noradrenergic system has recently yielded promising agents (e.g. [^{11}C]-O-methylreboxetine), with intriguing results shown in cocaine addicts (Ding et al. 2010) and also in patients with ADHD (Ulke et al. 2019; Sigurdardottir et al. 2019) and trait impulsivity (Hesse et al. 2017). However, despite the abundance of PET ligands targeting 5-HT (e.g. the SERT tracer [^{11}C]-DASB, the 5-HT_{2A} receptor antagonist [^{18}F]-altanserin, and the 5-HT_{1A} receptor antagonist [^{11}C]-WAY-100635), with only a few studies assessing nicotine dependence (e.g. Zhao et al. 2016), serotonin radiotracers have not been comprehensively evaluated in addiction despite preclinical evidence indicating that 5-HT is a promising candidate for mediating compulsive drug seeking (Pelloux et al. 2012). Recently, it has become possible to visualise cannabinoid CB_1 receptors in the living brain using the selective inverse agonist [^{18}F]-MK9470 which may prove to be a useful compound for the assessment of novelty-seeking traits (Van Laere et al. 2009) and putatively impulsivity as well (Wiskerke et al. 2011). Indeed, CB1 receptors are reportedly downregulated in male tobacco smokers (Hirvonen et al. 2018). The application of PET to investigate the endocannabinoid systems in psychiatry has recently been reviewed (Sloan et al. 2019).

Finally, and not least, there has been considerable progress in the development of molecular probes for opioid receptors with utility in addiction research. For example, the distribution volume of the non-selective opioid receptor antagonist [^{11}C]-diprenorphine was globally elevated in acutely abstinent alcoholics, in whom there was a positive correlation with craving, even after prolonged abstinence (Williams et al. 2009). Similar effects have been reported for the selective μ-opioid receptor agonist ligand [^{11}C]-carfentanil, specifically as a predictor for increased relapse rates in acutely abstinent cocaine users (Gorelick et al. 2008), as well as in former alcoholics, where an interaction between decreased binding in the ventral striatum and the OPRM1 gene variant was found to modulate relapse risk (Hermann et al. 2017). In addition, the involvement of the kappa-opioid receptor system in stress-induced relapse has been investigated. For example, binge exposure to cocaine produced a significant reduction in kappa-opioid receptors in the striatum and more globally throughout the brain (Martinez et al. 2019). In a further development, a positive correlation was found between [^{18}F]-fluoroethyl-diprenorphine binding in the ventral striatum and scores on the Cloninger personality dimension of reward dependence, an inventory that predicts drug-seeking propensity (Schreckenberger et al. 2008). Further advances in opioid receptor imaging will undoubtedly be forthcoming with the development of low-potency agonists for use in small animals, as reported recently (Riss et al. 2013), and also reviewed in Cumming et al. (2019).

This chapter has surveyed the unique contribution made by translational neuroimaging to the discovery of biomarkers in stimulant addiction. Although much of this research has inevitably focused on brain DA systems, the recent and rapid increase in the number of molecular probes available for the investigation of other neurotransmitter systems offers exciting prospects for research into entirely novel mechanisms underlying individual risks for addiction.

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SPECT and PET in Eating Disorders

23

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Abstract

Medical imaging techniques like PET and SPECT have been applied for investigation of brain function in anorexia and bulimia nervosa. Regional abnormalities have been detected in cerebral blood flow, glucose metabolism, the availability of several neurotransmitter receptors (serotonin 1A and 2A, dopamine D2/D3, histamine H1, mu-opioid, GABA(A)-benzodiazepine, and cannabinoid CB1), stimulant-induced dopamine release, presynaptic FDOPA influx, and the density of serotonin transporters. Different subtypes of eating disorders appear to be associated with specific functional changes. It is hard to judge whether such changes are a consequence of chronic dietary restrictions or are caused by a putative anorexia (or bulimia) nervosa endophenotype. Many abnormalities (particularly those of glucose metabolism) appear to be reversible after restoration of weight or normal patterns of food intake and may represent consequences of purging or starvation. However, some changes of regional flow and neurotransmitter systems persist even after successful therapy which suggests that these reflect traits that are independent of the state of the illness. Changes of the serotonergic system (altered activity of 5-HT_{1A} and 5-HT_{2A} receptors and 5-HT transporters) may contribute to dysregulation of appetite, mood, and impulse control in eating disorders and may represent a trait which predisposes to the development of anxiety, obsessionality, and behavioral inhibition. Assessment of functional changes in the brain with PET or SPECT may have prognostic value and predict neuropsychological status after several years of therapy.

23.1 Introduction

Anorexia nervosa (AN, literally nervous inability to eat) is a psychiatric disorder with four important diagnostic features:

1. An unrealistic but intense fear of weight gain.
2. A conspicuous distortion of body image. Even though serious underweight is present, the patient feels fat and is obsessed with becoming thinner.
3. A body weight smaller than 85% of the value expected for the individual's height and age or—in the case of children—a failure to gain weight with increasing age. Food intake is limited so much that health is compromised—in some cases to the point of death.
4. Amenorrhea (females missing at least three subsequent menstrual periods after menstruation has been established) or a delayed puberty (the first menstruation occurring at an exceptionally advanced age) (American Psychiatric Association 2000). This last criterion was removed in DSM-5.

Two major subtypes of anorexia have been distinguished. Restrictive anorexics rigorously limit their food intake. They may also exercise excessively or abuse drugs which promote weight loss, but they never engage in binge eating. Purge-type

anorexics show repeated cycles of binge eating and purging. For short periods of time (usually less than 2 h), they eat excessively large amounts of food. Subsequently, they initiate a purging process which may involve heavy exercise, self-induced vomiting, and misuse of laxatives (or enemas) and diuretics.

Most subjects with anorexia nervosa are women (>90%). The onset of the disorder is usually either at adolescent age (13–18 years) or at midlife (age 40–50 years).

Bulimia nervosa (BN, literally nervous extreme hunger) shares many characteristics with purge-type anorexia (Russell 1979). However, bulimic individuals are typically at normal or high normal weight, in contrast to anorexics which are emaciated. In order to be characterized as bulimics, subjects should engage in cycles of binge eating and purging at least two times per week for a period of at least 3 months. During episodes of binge eating, they consume excessive amounts of calories, up to four times as much as healthy volunteers, but during non-binge meals, they eat significantly less than controls (Heaner and Walsh 2013). In DSM-5, the threshold for the diagnosis of BN has been lowered, so that once-a-week binge eating and purging is sufficient to be diagnosed as a bulimic.

Both eating disorders are considered as a serious public health problem in Western societies. Self-imposed food restriction may lead to health complications, such as growth retardation, dental problems, constipation, stomach rupture, anemia, congestive heart failure, kidney failure, electrolyte imbalance, and osteoporosis. Repeated purging can result in heartburn (a burning feeling in the chest because of acid entry in the esophagus), esophageal inflammation, damage to tooth enamel, and acid-related scarring of the fingers. Most anorexics (and bulimics) experience depression and anxiety. Anorexia has one of the highest mortality rates of any psychiatric disorder (estimated as at least 5%) (Roux et al. 2013).

Binge eating disorder (BED) resembles BN in many respects, but is not associated with purging. Thus, individuals with BED display loss of control, repetitive binge eating episodes, and marked distress concerning binge eating (de Zwaan et al. 1993). However, the definition of precise criteria to identify BED as a psychiatric syndrome has remained difficult (Williamson and Martin 1999; Cooper and Fairburn 2003; Klein et al. 2016).

Medical imaging techniques such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) can provide insights into the physiological and biochemical alterations of the human brain that are associated with eating disorders. Because of the aim of this book series, the current chapter is focused on observations made with PET and SPECT. Comprehensive reviews on imaging findings in AN and BN were published in recent years (Donnelly et al. 2018; Bargiacchi 2014; Phillipou et al. 2014; Frank 2012; Frank and Kaye 2012; Jauregui-Lobera 2011; Kaye 2008).

23.2 Anorexia and Brain Perfusion

Several SPECT studies have focused on abnormalities of cerebral perfusion in anorexia nervosa. The initial study of this kind was already performed in 1989. Regional cerebral blood flow (rCBF) was measured in the resting state using a ^{133}Xe

inhalation method. The study population consisted of 12 female patients (age 16–27) and a healthy control group (age 19–37 years, 5 females and 7 males). The patients were examined both at the time of admission and after a period of treatment and weight gain. No significant differences between patients and controls (or between the two patient scans) were observed (Krieg et al. 1989). It should be noted that the average age of the control group was 10 years higher than the patient group; moreover, the control group was not sex matched.

A subsequent study measured the flow response to a food stimulus (eating of a custard cake). The hypothesis of this paradigm is that rCBF in certain cortical areas will increase after presentation of the stimulus, and the magnitude or regional extent of that increase may be different in patients and healthy controls. The study population consisted of seven female AN patients (age 19 ± 5 years) and five gender- and age-matched healthy subjects. Cerebral blood flow was measured with the tracer ^{99m}Tc-hexamethylpropylene amine oxime (HMPAO), before and after presentation of the stimulus, both at the time of admission and after 2–3 months of therapy. Before therapy, anorexics demonstrated a significant 7–9% increase in rCBF in the inferior frontal cortex in response to the food stimulus. After therapy, the response was no longer observed, and it was also absent in the control group (Nozoe et al. 1993). The study data can be interpreted as evidence for activation of the arousal system in untreated patients (who, in contrast to normal subjects, felt discomfort while eating the cake).

A later study examined the regional pattern of cerebral perfusion (^{99m}Tc-HMPAO-SPECT) in two female anorexia patients at the time of diagnosis and after remission of symptoms, which involved more than 1 year of therapy. Diffuse, bilateral hypoperfusion was observed during the first SPECT scan in frontal, parietal, and frontotemporal areas, particularly in the left hemisphere. After symptom remission, the pattern of rCBF became normal (Kuruoglu et al. 1998). Thus, there seems to be state-related hypoperfusion in AN. A Swedish study (Rastam et al. 2001) compared ^{99m}Tc-HMPAO-SPECT scans in 21 patients with adolescent-onset AN (19 females, 2 males, mean age 22 years) to similar scans in a very young patient group without neuropsychiatric disorder who underwent SPECT for cardiovascular or oncologic indications (5 females, 4 males, age 10 years). Anorexic patients showed reduced perfusion in temporal, parietal, occipital, and orbitofrontal lobes compared to the control group. This finding was suggestive of AN-related hypoperfusion, although some of the flow changes could also be related to the age difference between the study groups. This study also showed reduced cerebral blood flow (to 66%) in temporal and associated areas, with no correlation with body mass index, residual eating disorder psychopathology, or intelligence quotient.

In a more extended activation study, ^{99m}Tc-HMPAO-SPECT was used to measure changes of rCBF in seven female patients with purely restrictive anorexia, seven female AN patients with habitual binge/purge behavior, and seven age-matched, healthy female volunteers. The stimulus consisted of visualizing a custard cake followed by imagining its eating. Binge/purge anorexics showed significant increases of flow in the inferior, superior, prefrontal, and parietal regions of the right hemisphere, in contrast to purely restrictive anorexics or healthy volunteers (Naruo et al.

2000). This observation may indicate that the perception of food is different in binge/purge anorexics, resulting in greater anxiety in this patient group. Indeed, binge/purge anorexics scored higher levels of apprehension in regard to food intake than either restrictive anorexics or healthy controls.

Using ^{99m}Tc-HMPAO-SPECT and statistical parametric mapping (SPM) analysis, a follow-up study (Naruo et al. 2001) examined cerebral perfusion patterns during the resting state in the same three subject groups as were mentioned above. Restrictive anorexics showed a significantly reduced rCBF in frontal areas (especially the anterior cingulate cortex), which was not noticed in binge/purge anorexics or healthy volunteers. Since the anterior cingulate cortex is involved in mood regulation, attention control, and the cognitive process of selection following somatosensory stimuli, reduced blood flow in this area may be related to disturbances of perception and emotional control in patients with restrictive anorexia. Similar findings were reported in a study which employed SPM, ^{123}I-iodoamphetamine (^{123}I-IMP), and SPECT to examine rCBF in eight restrictive anorexics, six binge/purge anorexics, and eight healthy controls (all female). Anorexics showed hypoperfusion in the medial prefrontal cortex and the anterior cingulate gyrus. In addition, they demonstrated increased perfusion in the thalamus, amygdala, and hippocampus (Takano et al. 2001). In a rather recent ^{99m}Tc-HMPAO study, involving 13 restrictive anorexics, 13 binge/purge anorexics, and a healthy control group (10 women), bilaterally decreased perfusion was noted during the resting state in the patients, but no significant differences were observed between the patient groups (Yonezawa et al. 2008).

Activation studies measuring, directly or indirectly, cerebral blood flow have shown changes in certain areas of the brain. When patients with anorexia nervosa are exposed to food and examined with functional MRI, SPECT, or PET, an activation was noted in the insula, orbitofrontal cortex, prefrontal cortex, anterior cingulate, and temporal lobes (Nozoe et al. 1993; Uher et al. 2004). An activation study with the tracer ^{15}O-CO_2, positron emission tomography (PET), and SPM analysis examined rCBF during exposure to three types of visual stimuli: high-calorie foods, low-calorie foods, and nonfood items. A group of eight female patients with anorexia nervosa was compared to eight healthy female control subjects. When high-calorie foods were presented, control subjects reported a significant desire to eat, whereas patients reported anxiety. The patient group showed bilateral elevations of rCBF in the medial temporal lobe compared to the control group. In the left occipital cortex and right temporo-occipital cortex of the patient group, high-calorie food induced greater increases of rCBF than the low-calorie stimulus. These findings resemble results obtained in patients with psychotic disorders, in the sense that food phobia appears to be associated with exaggerated responses in the visual association cortex (Gordon et al. 2001).

Three studies employed ^{99m}Tc-HMPAO and SPECT to examine rCBF in anorexic children. More than half of the patients showed a left temporal lobe hypoperfusion, which did not disappear after regaining normal weight (Gordon et al. 1997). This might reflect primary functional changes related to the disorder rather than brain starvation. In the second study (Chowdhury et al. 2003), asymmetric hypoperfusion

was sometimes also noticed in the parietal lobe, frontal lobe, thalamus, and caudate nuclei. Patients with a deficit of perfusion had higher median Eating Disorders Examination subscale scores than those without. Temporal lobe asymmetry may thus reflect a neurologic abnormality that contributes to the development of anorexia. In the third study, 75% of the patients with early-onset AN were found to show a unilateral reduction of blood flow in the temporal lobe. This reduction was not associated with nutritional status, length of illness, and mood or eating disorder psychopathology, but significantly associated with impaired visuospatial ability, impaired complex visual memory, and enhanced speed of information processing in the patient group (Lask et al. 2005).

A later ^{99m}Tc-HMPAO-SPECT study examined changes in resting rCBF before and after weight gain in 12 female patients with restrictive anorexia nervosa (age 18.6 ± 3.5 years). A control group of 11 normal females (age 21.8 ± 2.1 years) was also included. At the time of the first scan, the patients had lower rCBF in the bilateral anterior lobes, right parietal lobe, insula, and occipital lobes. After weight gain, flow in the right parietal lobe was increased, but reduced flow in the anterior cingulate cortex persisted. Lower body mass index in the patient group was associated with lower rCBF in the occipital lobes. Apparently, rCBF in some brain areas of anorexic individuals normalizes after weight gain. Decreases of flow in these areas may thus be state-related. However, rCBF in the anterior cingulate cortex appears unaffected by treatment and may reflect abnormal brain function related to the clinical features of restrictive anorexia (Kojima et al. 2005). This should be considered as a tentative conclusion, since the recovery of body weight by the patients after treatment was far from complete. Another study which employed ^{123}I-IMP SPECT to assess rCBF in anorexic patients reported increases of flow after inpatient-behavioral therapy in several brain areas, including the anterior cingulate cortex (Matsumoto et al. 2006). However, this study was limited by the small size (n = 8) and heterogeneous character of the patient group, three patients being restrictive and the other five binge/purge anorexics. A third SPECT study of this kind was performed in ten young girls (average age 13 years) with anorexia nervosa. Because of the young age of the patient group, a similar group of healthy controls could not be included for ethical reasons. Relative increases of rCBF during recovery were observed in the bilateral parietal lobe and limbic lobe including the posterior cingulate cortex. Flow changes in the last area could reflect affective changes related to eating motivation after successful therapy (Komatsu et al. 2010). Another ^{99m}Tc-HMPAO-SPECT study involved nine patients with early-onset AN (at age lower than 15 years) who were scanned again after 4.2 years of treatment. Seven out of these nine patients showed reductions of cerebral blood flow which persisted even after long-term therapy, particularly in the medial temporal region. Thus, this study suggested that in a substantial number of cases, rCBF does not return to normal after weight restoration (Frampton et al. 2011).

The Stroop interference task (SIT) is a popular neuropsychological test examining the ability of a subject to correctly process information in the presence of interfering stimuli. An interesting SPECT study using ^{99m}Tc-ethyl cysteinate dimer

(ECD) compared brain perfusion in the resting state with scores in the SIT test in 16 patients with anorexia nervosa (11 restrictive, 5 binge/purge individuals). Four patients scored abnormally low in the neuropsychological test, and within the entire group, a significant correlation was observed between the SIT score and rCBF in the superior frontal gyrus of both hemispheres. These findings can be interpreted as evidence for impaired error detection and immediate correction in anorexic individuals (Ferro et al. 2005).

A final ^{99m}Tc-HMPAO-SPECT study examined whether rCBF at initial presentation predicts neuropsychological status after 4 years of therapy. The study group consisted of 15 children with early-onset anorexia nervosa and 15 healthy controls. Some patients with early-onset anorexia nervosa appeared to have no measurable perfusion abnormalities. Patients with hypoperfusion in the SPECT scan showed significantly lower scores for delayed visual recall and higher scores for verbal inhibition than healthy controls after 4 years. However, patients with normal perfusion in the SPECT scan showed similar scores as controls for delayed visual recall, visual object recognition, verbal fluency, cognitive inhibition, switching, planning, and verbal inhibition in all neuropsychological tests after 4 years, even though some of them suffered from a persistent eating disorder. Thus, rCBF at initial presentation seems to predict neuropsychological status at 4-year follow-up (Frampton et al. 2012).

An interesting arterial spin labeling MRI study investigated whether former AN patients (21 women remitted from restricting-type AN, age 24 ± 2 years) and healthy female control subjects (n = 16, age 27 ± 2 years) showed a different response of cerebral blood flow to hunger and satiety. All subjects were scanned after a 16-h period of fasting and just after eating a meal. In three brain regions (right ventral striatum, right subgenual anterior cingulate cortex, and left posterior insula), the former AN patients demonstrated a significantly different flow response to hunger than the control group. Whereas healthy subjects showed an increased flow in the hungry compared to the fed condition, former AN patients had decreased flow when hungry compared to being fed. Decreased flow in the left insula was associated with higher self-report assessments of hunger on the fasting day in the former patient group (Wierenga et al. 2017). This study indicated that even after successful treatment, women remitted from AN have aberrant blood flow changes in homeostatic neural circuits in response to hunger.

In conclusion, most studies suggest that AN is associated with hypoperfusion in several brain areas (Table 23.1). Blood flow may normalize in most regions after successful therapy but remain low in others, particularly the anterior cingulate cortex. A subgroup of patients appears to display a normal pattern of regional blood flow even prior to therapy. Reductions of flow in early-onset anorexia may be predictive of persisting neuropsychological problems at adolescent age. An extensive review of functional neuroimaging in anorexia nervosa (SPECT, PET, and fMRI) was published in 2009 (van Kuyck et al. 2009).

It should be noted that intracranial tumors may masquerade as early-onset anorexia nervosa. Such tumors can be detected using SPECT, PET, or other medical imaging techniques (O'Brien et al. 2001).

Table 23.1 Studies of rCBF in the resting state

Study groups	Study moment	Tracer	Findings	After therapy	Reference
AN, control	Pre-/post-therapy	^{133}Xe	No difference	No difference	Krieg et al. (1989)
AN	Pre-/post-therapy	^{99m}Tc-HMPAO	↓ fro, par, frotem (bilateral)	Normalization	Kuruoglu et al. (1998)
AN, control	Only 1 session	^{99m}Tc-HMPAO	↓ tem, par, occ, orbfro	–	Rastam et al. (2001)
R-AN, BP-AN, control	Only 1 session	^{99m}Tc-HMPAO	↓ fro (acc) in R-AN only	–	Naruo et al. (2001)
R-AN, BP-AN, control	Only 1 session	^{123}I-IMP	↓ acc, mpc ↑ th, am, hip	–	Takano et al. (2001)
R-AN, BP-AN, control	Only 1 session	^{99m}Tc-HMPAO	↓ bilaterally (R-AN, BP-AN)	–	Yonezawa et al. (2008)
AN	Pre-/post-therapy	^{99m}Tc-HMPAO	↓ left tem	Persisting	Gordon et al. (1997)
AN	Only 1 session	^{99m}Tc-HMPAO	↓ left tem a.o.	–	Chowdhury et al. (2003)
AN	Only 1 session	^{99m}Tc-HMPAO	↓ left tem lobe	–	Lask et al. (2005)
R-AN, control	Pre-/post-therapy	^{99m}Tc-HMPAO	↓ ant, right par, ins, occ	Persisting in acc	Kojima et al. (2005)
AN	Pre-/post-therapy	^{123}I-IMP	↓ many brain areas	Normalization	Matsumoto et al. (2006)
AN	Pre-/post-therapy	^{123}I-IMP	↓ many brain areas	Normalization	Komatsu et al. (2010)
Early-onset AN	Pre-/post-therapy	^{99m}Tc-HMPAO	↓ many brain areas	Persisting (med tem)	Frampton et al. (2011)
R-AN, BP-AN	SIT test	^{99m}Tc-ECD	↓ sup fro gyrus = ↓ test score	–	Ferro et al. (2005)
Early-onset AN, control	Only 1 scan session	^{99m}Tc-HMPAO	↓ only in some patients	Lower test scores	Frampton et al. (2012)
R-AN, control	Post-therapy, hungry vs fed	None (MRI)	↓ when hungry, controls ↑ when hungry (compared to fed)	–	Wierenga et al. (2017)
BN, AN, control	Only 1 session	^{99m}Tc-HMPAO	↓ AN left par, ↑ BN left tem a.o.	–	Nozoe et al. (1995)
BN (1 subject)	No therapy	^{123}I-IMP	↑ in binge than in purge phase; asymmetry only in purge phase	–	Hirano et al. (1999)

Table 23.1 (continued)

Study groups	Study moment	Tracer	Findings	After therapy	Reference
BN, control	Post-therapy	^{15}O-Water	No differences any more	Normalization (from ↑ in ctx and left th)	Frank et al. (2000)
BN, BP-AN, R-AN, control	Post-therapy	^{15}O-Water	No differences any more	Normalization (from ↑ in BN and ↓ in AN)	Frank et al. (2007)
BN, BP-AN, R-AN	Only 1 session	^{99m}Tc-ECD	Perfusion covaries only with body dissatisfaction/ ineffectiveness	–	Goethals et al. (2007a)

acc anterior cingulate cortex, *am* amygdala, *AN* anorexia nervosa, *ant* anterior, *BN* bulimia nervosa, *BP-AN* binge/purge type of anorexia nervosa, *ctx* cortex, *ECD* ethyl cysteinate dimer, *fro* frontal, *frotem* frontotemporal, *gyr* gyrus, *hip* hippocampus, *HMPAO* hexamethylpropylene amine oxime, *IMP* iodoamphetamine, *ins* insula, *med* medial, *mpc* medial parietal cortex, *occ* occipital, *orbfro* orbitofrontal, *par* parietal, *R-AN* restrictive type of anorexia nervosa, *sup* superior, *tem* temporal, *th* thalamus

23.3 Bulimia and Brain Perfusion

An initial ^{99m}Tc-HMPAO-SPECT study in bulimia nervosa compared rCBF in five patients with bulimia (age 21.0 ± 2.9 years), eight patients with anorexia (age 24.1 ± 7.8 years), and nine healthy controls (age 20.3 ± 1.0 years). Blood flow was measured before and after eating a custard cake. Flow was expressed as ratio units, by comparing tracer uptake in a brain region to uptake in the cerebellum. Differences between the groups were observed only during the first scan. Whereas anorexics showed *reduced* flow in the left parietal region, bulimics demonstrated significantly *increased* flow in the bilateral inferior frontal and left temporal regions compared to the control group. Flow increases were noted in anorexics, and flow decreases in bulimics after eating; thus, any differences between the groups were abolished by the food stimulus (Nozoe et al. 1995). Since the frontal cortical area of the brain controls feeding together with the hypothalamus, flow differences in frontal regions may reflect disease-related differences in cortical function. Frontal lobe damage can result in hyperphagia; thus, dysfunction of this brain area could be related to binge eating in bulimics.

A case report examined rCBF in a male patient with bulimia nervosa (age 27 years), first during a period of purging and, 22 days later, during binge eating, using ^{123}I-IMP and SPECT. Global CBF was higher during the binge eating phase than during the purge phase. In the purge phase, an asymmetric pattern was noted, with lower values for rCBF in the right temporal, parietal, and occipital lobe. This asymmetry disappeared during binge eating. Thus, rCBF differs between the two phases of bulimia nervosa, and flow asymmetry is dependent on the eating state (Hirano et al. 1999).

A subsequent study examined rCBF in nine women with bulimia nervosa who had recovered from their disorder by showing stable food intake, normal weight, and regular menses for a period of more than 1 year. rCBF was measured with the tracer [^{15}O]water and PET, and flow patterns were compared to those of an age-matched healthy control group (13 females). Significant differences between the groups were not observed, but rCBF in several cortical areas and the left thalamus was significantly and inversely related to length of recovery in the patient group (Frank et al. 2000). Apparently, differences in rCBF between bulimics and controls are state-related and disappear during recovery.

A later [^{15}O] water PET study compared rCBF in 10 women who had recovered from restrictive anorexia, 8 women who had recovered from binge/purge anorexia, 9 women who had recovered from bulimia, and 18 healthy control subjects. Partial volume-corrected rCBF values in the four groups were not significantly different in any brain region. Thus, rCBF appears to normalize after recovery not only in bulimics but also in subjects with anorexia nervosa (Frank et al. 2007).

An interesting PET study with ^{15}O-water has suggested a vagal pathophysiology for bulimia nervosa and the accompanying depressive symptoms. Mechanical distention of the stomach with a balloon in female healthy volunteers and the associated vagal stimulation was shown to result in activation of several brain areas, including areas which are involved in the emotional aspects of eating (lateral inferior frontal and orbitofrontal cortex) and in the symptoms of depression (anterior cingulate cortex). The hypothesis that vagal afferent activity is involved in the cycles of binge eating and vomiting in bulimia nervosa with their associated symptoms of depression was subsequently tested in two ways: first, pain detection thresholds were examined in patients with BN and were found to fluctuate in association with bulimic episodes, suggesting fluctuation of vagal activity. A double-blind treatment protocol of bulimic individuals was then carried out with the serotonin 5-HT$_3$ antagonist ondansetron. This treatment significantly decreased binge eating and vomiting in BN patients, abolished the fluctuation in pain thresholds, and reduced the depressive symptoms. These findings were interpreted as evidence for the hypothesis that cyclic increases in vagal activity drive the urge to binge eat and vomit (Faris et al. 2006).

A large ^{99m}Tc-ECD SPECT study examined rCBF in 67 female patients with eating disorders (31 restrictive anorexics, 16 binge/purge anorexics, and 20 bulimics). SPM analysis was applied to the SPECT data, and brain areas were identified in which perfusion covaried with symptoms measured by the Eating Disorder Inventory. The only significant correlation observed was a positive correlation between scores on body dissatisfaction and ineffectiveness and rCBF in the prefrontal and parietal cortex (Goethals et al. 2007a). Based on this finding, the authors argued that neurobiological findings in eating disorders, such as changes in the serotonergic system, may reflect not only emotional and behavioral factors (e.g., decreased impulse control) but also cognitive-evaluative features: attention, memory, and judgment being continuously affected by an overconcern with eating, body size, and shape.

This hypothesis was explored in a later study in which rCBF was measured with ^{99m}Tc-HMPAO and SPECT in 34 subjects (9 restrictive anorexics, 13 bulimics, and 12 healthy controls) under three different conditions: at rest, after viewing a neutral stimulus (landscape video), and after viewing their own-filmed body image (positive stimulus). Anorexics showed a hyperactivation of the left parietal and right superior frontal cortex by the positive as compared to the neutral stimulus. Bulimics showed a hyperactivation of the right temporal and right occipital areas. Activation of the right temporal lobe may reflect an aversive response and abnormal activation of the left parietal lobe the storage of a distorted prototypical image of the body (Beato-Fernandez et al. 2009). In a follow-up study performed in the same subjects, the right temporal lobe activation in bulimics was shown to persist even after 1 year of participation in a treatment program for eating disorders (Rodriguez-Cano et al. 2009). Thus, although progress was made in the control of purging symptoms, mood (depression), and self-esteem, the aversive response of the patients toward their own body shape was still present after 1 year, and more specific long-term therapies are needed for the treatment of body dissatisfaction.

In summary, using either SPECT or PET, abnormal activation of certain brain areas has been detected both in BN and AN after presentation of various stimuli, related either to food intake or body shape (Table 23.2). These responses have been interpreted as symptoms of anxiety or phobia. Most abnormalities disappear after successful treatment, but abnormal activation of the right temporal lobe may persist in BN and reflect persistence of body dissatisfaction.

Table 23.2 Studies of rCBF (activation paradigm)

Study groups	Study moment	Stimulus	Tracer	Findings	After therapy	Reference
AN, control	Pre-/post-therapy	Cake eating	^{99m}Tc-HMPAO	↑ inf fro ctx in AN	Normalization	Nozoe et al. (1993)
R-AN, BP-AN, control	Only 1 session	Imagined eating	^{99m}Tc-HMPAO	↑ right hs in BP-AN	–	Naruo et al. (2000)
AN, control	Only 1 session	Visual (food)	$^{15}O–CO_2$	↑ med temp	–	Gordon et al. (2001)
BN, R-AN, control	Pre-therapy	Visual (body)	^{99m}Tc-HMPAO	↑ fro ctx (AN), ↑ ri tem occ (BN)	–	Beato-Fernandez et al. (2009)
BN, R-AN, control	Post-therapy	Visual (body)	^{99m}Tc-HMPAO	↑ ri tem (BN only)	Normalization AN, persisting BN	Rodriguez-Cano et al. (2009)

AN anorexia nervosa, *BN* bulimia nervosa, *BP-AN* binge/purge type of anorexia nervosa, *Ctx* cortex, *HMPAO* hexamethylpropylene amine oxime, *hs* hemisphere, *Inf* inferior, *med* medial, *occ* occipital, *R-AN* restrictive type of anorexia nervosa, *ri* right, *tem* temporal

23.4 Anorexia and Cerebral Metabolism of Glucose

The first study of cerebral glucose metabolism in anorexia nervosa was published in 1987. Five female anorectic patients were scanned with PET and the tracer FDG, both during the anorectic state and after behavioral therapy. Scans were made in the resting state, with eyes closed and ears unplugged. Significant bilateral hypermetabolism in the caudate nucleus was observed in the anorectic state in comparison with results obtained after weight gain (Herholz et al. 1987). A subsequent study included nine patients with bulimia and seven patients with anorexia. Relative glucose metabolism in the caudate, compared to the rest of the brain, was significantly higher in anorexia than in bulimia (Krieg et al. 1991). These findings could be interpreted as high motor activity in the anorexic patients resulting in increased dopamine turnover in the caudate nucleus and metabolic hyperactivity.

A more extensive study appeared in 1995. FDG-PET scans were made during rest, with eyes closed and with low ambient noise, in 20 underweight anorectic girls and 10 age-matched healthy female volunteers. Compared to controls, the patients showed a global hypometabolism, the most striking difference being present in the frontal and parietal cortex (Delvenne et al. 1995). The observed hypometabolism might reflect a primary cortical dysfunction underlying anorexia nervosa, but it could also be related to physiological or morphological changes as a consequence of starvation or to depression in the patient group. A subsequent study examined cerebral glucose metabolism in ten anorectic girls, both at the onset of therapy and after weight gain. Ten age-matched healthy females were used as controls. In the underweight state, patients showed the same hypometabolism as was observed previously, but after weight gain, cerebral glucose metabolism normalized, and patient data were no longer significantly different from those acquired in controls although a trend toward inferior metabolism in some brain areas was still apparent (Delvenne et al. 1996). For this reason, glucose hypometabolism appears to be state- rather than trait-related. A third FDG-PET study included ten underweight females with anorexia nervosa, ten underweight depressed patients, and ten depressed patients with normal weight (all age- and sex-matched). Absolute values for glucose metabolic rate were significantly correlated with body mass index in all subjects; the lowest values were observed in the anorexic group. Thus, glucose hypometabolism seems to be a consequence of low weight (Delvenne et al. 1997a). The hypothesis that cerebral hypometabolism of glucose is a consequence of starvation was confirmed in a further study which compared FDG-PET scans of ten young depressed patients with low weight without anorexia nervosa with those of ten age- and sex-matched healthy volunteers. Absolute global and regional metabolic rates of glucose were significantly lower in the patient group than in the control group (Delvenne et al. 1997b). One factor that could partially explain the described findings is the downregulation of glucose transporters under nutrient starvation (Merrall et al. 1993), since these proteins are involved in uptake of FDG from the blood.

A more recent PET study involved 14 women with anorexia nervosa, 20 aged-matched healthy control subjects, and the same group of anorexics after randomization to 3 weeks of low-dose replacement testosterone therapy or placebo. The study

confirmed that cerebral glucose metabolism is significantly reduced in several cortical areas of anorexics as compared to controls. Testosterone therapy resulted in increases of metabolism in many areas including one region (posterior cingulate) which had previously shown hypometabolism (Miller et al. 2004). The clinical significance of this finding should be further examined.

In several PET studies (Delvenne et al. 1997a, 1999), relative glucose metabolism in the parietal cortex of anorexics was shown to be significantly decreased compared to controls and significantly increased in the caudate nucleus. Similar decreases of relative glucose metabolism were also noted in the parietal cortex of patients with bulimia; thus, it appears to be a common feature in both eating disorders (Delvenne et al. 1999).

Two PET studies have examined changes of cerebral glucose metabolism in an animal model of anorexia nervosa. In the first study, female Wistar rats received either free access to food or were severely restricted in their food intake until a 30% weight loss occurred. Body weight was then maintained at 70% of the control value by adjusting daily food intake and by providing free access to a running wheel. The tracer ^{18}F-FDG was administered intraperitoneally and was allowed to be distributed in the body of the awake animals for 50 min before the rats were anesthetized and scanned. Absolute values for glucose metabolic rate could not be determined by this protocol (since an arterial input function was missing), but relative glucose metabolism was found to be significantly altered in the food-deprived animals, decreases being noted in the hippocampus and striatum and increases in the cerebellum (Barbarich-Marsteller et al. 2005). The second study used a somewhat different approach. Here, food restriction (1.5 h instead of 24 h/day) and running wheel access were combined from the beginning. Animals were scanned after 9 days, when body weight in the food-restricted/exercised group had declined by 20%. FDG was not allowed to be distributed in awake but in pentobarbital-anesthetized rats, and the study used male animals rather than females. Decreases of glucose metabolic rate were observed in cortical areas and striatum, whereas increases occurred in the mediodorsal thalamus, ventral pontine nuclei, and cerebellum. Brain metabolism in the cingulate and the surrounding motor and somatosensory cortex was positively correlated to weight loss (van Kuyck et al. 2007). Both studies suggested that changes of cerebral metabolism can be detected with PET in animal models of anorexia nervosa and that these changes are related to loss of body weight.

A Chinese study used ^{18}F-FDG-PET and SPM to detect regional differences of glucose metabolism in the brain of AN patients ($n = 6$, all female, age 17 ± 1 years) compared to healthy controls ($n = 12$, all female, age 24 ± 3 years). The patients demonstrated increased metabolism in the frontal lobe, bilateral hippocampus, amygdala, and lentiform nucleus, left insula, and left subcallosal gyrus. Decreased metabolism was observed in the parietal lobe (on both sides of the brain). Four patients were subsequently treated with deep brain stimulation (DBS) in the nucleus accumbens, for a period of 3–6 months. DBS reduced the hypermetabolism in the frontal lobe, hippocampus, and lentiform nucleus in this patient group (Zhang et al. 2013). The observed metabolic differences between AN patients and controls may be related to AN symptoms such as a distorted perception of body image, lack of

recognition of the symptoms of malnutrition, distorted emotions associated with food-related stimuli, and aberrant responses to these stimuli.

A Canadian pilot study evaluated how cerebral glucose metabolism correlates with clinical improvement after DBS of the subcallosal cingulate in patients with anorexia nervosa. The authors showed that reversal of abnormalities seen in the anterior cingulate, insula, and parietal lobe at baseline (i.e., before DBS) is strongly correlated with the clinical benefits caused by this kind of therapy besides some adverse effects associated with DBS (Lipsman et al. 2013). A follow-up study from the same group monitored the impact of DBS of the subcallosal cingulate after a treatment period of 1 year in 16 patients with treatment-refractory AN. Although adverse events occurred in a substantial number of patients ($n = 7$), mean body mass index was significantly increased (from 13.8 ± 1.5 to 17.3 ± 3.4), and measures of depression, anxiety, and affective regulation were significantly improved. These beneficial consequences of treatment were associated with decreases of cerebral glucose metabolism (^{18}F-FDG-PET) in several brain areas (frontal gyri, caudate/putamen, thalamus, globus pallidus, cerebellum) and increases in some posterior cortical regions (Lipsman et al. 2017). The authors concluded that in patients with chronic (avg 18 years) treatment-refractory AN, DBS is well tolerated and associated with significant improvement of many disease symptoms.

Various studies, both in experimental animals and humans, have indicated that both DBS and electroacupuncture at acupoints result in changes of cerebral glucose metabolism and may be beneficial in the treatment of refractory AN. Thus, Chinese authors hypothesized that changes of regional ^{18}F-FDG uptake after electroacupuncture may serve as a biomarker to predict the therapeutic effect of DBS (Liu et al. 2015). Since DBS is an invasive form of therapy with associated risks, it seems important to apply DBS only in subjects which may benefit from this approach. However, the Chinese hypothesis has not yet been tested.

To summarize the findings in humans, most PET studies have reported cerebral hypometabolism in patients with AN as compared to controls, particularly in the frontal and parietal cortex (Table 23.3). Such hypometabolism appears to be a consequence of starvation rather than a trait leading to the development of anorexia. The ratio of metabolism in caudate nucleus to the rest of the brain is increased in anorexia. This may be a symptom of excessive motor activity in anorexics.

23.5 Anorexia and Brown Fat Activity

For a long time, brown adipose tissue was considered to exist only in young children. However, whole-body ^{18}F-FDG-PET scans revealed that brown fat also exists in some human adults where it may play a significant role in total body metabolism. For this reason, Italian researchers examined several groups of young females in underweight condition: seven subjects with constitutional leanness (CL), seven subjects with AN, seven subjects with AN after stable refeeding, and an aged-matched control group with normal weight ($n = 24$). In CL subjects, the body does not store significant amounts of fat, even in overfeeding conditions. The PET scans revealed the presence of brown fat in all subjects with CL and in

Table 23.3 Studies of CMR glucose in the resting state

Study groups	Study moment	Tracer	Findings	After therapy	Reference
AN	Pre-/post-therapy	^{18}F-FDG	Rel ↑ cau nuc	Normalization	Herholz et al. (1987)
AN, BN	Only 1 session	^{18}F-FDG	Rel ↑ cau nuc in AN	–	Krieg et al. (1991)
AN, control	Only 1 session	^{18}F-FDG	↓ globally in AN	–	Delvenne et al. (1995)
AN, control	Pre-/post-therapy	^{18}F-FDG	↓ globally in AN	Normalization	Delvenne et al. (1996)
AN, dep uw, dep nw	Only 1 session	^{18}F-FDG	CMRglucose correlates with BMI	–	Delvenne et al. (1997a)
Dep uw, control	Only 1 session	^{18}F-FDG	↓ in uw group	–	Delvenne et al. (1997b)
AN, control	Pre-/post-therapy	^{18}F-FDG	↓ in AN ctx areas	Normalization	Miller et al. (2004)
AN, control	Pre/post DBS	^{18}F-FDG	↑ fro lobe, hip, amy, lentiform nuc, left ins, left sc ↓ par lobe	Normalization (fro lobe, hip, lentiform nuc)	Zhang et al. (2013)
AN, BN, control	Only 1 session	^{18}F-FDG	Rel ↓ par ctx, rel ↑ cau nuc AN, BN	–	Delvenne et al. (1997a, 1999)
BN, control	Only 1 session	^{18}F-FDG	Not different, ant prefro correlated to depression	–	Andreason et al. (1992)
BN, control	Only 1 session	^{18}F-FDG	↓ globally in BN, rel ↓ in par ctx. CMRglucose *not* correlated with BMI or depression	–	Delvenne et al. (1997c)

AN anorexia nervosa, *ant* anterior, *BN* bulimia nervosa, *cau* caudate, *dep* depressive individuals, *nw* normal weight, *nuc* nucleus, *ob* obese, *occ* occipital, *par* parietal, *prefro* prefrontal, *uw* underweight

3 out of 24 normal subjects, but brown fat was completely absent in the AN or refed AN groups. Thus, brown adipose tissue may play a role in resistance of the human body against lipid storage and may be lacking in subjects with AN (Pasanisi et al. 2013).

23.6 Bulimia and Cerebral Metabolism of Glucose

In an early FDG-PET study, cerebral metabolic rate of glucose was examined in eight women with bulimia and eight normal healthy females during the performance of a visual vigilance task. Healthy subjects showed asymmetry with higher glucose

metabolism in the right than in the left hemisphere, but this asymmetry was absent in the patient group suggesting absence of the normal right activation and impaired processing of the visual task (Wu et al. 1990). In a subsequent publication, an additional group of eight women with major affective disorder was included. In contrast to the bulimics, depressed subjects showed normal activation in the right hemisphere during processing of the visual task, but they had decreased metabolism in the basal ganglia. Thus, although bulimics frequently suffer from symptoms of depression, their regional pattern of brain activation differs from that observed in major affective disorder (Hagman et al. 1990).

A later FDG-PET study examined the cerebral metabolic rate of glucose in 11 women with bulimia nervosa and 18 healthy age- and sex-matched control subjects. The bulimics were also tested for symptoms of major depression and obsessive-compulsive disorder. No group differences in orbitofrontal glucose metabolism were detected, but lower metabolism in the left anterolateral prefrontal cortex was correlated to greater depressive symptoms in the patient group (Andreason et al. 1992).

Another imaging study with PET and FDG examined cerebral glucose metabolism at rest (eyes closed, ears unplugged) in 11 normal-weight bulimic girls and 11 age- and sex-matched healthy volunteers. In contrast to the previous study, both global and regional levels of glucose metabolism were significantly lower in bulimics than in healthy controls. Relative levels of metabolism (compared to the rest of the brain) were reduced only in the parietal cortex. No correlations were found between absolute or relative glucose metabolic rates, body mass index, anxiety scores, or scores of depression (Delvenne et al. 1997c). The observed reductions in glucose metabolism could either be a consequence of nutritional deficiencies or a brain dysfunction underlying eating disorders.

In summary, most PET studies have reported that cerebral glucose metabolism in bulimics is either decreased or not significantly different from that in healthy controls (Table 23.3). However, data from FDG studies using an activation paradigm suggest that the processing of visual tasks may be impaired in BN (Table 23.4).

Table 23.4 Studies of CMR glucose (activation paradigm)

Study groups	Study moment	Stimulus	Tracer	Findings	After therapy	Reference
BN, control	Only 1 session	Visual task	^{18}F-FDG	Asymmetry in controls No right activation in BN	–	Wu et al. (1990)
BN, MAD, control	Only 1 session	Visual task	^{18}F-FDG	As above (BN, controls) Normal asymmetry in MAD, plus ↓ in bas gan	–	Hagman et al. (1990)

bas gan basal ganglia, *BN* bulimia nervosa, *MAD* major affective disorder

23.7 Alterations of the Serotonergic System in Eating Disorders

Several observations suggest that eating disorders may be associated with altered serotonergic neurotransmission in the brain. Serotonergic signaling in the hypothalamus is known to be involved in the control of food intake and body weight, serotonin acting as an eating-inhibitory substance (Leibowitz 1986). Serotonin (5-HT) uptake in platelets of bulimia nervosa patients is increased compared to healthy controls (Goldbloom et al. 1990), and selective serotonin reuptake inhibitors (SSRIs) like fluoxetine can suppress bulimic symptoms (Freeman and Hampson 1987). Such observations (and many others, including the role of serotonin in regulation of mood and impulse control) have prompted imaging studies of 5-HT receptors and transporters in the brain of patients with eating disorders (Table 23.5; reviewed in (Bailer and Kaye 2011; Barbarich et al. 2003; Kasper et al. 2002; Kaye et al. 2005a, 2005b).

An initial study used the tracer [^{123}I]-2β-carbomethoxy-3β-(4-iodophenyl)tropane (β-CIT) and SPECT to quantify 5-HT transporter binding in the thalamus and hypothalamus and dopamine (DA) transporter binding in the striatum of ten medication-free, female bulimic patients and ten age-matched healthy controls. A significant (17%) reduction of both 5-HT and DA transporter binding was noted in patients compared to controls, and 5-HT transporter availability was negatively correlated to the duration of illness (Tauscher et al. 2001). Similar findings were

Table 23.5 Studies of the serotonergic system

Study groups	Study moment	Tracer	Findings	After therapy	Reference
5-HT transporter binding					
BN, control	Only 1 session	^{123}I-β-CIT	↓	–	Tauscher et al. (2001)
ob BN, ob control	Only 1 session	^{123}I-β-CIT	↓ midbr	–	Kuikka et al. (2001)
ob BN, ob control	Pre-/post-therapy	^{123}I-β-CIT	↓ midbr	Normalization	Tammela et al. (2003)
BN, BP-AN, R-AN, control	Post-therapy	^{11}C-McN5652	Differences between groups	Persisting	Bailer et al. (2007a)
BN, control	Post-therapy	^{11}C-DASB	↓ midbr, cin ↑ acc, sup tem gyr	Persisting	Pichika et al. (2012)
BED, control	Only 1 session	^{11}C-MADAM	↓ n ac, inf tem gyr, orbfro ctx ↑ par-occ ctx	–	Majuri et al. (2017a)

(continued)

Table 23.5 (continued)

Study groups	Study moment	Tracer	Findings	After therapy	Reference
5-HT $_{2A}$ receptor binding					
BN, control	Post-therapy	^{18}F-altanserin	↓ med fro ctx	Persisting	Kaye et al. (2001)
BP-AN, control	Post-therapy	^{18}F-altanserin	↓ cin amy hip occ, par ctx	Persisting	Frank et al. (2002)
BP-AN, control	Post-therapy	^{18}F-altanserin	↓ cin, le par, ri occ ctx	Persisting	Bailer et al. (2004)
AN, control	Only 1 session	^{18}F-altanserin	No significant differences	–	Bailer et al. (2007b)
AN, control	Only 1 session	^{123}I-5-I-R91150	↓ le fro ctx, par, occ ctx	–	Audenaert et al. (2003)
BN, control	Only 1 session	^{123}I-5-I-R91150	No significant differences	–	Goethals et al. (2004)
R-AN, BP-AN	Only 1 session	^{123}I-5-I-R91150	↓ par ctx (BP-AN)	–	Goethals et al. (2007b)
5-HT $_{1A}$ receptor binding					
BN, control	Only 1 session	^{11}C-WAY100635	↑ ang gyr, med prefro, pos cin	–	Tiihonen et al. (2004)
BP-AN, R-AN, control	Post-therapy	^{11}C-WAY100635	↑ many regions in BP-AN only	Persisting in BP-AN	Bailer et al. (2005)
AN, control	Only 1 session	^{11}C-WAY100635	↑ many ctx regions, dorsal raphe	–	Bailer et al. (2007b)
BN, control	Post-therapy	^{11}C-WAY100635	↑ many ctx regions	Persisting	Bailer et al. (2011)
R-AN	Pre-/post-therapy	^{18}F-MPPF	↑ right ctx both pre/post	Persisting	Galusca et al. (2008)

acc anterior cingulate cortex, *AN* anorexia nervosa, *ang* angular, *BN* bulimia nervosa, *BP-AN* binge/purge type of anorexia nervosa, *cin* cingulate, *CIT* carbomethoxy-3β-(4-iodophenyl)tropane, *ctx* cortex, *fro* frontal, *gyr* gyrus, *hip* hippocampus, *inf* inferior, *le* left, *med* medial, *midbr* midbrain, *mpc* medial parietal cortex, MPPF 2′-methoxyphenyl-(*N*-2′-pyridinyl)-*p-fluorobenzamidoethyipiperazine*, *n ac* nucleus accumbens, *ob* obese, *occ* occipital, *orbfro* orbitofrontal, *par* parietal, *pos* posterior, *prefro* prefrontal, *R-AN* restrictive type of anorexia nervosa, *ri* right, *sup* superior, *tem* temporal, *WAY100635* *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridyl)cyclohexanecarboxamide

reported in a Finnish study using the same approach. Obese binge eating women showed a significantly (28%) reduced β-CIT binding in the midbrain compared to obese controls (Kuikka et al. 2001). In a subsequent study from the same group, seven obese women with binge eating disorder were scanned with β-CIT before and after successful treatment which consisted of psychotherapy and fluoxetine medication. A repeated scan was also made in a group of six obese control subjects. After treatment, the symptoms of binge eating in the patient group had completely

disappeared, and 5-HT transporter density was significantly (24%) increased. In the control group, the binding of β-CIT was unchanged during the study period (Tammela et al. 2003).

Although 5-HT transporter density in the brain of bulimic women seems to increase after successful therapy, a PET study with the 5-HT transporter ligand [^{11}C]McN5652 indicated that altered transporter function may persist in some brain regions after recovery from eating disorders. The study involved 11 females who had recovered from restrictive anorexia, 7 who had recovered from binge/purge anorexia, 9 who had recovered from bulimia, and 10 healthy control women. Differences in transporter expression were noted between the three patient groups. The group which had recovered from restrictive anorexia showed a greater binding potential in the dorsal raphe and anteroventral striatum than the one which had recovered from binge/purge anorexia. Moreover, individuals who had recovered from binge/purge anorexia had a lower binding potential of [^{11}C]McN5652 in the anteroventral striatum than individuals who had recovered from bulimia nervosa (Bailer et al. 2007a). Apparently, patients with different eating disorders show differences in transporter function even after a recovery period of more than 1 year, and these differences could be related to differences in affective regulation and impulse control. A PET study with another 5-HT transporter ligand, [^{11}C]DASB, provided evidence for reductions of transporter availability in the brain of bulimic individuals even after complete recovery. When [^{11}C]DASB scans of eight females who had recovered from bulimia nervosa were compared to scans of eight healthy control women, the patient group had lower binding potential in the midbrain (containing the dorsal raphe) and superior and inferior cingulate and higher binding potential in the anterior cingulate and superior temporal gyrus (Pichika et al. 2012).

Another interesting study evaluated serotonin transporter binding in six patients with night eating syndrome (NES). NES is manifested by evening hyperphagia (consuming > 25% of the total daily food intake after the evening meal). Significantly higher binding of the serotonin transporter ligand ^{123}I-ADAM was observed in patients with NES as compared to six normal volunteers (Lundgren et al. 2008). A more recent PET study examined serotonin transporter density in 7 subjects with BED, 13 subjects with pathological gambling, and 16 healthy controls. Subjects with BED showed increased binding of the 5-HT transporter ligand ^{11}C-MADAM in the parieto-occipital cortex, but decreased binding in the nucleus accumbens, inferior temporal gyrus, and lateral orbitofrontal cortex compared to controls. In subjects with a pathological addiction to gambling, the regional density of the 5-HT transporter was not significantly different from healthy controls (Majuri et al. 2017a).

An early PET study examined ^{18}F-altanserin (5-HT$_{2A}$ receptor) binding in the brain of ten healthy volunteers and nine women who had recovered from bulimia nervosa. Former patients had reduced tracer binding in the medial frontal cortex. An age-related decline of 5-HT$_{2A}$ binding was noted in the brain of healthy controls but not in subjects who had recovered from bulimia (Kaye et al. 2001). Reduced binding in the frontal lobe of patient brains could be related to disturbed self-control (impulsive/obsessive behavior) and dysphoric mood states in individuals vulnerable for eating disorders. A more extensive study using the same approach was published

in the following year. That study involved 23 female healthy volunteers and 16 women who had recovered from the binge/purge type of anorexia nervosa by showing normal weight, regular menses, and stable food intake for at least 1 year. Reduced binding of [^{18}F]altanserin was observed in several areas of the patient brains (cingulate cortex, amygdala, and hippocampus). SPM analysis revealed additional reductions of 5-HT$_{2A}$ binding in the occipital and parietal cortex (Frank et al. 2002). A later [^{18}F]altanserin-PET study from the same group confirmed that 10 women who had recovered from the binge/purge type of anorexia had a significantly reduced binding potential of the tracer in several brain areas (left subgenual cingulate, left parietal cortex, and right occipital cortex) compared to 16 healthy controls. In the former patients but not in the healthy control group, 5-HT$_{2A}$ binding potential in cingulate and parietal regions was positively related to harm avoidance and negatively to novelty seeking. Moreover, 5-HT$_{2A}$ binding potential in several cortical regions was negatively correlated to drive for thinness in the patient group (Bailer et al. 2004). Since robust decreases of 5-HT$_{2A}$ binding were observed even after long-term recovery in several studies, such decreases may reflect a trait-related disturbance that contributes to the pathophysiology of anorexia nervosa. However, some of the observed differences (e.g., those in subgenual cingulate) could also be related to depressive disorder in the patient group.

A SPECT study with the 5-HT$_{2A}$ receptor antagonist 4-amino-*N*-[1-[3-(4-fluorophenoxy)propyl]-4-methyl-4-piperidinyl]-5-^{123}I-iodo-2-methoxybenzamide (^{123}I-5-I-R91150) examined tracer binding in the brain of 15 patients with anorexia nervosa and 11 age-matched healthy volunteers. Reduced availability of 5-HT$_{2A}$ receptors was observed in the left frontal cortex, the left and right parietal cortex, and the left and right occipital cortex of the patients as compared to controls. The frontal cortex in the patient brains showed a significant left-right asymmetry, lower levels of tracer binding occurring in the left hemisphere (Audenaert et al. 2003). However, when similar SPECT scans were made in ten patients with bulimia nervosa, 5-HT$_{2A}$ binding in such patients was found to be not significantly different from that in the healthy control group (Goethals et al. 2004). In a later study with the same tracer, SPECT scans of nine subjects with restrictive anorexia were compared to scans of seven individuals with binge/purge anorexia. Relationships between binding index and temperament scores were also explored. Patients with binge/purge anorexia showed a significantly lower 5-HT$_{2A}$ binding index in the parietal cortex than patients with restrictive anorexia. A positive correlation was noted between parietal 5-HT$_{2A}$ binding and reward dependence, suggesting that these variables could be associated with the patient groups (Goethals et al. 2007b).

Since SSRIs are potential tools for the treatment of bulimia nervosa, and the serotonin 5-HT$_{1A}$ receptor is involved in the action of these compounds by causing negative feedback inhibition of serotonin release, a Finnish group examined cerebral 5-HT$_{1A}$ receptor binding of the PET tracer [^{11}C]WAY-100635 in eight unmedicated patients with bulimia and ten healthy control subjects. The patients showed greater binding potential values in all studied brain regions, particularly the angular gyrus, the medial prefrontal cortex, and the posterior cingulate cortex. Increased 5-HT$_{1A}$ expression in patients as compared to controls could be associated with reduced serotonin release and impaired control of food intake during binge eating.

In addition, such increases could be related to anxiety in the patient group (Tiihonen et al. 2004). A later study from the USA examined the binding of [^{11}C]WAY-100635 in the brain of 13 women who had recovered from restrictive anorexia, 12 women who had recovered from binge/purge anorexia, and 18 healthy control women. All patients had shown normal weight, regular menstrual cycles, and absence of binge/purge behavior for more than 1 year. Women who had recovered from binge/purge anorexia showed increased [^{11}C]WAY-100635 binding potential in many cortical regions (cingulate, lateral and mesial temporal, lateral and medial orbital frontal, parietal, and prefrontal) and in the dorsal raphe as compared to healthy controls. However, no significant differences were detected between the brain of women who had recovered from restrictive anorexia and the brain of healthy subjects, although 5-HT$_{1A}$ receptor binding after recovery from restrictive anorexia was positively correlated with harm avoidance and with a measure of anxiety (Bailer et al. 2005). A subsequent study applied three different PET tracers ([^{11}C]WAY-100635 for imaging of 5-HT$_{1A}$ receptors, [^{18}F]altanserin for imaging of 5-HT$_{2A}$ receptors, [^{15}O]water for measurement of cerebral blood flow) in 15 women with anorexia nervosa and 29 healthy controls. Compared to controls, the patients showed strong (30–70%) increases of 5-HT$_{1A}$ binding potential in various cortical regions and dorsal raphe nuclei. 5-HT$_{2A}$ binding potential and cerebral blood flow in the patient group were normal, but the binding potential of [^{18}F]altanserin in the supragenual cingulate and frontal and parietal cortex was positively related to harm avoidance in this group (Bailer et al. 2007b). Another study from the same group examined [^{11}C]WAY-100635 binding in the brain of 13 women who had recovered from bulimia nervosa and 21 healthy control subjects. The patient group showed significant elevations (23–34%) of 5-HT$_{1A}$ binding potential in the subgenual cingulate, mesial temporal, and parietal cortex. Binding potential values were positively related to harm avoidance and negatively to sensation seeking. In the healthy control group, 5-HT$_{1A}$ binding potential was also related negatively to novelty seeking (Bailer et al. 2011). The increased activity of 5-HT$_{1A}$ receptors in bulimic and anorexic individuals, which was detected in several PET studies, may explain why such patients show a rather poor response to serotonergic medication.

A PET study with another 5-HT$_{1A}$ receptor ligand, [^{18}F]MPPF, detected increases of tracer binding in a selective area of the right cortex both in lean and recovered patients with restrictive anorexia. Elevated perfectionism and interpersonal distrust scores were noted even in the recovered patient group (Galusca et al. 2008). The findings of this PET study indicate that anxiety symptoms and serotonergic alterations persist after recovery from eating disorders and may reflect a personality trait that contributes to their pathogenesis.

23.8 Alterations of Other Neurotransmitter Systems in Eating Disorders

Various PET studies have examined dopamine receptor binding in the brain of patients with eating disorders (Table 23.6). An early study included 10 women who had recovered from anorexia nervosa and 12 healthy control subjects. The patient

Table 23.6 Studies of other neurotransmitter systems

Study groups	Study moment	Tracer	Findings	After therapy	Reference
D_2/D_3 receptor binding					
AN, control	Post-therapy	^{11}C-raclopride	↑ ant ven str	Persisting	Frank et al. (2005)
BN, control	1 session, methylphenidate challenge	^{11}C-raclopride	↓ str, ↓ response to challenge	–	Broft et al. (2012)
AN, control	Post-therapy, amphetamine challenge	^{11}C-raclopride	Tracer binding same but mood changes different	Persisting mood differences	Bailer et al. (2012)
BP-AN, R-AN, BN, control	Post-therapy	^{11}C-raclopride	dor cau, put BP related to harm avoidance	Character-trait-related differences	Bailer et al. (2013)
AN, control	Before and after weight restoration	^{11}C-raclopride	No differences between AN and controls	Still no differences	Broft et al. (2015)
AN (treated, recovered)	Only 1 session	^{11}C-raclopride, fMRI	Increased BP in dor cau related to enhanced response to loss in a game	–	Bailer et al. (2017)
Dopamine release					
BED, control	During neutral and food stimuli, with and without oral methylphenidate	^{11}C-raclopride	Food stimuli combined with methylphenidate increase dopamine release in binge eaters but not in nonbinge eating obese subjects	–	Wang et al. (2011)
Fluoro-DOPA influx					
BED, control	Only 1 session	^{18}F-DOPA	Striatal influx reduced (by 20% in nuc accumbens)	–	Majuri et al. (2017b)
μ-Opioid binding					
BN, control	Only 1 session	^{11}C-carfentanil	↓ le ins ctx	–	Bencherif et al. (2005)
BED, control	Only 1 session	^{11}C-carfentanil	↓ many cortical and subcortical regions	–	Majuri et al. (2017b); Joutsa et al. (2018)

Table 23.6 (continued)

Study groups	Study moment	Tracer	Findings	After therapy	Reference
Histamine H_1 binding					
AN, control	Only 1 session	^{11}C-doxepin	↑ am, len nuc control ♀ ↑ than ♂	–	Yoshizawa et al. (2009)
Cannabinoid CB_1 binding					
BN, AN. control	Only 1 session	^{18}F-MK9470	↑ globally in AN	–	Gerard et al. (2011)
			Relative ↑ ins AN, BN		
AN animal model	During model and upon recovery	^{18}F-MK9470	↑ in all cortical and subcortical areas, in ♀ also relative increases in hip, inf col, ent ctx	Normalization	Casteels et al. (2014)
AN, BN, control	Only 1 session	^{18}F-MK9470	Binding in hyp, bs inversely associated with BMI. In AN, BN groups also inverse association of binding in mb, str, ins, am, orb fro ctx, and BMI		Ceccarini et al. (2016)
GABA(A)-benzodiazepine binding					
AN	At onset of therapy and after 4 months	^{123}I-iomazenil	↓ in cin, le fro, par ctx correlated with EAT-26 and mood scores	↑ in pos cin ctx, occ gyr	Nagamitsu et al. (2016)

am amygdala, *AN* anorexia nervosa, *ant* anterior, *BN* bulimia nervosa, *BMI* body mass index, *BP-AN* binge/purge type of anorexia nervosa, *bs* brainstem, *cau* caudate, *cin* cingulate, *CIT* carbomethoxy-3β-(4-iodophenyl)tropane, *col* colliculus, *ctx* cortex, *dor* dorsal, *ent* entorhinal, *fro* frontal, *gyr* gyrus, *hip* hippocampus, *hyp* hypothalamus, *inf* inferior, *ins* insula, *le* left, *mb* midbrain, *nuc* nucleus, *occ* occipital, *orb* orbito, *pos* posterior, *R-AN* restrictive type of anorexia nervosa, *str* striatum, *ven* ventral

group had significantly higher binding potential of [^{11}C]raclopride in the anterior-ventral striatum than the control group. In women who had recovered from anorexia nervosa, [^{11}C]raclopride binding potential in the dorsal caudate and dorsal putamen was positively related to behavioral scores for harm avoidance (Frank et al. 2005). These findings could be interpreted as evidence for disturbed dopamine-related reward mechanisms in subjects with anorexia nervosa which may contribute to altered feeding behavior.

In a more recent PET study, 15 women with bulimia nervosa and 15 healthy control subjects were scanned with [^{11}C]raclopride before and after administration of methylphenidate, a drug which inhibits dopamine reuptake and stimulates dopamine release from dopaminergic terminals. Bulimic individuals tended to have lower values than healthy controls for dopamine D_2 receptor binding in two subregions of the striatum in the first scan. The reduction of [^{11}C]raclopride binding after administration of methylphenidate was significantly smaller in patients compared to controls, and a smaller response to the psychostimulant challenge was associated with a higher frequency of binge eating in the patient group (Broft et al. 2012). These data were interpreted as evidence for reduced release of dopamine in bulimia nervosa. Reduced dopamine release has also been observed in substance abuse, e.g., cocaine or alcohol dependence. However, in contrast to the findings in substance abuse, impaired dopamine release in bulimic individuals was observed only in the putamen and not in the caudate (Broft et al. 2012). This study indicates disturbances of dopamine-related reward mechanisms in bulimia which differ both from those observed in anorexia and in substance abuse.

Another PET study examined amphetamine-induced dopamine release in ten women who had recovered from anorexia and nine healthy control women. Binding potential of the PET tracer [^{11}C]raclopride was identical in the two study groups, both before and after the amphetamine challenge. However, mood changes in the groups associated with amphetamine-induced dopamine release were strikingly different. In the healthy control group, the amphetamine-induced change of [^{11}C]raclopride binding potential in the ventral striatum was significantly associated with amphetamine-induced euphoria. In the patient group, the change of [^{11}C]raclopride binding potential in the precommissural dorsal caudate was significantly associated with amphetamine-induced anxiety (Bailer et al. 2012). Apparently, food-related dopamine release produces anxiety in patients with AN, whereas feeding is pleasurable in healthy subjects. An extensive PET study examined striatal dopamine D_2/D_3 receptor availability in 25 women with AN before and after weight restoration, in comparison to an age-matched control group of 25 healthy female subjects. Binding potential values in the patient group were again found to be identical to those in the control group, both in the underweight and weight-restored condition (Broft et al. 2015).

Interesting data were acquired in a PET study concerning dopamine release in patients with BED. Ten obese subjects with BED and eight obese control subjects without BED were included in this investigation. Neutral and food stimuli were presented to the subjects which were treated either with oral methylphenidate (in order to amplify dopamine release) or with placebo, and subjects were scanned with the D_2/D_3 receptor ligand ^{11}C-raclopride which is sensitive to dopamine competition. Neutral stimuli (with or without methylphenidate) and food stimuli (with placebo) were found to not increase extracellular dopamine. However, food stimuli combined with methylphenidate increased striatal dopamine release in the binge eaters, but not in the obese control subjects. The authors concluded that dopamine release alone does not predict obesity, but it may predict binge eating (Wang et al. 2011).

Another PET study examined both dopamine D_2/D_3 receptor ([^{11}C]raclopride) and serotonin transporter ([^{11}C]McN5652) binding in 7 individuals who had recovered from binge/purge anorexia, 11 individuals who had recovered from restrictive anorexia, 9 individuals who had recovered from bulimia, and 9 control women. This tracer combination was chosen because the dopaminergic system is believed to be involved in appetite and the serotonergic system in aversion; thus, these neurotransmitter systems could have opposed actions. In patients but not in healthy controls, a significant positive correlation was observed between the binding potential values of both tracers in various regions of the striatum. Scores for harm avoidance were significantly related to dopamine D_2/D_3 but not 5-HT transporter binding potential in the dorsal caudate and putamen. The interaction between 5-HT transporter and D_2/D_3 receptor binding in the dorsal putamen was a significant predictor of harm avoidance. These data suggest that serotonin/dopamine interactions contribute to harm avoidance behavior in eating disorders (Bailer et al. 2013). In a later study of the same group, blood flow responses in the striatum to wins and losses in a game (assessed by blood-oxygen-level-dependent fMRI) were compared to dopamine D_2/D_3 receptor binding potential (measured with PET and ^{11}C-raclopride). Increased D_2/D_3 binding in the dorsal striatum was found to be associated with an enhanced blood flow response to loss. This finding was tentatively interpreted as evidence for a relationship between increased dopamine receptor availability and anxious anticipation of consequences in the subject group, who consisted of individuals recovered from AN (Bailer et al. 2017).

In an interesting study from Finland, 7 subjects with BED, 15 subjects with pathological gambling, and 17 healthy control subjects were scanned with the false neurotransmitter ^{18}F-DOPA. The striatal influx of this tracer (K_1) was significantly decreased in BED with respect to controls (by 20% in the nucleus accumbens), but was not altered in the morbid gamblers. Thus, BED patients show marked presynaptic dopaminergic defects (Majuri et al. 2017b).

In comparison to healthy volunteers, bulimic individuals show significantly decreased mu-opioid receptor binding in the left insular cortex, a brain area involved in taste discrimination and eating reward (Bencherif et al. 2005). This decrease may reflect downregulation of μOR in the bulimic state as a consequence of chronically increased release of opioid peptides or a personality trait that increases the reward value of dieting. In the abovementioned ^{18}F-DOPA study from Finland, subjects were also scanned with the μ-opioid ligand ^{11}C-carfentanil. BED patients showed reductions of binding potential in many cortical and subcortical areas of the brain, whereas pathological gamblers displayed a 30–34% reduction of binding in the anterior cingulate. Thus, these two forms of addiction were associated with distinct neurobiological changes (Majuri et al. 2017b). A later study from the same group compared μ-opioid binding in the brains of BED patients, subjects with morbid obesity, and healthy controls. Both BED and morbid obesity were found to be associated with widespread reductions of μ-opioid receptor binding potential, and there were no significant differences between these two patient groups (Joutsa et al. 2018).

An interesting PET study compared binding potential of the histamine H1-receptor ligand [^{11}C]doxepin in 12 women with anorexia nervosa, 11 healthy

male volunteers, and a control group of 12 healthy females. Females showed significantly higher binding potential than males in the amygdala, hippocampus, medial prefrontal cortex, orbitofrontal cortex, and temporal cortex. Anorexia patients showed even higher binding potential in the amygdala and lentiform nucleus than the healthy control group. Correlations were observed between [^{11}C]doxepin binding in several brain areas and scores for abnormal eating behavior, depression, and anxiety. Thus, women appear to have higher histamine H1-receptor densities in the limbic system than men, and anorexia is associated with increases of H1-receptor density, particularly in the amygdala (Yoshizawa et al. 2009).

The endocannabinoid system which is located in many areas of the body is involved in the maintenance of body homeostasis via regulation of food intake and energy expenditure (Marco et al. 2012). One interesting PET study employed the tracer [^{18}F]MK9470 to assess regional cannabinoid CB_1 receptor density in the brain of 16 female patients with BN, 14 female patients with AN, and 19 age-matched healthy female volunteers. Global increases of CB_1 receptor availability were detected in anorexics as compared to healthy controls. Regional (relative) increases of CB1 receptors were detected in the insula of both patient groups and in the inferior frontal and temporal cortex in AN patients only (Gerard et al. 2011). These findings were interpreted as upregulation of CB1 receptors compensating for underactivity of the endocannabinoid system in anorectic conditions. Very similar findings were reported in an activity-based rat model of AN. This model offers the advantage that the impact of several variables (gender, diet, exercise) on the scan results can be independently assessed. In the animal model of AN (diet restriction combined with wheel exercise), strong increases of CB1 receptor binding were noted in all cortical and subcortical brain regions (+67% in males, >51% in females). Females showed in addition relative increases of CB1 receptor availability in the hippocampus, inferior colliculus, and entorhinal cortex. Diet restriction had a greater impact on the CB1 receptor population than physical exercise (wheel running), and the combination of diet restriction and exercise had the greatest effect. The observed changes of [^{18}F]ML9470 binding were normalized during recovery, when animals returned to their normal weight (Casteels et al. 2014). These PET data suggested that the rat model mimics many aspects of the human disease, and gender affects the response of the endocannabinoid system. A later, extensive PET study in humans examined CB1 receptor availability in 54 patients with various eating disorders (AN, BN, functional dyspepsia with weight loss, obesity) and an age- and gender-matched control group ($n = 26$). In all subjects, including the healthy control group, the binding of [^{18}F]ML9470 in the hypothalamus and brainstem was found to be inversely correlated with body mass index (BMI). However, in the subjects with eating disorders but not in the control group, an additional negative correlation was observed between BMI and tracer binding in the midbrain, striatum, insula, amygdala, and orbitofrontal cortex (Ceccarini et al. 2016). These findings were interpreted as evidence for a link between BMI and the cerebral endocannabinoid system in brain regions involved in the maintenance of body homeostasis, with additional involvement of the endocannabinoid system in reward areas in the patient groups.

A Japanese study examined GABA(A)-benzodiazepine receptor binding in subjects with AN, since anxiety plays an important role in the development of this disorder. Sixteen female patients were scanned with the SPECT tracer ^{123}I-iomazenil, both at the onset and after 4 months of therapy. The scan data could be compared with behavioral scores (that were acquired at the onset of therapy) and with therapeutic outcome (that was evaluated after 1 year). Higher scores in the Eating Attitudes Test with 26 items (EAT-26) corresponded with lower tracer binding in the anterior and posterior cingulate cortex. Higher scores in a Profile of Mood States (POMS) short form were associated with reduced binding in the left frontal, parietal, and posterior cingulate cortex. Decreased tracer binding in the anterior cingulate and left parietal cortex corresponded with poor therapeutic outcome. Subjects with weight gain demonstrated increases of tracer binding in the posterior cingulate cortex and occipital gyrus. These findings were interpreted as evidence for decreased GABA(A)-benzodiazepine binding in AN, related to anxiety, which normalizes after successful treatment (Nagamitsu et al. 2016).

23.9 Conclusion

PET and SPECT imaging findings provide evidence that individuals with eating disorders have altered brain function in regions that constitute limbic circuits. Fear-related responses to food and body-related stimuli have been detected, a changed reward response and sensory taste response (Frank et al. 2006) have been noted, and the availability of 5-HT transporters, serotonin 5-HT_{1A} and 5-HT_{2A}, dopamine D_2/D_3, histamine H_1, cannabinoid CB_1, GABA(A)-benzodiazepine, and mu-opioid receptors is altered. Many of these alterations persist after long-term therapy and behavioral or weight recovery. Hopefully, some of the biochemical changes detected with PET may lead to the identification of targets for pharmacological intervention. Recent functional neuroimaging studies have helped to indicate that a few experimental treatments show promise, such as ondansetron in BN and deep brain stimulation in AN.

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Impulsivity Imaging

24

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Contents

Abstract

Impulsivity is a complex and multidimensional trait that represents a core aspect of several neuropsychiatric conditions and, as such, provides an interesting target for diagnosis, appropriate treatment selection and response evaluation.

It is conceived as the result of a variety of dysfunctions and dysregulations within an intricate network of neurotransmitter systems, including dopamine (DA), serotonin (5-HT) and noradrenaline (NA). Hence, regional investigations of one single neurotransmitter may not be sufficient to disentangle the patho-

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physiology of impulsivity. Thus individual variation in limbic striatal D_2/D_3 receptor availability, diminished functioning of the highly diverse serotonergic system and the variation in norepinephrine density appear to be central to gaining insight into the aetiology and treatment of impulsivity.

Convergent data from neuroimaging and neuropsychology studies consistently point to the aberrations in especially the fronto-striatal, parieto-temporal and fronto-cerebellar networks. Functional imaging with SPECT and PET provides a useful tool in elucidating the neurobiological underpinnings of impulsive-aggressive behaviour in ADHD, Parkinson's disease (PD), bipolar disorder (BP), conduct disorder (CD), substance abuse/dependence and schizophrenia.

Although findings are still heterogeneous, functional brain imaging may provide novel insight into the underlying neural disturbances of pathological impulsivity. In addition, its role in the monitoring of treatment response in the various neuropsychiatric disorders, characterized by impulsive behaviour, is emerging as a potentially valuable tool in the long-term management of these patients.

24.1 Overview

24.1.1 Introduction/Definition

"Impulsivity" is a broad term, which in general refers to an inability to resist an impulse, drive or temptation to perform an action. It tends to occur without the necessary expected forethought, planning or consideration of long-term effects and therefore frequently results in unwanted or harmful outcomes to self or others.

The *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association 2000) defines impulsivity as "the failure to resist an impulse, drive or temptation to perform an act that is harmful to the person or to others".

Impulsive individuals have a tendency to express repetitive deliberate self-destructive acts, such as self-mutilation and suicidal behaviour, and/or outward aggression to others. Impulsivity is considered central to neuropsychiatric conditions such as attention deficit hyperactive disorder in relation to depression and anxiety and cluster B personality disorders, such as antisocial and borderline.

Impulsivity appears to be a complex multidimensional concept (Moeller et al. 2001), which consists of cognitive, behavioural, attention, motor and non-planning aspects for which to date no consensus over a single precise definition exists. Some authors have made a distinction between motor (or behavioural) and cognitive (or choice) impulsivity in an attempt to separate causes from consequences of impulsivity and in an attempt to improve the validity of measurements.

In a 2006 review on impulsivity, Estíbaliz Arce and Carmen Santisteban provided an in-depth exploration of the various definitions and aspects of impulsivity (Arce and Santisteban 2006).

The following excerpts are from the aforementioned review:

- Kagan (1994) proposed behavioural inhibition as a type of temperament in the child that presents a unique combination of behavioural and physiological responses to novelty. Furthermore, he believed this temperament was associated with future development of anxiety disorders in adulthood. From a behavioural perspective, impulsivity can be defined as "a wide range of actions that are poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situations and that often result in undesirable outcomes" (Evenden 1999).
- More simply, it is described as the inability to delay gratification or the inverse of self-control (Monterosso and Ainslie 1999). In the context of experimental behavioural science, impulsivity is commonly viewed as a trait shown by some subjects that, when presented with a variety of outcomes, choose poorer immediate rewards rather than greater delayed rewards (Ainslie 1975). Ho and colleagues include in their definition the importance of punishment, "the selection of small immediate gains in preference to larger delayed gains, or the selection of large delayed penalties in presence to smaller immediate penalties" (Ho et al. 1998).
- Brunner and Hen (1997), Evenden (1999), Bechara et al. (2000) and Bechara (2002) have distinguished motor (or behavioural) from cognitive (or choice) impulsivity. The former is usually studied in animals and is equivalent to response inhibition. Cognitive impulsivity is considered the inability to weigh the consequences of immediate and future events and, consequently, delay gratification. This has been measured in tasks of decision-making such as the Iowa gambling task (Bechara et al. 1994).
- Brunner and Hen (1997) further distinguish between an impulsive act (behaviour) and impulsivity per se (underlying psychological process) (Brunner and Hen 1997).
- From a bio-psycho-social perspective, and in an attempt to combine the various aspects, Moeller et al. (2001) pointed out that a general definition of impulsivity should include the following aspects: "(1) decreased sensitivity to negative consequences; (2) rapid, unplanned reactions to stimuli before complete processing of information; and (3) lack of regard for long-term consequences". In the context of psychopathology, impulsivity has been defined in three different ways: (1) "swift action without forethought or conscious judgment, (2) behaviour without adequate thought, and (3) the tendency to act with less forethought than most individuals of equal ability and knowledge" (Arce and Santisteban 2006).

The focus of this chapter is on the imaging of impulsivity as its different aspects manifest in the various neuropsychiatric disorders (notably ADHD, PD and cluster B personality disorders).

24.1.2 Why Is the Study of Impulsivity Important?

Impulsivity forms an integral part of several neuropsychiatric disorders, such as ADHD, Parkinson's disease (PD), bipolar disorder (BP), conduct disorder (CD),

substance abuse/dependence and schizophrenia, or as part of a personality disorder (antisocial and borderline personality disorders). Clearly, these disorders may result in significant functional and occupational impairment with important social and judicial implications.

Assessment of impulsivity forms a crucial part in establishing whether a neuropsychiatric patient poses a potential threat to himself or others. It also provides an important target for choosing the most appropriate treatment and in the subsequent evaluation of treatment response (Moeller et al. 2001).

24.1.3 How Is Impulsivity Currently Diagnosed or Measured?

Non-imaging measurements that are currently available and widely used include self-report measures such as the Barratt Impulsiveness Scale, behavioural laboratory measures and event-related potentials in addition to the history and patient interview. The most important human measurement tools will be briefly mentioned here as discussed in recent publications by Aichert et al. (2012) and Arce and Santisteban (2006). However, since the focus of this chapter is on the imaging of impulsivity as a potential measurement tool, readers are referred to the aforementioned publications for more in-depth information.

Self-report measures of impulsivity are useful in allowing the measurement of a broad range of cognitive and behavioural styles in different social contexts. The Barratt Impulsiveness Scale is one of the most commonly used self-report measures and consists of a three-factor model that includes both motor and cognitive impulsivity. The scale has 30 items, which are grouped into 3 subscales of factors: attentional (inattention and cognitive instability), motor (motor impulsiveness and lack of perseverance) and non-planning (lack of self-control and intolerance of cognitive complexity). Due to its simplicity and rapid administration, this instrument has been widely used in studies of bipolar disorder, alcohol and substance use and personality disorders, amongst others (Patton et al. 1995).

A variety of experimental, multifaceted paradigms have been developed to assess other components of impulsivity such as the ability to inhibit impulsive or inappropriate responses. These paradigms assess cognitive, motor and emotion disinhibition and delay discounting in reward choices, decision-making processes or time estimation biases.

In their recent publication, Aichert et al. focused on prepotent response inhibition due to the importance of these in the cognitive and clinical neuroscience literature. The table below from the aforementioned article provides a summary of the prepotent response inhibition measures. The complete table also provides neural correlates to which readers are hereby referred to for a more detailed discussion (Aichert et al. 2012) (Table 24.1).

The above-mentioned measures of impulsivity suffer from several limitations to varying degrees. There appears to be a lack of clear unidimensional definitions with significant conceptual overlap between self-report and behavioural lab tasks used to measure impulsivity. These issues were explored in a recent publication by Cyders

Table 24.1 Non-imaging measurement tools of impulsivity

Task/ questionnaire	Characteristics of the task/questionnaire
Antisaccade task	The antisaccade task is considered a measure of oculomotor response inhibition
	Participants are required to avoid a prosaccade to a sudden-onset peripheral target and instead initiate a volitional saccade towards the mirror image position
	The key dependent variable of oculomotor response inhibition is the percentage of directional errors
Stroop task	Colour words are presented in different ink colours (e.g. *green* is printed in red ink)
	Participants are required to name the word colour and avoid the automated response of reading the word
	The "Stroop effect", a measure of interference inhibition, is indicated by longer RT to congruent than incongruent stimuli (MacLeod 1991; van Mourik et al. 2005)
Go/no-go task	The go/no-go task is considered a measure of selective motor response inhibition
	Participants are required to respond with a fast motor response when a frequent go stimulus appears but to withhold the motor response when an infrequent no-go stimulus is presented
	The key dependent variable is the frequency of commission errors, i.e. failures to suppress the response to the no-go stimulus
Stop-signal task	In stop-signal tasks, a stop-signal sometimes appears unpredictably shortly after the go signal, demanding the later stage inhibition process of interrupting a motor response that is already triggered and under way
	Inhibitory performance in this task is estimated by the latency of the stopping process known as the stop-signal reaction time (SSRT; Logan et al. 2014)
BIS-11 questionnaire	BIS-11 (Patton et al. 1995) is a 30-item self-report questionnaire designed to assess trait impulsivity
	It comprises six first-order factors: attention, motor impulsiveness, self-control, cognitive complexity, perseverance, cognitive instability
	These first-order factors were combined to three second-order factors: attentional impulsiveness (inability to focus attention or concentrate), motor impulsiveness (acting without thinking) and non-planning impulsiveness (lack of "futuring" or forethought)

Aichert et al. (2012)

and Coskunpinar (2011). Other methodological problems with the study of impulsivity include the lack of control for potentially confounding variables such as age, IQ, socio-economical status and gender in some instances (Brunner and Hen 1997).

An in-depth discussion of the various limitations of individual assessment tools falls outside the scope of this chapter. It does appear, however, that there is a need for a standard, objective, quantifiable, non-invasive and repeatable diagnostic modality, which corresponds to the underlying brain function. Neuroimaging in the forms of SPECT, PET and functional MRI may provide such a diagnostic or measurement tool.

24.1.4 What Is the Pathophysiology of Impulsivity?

Various anatomical structures and functional areas or circuits have been implicated in the pathophysiology of impulsivity although a complete explanation remains elusive for now. The following structures or areas appear crucial in impulse control: the sub-thalamic nucleus, the orbito-frontal and right inferior frontal gyrus and the nucleus accumbens.

The frontal cortex is one of the association cortices and has been implicated in cognitive behaviour and complex motor actions. Lesions in the prefrontal cortex have been shown to produce disinhibition and to cause personality changes. This cortex is also the main source of input to the midbrain serotonergic neurons of the dorsal raphe nuclei. This is important since the serotonin system has been implicated in the evolution of impulsive behaviour (Yang and Raine 2009).

Although many (especially earlier studies) have focused on the role of serotonin regulation, the current emphasis appears to have shifted to the importance of the dopaminergic and noradrenergic systems.

24.1.5 The Role of Functional Imaging

Functional imaging has played an important role in establishing the underlying aetiology and pathophysiology in many neuropsychiatric conditions.

Both PET and SPECT imaging allow for the selection of radiotracers based on the aspect of the pathophysiology of interest, which can then be quantified. These include tracers for cerebral perfusion, metabolism, blood-brain barrier integrity testing, neurotransmitters and a multitude of receptor targets. These are then labelled to a radioactive isotope suitable for either PET or SPECT imaging, taking into account the availability, expertise and economic implications. Radioisotopes that are typically used include ^{11}C, ^{13}N, ^{15}O and ^{18}F for PET and ^{99m}Tc and ^{123}I for SPECT. Radioisotopes for the imaging of brain neurotransmitter receptors and transporters are based structurally on receptor agonists or antagonists (a vast majority of tracers used) and do not elicit pharmacological effects due to the very low (tracer) doses used.

24.1.6 How Can We Image Impulsivity?

The role of dopamine (DA) and its regulation and, to a lesser degree, those of serotonin (5-HT) and noradrenaline (NA) appear central in impulsivity. An important starting point, therefore, would be an overview of the functional imaging of these neurotransmitters and their receptors.

24.1.6.1 Dopaminergic Neurotransmission

The function of dopamine (DA) in the brain includes the mediation of cognition, emotion and movement, and it is involved in both the production and inhibition of

several primary biological drives. Removal of free dopamine from the synaptic cleft is one of the primary mechanisms for regulating dopaminergic tone, with the reuptake of free dopamine from the synaptic cleft mediated by a macromolecular transporter located in the axonal membrane (DAT).

The majority of neuropsychiatric diseases and drugs cause compensatory changes in the dopamine transporter before affecting the concentration of the postsynaptic dopaminergic receptors. These striatal transporters are present exclusively on dopamine-producing neurons where they play a key role in the regulation of DA levels in the synaptic cleft. Dopamine transporters are markers of the integrity of presynaptic dopaminergic neurons and as such provide an ideal target for imaging with either SPECT or PET. Figure 24.1 provides an overview of the most important functional imaging targets and some of the more commonly used SPECT and PET tracers.

There is growing evidence to suggest that impulsiveness is caused by dysregulation of brain dopaminergic neurotransmission (Dalley et al. 2008). Areas that are often implicated include the dopaminergic neuronal projections from the midbrain to the ventral striatum (nucleus accumbens). These are associated with the

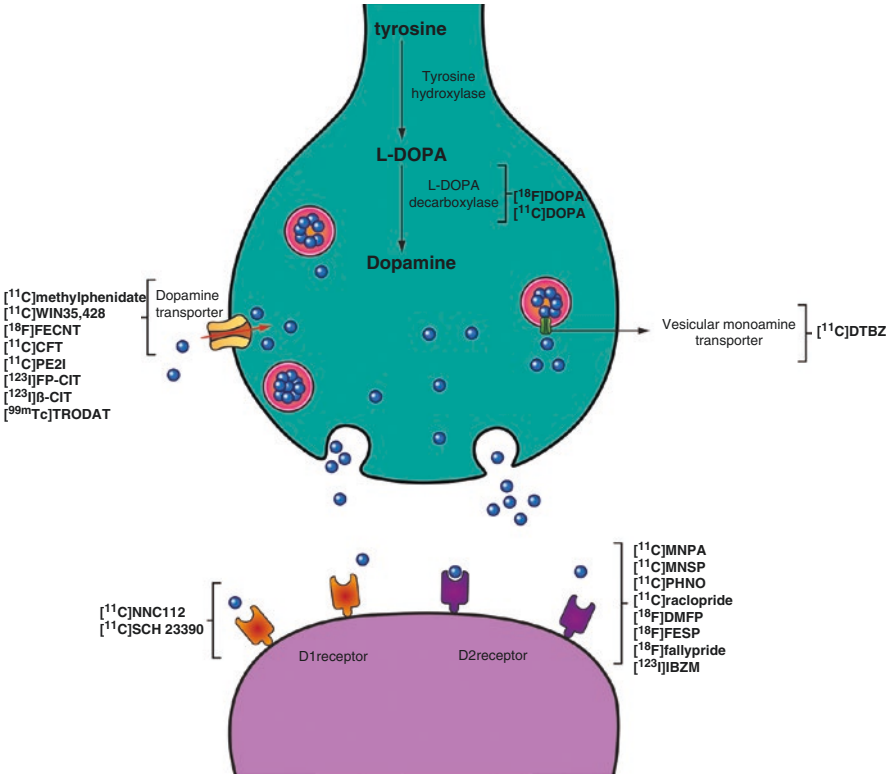

Fig. 24.1 The dopaminergic synapse

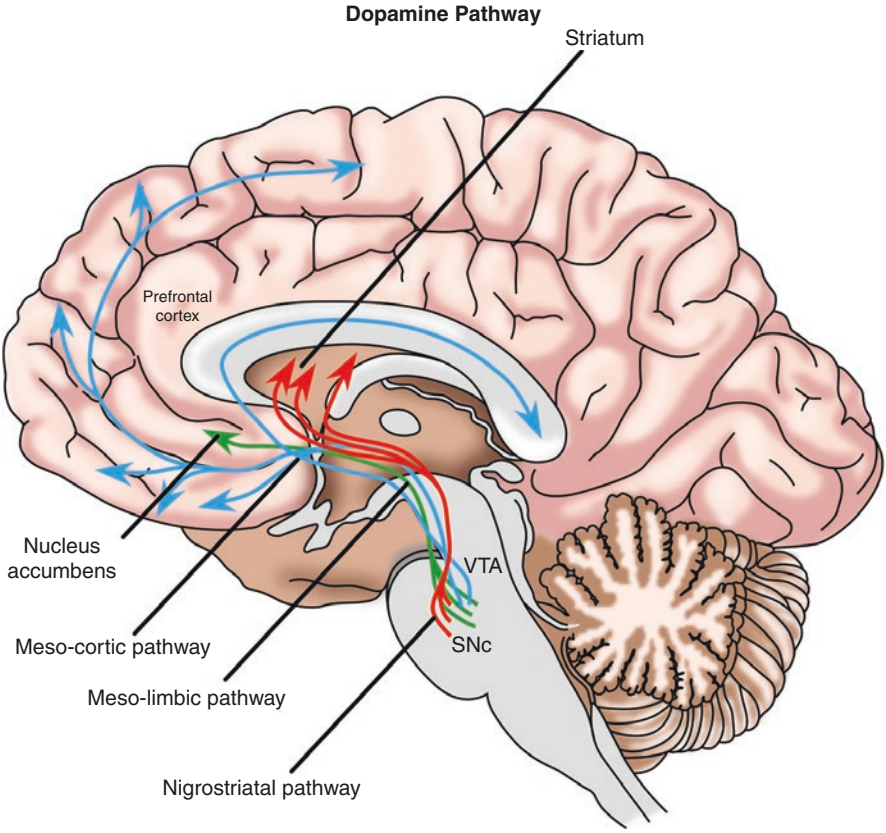

Fig. 24.2 The dopaminergic pathways

integration of motivational and reward-based processing (Cardinal et al. 2004). Figure 24.2 shows the dopaminergic nerve projections from the midbrain to other areas of the brain.

There has been a rapid growth in the literature describing the dopaminergic basis of human behaviour, with a parallel increase in tracer development for quantification of dopamine release via D_2/D_3 receptor occupancy imaging.

In a publication by Reeves et al. (2012), the association between reduced striatal D_2/D_3 receptor availability and higher levels of impulsivity was explored in 23 healthy volunteers. The authors wanted to evaluate whether a relationship between limbic (ventral) striatal D_2/D_3 receptor availability and the individual components of impulsivity exists. They made use of ^{11}C-raclopride PET imaging in 23 healthy volunteers which was compared to the various components of impulsivity (attention, motor and non-planning), assessed using the Barratt Impulsiveness Scale. After the exclusion of potential dissimulators, a significant association was found between non-planning impulsiveness and limbic D_2/D_3 receptor availability. The authors concluded that non-planning impulsiveness may be associated with

individual variation in limbic striatal D_2/D_3 receptor availability and that different facets of impulsivity may have specific neurochemical correlates (Reeves et al. 2012).

In another recent study, Costa et al. (2013) investigated the dopaminergic basis of impulsivity and other ADHD-related traits in healthy individuals by evaluating the association of such traits with striatal dopamine transporter availability. The group imaged 38 healthy males with ^{123}I-FP-CIT SPECT; they measured impulsivity with the Barratt Impulsiveness Scale (BIS) and hyperactivity-impulsivity and inattention with the Adult ADHD Self-Report Scale (ASRS). The authors found that greater dopamine transporter availability was associated with higher impulsivity as measured on BIS but was not associated with ADHD-related traits. This association with BIS was significant even after accounting for individual differences in age and neuroticism. The authors suggested in conclusion that individual differences in the dopamine system may be a neural correlate of trait impulsivity in healthy individuals (Costa et al. 2013).

24.1.6.2 Serotonergic Neurotransmission

The serotonergic system is one of the most important and complex neurotransmitter systems in the human brain, with 14 receptors identified to date, many of whose functions remain elusive and many of which play a role in several different processes. Serotonin transmission also plays an important role in several neuropsychiatric conditions and has been strongly implicated in impulsivity, together with the dopaminergic system.

Extensive investigation of the role of serotonin followed the discovery that the metabolite 5-HIAA is often low in the CSF of people with impulsive and aggressive behaviour. The incidence of suicidal acts was also related to the level of 5-hydroxyindoleacetic acid (5HIAA) in the cerebrospinal fluid, where patients with low levels of 5-HIAA (below 15 ng/mL) attempted suicide significantly more often than those with high levels and used more violent means (Åsberg et al. 1976). Figure 24.3 is a schematic diagram of the serotonergic synapse showing the synthesis, synaptic release, receptor binding and reuptake mechanism of serotonin.

In the CNS, 5-HT is synthesized in the raphe nuclei of the human midbrain and brainstem as well as their projection sites. From the raphe nuclei, projections run to the forebrain, reaching nearly all parts of the brain (Fig. 24.4). Tryptophan hydroxylase (TPH) plays an important role in the synthesis of serotonin by metabolizing L-tryptophan to 5-hydroxy-L-tryptophan, which in turn is metabolized by amino acid decarboxylase to serotonin. Serotonin reuptake from the extracellular space and the synaptic cleft is carried out by the SERT, which is an important therapeutic target in the treatment of many psychiatric disorders. The vesicular monoamine transporter type 2 (VMAT2) is a non-serotonin-specific transporter, which also transports other neurotransmitters such as dopamine, norepinephrine and histamine. The enzyme monoamine oxidase A (MAO-A) is responsible for the degradation of serotonin, and the resulting aldehyde is oxidized by aldehyde dehydrogenase to 5-hydroxyindoleacetic acid (5-HIAA). Figure 24.5 shows the enzymatic degradation of serotonin at the synaptic cleft.

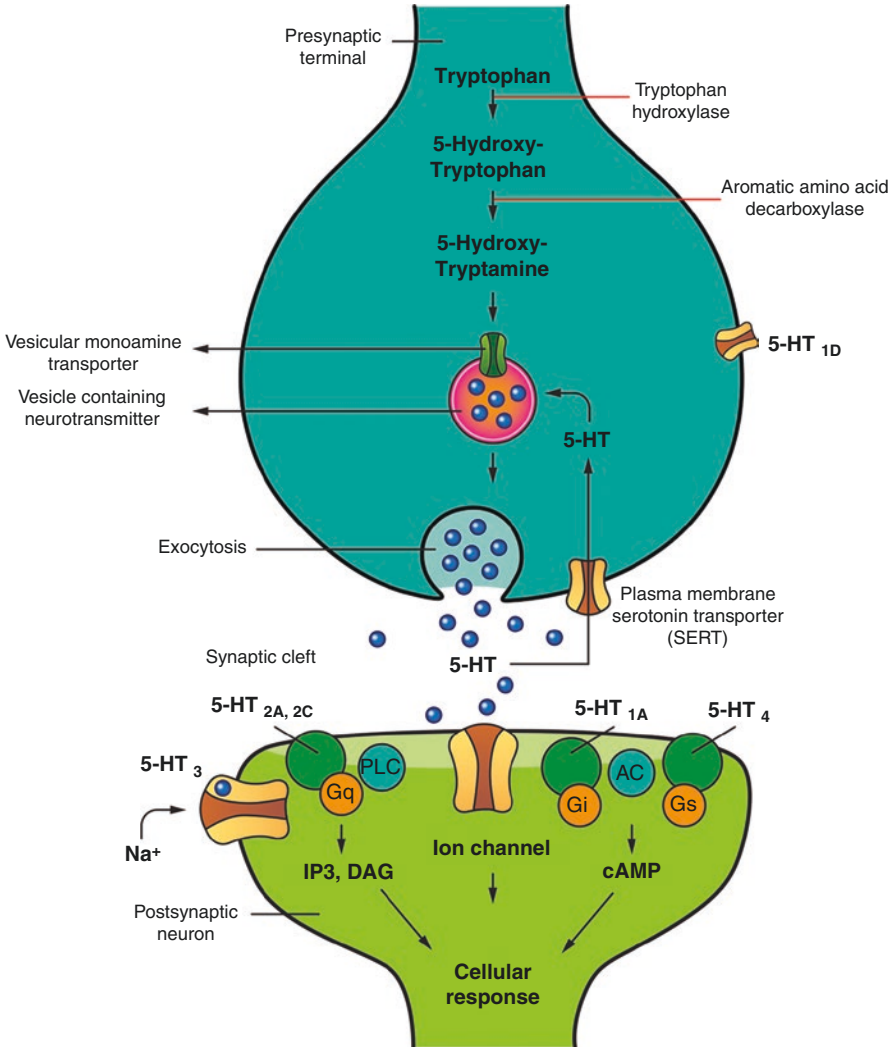

Fig. 24.3 The serotonergic synapse

Paterson and co-workers (2013) reviewed the history and current status of radioligands used for both SPECT and PET imaging of the human serotonin receptors, the serotonin transporter (SERT) and 5-HT synthesis rate. Table 24.2 was adapted from their paper and provides a summary of the imaging options and studies so far (Paterson et al. 2013).

Saulin et al. (2012) have summarized the distribution and main functions of the serotonin (5-hydroxytryptamin, 5-HT) receptors as well as that of the serotonin transporter (SERT, 5-HTT), the vesicular monoamine transporter 2, monoamine oxidase type A and 5-HT synthesis in the human brain. They included recent

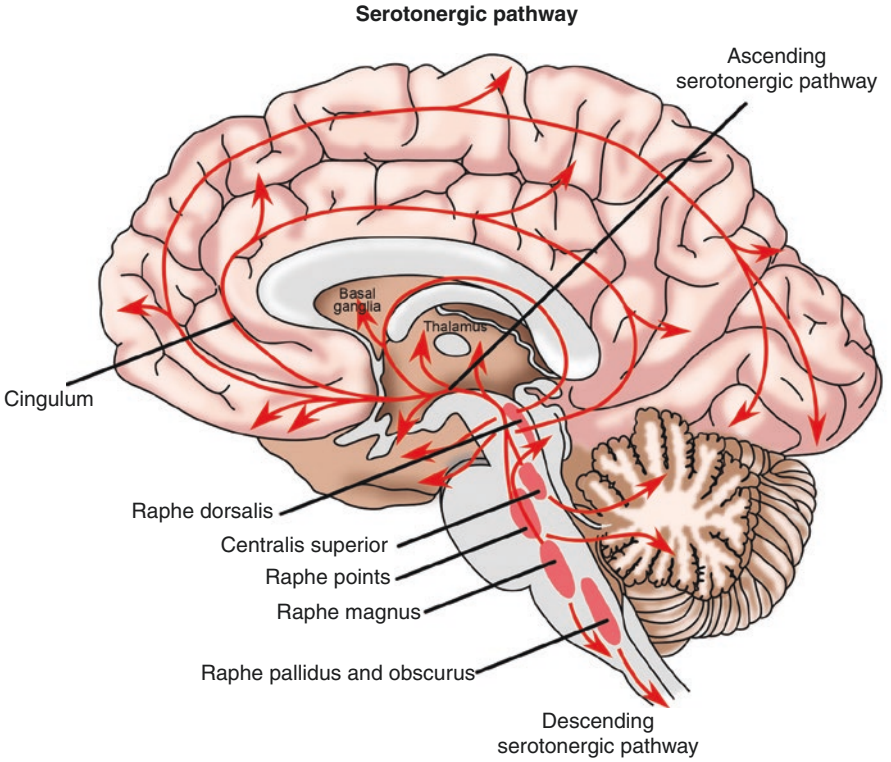

Fig. 24.4 The serotonergic pathway

advances in in vivo quantification of these different receptors and enzymes that are part of the serotonergic system using PET. A summary from their publication can be found below (Saulin et al. 2012) (Table 24.3).

Several important studies have provided evidence supporting the role of serotonergic disturbances in patients with disorders of impulsivity. For example, in 5-HT_{1B} knockout mice, an increase in impulsive behaviour and defective regulation of impulsivity have been reported (Meneses 2007; Meneses and Perez-Garcia 2007). The 5-HT_{1B} receptor has also been reported to play a role in several other psychiatric disorders. Studies have found it to be involved in alcoholism (Hu et al. 2010; Soyka et al. 2004) and substance abuse (Huang et al. 2003; Neumaier et al. 2002) (but see Cigler et al. (2001) for different findings). It has also been implicated in disorders such as attention deficit hyperactivity disorder (ADHD) (Quist et al. 2003) and aggression (Olivier and van Oorschot 2005; Saudou et al. 1994). In studies by Knudsen and co-workers, OCD has been linked to elevated levels of 5-HT_{2A} binding in the caudate nucleus (Adams et al. 2005), as well as to Tourette's syndrome which was associated with increased binding in the orbitofrontal cortex, anterior cingulate and frontal cortex and other regions of the brain (Haugbøl et al. 2007).

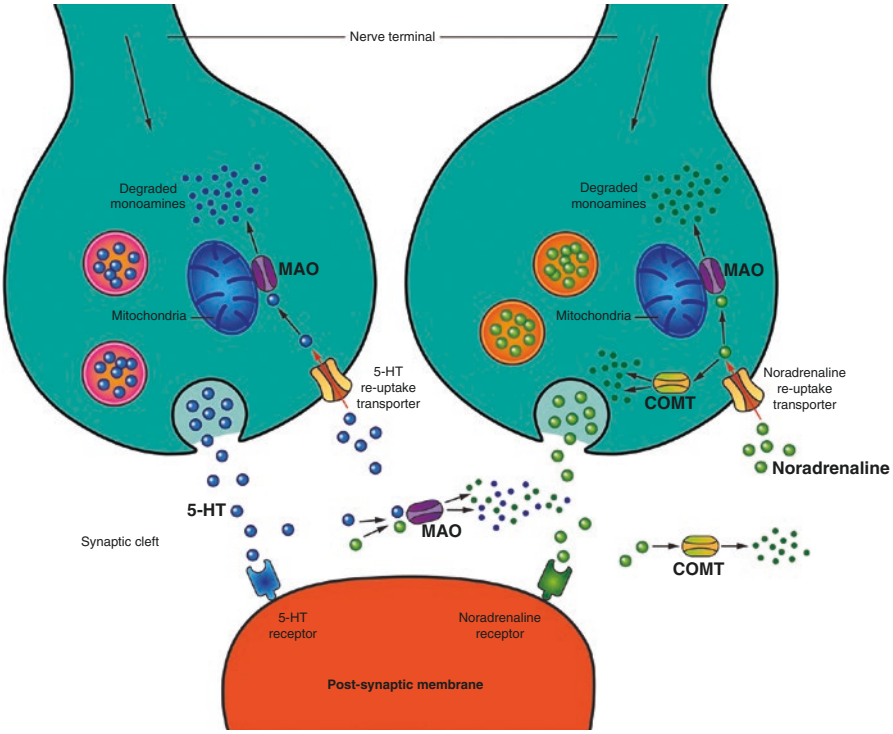

Fig. 24.5 A schematic diagram showing synaptic breakdown of neurotransmitters

By means of the highly specific radioiodinated 5-HT_{2A} receptor antagonist 4-amino-*N*-[1-[3-(4-fluorophenoxy) propyl]-4-methyl-4-piperidinyl]-5-iodo-2-methoxybenzamide or ^{123}I-5-I-R91150, Audenaert and co-workers demonstrated with high-resolution SPECT that the 5-HT_{2A} receptor in deliberate self-harm patients was significantly reduced in the frontal cortex (after correction for age) when compared with healthy controls. They also found that the reduction was more pronounced amongst deliberate self-injury patients (Audenaert et al. 2001).

Rylands et al. also conducted a study in which ^{11}C-MDL100907 was used to measure the availability of 5-HT_{2A} receptor in males with impulsive aggression. These patients fulfilled the DSM-IV diagnostic criteria of antisocial personality disorder (ASPD) and borderline personality disorder (BPD) and were divided into a high-impulsive aggression (high-IA) and a low-impulsive aggression (low-IA) group. Those with a history of past alcohol and drug dependence, current or past DSM-IV Axis I disorder, current Axis II cluster A personality disorder or use of 3,4-methylenedioxymethamphetamine (ecstasy) were excluded from the study. PET imaging was performed, which demonstrated that 5-HT_{2A} receptors were lower throughout the brain cortex of highly impulsive individuals. This indicates abnormal postsynaptic mechanisms of serotonin in these impulsive patients (Rylands et al. 2012).

Table 24.2 Promising SPECT and PET tracers for serotonergic imaging

Target	Radioligand	First in man	Animal studies	Human studies	Research institutions
5-HT_{1A}	[^{11}C]WAY-100635	1995	10	80	12
	[^{18}F]MPPF	2000	27	21	6
	[^{18}F]FCWAY	2000	7	11	1
	[^{11}C]CUMI-101	2008	2	1	1
5-HT_{1B}	[^{11}C]AZ10419369	2008	3	1	1
	[^{11}C]P943	2009	1	3	1
5-HT_{2A}	[^{123}I]-5-I-R91150	1997	9	19	6
	[^{18}F]Setoperone	1990	3	36	7
	[^{18}F]Altanserin	1994	5	51	10
	[^{18}F] Deuteroaltanserin	1998	2	5	1
	[^{11}C]MDL100907	1998	5	6	5
5-HT_4	[^{11}C]SB207145	2008	3	3	2
5-HT_6	[^{11}C]GSK215083	2008	1	2	1
SERT	Beta-[^{123}I]CIT	1993	20	87	18
	[^{123}I]ADAM	2005	11	28	12
	[^{11}C]DASB	2000	17	48	16
	[^{11}C]MADAM	2005	1	7	2
5-HT	[^{11}C]-AMT	1997	2	17	2
Synthesis	[^{11}C]-HTP	1991	4	10	3

Paterson et al. (2013)

Abnormalities of 5-HT_2 receptors in the brain cortex are viewed as representative of 5-HT_{2A} receptors in the cortex due to the extremely low density and binding of the other two subtypes, 5-HT_{2B} and 5-HT_{2C} (Meyer et al. 2008).

In schizophrenia, increased binding was observed in the caudate nucleus (Erritzoe et al. 2008), but decreased levels were found in the dorsolateral prefrontal cortex (dlPFC) and the parahippocampal gyrus (Burnet et al. 1996). Moreover, the 5-HT_{2A} polymorphism-1438G/A has been suggested to play a role in OCD (Enoch et al. 1998).

Most prominently in the clinical population (for review, see Daws and Gould (2011)), SERT has been found to play a major role in depression (e.g. Tsao et al. 2006) and bipolar disorder (e.g. Lesch et al. 1995). Other studies suggested SERT to be implicated in OCD (Hesse et al. 2011; Simpson et al. 2003) and substance abuse (Brown et al. 2007), especially MDMA (McCann et al. 2005; Selvaraj et al. 2009). SERT has further been linked to obesity (Erritzoe et al. 2010) and Parkinson's disease (e.g. Wang et al. 2010).

Changes in 5-HT synthesis have been associated with the treatment of major depression, showing lower 5-HT synthesis rates in patients with major depression (Rosa-Neto et al. 2004). A decrease of tryptophan has also been associated with Parkinson's disease, especially in the caudate (Kish et al. 2008). Leyton and colleagues found borderline personality disorder to be negatively linked to 5-HT

Table 24.3 Overview of the frequently used PET radioligands for measurement of the serotonergic system in the human brain, as well as recent promising radioligands from animal and human PET studies

Receptor/ transporter/enzyme	Frequently used PET ligands in humans	Recent promising PET ligands (animal, humans)	References
5-HT_{1A}	[*Carbonyl*-^{11}C]-WAY	[^{18}F]MefWAY (primate)	Wooten et al. (2011)
	[^{11}C]WAY100635	[^{11}C]CUMI-101, (baboon, *Papio anubis*, human)	Milak et al. (2008, 2010, 2011)
5-HT_{1B}	[^{11}C]AZ10419369	–	Varnäs et al. (2011a)
	[^{11}C]P943		Murrough et al. (2011)
5-HT_{1C}	–	–	–
5-HT_{1E}	–	–	–
5-HT_{1F}	–	–	–
5-HT_{2A}	[^{18}F]Altanserin	[^{11}C]CIMBI-36 (pig)	Ettrup et al. (2011)
	[^{11}C]MDL100,907	(R)-[^{18}F]MH.MZ (rodent)	Debus et al. (2010)
5-HT_{2B}	–	–	–
5-HT_{2C}	–	–	–
5-HT_{3}	–	–	–
5-HT_{4}	[^{11}C]SB207145	[^{11}C]**13** (guinea pig)	Xu et al. (2010)
5-HT_{5}	–	–	–
5-HT_{6}	–	[^{11}C]GSK210583 (pig, human)	Parker et al. (2012)
5-HT_{7}	–	–	–
SERT	[^{11}C]DASB	[^{18}F]FPBM (rat)	Wang et al. (2010)
	[^{11}C]MADAM	[^{18}F]ADAM (rat, monkey)	Huang et al. (2010)
VMAT2	[^{11}C]DTBZ	[^{18}F]AV133 (mouse, human)	Zhu et al. (2010)
	[^{11}C]MTBZ		Okamura et al. (2010)
MAO-A	[^{11}C]Harmine	[^{11}C]RS 2360 (mouse)	Soliman et al. (2011)
	[^{11}C]Clorgyline		Fowler et al. (2005)
	[^{11}C]Befloxatone		Bottlaender et al. (2003)
			De Bruyne et al. (2010)
5-HT synthesis	[^{11}C]AMT	–	Visser et al. (2011)
	[^{11}C]5-HTP		
Endogenous 5-HT	[^{18}F]MPPF	–	Derry et al. (2006)
			Yatham et al. (2001)
			Varnäs et al. (2011b)

Saulin et al. (2012)

synthesis rates as measured with PET in the medial frontal gyrus, anterior cingulate gyrus, superior temporal gyrus and corpus striatum. They also found reduced synthesis rates in the medial frontal gyrus, anterior cingulate gyrus, temporal gyrus and striatum in subjects scoring high on measures of impulsivity (Leyton et al. 2001).

Drug-free suicide attempters compared with matched controls showed a negative correlation between SERT and impulsiveness with no significant difference demonstrated concerning the regional levels of SERT binding potentials and DAT binding potentials in the two groups. However, a significant regional correlation was seen in the suicide attempters between Marke-Nyman temperament test (which assesses the level of impulsiveness and mental energy) and the SPECT findings. This finding was not evident in the control group and was attributed to an inability of the suicide attempters to regulate their serotonin and dopamine levels in response to external stress (Ryding et al. 2006).

^{123}I-β-CIT, a mixed monoamine transporter tracer which is a potent ligand for both dopamine and serotonin reuptake sites, was used by Lindstrom et al. to evaluate 12 patients (10 men and 2 women) who previously had a serious suicide attempt and their matched healthy controls. SPECT imaging demonstrated a correlation between SERT and DAT in the suicide attempters which was not evident in the control group indicating that both systems may play a role in impulsivity (Lindström et al. 2004).

24.1.6.3 Noradrenergic Neurotransmission

The noradrenaline transporter (NAT) is located at the presynaptic terminal of noradrenergic neurons where it plays an integral role in noradrenergic neurotransmission. It regulates the concentration of noradrenaline in the synaptic cleft via a reuptake mechanism. Brain structures known to be rich in norepinephrine (NET) include the locus coeruleus, thalamus, hippocampus and entire cerebral cortex, whereas low levels are found in the cerebellum and striatum (Fig. 24.6).

Alterations in synaptic noradrenaline levels have been implicated in various neuropsychiatric and neurodegenerative disorders (such as ADHD, anxiety and Alzheimer's disease). More importantly, NAT is a major therapeutic target for these disorders and provides SPECT and PET with an imaging target to assess drug occupancy levels, amongst other applications.

Most of the initial work on SPECT radiotracers for imaging of the noradrenaline transporter (NAT) has focused on the development of radioiodinated analogues of the noradrenaline reuptake inhibitor, reboxetine. It has lagged behind the tracer development for DAT and SERT somewhat, due to the limited availability of suitable radioligands. A few tracers that are selective for NET have recently emerged with several research groups having found the reboxetine derivatives are preferable to the nisoxetine series.

Tamagnan and co-workers (2007) worked on the development of SPECT imaging agents for the norepinephrine transporter. They synthesized a series of reboxetine analogues, which was then evaluated for in vitro binding as racemic mixtures. [^{123}I]INER was considered to be the best candidate and was synthesized as the optically pure (S,S) enantiomer. The in vivo binding of [^{123}I]INER was determined by

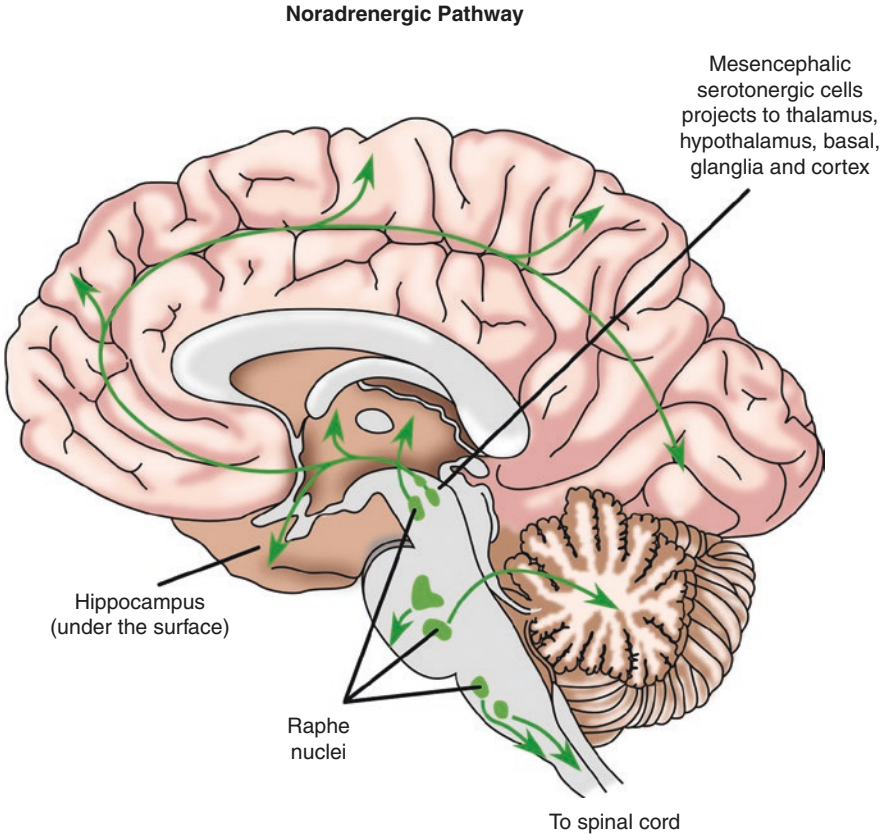

Fig. 24.6 Noradrenergic pathway

SPECT imaging in an animal model, and the authors found that the tracer's in vivo specificity, selectivity and kinetics made it a promising agent for SPECT imaging of norepinephrine in vivo (Tamagnan et al. 2007).

Jobson and co-workers (2008) developed a new route for the synthesis of iodinated reboxetine analogues to image the noradrenaline transporter (NAT) with SPECT. The authors prepared 2S,3S- and 2R,3R-iodoreboxetine and performed biological testing against various monoamine transporters, which demonstrated these compounds to be potent and selective for NAT (Jobson et al. 2008).

A specific tracer for quantification of the variation in norepinephrine density will be valuable in gaining insight into the aetiology and pathophysiology of neuropsychiatric disorders such as ADHD and Alzheimer's. This will especially be of value in identifying therapeutic targets and monitoring treatment response in newly emerging drug treatments, such as atomoxetine. This is the first selective, non-stimulant treatment for ADHD.

24.1.6.4 The Potential Role of PET and SPECT in Evaluating Response to Treatment, Prognosis and Drug Development

Although clinical application may include a primary role in diagnosis, the most promising role of functional imaging seems to be in the fields of drug development, in the evaluation of treatment response and in providing an idea of the severity and prognosis of disease conditions.

In addition to the role of functional neuroimaging in the assessment of neural connections involved in impulsivity, several authors have also reported the potential role of molecular imaging in treatment response assessment. By labelling an appropriate tracer with an affinity and selectivity for the molecular target in question to a suitable radioisotope, it is possible to evaluate the kinetics, biodistribution, metabolism and toxicity of particular drugs (Guilloteau and Chalon 2005).

New et al. used ^{18}F FDG-PET/CT to assess metabolic changes in specific cortical areas in patients with impulsive aggression following treatment with selective serotonin reuptake inhibitors (SSRIs). This group demonstrated increased metabolism in the prefrontal and medial temporal regions (commonly implicated in impulsive aggression) in patients treated with fluoxetine. These patients demonstrated decreased tracer uptake in the aforementioned areas on their baseline scans during their treatment-naïve state (New et al. 2004).

Rosa-Neto et al. and Krause and co-workers also used molecular imaging in assessing response to methylphenidate in patients diagnosed with ADHD (Rosa-Neto et al. 2004; Krause et al. 2000). Dose-dependent occupancy of DAT with methylphenidate had been demonstrated by Volkow et al. (1998). Therapeutic doses of this drug have been shown to increase extracellular dopamine concentration. Using ^{11}C-raclopride PET, Rosa-Neto et al. went on to demonstrate a 12% reduction in the binding potential of striatal dopamine D_2/D_3 receptors during treatment with methylphenidate compared to the baseline pretreatment assessment of adolescents with ADHD. The binding potential assessed with ^{11}C-raclopride PET was found to correlate with the cognitive measures using the TOVA test. They further demonstrated a correlation between the severity of the impulsivity and the magnitude of the binding potential of ^{11}C-raclopride in the striatum of these patients, suggesting a potential role in the evaluation of the prognosis of patients with impulsivity with molecular imaging (Rosa-Neto et al. 2004).

The role of molecular imaging may further be extended to the development of drugs for neuropsychiatric disorders. This was discussed by Guilloteau and Chalon who explored the potential role of PET and SPECT imaging through in vivo exploration of monoamine transporters. (These are believed to be responsible for the homeostasis of the neurotransmitter pools at the nerve endings.) The authors concluded that in vivo molecular imaging could be used to define the involvement of a specific neurotransmitter and therefore to explain the mechanism of action of drugs through binding site occupancy studies. This therefore makes it possible to evaluate disease evolution and therapeutic effects of treatment and to elucidate the mechanism of action of new drugs (Guilloteau and Chalon 2005).

24.2 Clinical Applications

As mentioned before, impulsivity represents a core aspect of several neuropsychiatric conditions and, as such, provides an interesting target for diagnosis, appropriate treatment selection and response evaluation. Attention deficit hyperactivity disorder (ADHD) is considered by many to be the "archetypal disorder of impulsivity", and as such it was considered an appropriate starting point for discussion. It should also serve as a model to illustrate the role of functional imaging in all of the aforementioned aspects of neuropsychiatric disease evaluation.

24.2.1 Neurology

24.2.1.1 Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is a common and debilitating neuropsychiatric disorder, which frequently starts in childhood and is characterized by age-inappropriate symptoms of hyperactivity, inattentiveness and impulsivity. According to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), there are three subtypes of ADHD: the predominantly inattentive subtype, the predominantly hyperactive-impulsive subtype and the combined subtype. However, evidence from various neuropsychological studies suggests that "poor inhibitory control is central to ADHD" (Durston 2003).

The understanding of the underlying pathophysiology is complicated by the variety of clinical symptoms with which the condition may present as well as the high incidence of comorbidity. Imaging studies of the past 20 years have shown aberrations in especially the fronto-striatal, parieto-temporal and fronto-cerebellar networks.

24.2.1.2 Pathophysiological Changes

Several anatomical studies have shown diffuse volume reductions, which affect the cerebrum and cerebellum. Studies of the basal ganglia have resulted in inconsistent results with some reporting reductions in the right caudate volume and others in the left and no changes noted in the putamen (Castellanos 1996). A meta-analysis by Nakao et al. (2011) has demonstrated that low grey matter in the basal ganglia is the most consistent abnormal finding (Nakao et al. 2011).

The central role of striatal dopamine levels appears undisputed. Hypotheses have linked cognitive impairments to a decrease in DA availability in the prefrontal cortex, while hyperactivity and impulsivity have been linked to a secondary increase in striatal DA (Solanto 2002).

A 2003 review by Sarah Durston provides a comprehensive overview on the anatomical and functional information obtained from various imaging studies prior to 2003, which is conveniently grouped and summarized in table form and which readers are hereby referred to (Durston 2003).

In a meta-analysis by Fusar-Poli et al. (2012), the authors evaluated the inconsistent results so far on striatal dopamine receptor density by combining the results of nine nuclear medicine imaging studies, involving either PET or SPECT.

This resulted in a total of 169 ADHD patients with 173 normal controls matched for age, gender and IQ. They extracted striatal binding potentials (BP) together with clinical, demographic and methodological variables from all publications. However, significant heterogeneity was present, and the authors had to use a random-effects model. No publication bias was present, and the robustness was proven by sensitivity analysis.

The following studies were included (Table 24.4).

The following observations were made (Fig. 24.7).

- Two (out of the nine) studies failed to demonstrate any significant difference in striatal DA transporter density between patients with ADHD and healthy controls.
- Five studies showed higher DAT density between ADHD and comparison groups.
- Two studies demonstrated lower DAT density in patients with ADHD.
- Pooled results from the meta-analysis indicated statistically significant increases in DAT density in patients with ADHD compared to healthy controls (on average a 14% increase).
- The type of imaging modality used (PET/SPECT) did not alter the results.
- In addition, post hoc analysis showed that lower DAT levels were associated with treatment-naïve subjects, while higher DAT levels were associated with treated patients.
- The authors suggested that high DAT levels might therefore be secondary to long-term psychostimulant treatment as an adaptive brain response, rather than representing an integral part of the pathophysiology in ADHD (Fusar-Poli et al. 2012).

24.2.1.3 Additional Studies Involving SPECT and PET Imaging

Kaya et al. evaluated regional perfusion changes in children with ADHD making use of ^{99m}Tc-HMPAO SPECT. They assessed 13 treatment-naïve children with established ADHD according to DSM-IV criteria and compared them to 7 age-matched healthy controls. The authors found decreased perfusion (visually and semi-quantified) in the right medial temporal cortex, which demonstrated a significant inverse correlation to Du Paul teacher's questionnaire rating scale (Kaya et al. 2002).

Szobot and co-workers sought to determine whether the presence of certain risk alleles at DRD4 and DAT1 genes could be correlated to regional cerebral perfusion changes as assessed by ^{99m}Tc-ECD SPECT imaging. They selected boys with a diagnosis of ADHD according to DSM-IV criteria and divided them into groups with and without the aforementioned risk genes. Brain perfusion patterns were analysed voxel by voxel with SPM-99. The authors found a pattern of significantly increased perfusion in the right middle temporal gyrus, which was associated with the presence of both DRD-4 and DAT1 genes. No associations were found between abnormal perfusion and single gene aberrations (Szobot et al. 2004).

Table 24.4 PET or SPECT studies included in a meta-analysis of striatal dopamine transporter density in ADHD patients and healthy comparison subjects

Study and group	Radiotracer	Technique	*N*		Age (years)		ADHD treatment status	ADHD/comparison ratio of dopamine transporters
			Total	Female	Mean	SD		
Dougherty et al. (1999)	[^{123}I] Altropane	SPECT					Drug-free	1.70[a]
ADHD			6	4	41.33	4.46		
Comparison			30	–	40.80	–[b]		
van Dyck et al. (2002)	[^{123}I]β-CIT	SPECT					8 drug-naïve, 1 drug-free	1.00
ADHD			9	3	41	11		
Comparison			9	3	41	11		
Cheon et al. (2004)	[^{123}I]IPT	SPECT					Drug-naïve	1.51[a]
ADHD			9	2	9.67	2.12		
Comparison			6	–	10.33	2.88		
Jucaite et al. (2005)	[^{11}C]PE2I	PET					9 drug-naïve, 3 drug-free	1.08
ADHD			12	0	13.8	1.2		
Comparison			10	0	29.5	5.8		
la Fougère et al. (2006)	[^{99m}Tc] TRODAT-1	SPECT					Drug-free	1.16[a]
ADHD			22	11	39.1	10.2		
Comparison			14	6	–[c]			
Larisch et al. (2006)	[^{123}I] FP-CIT	SPECT					Drug-naïve	1.06[a]
ADHD			20	11	35	7		
Comparison			20	11	32	8		
Spencer et al. (2007)	[^{11}C] Altropane	PET					Drug-naïve	1.15[a]
ADHD			21	7	34.4	9.2		
Comparison			26	15	27.4	7.6		
Volkow et al. (2009)	[^{11}C] cocaine	PET					Drug-naïve	0.80[a]
ADHD			53	26	32	8		
Comparison			44	14	31	6		
Hesse et al. (2009)	[^{123}I] FP-CIT	SPECT					Drug-naïve	0.81[a]

Table 24.4 (continued)

Study and group	Radiotracer	Technique	*N*		Age (years)		ADHD treatment status	ADHD/ comparison ratio of dopamine transporters
			Total	Female	Mean	SD		
ADHD			17[d]	9	32	8		
Comparison			14	6	32	9		

Fusar-Poli et al. (2012)
[a]Statistically significant
[b]Age range = 21–60
[c]Age range = 21–63
[d]With psychiatric or neurological comorbidity

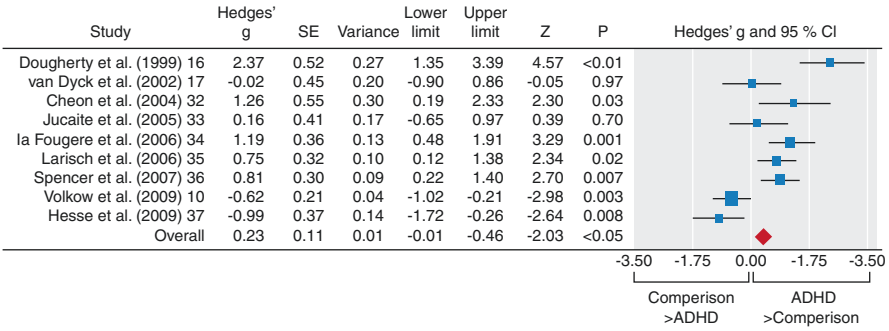

Fig. 24.7 Meta-analysis of striatal dopamine transporter density in ADHD patients and healthy comparison subjects employing random-effects models. (Fusar-Poli et al. 2012)

Zimmer published a review in 2009, which provides a comprehensive overview of the role of PET and SPECT imaging in the explanation of the pathophysiology of ADHD as well as in the therapeutic drug development. Studies (involving SPECT and PET imaging) are discussed under the headings of perfusion, glucose metabolism, dopaminergic and noradrenergic neurotransmission, to which readers are hereby referred (Zimmer 2009).

24.2.1.4 Promising Future Roles of SPECT and PET

Treatment and Response Evaluation in ADHD

Methylphenidate is a highly effective form of treatment in ADHD and is believed to exert its action by blockade of striatal dopamine transporters, causing an increase in the prefrontal DA transmission, which then results in an improvement in both cognition and behavioural symptoms. When given orally at a therapeutic dose, methylphenidate blocks around 70% of the dopamine transporters in the striatum (Dougherty et al. 1999).

Krause and co-workers made use of ^{99m}Tc-TRODAT-1 SPECT imaging for evaluation of DAT-1 and found a reduction of dopamine transporter sites after 4 weeks of treatment with methylphenidate (Krause et al. 2000).

Volkow et al. evaluated the effects of an acute therapeutic dose of oral methylphenidate with ^{11}C-raclopride PET imaging and found that this leads to marked increases of extracellular striatal dopamine (Volkow et al. 2001).

Rosa-Neto et al. used a pharmacological challenge with therapeutic doses of methylphenidate (MP) to assess whether the magnitude of the changes induced in extracellular DA concentrations could be used as a measure of the severity of impulsivity and inattention. They evaluated nine unmedicated adolescents with ADHD who each underwent a baseline ^{11}C-raclopride PET scan, followed by a second PET 30 min after MP administration. The binding potential of ^{11}C-raclopride provides an estimate of free D_2D_3 receptor binding sites and should decrease following methylphenidate administration. A striatum to cerebellar ratio was calculated at 30–45 min postinjection in order to reflect steady-state conditions. Image findings were then compared to severity of clinical symptoms as assessed by the Test of Variables of Attention (TOVA), which is a widely used tool for this purpose. The authors found a significant correlation between the magnitude of the change in percentage binding potential in the right striatum and the severity of inattention and impulsivity (Rosa-Neto et al. 2005).

It has recently been postulated that methylphenidate may be associated with an adaptive secondary up-regulation of DAT in response to long-term blockade, which could explain its loss of effectiveness during long-term use (Fusar-Poli et al. 2012).

Genetic Imaging

The imaging of genetics is an exciting emerging field, where various forms of functional imaging are used to evaluate the association of certain "risk genes" with brain function, structure and chemistry. This follows a recent trend in psychiatry towards the identification of specific psychiatric endophenotypes.

ADHD is a highly prevalent neuropsychiatric disorder in both children and adults with a well-established hereditary component. The two best-studied and validated risk genes appear to be the DRD4 and DAT1 genes (Waldman and Gizer 2006).

Norepinephrine neurotransmission plays an important role in the pathogenesis of ADHD as evident by its targeting in the pharmacotherapy of ADHD. Methylphenidate and atomoxetine are effective drugs for ADHD that inhibit norepinephrine reuptake (Asherson et al. 2014; Kowalczyk et al. 2019). Using [^{18}F]FMeNER-D2 PET imaging, Sigurdardottir et al. (2016) recently evaluated the effects of single-nucleotide polymorphisms (SNPs) within the NET gene on NET nondisplaceable binding potential (BP_{ND}) in patients with ADHD. The authors reported significant differences in cerebellar and thalamic NET binding between ADHD patients and healthy controls, the observations of which were dependent on the differences in genotypes. In ADHD patients, there was a high correlation between hyperactivity/impulsivity and NET BP_{ND} in the cerebellum, an effect that was strongly moderated by the patients' genotype. These findings support the results from an earlier longitudinal

study indicating that individuals with a certain gene encoding for the norepinephrine transporter are at increased risk of ADHD lifetime diagnosis (Hohmann et al. 2015). The genetic variation in the norepinephrine system contributes to the differences in the symptoms of ADHD.

Sarah Durston (2010) reviewed the early works on the subject, which is summarized in the following tables (Durston 2010) (Table 24.5):

Table 24.5 Studies on imaging genetics in ADHD

Authors	Participants	Modality and methods	Results
Brain structure			
Castellanos et al. (1998)	41 ADHD (9.7 ± 2.6 yrs; all psychoactive meds)	Structural MRI (1.5 T); semiautomated volumes of TB, cerebellum, PFC; manual volumes of CN, PAL	No genotype effects
	57 NC (17.6 ± 9.1 yrs)	DRD4 VNTR exon 3; 7R-car vs not: 17	No group × genotype interactions
	Mixed ethnicity; US study	ADHD-7R; 22 NC-7R	
Bobb et al. (2005)	163 ADHD (86 M; 9.0 ± 2.2 yrs; meds not reported)	Structural MRI (1.5 T); fully automated volumes of TB, lobes, BG, cerebellum	No genotype effects
	129 NC (74 M; 16.0 ± 8.1 yrs)	DRD1; rs4532 C-car vs not: 64 ADHD C-car and 36 NC C-car; rs265981 T-car vs not: 62 ADHD T-car and 36 NC T-car	No group × genotype interactions
	Mixed ethnicity; US study	NET1; rs998424 C-car vs not: 112 ADHD C-car and 90 NC C-car; rs3785157 T-car vs not: 114 ADHD T-car and 92 NC T-car	
Durston et al. (2005)	26 ADHD (30 M; 12.1 ± 2.5 yrs; all MPH)	Structural MRI (1.5 T); automated volume of PFC GM; manual volume of CN	Main effects: DAT1 on CN: 9R > 10R DRD4 on PFC GM: 4R < car variant alleles
	26 unaffected siblings (30 M; 11.6 ± 3.2 yrs)	DRD4 VNTR exon 3; 4R/4R vs not: 34 4R/4R	
	20 NC (30 M; 10.7 ± 1.9 yrs)	DAT1 3′ VNTR; 10R/10R vs carrier 9R: 40 10R/10R	
	Caucasian sample; Dutch study		

(continued)

Table 24.5 (continued)

Authors	Participants	Modality and methods	Results
Shaw et al. (2007)	105 ADHD (50 M; 10.1 ± 2.8 yrs; 85 stimulant meds)	Structural MRI (1.5 T); longitudinal	Main effect of diagnosis in OFC, sup/med PFC and post parietal cortex: ADHD < NC main effect of DRD4-7R in similar regions: ADHD 7R < ADHD not-7R < NC 7R < NC not-7R
	103 NC (58 M; 10.0 ± 2.9 yrs)	Automated cortical thickness	
	Mixed ethnicity; US study	DRD4 VNTR exon 3; 7R-car vs not:	
		43 ADHD 7R and 35 NC 7R	
Monuteaux et al. (2008)	24 ADHD (12 M; 38.1 ± 10.8 yrs; meds not reported)	sMRI (1.5 T) volumes of sup frontal, mid frontal, ACG, cerebellar cortices	Main effect of genotype in frontal and cerebellar cortex for ADHD only: 7R-car < not
	19 ADHD and BD (13 M; 35.8 ± 14.1 yrs)	DRD4 VNTR exon 3; 7R-car vs not: 6 ADHD; 7 ADHD and BD; 6 NC 7R	
	20 NC (13 M; 33.2 ± 10.0 yrs)		
	Mixed ethnicity; US study		
Brain chemistry			
Cheon et al. (2005)	11 ADHD (9 M; 9.8 ± 1.3 yrs; all med naïve)	I[^{123}I]IPT SPECT (to assess DAT availability) DAT1 3′ VNTR; 9R-car vs 10R/10R: 4 10R/10R	Striatal DAT availability:
	Pharmacogenetics study: 8-wk MPH treatment		10R >9R 10R associated with poorer MPH response
	Ethnicity not reported; Korean study		
Krause et al. (2006)	29 ADHD (19 M; 37.6 ± 10 yrs; all med naïve)	[(^{99m})Tc]TRODAT-1 SPECT (to assess DAT availability) DAT1 3′ VNTR; 9R-car vs not: 12 9R	No effect of genotype on striatal DAT availability
	Caucasian sample; German study		
Brain function			
Rohde et al. (2003)	8 ADHD (8 M; range 8–12 yrs; all MPH-naïve)	^{99m}Tc-ECD SPECT during CPT (rCBF in 5 ROIs; 3 PFC; 2 BG) DAT1 3′ VNTR; 10R/10R vs carrier 9R: 4 10R/10R	PFC and BG:
	Pharmacogenetics study: 4-day MPH treatment		10R/10R > carrier 9R
	Ethnicity not reported; Brazilian study		

Table 24.5 (continued)

Authors	Participants	Modality and methods	Results
Loo et al. (2003)	27 ADHD (18 M; 10.1 ± 1.5 yrs; 48 hr med washout)	EEG CPT task during MPH challenge DAT1 3′ VNTR; 10R/10R vs carrier 9R: 17 10R/10R	10R/10R: increased parietal/central beta-power, decreased frontal theta, decreased theta/beta ratios Carrier 9R: reverse pattern
	Pharmacogenetics study: single dose MPH		
	Ethnicity not reported; US study		
Szobot et al. (2005)	34 ADHD (34 M; 11.6 ± 2.5 yrs; all med naïve)	^{99m}Tc-ECD SPECT during CPT (whole-brain rCBF) DRD4 VNTR exon 3; 7R-car vs not: 13 7R DAT1 3′ VNTR; 10R/10R vs carrier 9R: 17 10R/10R	rCBF R medial temporal gyrus: carriers both risk alleles >not
	Ethnicity not reported; Brazilian study		
Baehne et al. (2009)	122 ADHD (72 M; 34.7 ± 9.6 yrs; all med free but not necessarily naïve)	EEG go/no-go task: No-go anteriorization (marker prefrontal functioning) tryptophan hydroxylase gene (TPH2); rs4570625 G/G: 76 ADHD; 57 NC G/G and rs11178997 T/T: 107 ADHD; 73 NC T/T	Both ADHD and controls:
	84 NC (44 M; 34.8 ± 10.3 yrs)		Homozygotes risk alleles at both TPH2 loci <non-homozygotes
	Ethnicity not reported; German study		
Durston et al. (2008)	10 ADHD (10 M; 14.6 ± 2.6 yrs; 1 med naïve; 24 hr meds washout)	fMRI (1.5 T) go/no-go task; whole-brain analysis of genotype DAT1 3′ VNTR; 10R/10R vs carrier 9R: 6 ADHD; 5 sibs; 6 NC 10R/10R	Main effect genotype:
	10 unaffected sibs (10 M; 14.8 ± 2.3 yrs)		9R ↑; activation in CN
	9 NC (9 M; 15.3 ± 2.1 yrs)		9R ↓; activation in vermis
	Caucasian sample; Dutch study		Group × genotype interaction: effect in CN related to ADHD and unaffected siblings—not NC
Brown et al. (2010)	42 ADHD (20 M; 35.2 ± 13.5 yrs; 16 med naïve; 24 hr meds washout)	fMRI (1.5 T) MSIT (interference) task; ACC ROI and whole-brain analysis of genotype DAT1 3′ VNTR; 10R/10R vs carrier 9R: 19 10R/10R	9R ↑; activation in ACC, vermis, PFC
	Caucasian sample; US study		

(continued)

Table 24.5 (continued)

Authors	Participants	Modality and methods	Results
Bédard et al. (2010)	33 ADHD (24 M; 11.1 ± 2.5 yrs; 21 med naïve; 2 wk meds washout)	fMRI (3.0 T) go/no-go task; whole-brain analysis of genotype DAT1 3′ VNTR; 10R/10R vs carrier 9R: 21 10R/10R	9R ↓; activation in striatum, premotor cortex, temporoparietal junction
	Mixed ethnicity; US study		

Sarah Durston (2010)

BD bipolar disorder, *car* carrier, *C-car* C-allele carrier, *CN* caudate nucleus, *CPT* continuous performance task, *EEG* electroencephalogram, *ERP* event-related potential, *G/G*G-allele homozygote, *GM* grey matter, *hr* hour; *med* medial, *med free* medication free, *med naïve* medication naïve, *meds* medications, *mid* middle, *MPH* methylphenidate, *MRI* magnetic resonance imaging, *NC* normal controls, *OFC* orbitofrontal cortex, *PFC* prefrontal cortex, *PAL* pallidum, *post* posterior, *PET* positron emission tomography, *rCBF* regional cerebral blood flow, *R* repeat, *ROI* region of interest, *SPECT* single-photon emission computed tomography, *sup* superior, *TB* total brain, *T* Tesla, *T-car* T-allele carrier, *T/T*T-allele homozygote, *US* United States, *wk* week, *yrs* years

The largest study involving genetic imaging with SPECT was done by Szobot et al. (2005), and readers are referred back to the earlier SPECT section for more detail on this study (Szobot et al. 2004).

Conduct disorder (CD) is one of the most frequent behavioural disorders comorbid with ADHD. CD is seen in about 20% of patients with ADHD (Loeber et al. 2000). Its presence may alter the course and prognosis of ADHD, may diminish the effectiveness of pharmacotherapy and may predispose affected patients to other conditions such as substance abuse, major depression, bipolar disorder and multiple anxiety disorder (Biederman et al. 1996; Loeber et al. 2000; Molina and Pelham Jr 2003). It is, therefore, important to identify CD as a comorbid condition in individuals with ADHD in order to institute appropriate therapy. Chang et al. (2017) demonstrated a reduction in SERT availability in the striatum and midbrain of adult males comorbid with ADHD and CD. The findings from this study suggest that disorder in the serotonergic transmission may be responsible for CD in patients with ADHD and may hold potential as a therapeutic target in drug development.

24.2.1.5 Parkinson's Disease (PD)

Patients with Parkinson's disease have a higher prevalence of impulse control disorders (ICD) when compared to the general population, which has been found particularly in association with dopaminergic treatment (Avanzi et al. 2006). Other impulsive-compulsive behaviours in association with PD include dopamine dysregulation syndrome (characterized by self-medication with inappropriately high doses of high-potency and short-acting medications driven by a desire to maintain a "high" or avoid the "low" state), punding (repetitive, purposeless behaviours that are characterized by an intense preoccupation with specific items or activities such as collecting, arranging or taking apart objects), hobbyism (a higher level of repetitive behaviours such as excessive exercise, Internet use, etc.), excessive aimless wandering and hoarding (acquisition and refusal to discard a large number of items

with little or no value) (Giovannoni et al. 2000; Evans et al. 2004; Dagher and Robbins 2009; O'Sullivan et al. 2010).

The DOMINION study found treatment with dopaminergic drugs (as a class) to be associated with a 2–3.5 times increase in the odds of having an ICD and reported a 6-month ICD prevalence of 13.6% (Weintraub et al. 2010a).

Impulse control disorders in PD (pathological gambling, hypersexuality, compulsive shopping or eating) appear to be underdiagnosed, under-reported and therefore frequently not treated in light of the predominant motor disturbances. Considering the potential negative effects of these disorders, attention should be paid to early diagnosis and treatment. Non-imaging diagnostic tools consist of various questionnaires (e.g. QUIP-Current-Short).

In light of the fact that not all patients who are treated with DA develop impulse control disorders and that early treatment changes are necessary in those who do develop them, there is a need for an objective early diagnostic tool in order to identify those at risk and evaluate the response to treatment change. Functional imaging appears promising in this setting; Vilas et al. (2012) published an overview on the relevant aspects of the above-mentioned issues to which readers are referred (Vilas et al. 2012).

Functional Imaging with SPECT and PET

Steeves et al. (2009) evaluated the DA function of patients with PD during pathological gambling with the use of ^{11}C-raclopride PET imaging. They found greater decreases in the binding potential in the ventral striatum compared to controls, which implies a greater release in DA during gambling, similar to that found with substance abuse.

Cilia and co-workers (2010) investigated whether presynaptic DA abnormalities could be used to identify patients with Parkinson's disease who have an increased likelihood of developing impulsive disorders (ICD). They determined striatal DAT density with the use of ^{123}I-FP-CIT SPECT imaging which was analysed with voxel-based SPM. Patients with PD on DA agonist therapy who did not develop impulse control disorders were compared to those who did as well as healthy age-matched controls. The authors enrolled eight patients with pathological gambling (as a prototype of ICD) and found differences in the dorsal and ventral striata bilaterally between all three groups. Patients with pathological gambling demonstrated reduced tracer binding in the ventral striatum compared to PD controls, possibly reflecting either a reduction of mesolimbic projections or, alternatively, a lower membrane DAT expression on presynaptic terminals. The authors concluded that the latter hypothesis was the most likely, since the functional reduction of presynaptic reuptake would be consistent with the increased dopamine levels in the ventral striatum that had recently been reported in PD gamblers (Cilia et al. 2010). Navalpotro-Gomez et al. (2019), in a recent study, similarly showed reduction in DAT availability by ^{123}I-FP-CIT SPECT imaging in the ventral striatum of PD patients with ICDs compared with PD patients without ICDs. Reduction in DAT availability showed a negative association with clinical severity of ICDs. In addition, there was

an associated decreased cortical metabolism by ^{18}F-FDG PET/CT imaging in the mesolimbic and mesocortical areas as well as functional brain regions involved with salience attribution, reward processing and inhibitory control. Findings from this study showed the integrated relationship between the reduction in DAT density in the ventral striatum in PD patients with ICD and an impairment in brain regions concerned with conflict resolution and inhibitory control.

In a more recent prospective study including 320 patients newly diagnosed with PD who were followed up for a mean period of 1.97 years (Smith et al. 2016), the rate of development of ICD symptoms increased with time. DAT availability evaluated by ^{123}I-FP-CIT SPECT imaging decreased from baseline to 1 year of follow-up. The degree of decrease in DAT availability was significantly associated with an increased risk of developing ICDs.

Functional imaging may provide suitable probes for early identification of individuals at risk for developing ICDs and for subsequent treatment response evaluation.

The role of the right inferior frontal cortex and the sub-thalamic nucleus (STN) appears crucial in response inhibition and as such provides interesting imaging targets. Ray et al. recently reviewed the role of the sub-thalamic nucleus in impulsivity and the imaging thereof. The authors concluded that despite the overall impression that stimulation of the sub-thalamic nucleus is associated with increased impulsivity, there is a need for larger prospective trials (Ray et al. 2011).

Updates on SPECT and PET imaging of impulse control and related disorders in PD were recently reviewed by Weintraub and Claassen (2017) and Meyer et al. (2019) to which readers are referred for detailed discussion.

Treatment of Impulsive Disorders in Parkinson's Disease

Improvement in ICDs has been reported upon a reduction in dose and discontinuation or a change to a different dopaminergic drug (Voon and Fox 2007). However, to the authors' best knowledge, there is no clear consensus or definite evidence to support such practices exist. Also, a significant proportion of these patients may experience a debilitating withdrawal syndrome upon dose reductions or discontinuation (Fig. 24.8).

Preliminary data suggest the use of amantadine (Weintraub et al. 2010b) or zonisamide in combination with psychotherapy (Bermejo et al. 2010). Dopamine-3 (D_3) receptors have been more closely associated with behavioural disorders and substance abuse, and therefore second-generation dopamine agonists such as pramipexole and ropinirole are gaining importance in impulse regulation (Brewer and Potenza 2008).

Considering the above-mentioned facts, it would be of significant clinical value to be able to predict which patients will develop ICDs and what would be the most appropriate treatment choice. Again, the ability to quantify receptor binding (and other aspects related to dopaminergic neurotransmission) with PET and SPECT imaging makes it an important clinical tool.

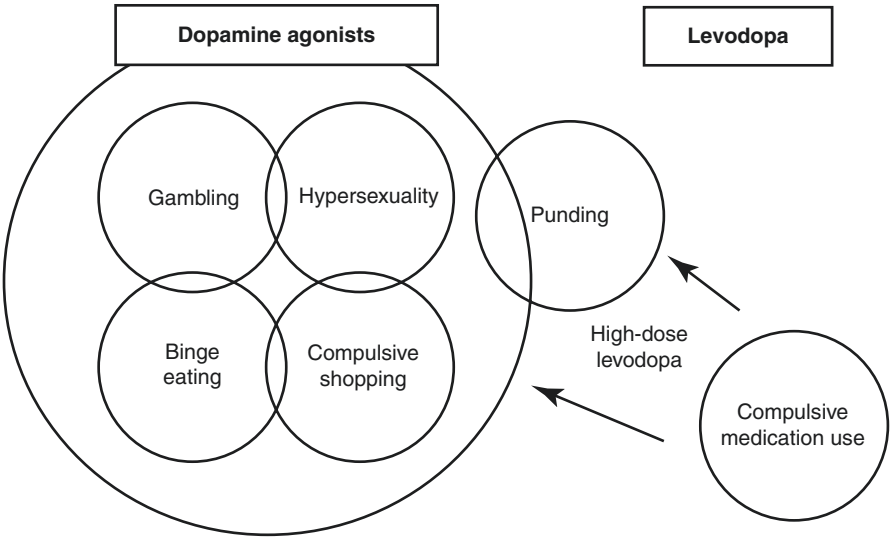

Fig. 24.8 Conceptualization of impulse control behaviour in Parkinson's disease as it relates to treatment (Voon and Fox 2007)

24.2.2 Psychiatry

24.2.2.1 Cluster B Personality Disorders and Bipolar Disorder

Despite some controversy, there is a growing evidence to suggest that considerable overlap between these disorders (especially between borderline personality disorder and bipolar disease) exists and that they are often indistinguishable (Coulston et al. 2012). According to Swann et al., "Cluster B personality disorders, including antisocial personality disorder (ASPD) and borderline personality disorder, share core features of impulsivity and affective instability with bipolar disorder" (Swann et al. 2013). The same group reported that a significant correlation was present in patients with ASPD, between the number of ASPD symptoms and impulsive errors made on testing of response inhibition (Swann et al. 2009). It has been suggested that ASPD and borderline personality disorders could be analogous disorders, which are just differently expressed, depending on the gender (Looper and Paris 2000).

Therefore, these conditions will be considered as a group and discussed simultaneously. Borderline personality disorder will be considered as the prototype for imaging of impulsivity in a psychiatric condition.

Diagnosis

According to the current psychiatric classification system in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), the essential feature of borderline personality disorder is a pervasive pattern of instability of interpersonal relationships, self-image and affect, with notable impulsivity that begins by early adulthood and is present in various contexts. It is a severe

psychiatric disorder characterized by a serious dysregulation of the affective system. Patients typically show instability of affect regulation, impulse control, interpersonal relationships and self-image. Nine criteria for BPD are described in the DSM, five of which are needed for an individual to be diagnosed as having BPD (Leichsenring et al. 2011).

Pathophysiology

The majority of the published evidence suggests an abnormality in serotonergic function, which underlies the impulsive-aggressive symptoms, and that this defect might be associated with specific genetic risk factors, but the precise molecular nature of this abnormality is not yet clear.

Impulsive aggression also forms an integral part of cluster B personality disorders with reduced serotonergic activity frequently implicated. Challenges with fenfluramine (that increases serotonergic activity) have been shown to be abnormal in patients with impulsive aggression and personality disorders (Coccaro et al. 1989).

The exact corresponding neuroanatomical location of this serotonergic dysfunction remains elusive, although preclinical and human studies suggest that the orbital frontal cortex and anterior cingulate cortex play an inhibitory role in the regulation of aggression. Functional imaging with FDG-PET, in conjunction with serotonergic agents such as fenfluramine or meta-chlorophenylpiperazine (m-CPP), can be used to assess the function of the serotonergic system and to localize brain areas with abnormal serotonergic function.

Recent studies done in patients with borderline personality disorder without comorbidity also demonstrated hyper-suppression of cortisol, which suggests yet another component in the already complex pathophysiology of this disorder (Leichsenring et al. 2011).

Neuroimaging

Several limitations exist when evaluating neuroimaging studies of borderline personality disorders (BPD) and other neuropsychiatric conditions. Inconsistencies within inclusion and exclusion criteria result in a heterogeneous study population that consists of various subtypes (often with significant comorbidity) of a specific order. In addition, sample sizes are often small, and the methodology and imaging modality used tend to vary greatly, which impedes meaningful comparisons.

Jana Mauchnik and Christian Schmahl published a comprehensive review of the neuro-functional imaging findings in borderline personality disorder to which readers are referred (Mauchnik and Schmahl 2010).

Anatomical Imaging

Structural imaging studies have frequently demonstrated predominantly smaller amygdala and hippocampal volumes in adult patients with impulsive-aggressive borderline personality disorder (Schmahl and Bremner 2006; Brambilla et al. 2004; Zetzsche et al. 2007).

Functional Imaging

Several functional neuroimaging studies have demonstrated abnormalities in fronto-limbic pathways when comparing borderline personality disorder (BPD) patients with controls, with the most consistent metabolic finding being changes in the frontal lobes, especially the medial frontal area. The following areas have frequently been implicated (Broadmann areas (BA) 24, 32 and 33), which include part of the cingulate (ACC; BA 24) and the dorsolateral prefrontal cortex (BA 9, 10 and 46) and ventromedial prefrontal cortex (VMPF) (including the medial orbitofrontal cortex (OFC) and subgenual cortex) (Lange et al. 2005; Goethals et al. 2005).

Studies that have made use of experimental paradigms have emphasized the integral role of dysfunction within the fronto-limbic circuit during emotion regulation in BPD (Koenigsberg et al. 2009). In summary, these studies have demonstrated hypo-activity of the orbital frontal cortex (OFC) including the ventromedial prefrontal (VMPF) cortex during cognitive-emotional tasks. Patients with borderline personality disorder also exhibit higher amygdala reactivity during emotionally negative stimulation when compared to controls (Minzenberg et al. 2007; Koenigsberg et al. 2009). These areas are known to be associated with the expression and control of two of the main behavioural dimensions of BPD, namely, emotional dysregulation and aggressive impulsivity.

Studies Involving Imaging with SPECT

In a study by Goethals et al., the authors evaluated cerebral perfusion patterns in patients with impulsivity-related personality disorders. They investigated 37 patients with either BPD or ASPD, which they compared to 34 healthy controls. Imaging was done with ^{99m}Tc-ECD SPECT using superhigh-resolution fan-beam collimators and analysed by statistical parametric mapping (SPM99). The key finding of this study was that patients with personality disorders (BPD and ASPD) who exhibited impulsive behavioural acts demonstrated reduced perfusion to the right lateral temporal cortex and the polar and ventrolateral parts of the right prefrontal cortex when compared to healthy controls (Goethals et al. 2005).

Audenaert et al. also demonstrated prefrontal hypoperfusion in patients who had recently attempted suicide, the majority of whom had been diagnosed with DSM-IV Axis II borderline personality disorder. These patients were compared with matched healthy controls. The left thalamus in these patients exhibited increased perfusion on ^{99m}Tc-ECD SPECT (Audenaert et al. 2006).

Koch and co-workers conducted the first study using ^{123}I-ADAM SPECT imaging to evaluate serotonin transporter (SERT) availability in patients with borderline personality disorder. ^{123}I-ADAM SPECT is a highly selective SERT ligand, with a 1000-fold higher selectivity for SERT than for transporters of NA and DA. This study was undertaken in order to substantiate the presumed underlying serotonergic dysfunction in BPD. Impulsivity was measured with the use of the Barratt Impulsiveness Scale (BIS). Their results demonstrated a 43% higher ADAM binding in the brainstem of patients, compared with control subjects, and a 12% higher binding in the hypothalamus. Significant correlations of ADAM binding with both

age and impulsiveness were found, and associations of BIS scores with ADAM binding remained significant even after controlling for age and depression. The authors concluded that the study provided evidence of a serotonergic dysfunction in patients with BPD and that SERT binding reflected the level of impulsiveness as an important feature in BPD (Koch et al. 2007).

Studies Involving Imaging with PET

Schmahl and Bremner evaluated the baseline brain metabolism of 12 treatment-naïve female patients with BPD compared to 12 healthy female controls with ^{18}F-FDG-PET imaging and statistical parametric mapping. They found significantly increased glucose metabolism in the anterior cingulate, the superior frontal gyrus bilaterally, the right inferior frontal gyrus and the opercular part of the right precentral gyrus in patients with BPD compared to controls. Decreased metabolism was found in the left cuneus and the left hippocampus (Schmahl and Bremner 2006).

New and co-workers, in a first-of-its-kind study, used a task, the Point Subtraction Aggression Paradigm (PSAP), to provoke aggression. Thirty-eight BPD patients with intermittent explosive disorder (BPD-IED) according to DSM-IV criteria were compared to 36 age-matched healthy control subjects. All study participants underwent two ^{18}F-FDG-PET scans on two separate occasions. One study was done with provocation and the other with a non-provocation version of the PSAP. They measured the mean relative glucose metabolism throughout the cortex and calculated various scores. The authors found that patients with BPD-IED were significantly more aggressive than controls on the PSAP. BPD-IED patients also had increased relative glucose metabolic rate (rGMR) in the OFC and amygdala when provoked, while controls had decreased rGMR in these areas. Healthy controls demonstrated increased rGMR in anterior, medial and dorsolateral prefrontal regions during provocation more than BPD-IED patients (New et al. 2009).

Salavert et al. (2011) sought to evaluate the regional cerebral metabolism with ^{18}F-FDG in euthymic patients with borderline personality disorder (and similar levels of impulsivity) and to compare it to socio-geographically matched healthy controls. They included eight patients with borderline personality disorder (based on a variety of scores) and eight healthy controls. Impulsivity in all patients was assessed based on the Barratt Impulsivity Scale (BIS-11) and the Sensation-Seeking Scale. PET images were acquired 45 min postinjection, and all psycho-stimulants and smoking were discontinued prior to the study. Medications such as SSRIs, anticonvulsants, antipsychotics and benzodiazepines were not discontinued. Comparisons were analysed voxel by voxel with the use of SPM2 software. The investigators found that on SPM voxel-by-voxel analysis, patients with BPD had pronounced hypometabolism in two areas and hypermetabolism in five areas. Hypometabolic areas correspond to the middle frontal right gyrus and middle frontal left gyrus, orbital part, and were linked to a possible higher level of impulsivity. Hypermetabolic areas correspond to the left middle occipital gyrus, right superior frontal gyrus, left cuneus, left superior parietal gyrus and left lingual gyrus (Salavert et al. 2011).

The PET serotonin transporter tracer, ^{11}C McN 5652 (butyryl thioester tartrate), was used in a study by Frankle et al. to evaluate the regional serotonin transporter

distribution in the brains of ten patients (five females and five males) who met the criteria for impulsive aggression (IA) and the DSM-IV criteria for BPD "impulsiveness" or "self-damaging". Patients with schizophrenia or other psychotic disorders were excluded, as well as patients who had alcohol and substance abuse in the preceding 6 months. This group found significantly reduced SERT and binding potential in the anterior cingulate cortex of the group with IA compared to the healthy group and concluded that the serotonergic innervations in the anterior cingulate cortex were lower in IA individuals. Unfortunately, this tracer demonstrates nonspecific binding which may limit the proper evaluation of regions of low SERT density such as the neocortex (Frankle et al. 2005).

^{11}C DASB, [^{11}C]3-amino-4-[2-[(dimethylamino)methyl]phenylthio) benzonitrile, a more SERT-selective tracer, was also used to image males with impulsive aggression who meet the DSM-IV diagnostic criteria for antisocial personality disorder (ASPD) and borderline personality disorder (BPD). Male patients were chosen to exclude the variations in impulsivity in BPD due to gender differences. These subjects were divided into a high-impulsive aggression (high-IA) and a low-impulsive aggression (low-IA) group. Those with history of past alcohol and drug dependence, current or past DSM-IV Axis I disorder and current Axis II cluster A personality disorder or use of 3,4-methylenedioxymethamphetamine (ecstasy), were excluded from the study. PET imaging was conducted on these patients and the images were co-registered to an MRI scan. SERT availability was significantly higher in high-IA group compared to the low-IA group in the brainstem, slightly higher in the subcortical and medial temporal lobe and lower in the cortical regions. The calculated binding potential of ^{11}C DASB was shown to be significantly higher in the high-IA group in the brainstem (Rylands et al. 2012).

Monoamine oxidase-A (MAO-A) is an enzyme localized in the outer mitochondrial membranes of glia and neurons which metabolizes amine neurotransmitters such as serotonin, norepinephrine and dopamine (Fig. 24.5). Low MAO-A binding has a strong relationship with impulsive aggression (Soliman et al. 2011). [^{11}C]Harmine is PET tracer that selectively binds to the MAO-A isoenzyme with a high affinity. Kolla et al. (2015) demonstrated lower MAO-A levels in the orbitofrontal cortex and ventral striatum in ASPD compared with controls without ASPD. Behavioural, self-report and clinically rated measures of impulsivity were all negatively associated with the level of MAO-A in the ventral striatum of patients with ASPD.

24.2.2.2 Substance Abuse

Comorbidity between substance abuse and impulsivity has been described extensively in the literature. In a review by Moeller and Dougherty, the authors explored the link between impulsivity and substance abuse. Impulsivity has been implicated in the development of substance abuse, and in turn, long-term substance abuse, for example, with cocaine, has been shown to alter the serotonin function in the brain. Evidence is also emerging to support the alteration of a number of neurotransmitter systems, following the long-term use of addictive substances. Subsequently,

long-term substance abuse appears to reduce the efficacy of medications used in treating impulsivity (Moeller and Dougherty 2002).

Dopamine is central to the brain's reward system, and substances of abuse are known to increase its levels resulting in intense euphoria. It has been suggested that reduced dopamine receptors and dopamine release (which results in under-stimulation of the reward circuits) is a risk factor for substance abuse.

Studies using radiotracers enable researchers to target different cellular elements of the brain dopamine system including the receptors, transporters, vesicular storage sites, precursors and enzymes. Labelling of the different drugs of abuse with a radioisotope provides information on the pharmacokinetics of these drugs in the brain as well as the distribution in various organs (Volkow et al. 2003). In their 2003 review, Volkow et al. explored the role of PET and SPECT in the study of substance abuse.

[^{11}C]Cocaine PET has been used to assess the pharmacokinetics of cocaine and demonstrated high, rapid brain uptake that was followed by rapid clearance. A decrease in dopamine D_2 receptors was also noted in cocaine abusers. High cardiac uptake could explain the complication of cardiotoxicity in cocaine abusers (Volkow et al. 2003).

Lee et al. used ^{18}F-fallypride PET to measure striatal dopamine D_2/D_3 receptor availability in methamphetamine-dependent and healthy individuals. Reduced D2/D3 receptor availability was noted in the caudate nucleus and putamen in the methamphetamine group. Similar findings were demonstrated using ^{11}C-raclopride (Lee et al. 2009). Beyond the striatum, dopamine release has been reported in the amygdala and hippocampus of cocaine users. Using ^{18}F-fallypride PET, high-craving users experienced cocaine cue-induced dopamine release in their amygdala and hippocampus (in addition to the ventral and dorsal striatum) compared with low-craving subjects (Fotros et al. 2013).

Ashok and colleagues recently performed a meta-analysis of SPECT and PET studies that have evaluated dopaminergic dysregulation in cocaine and amphetamine-like stimulant users. Seven studies that evaluated dopamine release found significantly reduced dopamine release in 164 stimulant users relative to 139 healthy controls with an effect size of −0.84 (95%CI: −1.08 to −0.60, $p < 0.001$). In 12 studies that evaluated dopamine transporter availability in stimulant users, there was a significant reduction in dopamine transporter availability in 177 stimulant users relative to 191 healthy controls with an effect size of −0.91 (95%CI: −1.50 to −0.32, $p < 0.01$). In 19 studies that evaluated dopamine receptor availability including 342 stimulant users and 321 healthy controls, there was an overall reduction in D2/D3 receptor availability in stimulant users relative to healthy controls with an effect size of −0.76 (95%CI: −0.92 to −0.60, $p < 0.001$) (Ashok et al. 2017).

SPECT and PET tracers have also been used to study the cause and effect of abuse of a variety of drugs. The following aspects have been assessed with various tracers: serotonin tracer density, alterations in brain perfusion and brain glucose metabolism and benzodiazepine receptor levels. These are just a few examples of the impact of molecular imaging in the study of this topic. Work has also been done

to evaluate the role of these tracers in the assessment of response to treatment in alcoholic patients (Volkow et al. 2003).

24.3 Conclusion

Functional imaging has an emerging, potentially important role in the evaluation and study of impulsivity. Available literature of work done in this field is contributing to the understanding of the pathophysiology of the disease processes and in selecting suitable target for pharmacotherapeutic intervention. In addition, its potential role in monitoring of treatment response in the various neuropsychiatric disorders, characterized by impulsive behaviour, is emerging as valuable tool in the long-term management of these patients.

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Brain SPECT in the Behaviourally Disordered Dog

25

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Abstract

Dogs can be used as research models in order to contribute to a better understanding of human neuropsychiatric disorders and to explore treatment options. In general, smaller laboratory animals, most often mice and rats, have been extensively used. Nevertheless, the implementation of larger animal (e.g. dogs) models has several important advantages. Their larger brain size omits the need for dedicated equipment (micro-PET or micro-SPECT), and the larger portion of the frontal cortex (crucial to behaviour regulation) in particular allows superior investigation of this area. They can further be used to investigate normal physiology and interaction of several neurotransmitter systems and the effects of drugs on brain function and chemistry. In this regard, they can also be used to obtain information on the pharmacokinetics and pharmacodynamics of newly developed drugs and the dosage at which maximal response and least side effects occur. Finally, natural animal behavioural models of disorders can be used to enlighten the biological base of several human neuropsychiatric disorders. In this chapter, an overview will be provided on the use of functional brain imaging in dogs suffering from impulsive aggression.

25.1 History of Behavioural Brain Research in Animal Models

Dogs have been loyal allies to man for a long time, starting from being a helping hand in hunting and herding to being a (usually) faithful companion and often a full member of the family in recent years. Their alliance with man has been recently amplified in their contribution to genetic and oncologic research as natural animal model for human disease (Breen and Modiano 2008; Casteleyn et al. 2013; Cyranoski 2010; Starkey et al. 2005).

Already in the nineteenth century, Roy and Sherrington demonstrated the link between neuronal activity, metabolism and perfusion in living dogs (Roy and Sherrington 1890). In the early and mid-twentieth century, most animal research was focused in general on unravelling function and functional interdependency of different brain regions in search of the topographic localisation of emotion and behaviour. Anatomical connections of the frontal lobe were investigated in non-human primates with autoradiography, immunohistochemical techniques and fluorescent dyes. Also, neurotransmitter systems and their receptors were mapped using the same methodology.

Apart from in vitro studies, in vivo studies were performed in animals based on ablation, electrical stimulation or cooling experiments (Fuster 1997). Some of these experiments were evaluated by pure observational recordings of behavioural changes; others were based on test performances in challenge tasks, such as go/no-go tasks. Although, in retrospect, some of these techniques were animal unfriendly and although not welcomed anymore in the modern era, they provided

invaluable contributions to the knowledge of brain function and behaviour today. Detailed reviews on the evolution of research concerning animal neuropsychology have been reported by Fuster (1997) and Joseph (1996) showing the now well-acknowledged link between the frontal cortex and the limbic system related to behaviour (Fuster 1997; Joseph 1996).

25.2 Studies on Canine Brain Pathophysiology

The availability of non-invasive functional imaging methods in the living animal is an important advantage in the investigation of behavioural pathophysiology. Moreover, since radioprotective measurements are not as stringent compared to human research, longitudinal studies with multiple measurements are possible. Using the appropriate tracers, both perfusion and metabolism can be visualised using single photon emission computed tomography (SPECT) or positron emission tomography (PET). Moreover, physiological and pathophysiological alterations in neurotransmitter systems can be investigated with specific neuroreceptor radioligands.

In general, primates are preferred as larger animal models, but, besides the advantages of the size of the brain and the closer resemblance to man, the disadvantages are prominent and often insurmountable in a lot of research centres. First, due to increasingly stringent ethical measures, the keeping of these animals is not obvious. Second, primates are expensive and not easy to handle compared to other more domesticated species such as the dog. Furthermore, the public interest in companion animals (pets) is growing rapidly both in Europe and the United States, which parallels the demand of more specialised veterinary health care, including more sophisticated diagnostic and therapeutic procedures. This also implies more investment in research on canine behavioural disorders and treatment, which offers an opportunity to use the dog as a natural model of some behavioural disorders similar to man (Overall 2000). Also, the nascence of veterinary specialists in aberrant behaviour in companion animals (Diplomates of the European College of Veterinary Behavioural Medicine (ECVBM) and the American counterpart, Diplomate of the American College of Veterinary Behaviour (ACVB)) has largely contributed to a better understanding, diagnostic approach and therapeutic management of problematic animals (Overall 1997). Canine aggression is probably the most relevant behavioural problem considering its consequences for public health (Langley 2009). More, it also poses a welfare problem as in many cases the shortcut solution is euthanasia without considering an alternative, and some countries have banned certain breeds, without hard scientific evidence. Dogs showing abnormal behaviour run also a higher risk of being abandoned or surrendered to animal shelters (Houpt et al. 1996). Understanding the biological underpinnings of "abnormal" aggression, as opposed to "normal" aggression (appropriate aggressive reaction in the context of the trigger (e.g. maternal aggression)), may provide tools to discern animals susceptible to this behaviour and may also be a helpful guide in unravelling the genetic base of aggression.

This chapter is dedicated to functional imaging (SPECT) in behaviour-disordered dogs. Brain perfusion and cortical serotonine-2A (5-HT_{2A}) receptor densities were evaluated in a population of severely impulsive-aggressive dogs. Further, the use of the 5-HT_{2A} receptor as a biomarker for differentiating impulsive aggression from aggression in the context of an anxiety disorder is expounded. The influence of SSRI treatment on this 5-HT_{2A} receptor in impulsive aggression will also be discussed. Finally, functional imaging (PET and SPECT) is used to assess the effect of transcranial magnetic stimulation (TMS) in healthy and anxious dogs. All owners of the dogs involved in all studies gave informed consent after receiving thorough information on the procedures. For the investigation in laboratory dogs, permission from the ethical committee of the Faculty of Veterinary Medicine, Ghent University, was obtained.

25.2.1 SPECT of the Impulsive-Aggressive Dog

One of the most replicated findings in biological psychiatry is the link between reduction of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF) and impulsive behaviour in man and animals (Asberg et al. 1976; Coccaro et al. 1997; Higley et al. 1996; Kavoussi et al. 1997; Oquendo and Mann 2000; Reisner et al. 1996).

From a conceptual viewpoint, one must strictly define the difference between aggressive and impulsive-aggressive behaviour. Aggressive behaviour in animals can be part of a survival strategy in order to have access to food and mating and to protect territory and offspring. Hence, this leads to the categorisation of normal animal aggression as predatory, dominance-related, intermale, territorial and maternal aggression (Volavka 1995). Aggressive behaviour in domesticated animals can be considered normal and tolerated as long as the acts are appropriate and foreseeable in relation to environmental conditions and stimuli. However, when a dog demonstrates aggressive behaviour, without classical warning signs such as growling or showing his teeth, and in unforeseen circumstances, this can be considered as abnormal. The biting events seem unpremeditated and as such may be the result of loss of impulse control. Moreover, these acts bear resemblance to the impulsive aggression demonstrated by primates leading to unnecessary and perilous fights. Behavioural observational studies combined with the investigation of biochemical parameters, such as the measurements of 5-HIAA in CSF, have shown that a difference in neuronal and biochemical function exists between breeds and individuals, which may lead to a less adapted and socially accepted form of aggression (Higley et al. 1996; Popova et al. 1976, 1991a, b; Reisner et al. 1996). This was elegantly demonstrated in behavioural studies in primates, showing a correlation between low CSF 5-HIAA and escalating aggression with wounds requiring medical intervention, excessive mortality due to aggressive interactions and high risk-taking behaviour (leaving the flock at a young, socially immature age; performing leaps at dangerous heights and over risky long distances) (Fairbanks et al. 2001; Higley et al. 1996; Mehlman et al. 1994; Westergaard et al. 1999). Lower 5-HIAA levels

were also found in aggressive dogs compared to normal behaving animals, with lowest levels in a subgroup demonstrating unexpected aggression, without the classical preceding warning signs (Reisner et al. 1996). Badino et al. (2004) performed a post-mortem study on the brain of aggressive dogs and found modifications in the adrenergic and serotonergic receptors with the high-affinity serotonin receptors increased in all areas examined (frontal cortex, thalamus, hippocampus and hypothalamus) compared to normal dogs (Badino et al. 2004). Decreased serum serotonin levels were reported in aggressive dogs (Leon et al. 2012), but debate exists whether peripheral measurements truly reflect central serotonergic activity.

Based on all this evidence, it can be concluded that a defective serotonergic system may be one of the biological bases for risk-taking and impulsive-aggressive behaviour.

In the following study, 19 impulsive-aggressive dogs (15 M (4 neutered), 4 F; mean age 2.6 years (range 12–84 m)) were included, without neurological or physical diseases, selected on the basis of a detailed examination by the referring behavioural specialist and a detailed questionnaire and based on a compilation of tests as proposed in literature (Goodloe 1996; Marder and Voith 1996) and adapted towards recognising especially impulsive behaviour. Repeated questions were included to control the objectivity of the answers of the owners (F. Odberg 2002, personal communication). Breeds were three Rottweilers, three Belgian shepherds, two Berger de Beauce, two Great Danes, two golden retrievers, one Jack Russell, one Caucasian shepherd, one Doberman, one bull mastiff, one Labrador retriever, one English bulldog and one pit bull. The main complaint in all cases was the unpredictability of the bite incidents and the disproportion between the provoking stimulus and the intensity of the attack and the association of the provoking stimulus with positive signals (e.g. petting) as well as with negative (e.g. punishment). Usually multiple bites were registered during the incident, not always leading to medical intervention. It is marked that the owner and family members were most often the assaulted persons. Concerning eating habits, most animals in the aggressive group were labelled greedy. Most owners reported decreased learning abilities of their dogs in the sense that it seemed difficult to teach them to do or not do things. It is noteworthy that the majority of included animals were males. All dogs were drug naïve.

Brain perfusion (^{99m}Tc-ethyl cysteinate dimer (ECD)) (Fig. 25.1) and the serotonin 2A (5-HT_{2A}) receptor radioligand binding were compared with a group of dogs (N = 12; 6 M, 6 F; mean age 4 years) not showing this behaviour. Perfusion studies were performed for several reasons: first, to exclude influence of perfusion on the radioligand binding index; second, to investigate whether perfusion alterations are present in these disordered animals; and, finally, to use them as anatomical reference for the radioligand data. The 5-HT_{2A} receptor was visualised using a tracer with antagonistic activity and high affinity (K_d = 0.11 nM) and selectivity for 5-HT_{2A} receptors (Fig. 25.2). The selectivity of the ligand for 5-HT_{2A} receptors with regard to other neurotransmitter receptors such as other 5-HT receptors, including 5-HT2C and 5-HT_{1A}, dopamine receptors (D1 and D2), adrenergic receptors (α1 and α2) and histamine receptors, is at least a factor of 50. The tracer is displaceable with the 5-HT2 antagonist ketanserin (Mertens et al. 1994; Peremans et al. 2002b; Terriere

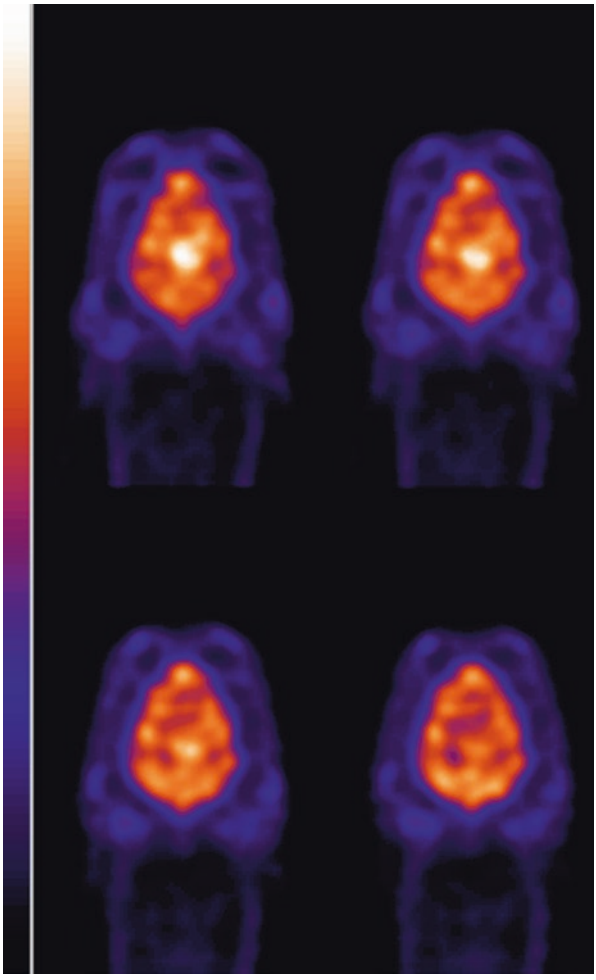

Fig. 25.1 Brain perfusion SPECT in a normal dog (horizontal/transverse slices). The colour scale gives information on the intensity of radioactivity registered in different areas: highest uptake is related with the colours at the top of the scale, low uptake with those at the bottom. The areas with highest radioactivity represent neuronal tracer uptake in the cortical and subcortical areas

et al. 1995). The optimal scanning time, the time when pseudo-equilibrium conditions are reached between free and bound radiotracer, necessary for semiquantification of the regional binding index, was first determined to be from 90 min onwards in a preliminary study (Peremans et al. 2002b). The radiopharmaceutical was therefore injected 90–100 min prior to image acquisition.

Individual perfusion data were automatically fit to a template, and a predefined volume-of-interest (VOI) map was used for semiquantification (Brain Registration and Automated SPECT Semiquantification, Hermes, NUD) (Fig. 25.3). Due to the inferior anatomical information on the radioligand images, individual data were manually matched with the corresponding perfusion data with multimodality software (Hermes, NUD). Regions of interest were defined on the perfusion data and automatically transferred to the radioligand data (Fig. 25.4). The cerebellum was

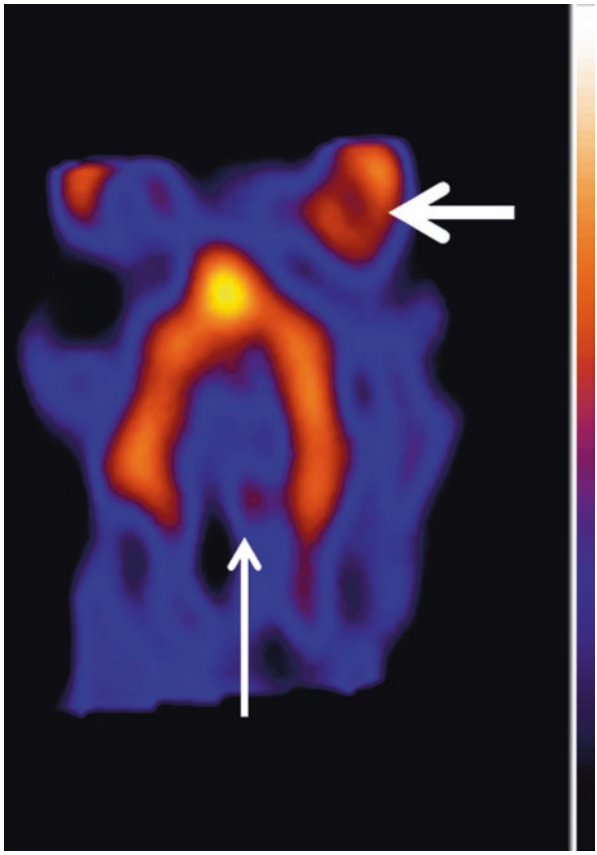

Fig. 25.2 A typical image of the distribution of the 5-HT_{2A} receptor radioligand in the cortical areas (horizontal/transverse slices). Note the lack of activity in the cerebellar area, a region void of 5-HT_{2A} receptors and used as a reference region for semiquantification (*arrow*). Note also the high physiological periorbital uptake (*thick arrow*)

used as reference area in the semiquantification procedure. The obtained binding indices provide an estimation of the receptor density in the different cerebral areas.

Although age difference was statistically not significant, age was taken into account as confounding factor as a previous study showed that, similar to man, age has profound effects on both perfusion and 5-HT_{2A} radioligand binding (Baeken et al. 1998; Meltzer et al. 1998; Peremans et al. 2002a; Rosier et al. 1996; Van Laere et al. 2001) (Fig. 25.5). In impulsive-aggressive dogs, a significantly increased binding of the 5-HT_{2A} radioligand was observed in the frontotemporal cortex. No significant perfusion alterations occurred in the different brain regions. There was also no correlation between perfusion and radioligand binding excluding perfusion effects on receptor radioligand binding (Peremans et al. 2003). The statistically higher 5-HT_{2A} binding index in the cortical regions confirms the involvement of the serotonergic system in impulsive-aggressive behaviour. In so far as methodological differences do not preclude the following comparisons, these results are in line with the higher levels of 5-HT_{2A} receptor binding measured with PET in impulsive-aggressive human patients (Rosell et al. 2010; Soloff et al. 2007) and with

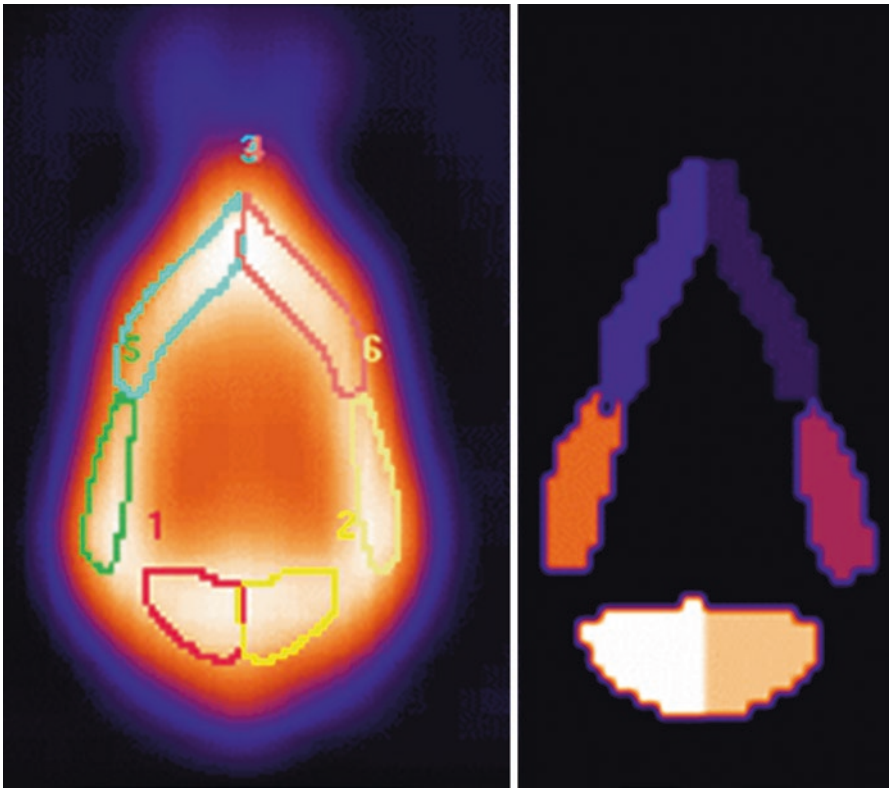

Fig. 25.3 Semiquantification of perfusion data is performed with BRASS software (Hermes, NUD) (normalisation to total brain counts). A template is created from the data of the group of normal dogs (*left panel*). A manually drawn volume-of-interest (VOI) map is created on this template (*right panel*) delineating the different cortical and subcortical regions. This template generates the average (with standard deviation) activity in the delineated areas in normal animals. New patient data can be introduced in this system and will be automatically compared with average activity in normal dogs. The regional activity in the patients' brain and differences with the template will be displayed. *1* Left occipital cortex, *2* right occipital cortex, *3* left frontal cortex, *4* right frontal cortex, *5* left temporal cortex, *6* right temporal cortex

post-mortem findings in the brain of suicide victims (Arango et al. 1990; Arora and Meltzer 1989; Stanley et al. 1983).

The increased 5-HT_{2A} receptor binding index could be the consequence of a reduced presynaptic availability of serotonin resulting in reduced synaptic serotonin concentration and therefore leaving more postsynaptic receptors available for radioligand binding or a compensatory upregulation of the number of postsynaptic 5-HT_{2A} receptors. However, no definite hypothesis can be put forward. First, no microdialysis was performed, and therefore no information is present on the concentration of serotonin in the synaptic cleft, and second, it is well-known that different neurotransmitter systems interact in general and the noradrenergic and

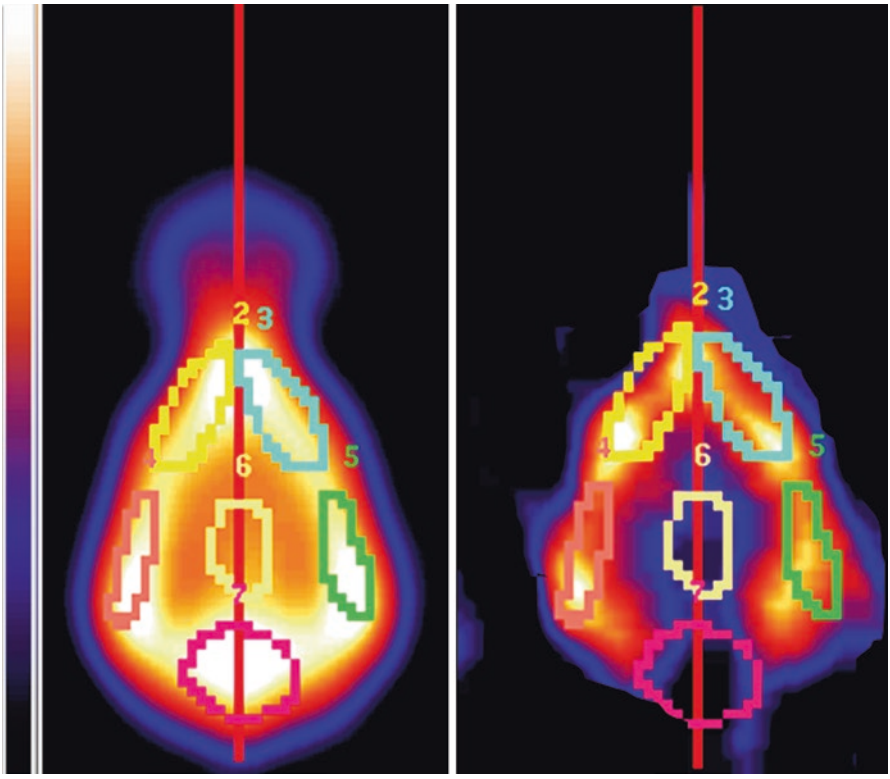

Fig. 25.4 The perfusion images of the same individual are used to define the VOIs on the serotonin-2A receptor radioligand data. Radioligand data are fused with the perfusion data, and the VOIs defined on the perfusion data are automatically applied to the radioligand images. The cerebellar area is used as the reference region in the semiquantification procedure. *2* Left frontal cortex, *3* right frontal cortex, *4* left temporal cortex, *5* right frontal cortex, *6* subcortical area; *7* cerebellum

serotonergic system in particular. As an example, upregulation of 5-HT_{2A} receptors without any modification of 5-HT or 5-HIAA concentrations in the brain can be induced in rats after administration of dexamethasone or exposure to stress (forced swimming) (Katagiri et al. 2001; Takao et al. 1995). The evidence for possible interactions of the noradrenergic and serotonergic systems in canine impulsive aggression was further provided by a post-mortem study measuring β-adrenergic receptor and serotonergic receptor concentrations. A decrease was detected in the β-adrenergic receptors next to an increase in the high-affinity serotonergic receptors in the frontal cortex, hypothalamus and thalamus of aggressive dogs (Badino et al. 2004). In rodents, an interactive role has also been attributed to the dopaminergic system in different research paradigms on impulsivity, albeit the results of these studies are not convergent and further research on the interplay of the serotonergic and dopaminergic system in impulsive behaviour remains mandatory (Dalley and Roiser 2012).

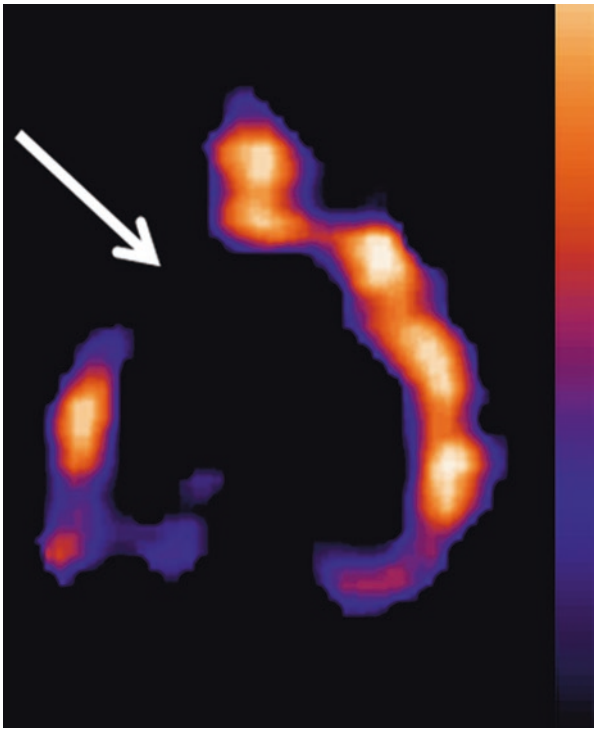

Fig. 25.5 A 5-HT_{2A} receptor SPECT in an aging dog (10 years). Note the decreased (*arrow*) radioactivity in the frontal cortex compared to the distribution of radioactivity in Fig. 25.2

25.2.2 5-HT_{2A}-Receptor Imaging as a Biomarker in Canine Behavioural Research

As previously mentioned in this chapter, aggressive behaviour is considered normal as long as it fits within the canine ethogram. However, distinguishing different types of aggression remains susceptible to subjective behavioural analysis. The challenge also remains to differentiate impulsive aggression from aggression originating from an anxiety disorder. In that respect, functional brain imaging was carried out to evaluate the 5-HT_{2A} receptor as an objective biomarker for differentiating impulsive-aggressive dogs from dogs with anxiety disorders. In the following study, a dual goal was aimed at. First, increasing the knowledge in canine behavioural problems will safeguard the human-dog bond which is under pressure in case of aggressive behaviour. Aggression, but also anxiety leading to aggressive behaviour, results in a low quality of life and expands the previously mentioned welfare issues to a safety issue as well. A second goal was to further investigate the value of behaviourally disordered dogs as a model for human behavioural disorders. Previous SPECT research already pointed out the value of this canine model in diagnostic and therapeutic aspects of impulsive-aggressive,

anxiety-disordered and compulsive-disordered dogs (Peremans et al. 2003, 2005; Vermeire et al. 2009a, b, 2010, 2012).

Sixty-six dogs were included and divided in three equally sized groups, i.e. 22 dogs with impulsive-aggressive behaviour (18 M (7 neutered), 4 F (all intact); mean age 2.73 years; range 12–84 m; breeds included are 3 Rottweilers, 3 Belgian shepherds, 2 Berger de Beauce, 2 golden retrievers, 2 Great Danes, 2 Labrador retrievers, 2 Dobermans, 1 Caucasian shepherd, 1 Jack Russell, 1 bull mastiff, 1 pit bull, 1 mongrel and 1 English bulldog), 22 dogs with severe anxiety (18 M (10 neutered), 4 F (2 neutered); mean age 3.67 years; range 14–86 m; breeds included are 4 mongrels, 3 golden retrievers, 3 Border collies, 2 German shepherds, 1 Staffordshire bull terrier, 1 Dutch decoy dog, 1 Berger de Beauce, 1 Bernese mountain dog, 1 Bleu de Gascogne, 1 Bordeaux dog, 1 boxer, 1 English bulldog, 1 miniature pinscher and 1 Shar Pei) and 22 normally behaving dogs (14 M (3 neutered), 8 F (all intact); mean age 3.17 years; range 12–84 m; breeds included are 4 German shepherds, 4 mongrels, 3 Border collies, 3 Belgian shepherds, 2 Boerboels, 2 Dutch decoy dogs, 1 dachshund, 1 French bulldog, 1 Rottweiler and 1 Labrador retriever). As in the previous study, ECVBM specialists selected the patients and categorised them based on behavioural analysis and a validated canine behavioural questionnaire CBARQ (Hsu and Serpell 2003). Possible neurological or physical illnesses were excluded (Haug 2008; Sherman and Mills 2008).

Age correction was performed for previously mentioned reasons. The comparison of the 5-HT_{2A} receptor binding revealed significant changes in both impulsive-aggressive and anxious behaving dogs in the frontal, temporal and occipital cortices (both hemispheres). Those changes were in opposing directions, with increased 5-HT_{2A} receptor binding for the impulsive-aggressive dogs and decreased 5-HT_{2A} receptor binding for the anxiety-disordered dogs, compared to the normal group. Brain perfusion changes were again excluded as the cause of the altered serotonin 2A receptor binding indices as no correlations were found between perfusion and radioligand data. The receiver operating characteristic (ROC) analysis of the data determined that the cut-off values for the frontal cortex had the highest statistical power to differentiate the separate groups (Fig. 25.6), a not surprising observation as the (pre)frontal cortex has been extensively identified as the key regulating region in behaviour (Fuster 1997). This region also contains the highest density of 5-HT_{2A} receptors of the brain in the human and canine species (Busatto et al. 1997; Peremans et al. 2002b), strengthening the role of the frontal cortex in behaviour. It is essential to realise that the proposed cut-off value is not rigid and a higher or lower cut-off value can be chosen depending on whether priority is given to risk assessment or to animal welfare issues. In case of risk assessment, one would prefer a high sensitivity (to avoid impulsive-aggressive animals ending in families); however, this would be at the expense of the specificity (more nonaggressive animals being labelled as impulsive aggressive). In case of animal welfare, one would prioritise a lower sensitivity with a higher specificity to avoid unnecessary euthanasia (Vermeire et al. 2011).

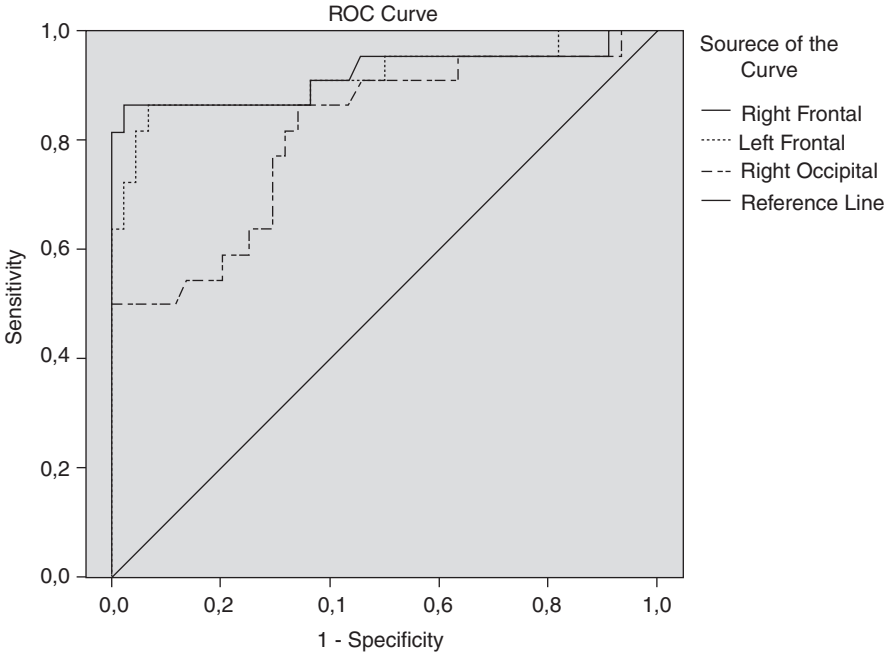

Fig. 25.6 Receiver operating curves (*ROC*) are shown for the group of impulsive-aggressive dogs. The sensitivity is plotted against (1-specificity) across a range of cut-off values. Binding indices of the right and left frontal cortex as well as the right occipital region are shown as examples of two valuable curves (frontal) and a less useful curve (occipital). The curves of the other brain regions are not shown because of their low sensitivity and specificity

Variations in the 5-HT_{2A} receptor gene have been suggested to play a role in anxiety and impulsive traits in man and could in theory affect radioligand binding due to conformational or functional alterations (Bjork et al. 2002; Giegling et al. 2006; Nomura et al. 2006; Unschuld et al. 2007). However, no variants in the HTR_{2A} gene were detected in aggressive golden retrievers, making a genetic modification as the cause of alterations found in the impulsive-aggressive dogs less likely (van den Bergh et al. 2008). No comparative studies have been performed in the anxiety-disordered dog up till now.

A correct differentiation of the underlying 5-HT_{2A} receptor imbalance is important in view of psychopharmacological and behavioural treatment choice (Moresco et al. 2007; Peremans et al. 2008; Vermeire et al. 2010; Zanardi et al. 2001). Hereby, the 5-HT_{2A} receptor neuroimaging and semiquantification is a more objective means to differentiate behaviour according to its biological underpinnings, in addition to the more subjective behavioural analysis.

25.3 Treatment Modalities in Behavioural Disordered Dogs

25.3.1 Selective Serotonin Reuptake Inhibitors in the Treatment of Impulsive-Aggressive Behaviour in Dogs

SSRIs are currently used to manage impulse control disorders and/or aggression in man and dogs (Dodman et al. 1996; Fuller 1996). In a pilot SPECT study, the effect of a single dose of citalopram on the canine serotonin reuptake transporters (SERT) was evaluated with the radioligand [^{123}I]-labelled 2 h-carboxymethoxy-3 h-(4-iodophenyl)tropane (^{123}I β-CIT), a nonselective competitive antagonist of norepinephrine, dopamine and serotonin transporters (Peremans et al. 2006) (Fig. 25.7a, b). A decreased binding was observed compared to the blank scan, providing proof that the SSRI, citalopram, binds to the canine serotonin reuptake transporters.

Nine impulsive-aggressive dogs were then treated daily with SSRIs (citalopram, 1 mg/kg) and were re-examined at 6 weeks of treatment (no behaviour therapy was allowed in this period). Both perfusion and 5-HT$_{2A}$ receptor radioligand binding were evaluated, and behavioural changes were assessed before and after treatment.

After treatment, a significant decreased binding of the 5-HT$_{2A}$ radioligand was evident in the frontotemporal and to a lesser extent in the occipital area without alterations in regional perfusion (Peremans et al. 2005). These findings show also

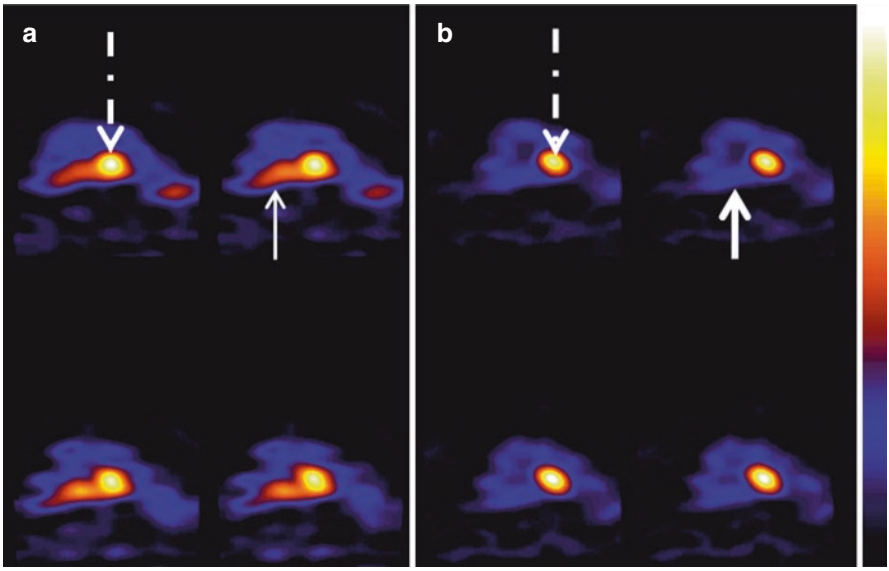

Fig. 25.7 SERT and DAT imaging with ^{123}I-β-CIT in a normal dog before (**a**) and after (**b**) administration of the SSRI Cipramil. Note the decreased activity in the area of the raphe nuclei where SERT are abundantly present (*thin arrow*). After blockade of the SERT by Cipramil, radiopharmaceutical uptake decreases substantially in this same area (*thick arrow*). The interrupted arrow points to the uptake of the radioligand in the basal ganglia, an area rich in dopamine transporters

resemblance with the results of a 5-HT_{2A} receptor PET study in depressed patients, where decreased binding of ^{18}F-setoperone was found in the cortex of young patients with depression, treated for 6 weeks with paroxetine (Meyer et al. 2001). An increased synaptic serotonin concentration due to chronic blockade of the SERT seems the most logical explication for the observed decreased radioligand binding, the decrease being invoked by either compensatory downregulation of the receptors or competition of endogenous serotonin with the radioligand. The extent of clinical behavioural recovery paralleled the extent of reduction of 5-HT_{2A} binding index. The possibility has been raised that even though downregulation of the receptors may not be a therapeutic effect in itself, the decreased numbers of 5-HT_{2A} receptor may reduce the agonistic impact on these receptors (Meyer et al. 2001). More, it is well-known in human depression that a lag period exists between initiation of SSRI treatment and the onset of their antidepressive effect. Initial agonistic activation of the 5-HT_{2A} receptor by blocking the SERT has been pointed at as one of the culprits for this phenomenon. In this regard, augmentation with a 5-HT_{2A}-receptor antagonist has been proposed as a potential alternative treatment strategy (Nemeroff 2005).

This study represents a nice example of the potency of functional imaging to evaluate receptor alterations after drug interventions in the canine brain and the therapeutic impact of psychopharmaca.

25.3.2 PET and SPECT Imaging in Canine Transcranial Magnetic Stimulation (TMS)

Transcranial magnetic stimulation (TMS), a non-invasive brain stimulation technique, is an FDA-approved treatment modality for treatment-resistant depression. This technique uses an alternating magnetic field to induce secondary electrical impulses in a targeted cortical region. Depending on the properties of the magnetic field, TMS may either stimulate or inhibit the underlying cortical region combined with remotely connected brain regions. An accelerated TMS treatment provokes a rapid improvement of the depressive symptoms and significantly reduces the treatment duration when compared to a classic TMS treatment (Holtzheimer et al. 2010; Hadley et al. 2011; McGirr et al. 2015). Because anxious dogs portray similar neuropathological changes (frontal neuronal asymmetry), display similar symptoms and receive the same treatment modalities (antidepressants and behavioural therapy) as depressed humans, it is feasible that they could benefit from this treatment as well. Therefore, two preclinical and one clinical TMS studies were carried out (Dockx et al. 2017, 2019).

First, healthy beagle dogs were randomly divided into three unequal groups: a control group and two treatment groups. The animals in the control group received five sham stimulation sessions during 4 consecutive days, whereas the animals in the treatment group got either five active stimulation sessions on either a single day or during 4 consecutive days. The sessions consisted of 40 trains each lasting 1.9 s. The intertrain interval was set at 12 s. Between two sessions, there was a 15-min

waiting period. This treatment protocol is an exact copy of an accelerated high-frequency repetitive TMS (aHF-rTMS) treatment protocol performed in patients suffering from depression. All aHF-rTMS treatments were applied over the left frontal cortex and administered under general anaesthesia. The outcome measurements were perfusion index (PI) of an [^{99m}Tc]HMPAO SPECT scan and serotonin transporter (SERT) binding index (BI) of [^{11}C]DASB PET scan. Scans were taken at baseline, 24 h, 1 month and 3 months after the last stimulation session was administered.

Onto each SPECT scan, a template holding 11 fixed, different brain regions (both frontal, temporal, parietal and occipital lobes, the cerebellum, olfactory bulb and the subcortical area) was fitted using BRASS software (Brain Registration and Automated SPECT Semiquantification, Nuclear Diagnostics, Sweden). The radioactivity in each region was normalised to the radioactivity of the entire brain. The control group did not display any changes in PI over time. An increase in PI was seen at 24 h in the left frontal cortex (stimulation site) for both active treatment groups. The observed effect after aHF-rTMS might result in normalisation of the hypoperfused left frontal cortex in dogs suffering from anxiety (Vermeire et al. 2009a). In humans, a normalisation of the PI in the left frontal cortex coincides with clinical improvement of depressed patients (Richieri et al. 2011).

In order to acquire the [^{11}C]DASB PET scans, an [^{11}C] DASB bolus was IV injected. Forty minutes after the bolus injection, a 20-min static scan was performed with the PET camera (Gemini PET/CT, Philips, Eindhoven, the Netherlands). The PET-CT data were fitted onto their corresponding MRI to provide anatomical information. Pmod (version 3.405, PMOD Technologies Ltd., Zurich, Switzerland) was used to calculate a non-displaceable binding potential (BI) for each ROI at each time point with the cerebellum (excluding the vermis) as reference region. No significant changes in SERT BI were found within the control group. Changes in SERT BI were noticed in both active aHF-rTMS treatment groups. The single-day aHF-rTMS treatment provoked SERT BI changes in the left frontal cortex, right parietal cortex and left temporal cortex. The 4-day aHF-rTMS treatment altered the SERT BI in the pons, left thalamic area, (pre)subgenual cortex and right parietal cortex.

Finally, during the clinical study, the single-day aHF-rTMS treatment was applied twice (3 weeks separated) over the left frontal cortex in a 5-year-old neutered male Malinois dog displaying anxious-aggressive behaviour towards objects, other animals and people. The dog's behaviour was assessed, before and after each stimulation session, using the validated canine behavioural questionnaire completed by the owner (Hsu and Serpell 2003; Duffy and Serpell 2012). [^{99m}Tc]HMPAO SPECT scans were taken to evaluate changes in rCBF: at baseline, one at 24 h and 3 weeks after the last aHF-rTMS session. Twenty-four hours after the aHF-rTMS treatment, normalisation of the left frontal cortex's rCBF was present combined with a decreased rCBF in the subcortical region. No abnormalities in rCBF were noticed 3 weeks after each treatment. These changes in rCBF were accompanied by an improvement of the dog's anxious-aggressive behaviour.

In summary, these studies indicate that [^{99m}Tc]HMPAO SPECT and [^{11}C]DASB PET imaging can be used to detect changes in rCBF and the SERT BI induced by arTMS in healthy and anxious dogs.

25.4 Confounding Factors in Canine Functional Brain Imaging Studies

25.4.1 Anaesthesia

In contrast to human studies, anaesthesia is generally required to perform animal imaging studies, although some recent studies report on investigations in the awake animal, employing fixing devices (Hassoun et al. 2003; Kakiuchi et al. 2000; Tokunaga et al. 2009). Sedatives and anaesthetics in general affect respiratory and cardiovascular dynamics and as such can influence peripheric tracer kinetics (Kersemans et al. 2006). In case of neuroimaging, interaction of the anaesthetics with the cerebral neurotransmission and metabolism may be an additional important confounder. Furthermore, through its influence on blood pressure and its effect on the ventilation, it has an impact on arterial carbon dioxide tensions and arterial oxygen tensions as well. All the aforementioned parameters, as well as the direct effect of anaesthetics on the cerebral blood vessels, can affect the (regional) cerebral blood flow (Waelbers et al. 2010). Due to those sometimes opposing effects, the ultimate result of anaesthesia on brain imaging studies is difficult to predict.

Although the influence of anaesthetics on brain imaging studies should never be neglected, it can sometimes be avoided. When performing SPECT brain perfusion studies, for instance, retention tracers can be used. After intravenous injection, these tracers are trapped in the cerebral neurons with a distribution pattern resembling the regional cerebral blood flow at the moment of the injection. A very interesting feature of these tracers is that their distribution is not altered by anaesthetic-induced brain perfusion changes occurring after tracer administration. Like in humans, the duration of this fixed distribution is long enough in dogs and cats as well, to allow induction of anaesthesia followed by the acquisition (Waelbers 2012; Waelbers et al. 2012a). This creates the possibility to visualise the brain perfusion without interference of the anaesthetics. In some situations, however, sedation or anaesthesia is required prior to tracer injection. This leads inevitably to global and regional perfusion alterations that have to be taken into account (Waelbers et al. 2011, 2012b).

Tracers that need to be injected simultaneous with the start of the acquisition and neuroreceptor radioligands, requiring acquisition during an equilibrium state, are more sensitive to anaesthetic-induced alterations. When tracers are used in animals under anaesthesia, blood flow changes are only one confounder (Lee et al. 2012). Other factors to consider are possible interactions of anaesthetics with the release and/or reuptake of neurotransmitters and direct actions of the anaesthetics on the neuroreceptors (Adriaens et al. 2012; Hassoun et al. 2003; Waelbers et al. 2012b).

In conclusion, it can be stated that the influence of anaesthesia on functional brain imaging should not be omitted and that careful selection of sedatives, anaesthetic agents and anaesthetic techniques is required. Furthermore, fixed anaesthetic protocols (agents and dosages) should be used throughout all studies.

25.4.2 Resolution Limits

The small size of the brain limits the resolution power of the conventional collimated camera system, and subdivision of the smaller subcortical areas is limited for gamma camera imaging. The use of animal-dedicated cameras (micro-PET and micro-SPECT) is gradually gaining field for research purposes. Unfortunately, the gantry opening is dedicated for small laboratory animals, such as mice and rats, and cannot be used for larger structures such as the cat and dog head. The potential of a micro-SPECT system (HiSPECT, Bioscan, USA) for use with a conventional gamma camera, based on multipinhole collimation, was investigated in cats and dogs (Martle et al. 2013; Waelbers et al. 2013). The advantage is that the gantry opening can be adapted to the size of the animal. A resolution of approximately 2.5 mm can be obtained with the multipinholes (six multi-focused holes, 3 mm ∅). Co-registration with MRI images then also allows localisation of the small subcortical areas, such as the basal ganglia and the thalamus (Fig. 25.8). An alternative is provided by resolution recovery software, available from several

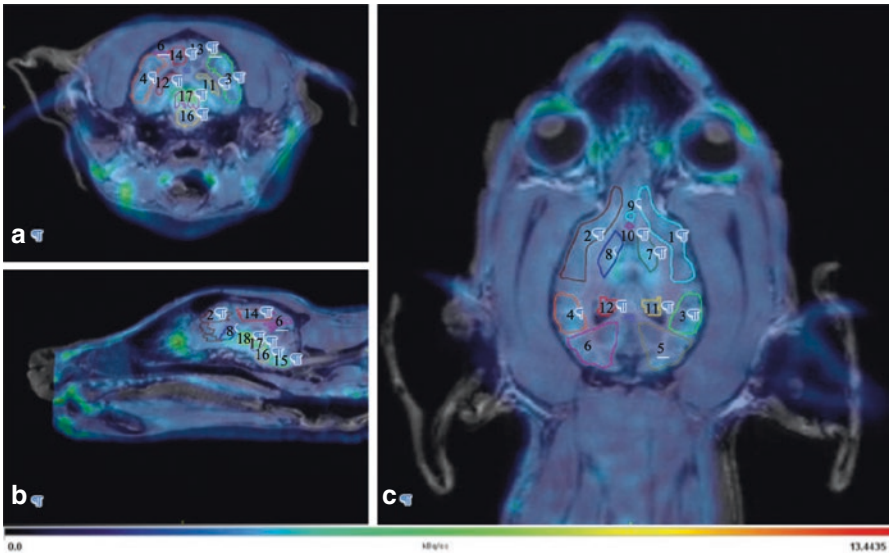

Fig. 25.8 Transversal (**a**), sagittal (**b**) and dorsal (**c**) fusion image ([^{11}C]DASB PET scan and MRI). *1* Right frontal cortex, *2* left frontal cortex, *3* right temporal cortex, *4* left temporal cortex, *5* right occipital cortex, *6* left occipital cortex, *7* right caudate nucleus, *8* left caudate nucleus, *9* presubgenual anterior cingulate cortex, *10* subgenual anterior cortex, *11* right hippocampus, *12* left hippocampus; *13* right parietal cortex, *14* left parietal cortex, *15* medulla oblongata, *16* pons, *17* midbrain, *18* left thalamus

firms, based on attenuation correction with CT data and collimator response correction which increases resolution to the extent that differentiation of the subcortical structures is facilitated (Fig. 25.9). PET(-CT/MRI) imaging is without any doubt preferable and will be used more and more, in line with accessibility, for this purpose (Fig. 25.10).

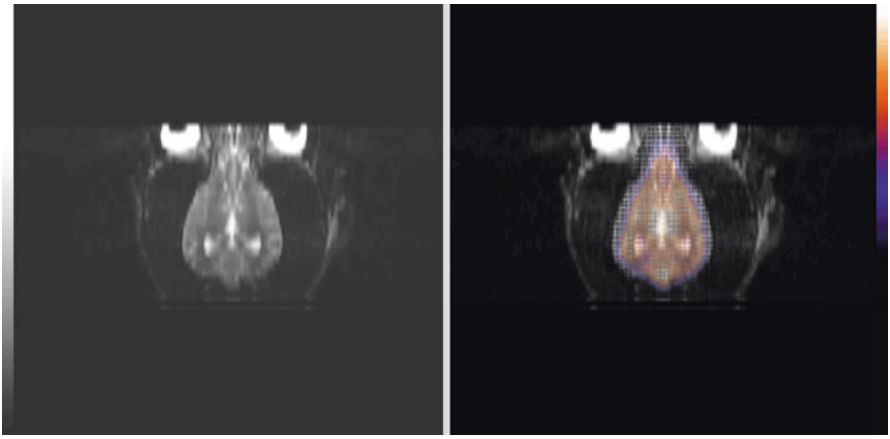

Fig. 25.9 Micro-SPECT perfusion images in a dog fitted to MRI data (*right panel*) to obtain anatomical reference for the delineation of the cortical and subcortical structures. Similar to conventional perfusion data, a VOI map can be created for the perfusion data based on the delineated regions on the MRI and used in the BRASS software program

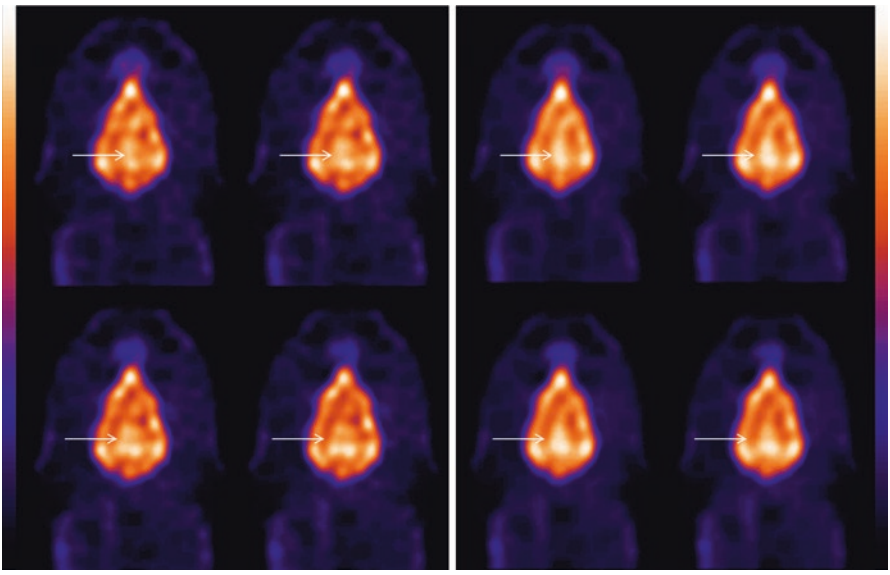

Fig. 25.10 An alternative solution to increase resolution is the use of resolution recovery software. Note the improved visualisation of the subcortical structures (*left panel*, *arrows*) compared to images obtained with conventional reconstruction (*right panel*, *arrows*). Filtering is the same in both reconstructions

25.5 Conclusion

In the last decades, the use of natural animal models has received much attention. The advantage of the canine model is that this species is easier to obtain and to handle, compared to primates. It has also been suggested that dogs develop behavioural conditions analogous to some human psychiatric disorders and may therefore serve as a natural model for human disease (Overall 2000). This has led to the investigation of canine models with behavioural and neuropathological similarities to human disease. In this context, canine aging and cognitive dysfunction (Adams et al. 2000; Peremans et al. 2002a), aggression and impulsivity (Peremans et al. 2003; Reisner et al. 1996) and anxiety and compulsive disorders (Rapoport et al. 1992; Vermeire et al. 2010, 2012) were reported to show clinical and/or neuropathological resemblance to human disease, respectively, dementia, personality disorders and anxiety disorders. Also, more and more psychogenic drugs, derived from the human psychopharmaceutical arsenal, are used in dogs for behavioural problems. The influence of medication on the 5-HT_{2A} receptor and the serotonin transporter visualised with SPECT is an example of the validity of a dog's model in the validation of drug treatment (Peremans et al. 2005, 2008; Vermeire et al. 2010). The recent growing interest in non-invasive neuromodulation modalities and stimulation protocols for depression and anxiety disorders in man has instigated more research on the canine species as translational model and to the benefit as veterinary patient.

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Obesity: An Addiction? Imaging of Neurotransmitter Systems in Obesity

26

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Contents

Abstract

The brain is important in the regulation of eating behavior and satiety signaling. There is also evidence that many neurotransmitters are involved in food intake regulation and eating behavior; consequently dysregulated neurotransmitter systems may be involved in the pathophysiology of obesity. This chapter presents an overview of results of neurotransmitter imaging studies in obese humans.

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Presently, the dopaminergic, serotonergic, noradrenergic, opioid and cannabinoid systems have been studied with molecular imaging techniques in obese humans. The major findings are increased serotonin (5-hydroxytryptamine; 5-HT) 5-HT_{2A} receptor availability in cortical regions, a complex relationship between dopamine $D_{2/3}$ receptor ($DRD_{2/3}$) availability and body mass index (BMI), probably an important role of the striatal and extra-striatal mu opioid receptor, and a possible role of the cannabinoid type 1 (CB_1) receptor. There is no disturbance in serotonin transporter (SERT) availability in the thalamus and midbrain or in striatal dopamine transporter (DAT) availability. The effects of bariatric surgery on neurotransmission and findings in subgroups such as patients with binge eating disorder or insulin resistance are also discussed.

26.1 Introduction

Obesity is an increasing health problem worldwide (Finucane et al. 2011). One of the major causes of the current obesity epidemic is thought to be increasing overconsumption of high-caloric foods, which are presented and available in abundance in present-day Western society. Overeating behavior can be considered a malfunction in the regulation of food intake with loss of control due to the combination of increased motivational salience and deficits in behavioral inhibition. In this respect, overeating and obesity have been compared with substance use disorders, and it has been hypothesized that similar mechanisms in the brain may be underlying both disorders (Volkow and Wise 2005).

It has long been recognized that the brain plays a central role in the regulation of food intake (Mayer and Thomas 1967). Therefore, brain function dysregulations may be an important factor in the aetiology of obesity and a possible target for prevention and treatment. Many brain structures participate in food intake regulation (Berthoud 2004; Berthoud 2007): the caudal brainstem is directly involved in ingestion, digestion, and absorption of food and largely controls autonomic signaling related to the ingestive and digestive processes; the hypothalamus is a key structure in the homeostatic regulation of food intake, which integrates internal state signals and drives pituitary-endocrine and autonomic outputs; corticolimbic regions are important in learning and processing food-related reward and exerting control over food intake with integration of non-metabolic signals. The striatum is an important structure within the corticolimbic system and is primarily involved in motivation for and reward processing of food.

Within the brain, many neurotransmitters play a role in the regulation of food intake, including dopamine, serotonin, noradrenalin, glutamate, gamma-aminobutyric acid (GABA), opioids and endocannabinoids (Berthoud 2004). The use of anti-obesity drugs, e.g. the serotonergic/noradrenergic blocker sibutramine and the inverse agonist for the cannabinoid-1 receptor rimonabant, has shown that manipulation of the serotonergic/noradrenergic and/or the cannabinoid system affects eating behavior and can induce weight loss. Drugs that increase dopamine

and noradrenalin levels, such as methylphenidate and amphetamines, have an anorexigenic effect, whereas dopamine D_2 receptor blockers (antipsychotics/neuroleptics) can lead to weight gain. In addition, it has been shown that food can induce dopamine release in the striatum (Bassareo and Di Chiara 1999; Small et al. 2003), therewith modulating the reward value of food (Volkow et al. 2011). Finally, in the key regulatory center for food intake, the hypothalamus, dopamine and serotonin also play an important role (Meguid et al. 2000). In short, it is plausible that (dysregulations of) neurotransmitter systems are associated with obesity either as a factor in the causal pathway or due to long-term overeating.

Using positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging techniques, it is possible to visualize and measure some of these molecular brain processes ***in vivo*** in humans. In this chapter, we review studies that focus on neurotransmitter systems in the brain of obese people. Furthermore, we will compare the findings in obesity with findings in substance abuse disorders, because behavioural and neuropharmacological similarities have been hypothesized (Volkow and Wise 2005; Volkow et al. 2017). A summary of the publications on molecular imaging in obesity (BMI > 30 kg/m^2) reviewed in this section can be found in Table 26.1.

Table 26.1 Studies on molecular imaging in obesity

First author	Year	Imaging method	Subjects	Primary outcome measures
Dopaminergic system				
Wang et al.	2001	[^{11}C]raclopride PET + [^{18}F]FDG PET	10 morbidly OB, 10 NW/OW	$DRD_{2/3}$ availability
Volkow et al.[a]	2008	[^{11}C]raclopride PET + [^{18}F]FDG PET	10 morbidly OB, 12 NW/OW	$DRD_{2/3}$ availability and metabolism
De Weijer et al.	2011	[^{123}I]IBZM SPECT	15 morbidly OB women 15 NW/OW women	$DRD_{2/3}$ availability
Dunn et al.	2012	[^{18}F]fallypride PET	14 OB, 8 NW	$DRD_{2/3}$ availability
Guo et al.	2014	[^{18}F]fallypride PET	20 OB, 23 NW	$DRD_{2/3}$ availability
Kessler et al.	2014	[^{18}F]fallypride PET	33 subjects, BMI 19-35	$DRD_{2/3}$ availability
Caravaggio et al.	2015	[^{11}C]-(+)-PHNO PET	26 subjects, BMI 23.7 ± 3.0	$DRD_{2/3}$ availability
Cosgrove et al.	2015	[^{11}C]-(+)-PHNO PET	12 subjects, BMI 28 ± 5	$DRD_{2/3}$ availability
Karlsson et al.	2015	[^{11}C]raclopride PET + [^{11}C]carfentanil	13 OB, 14 NW	$DRD_{2/3}$ and MOR availability
Eisenstein et al.	2015	[^{11}C]NMB PET	22 OB, 22 NW	$DRD_{2/3}$ availability
Gaiser et al.	2016	[^{11}C]-(+)-PHNO PET	14 OB, 14 OW, 14 NW	$DRD_{2/3}$ availability
Dang et al.	2016	[^{18}F]fallypride PET	130 subjects, BMI 25.5 ± 8	$DRD_{2/3}$ availability

(continued)

Table 26.1 (continued)

First author	Year	Imaging method	Subjects	Primary outcome measures
Haltia et al.	2008	[^{11}C]raclopride PET	12 OW/OB, 12 NW	Dopamine release after glucose injection
Steele et al.	2010	[^{11}C]raclopride PET	5 morbidly OB women	$DRD_{2/3}$ availability after bariatric surgery
Haltia et al.	2007	[^{11}C]raclopride PET	12 OW/OB, 12 NW	Dopamine release after glucose expectancy
Wang et al.	2011	[^{11}C]raclopride PET	8 OB, 10 OB with BED	Dopamine release after food stimulation
van de Giessen et al.	2014	[^{123}I]IBZM SPECT	15 OB, 15 OW	Dopamine release after amphetamine
Dunn et al.	2010	[^{11}C]raclopride PET	5 morbidly OB women	$DRD_{2/3}$ availability after bariatric surgery
Karlsson et al.	2016	[^{11}C]raclopride PET + [^{11}C]carfentanil	16 morbidly OB, 14 NW	$DRD_{2/3}$ and MOR availability after bariatric surgery
van der Zwaal et al.	2016	[^{123}I]IBZM SPECT	20 morbidly OB women	$DRD_{2/3}$ availability after bariatric surgery
Chen et al.	2008	[^{99m}Tc]TRODAT-1 SPECT	50 subjects, BMI 18.7–30.6	DAT availability
Koskela et al.	2008	[^{123}I]nor-β-CIT SPECT	16 monozygotic twin pairs, BMI 19.1–31.9	DAT and SERT availability
van de Giessen et al.	2012	[^{123}I]FP-CIT SPECT	123 subjects, BMI 18.2–41.1	DAT availability
Thomsen et al.	2013	[^{123}I]PE21 SPECT	33 subjects, BMI 21.0–49.5	DAT availability
Nam et al.	2018	[^{123}I]FP-CIT SPECT	142 NW/OW, BMI 25.1 ± 2.8 40 OB, BMI 32.9 ± 3.0	DAT availability
Wilcox et al.	2010	6-[^{18}F]FMT PET	3 OB, 3 OW, 9 NW	Dopamine synthesis capacity
Serotonergic system				
Adams et al.	2004	[^{18}F]altanserin PET	52 subjects, BMI 24.8 ± 3.7	$5HT_{2A}$ receptor availability
Erritzoe et al.	2009	[^{18}F]altanserin PET	136 subjects, BMI 18.4–42.8	$5HT_{2A}$ receptor availability
Haahr et al.	2015	[^{18}F]altanserin PET [^{11}C]DASB PET	21 OB (14 surgery), 10 NW/OW	$5HT_{2A}$ receptor availability and SERT availability after bariatric surgery
Haahr et al.	2012	[^{11}C]SB207145 PET	28 subjects, BMI 20.5–40.0	$5HT_4$ receptor availability
Erritzoe et al.	2010	[^{11}C]DASB PET	7 OB, 36 OW, 17 NW	SERT availability
Koskela et al.	2008	[^{123}I]nor-β-CIT SPECT	16 monozygotic twin pairs, BMI 19.1–31.9	DAT and SERT availability

Table 26.1 (continued)

First author	Year	Imaging method	Subjects	Primary outcome measures
Kuikka et al.	2001	[^{123}I]nor-β-CIT SPECT	7 OB women, 11 OB women with BED	SERT availability
Tammela et al.[b]	2003	[^{123}I]nor-β-CIT SPECT	6 OB women, 6 OB women with BED	SERT availability
Hesse et al.[c]	2014	[^{123}I]FP-CIT SPECT	127 subjects, BMI 18.2–41.1	SERT availability
Hesse et al.	2016	[^{11}C]DASB PET	30 morbidly OB, 15 NW/OW	SERT availability
Hinderberger et al.[d]	2016	[^{11}C]DASB PET	24 morbidly OB, 14 NW/OW	SERT availability, 5-HTTLPR genotype, BDNF
Versteeg et al.	2017	[^{123}I]FP-CIT SPECT	12 OB (6 IR, 6 IS), 8 NW	SERT availability
Nam et al.	2018	[^{123}I]FP-CIT SPECT 40 OB, BMI 32.9 ± 3.0	142 OB, BMI 25.1 ± 2.8	SERT availability
Noradrenergic system				
Hesse et al.	2017	[^{11}C] O-methylreboxetine	20 morbidly OB, 10 NW/OW	NAT availability
Melasch et al.	2016	[^{11}C] O-methylreboxetine	20 subjects, BMI 33.2 ± 9.7	NAT availability
Opioid system				
Karlsson et al.	2015	[^{11}C]carfentanil + [^{11}C] raclopride PET	13 morbidly OB, 14 NW	MOR and $DRD_{2/3}$ availability
Karlsson et al.	2016	[^{11}C]carfentanil + [^{11}C] raclopride PET	16 morbidly OB, 14 NW	MOR and $DRD_{2/3}$ availability after bariatric surgery
Tuominen et al.	2015	[^{11}C]carfentanil + [^{11}C] raclopride PET	25 morbidly OB, 20 NW	Correlation MOR and $DRD_{2/3}$ availability
Joutsa et al.	2018	[^{11}C]raclopride PET	19 morbidly OB, 7 BED, 30 NW	MOR availability
Cannabinoid system				
Ceccarini et al.	2016	[^{18}F]MK-9470 EPT 26 NW/OW	54 food intake disorder, BMI 12.5–40.6	Cannabinoid 1 receptor availability

PET positron emission tomography, *SPECT* single-photon emission computed tomography, *OB* obese (BMI > 30 kg/m^2), *NW* normal weight (BMI < 25), *OW* overweight (BMI 25–30), *BMI* body mass index, *BED* binge eating disorder, *$DRD_{2/3}$* dopamine $D_{2/3}$ receptor, *DAT* dopamine transporter, *MOR* mu opioid receptor, *PET* positron emission tomography, *SPECT* single photon emission computed tomography, *OB* Obese (BMI > 30 kg/m^2), *NW* Normal weight (BMI < 25), *OW* Overweight (BMI 25–30), *BMI* body mass index, *BED* binge eating disorder, *5-HT* serotonin, *SERT* serotonin transporter, *BDNF* brain derived neurotrophic factor, *IR* insulin resistant, *IS* insulin sensitive, *NAT* noradrenaline transporter, *MOR* mu opioid

[a]Sample overlap with Wang et al. (2001)
[b]Sample overlap with Kuikka et al. (2001)
[c]Sample overlap with van de Giessen et al. (2012)
[d]Sample overlap with van de Giessen et al. (2014)
[e]Sample overlap with Hesse et al. (2016)

26.2 Imaging Findings on Neurotransmitter Systems in Obesity

26.2.1 The Dopaminergic System

Most neuroimaging studies on neurotransmitter systems in obese subjects focus on the dopaminergic system. The earliest imaging study demonstrating abnormalities in the dopaminergic system focused on dopamine $D_{2/3}$ receptor ($DRD_{2/3}$) binding in obese humans (Wang et al. 2001). Wang et al. (2001) conducted a [^{11}C]raclopride PET imaging study in ten morbidly obese subjects (BMI > 40 kg/m^2) and ten age-matched controls (BMI < 30 kg/m^2). They showed that $DRD_{2/3}$ binding was lower in the striatum of obese participants and that there was a negative correlation between BMI and $DRD_{2/3}$ availability in the obese subjects. The finding of decreased striatal $DRD_{2/3}$ availability in obese subjects was confirmed by the same research group in a sample (BMI mean ± SD: 51 ± 5 kg/m^2) that partly overlapped with the previous one (Volkow et al. 2008). This finding was also replicated in an independent sample of 15 morbidly obese women (BMI mean ± SD: 46.8 ± 6.5 kg/m^2) and 15 control women (de Weijer et al. 2011). In this sample, striatal $DRD_{2/3}$ availability was measured with [^{123}I]iodobenzamide ([^{123}I]IBZM) SPECT, and, in line with previous PET studies, striatal IBZM binding was lower in the obese compared to the control women. Another research team (Haltia et al. 2007) conducted [^{11}C]raclopride PET scans in a sample of normal weight, overweight/obese subjects (BMI mean ± SD: 33.1 ± 4.4 kg/m^2). In a voxel-based analysis, they showed that the overweight/obese participants had significantly lower $DRD_{2/3}$ binding in left and right striatal and thalamic subregions, although this difference was not significant in the region of interest (ROI) analysis (Haltia et al. 2007). However, in this study the overweight and obese subjects had substantially lower BMIs than the subjects of the three previously described studies, which could be an explanation for the fact that it was not found in the ROI, but only in the voxel-based analysis. Steele et al. (2010) reported a comparison of [^{11}C]raclopride PET scans in five morbidly obese subjects (BMI > 40 kg/m^2) to an historical control sample of five females and found no significant difference in $DRD_{2/3}$ availability between the two groups. However, this study is limited by several factors, such as its small sample size, the 10-year difference in average age between groups, and the use of an external control group. After these initial studies, there have been a number of studies using different types of tracers for imaging the $DRD_{2/3}$ with seemingly conflicting results. One study using [^{123}I]IBZM SPECT demonstrated lower striatal $DRD_{2/3}$ availability in morbidly obese subjects (van de Giessen et al. 2013a), whereas two studies with [^{11}C]raclopride PET (Karlsson et al. 2015) and [^{11}C]NMB PET (NMB is a selective DRD_2 receptor tracer; Eisenstein et al. 2015) showed no difference, and two studies using [^{18}F]fallypride (Guo et al. 2014) and [^{11}C]-(+)-PHNO PET (Gaiser et al. 2016) found higher $DRD_{2/3}$ availability in obesity. Other studies only reported correlations with BMI, but again results are conflicting. One study with [^{18}F]fallypride PET showed a negative correlation (Kessler et al. 2014), and two studies with [^{18}F]fallypride PET (Dunn et al. 2012; Dang et al. 2016) and two with [^{11}C]-(+)-PHNO

PET showed positive correlations (Cosgrove et al. 2015; Caravaggio et al. 2015). It is important to note that the studies showing higher striatal $DRD_{2/3}$ availability in obesity and positive correlations with BMI are all performed with either the high-affinity antagonist tracer [^{18}F]fallypride or with the tracer [^{11}C]-(+)-PHNO, which binds to the high-affinity state of the D_2 and D_3 receptors and has preferential binding to the D_3 receptor. This may suggest that there are relatively fewer D_2 receptors in low-affinity state and relatively more in high-affinity state in obesity or that there are relatively more D_3 receptors in the ventral striatum. Furthermore, it should be noted that studies showing a decrease in $DRD_{2/3}$ availability all included subjects with very high BMI (>40 kg/m^2), suggesting that there might be a spectrum of $DRD_{2/3}$ availability within the obese group.

Further work investigating the dopaminergic system focused on dopamine release in the striatum. Dopamine release can be induced by a stimulus or pharmacological challenge (e.g., dexamphetamine). Quantifying the displacement of a dopamine receptor binding radiotracer through dopamine is thought to reflect the size of the dopamine release (although it also reflects processes such as dopamine receptor internalization). Based on the hypothesis that the dopaminergic system in obese people is hyporeactive, as suggested by the reward deficiency syndrome theory (Blum et al. 2000), Haltia et al. (2007) tried to demonstrate a blunted dopamine release in overweight and obese people after intravenous glucose administration that serves to mimic recent food intake. To test this hypothesis, they conducted a post-placebo injection and a post-glucose injection [^{11}C]raclopride PET scan in overweight/obese and normal weight subjects after an overnight fasting period. Any difference measured in $DRD_{2/3}$ levels between the baseline and post-glucose injection scan could reflect a change in the intrasynaptic dopamine level and thus indicate dopamine release. However, Haltia et al. (2007) were not able to show a significant difference in dopamine release between the normal weight and overweight/obese (BMI mean ± SD: BMI 33.1 ± 4.4 kg/m^2) group. What they did find, however, was a significant gender effect in the response to the intravenous glucose injection: while men showed a decrease in binding of [^{11}C]raclopride to $DRD_{2/3}$ after intravenous glucose injection, reflecting a dopamine release, women showed an increase in binding. This suggests that increasing glucose levels can have a different effect on the brain depending on gender. Haltia et al. also demonstrated the importance of expectancy for the effect, at least in male participants (Haltia et al. 2008). Using the same sample as before, the team also compared two [^{11}C]raclopride PET scans after placebo injection, one in which the subject was expecting glucose or placebo injection and one with an open placebo expectation. Men showed higher dopamine levels after the placebo injection with glucose expectancy compared to the open placebo injection, revealing an effect of glucose expectancy that seems to facilitate dopamine release. Again, there was no difference between the normal weight and overweight/obese participants. However, another study showed that within a group of obese subjects, those with binge eating disorder had increased striatal dopamine release after food stimulation (Wang et al. 2011). Furthermore, the dopamine release in the caudate nucleus in response to a food cue in this study correlated with binge eating severity scores in the obese binge eaters. Also, in this

study there was no association between BMI and dopamine release. Another study showed a significant amphetamine-induced dopamine release in lean controls, but not in morbidly obese subjects, whereas the dopamine release in the obese subjects correlated positively with food craving scores (van de Giessen et al. 2014). Taken together, studies failed to show a significant relationship between striatal dopamine release and BMI, although in subjects with a (very) high BMI, dopamine release tends to be lower, and binge eating may be associated with relatively higher dopamine release.

It has further been questioned whether weight loss in obese people will lead to a normalization (i.e., increase) of striatal $DRD_{2/3}$ availability. Bariatric surgery can lead to serious weight loss and influences eating behavior and, thus, may affect dopaminergic neurotransmission in the brain. Two small studies have addressed the question whether dopaminergic neurotransmission and $DRD_{2/3}$ availability change after bariatric surgery in morbidly obese subjects (Steele et al. 2010; Dunn et al. 2010). Steele et al. (2010) performed [^{11}C]raclopride PET imaging in five female subjects (preoperative BMI > 40 kg/m^2) before and 6 weeks after laparoscopic Roux-en-Y gastric bypass. They found that $DRD_{2/3}$ availability increased in four of the five subjects after bariatric surgery, although no statistical test was performed to test significance, and the subject with the highest BMI showed a strong postoperative decrease in $DRD_{2/3}$ availability. In a similar study, Dunn et al. (2010) compared $DRD_{2/3}$ availability before and 6 weeks after bypass surgery in five female patients (BMI > 40 kg/m^2) and found a significant decrease of $DRD_{2/3}$ availability in several areas of interest (caudate nucleus, hypothalamus, medial thalamus, and amygdala). However, in a recent study, Karlsson et al. (2016) showed no change in striatal $DRD_{2/3}$ availability with [^{11}C]raclopride PET 6 months after bariatric surgery in a larger sample of 16 morbidly obese women. It should be noted that these patients did not have a lower level of striatal $DRD_{2/3}$ availability at baseline compared to controls. Van der Zwaal et al. (2016) also showed no change in striatal $DRD_{2/3}$ availability using [^{123}I]IBZM SPECT at 6 weeks after bariatric surgery, but at long term (>2 years) there was an increase in 14 morbidly obese women who initially had lower $DRD_{2/3}$ levels than controls. Given the conflicting results, no definitive conclusion can be reached, although it seems that there might be no change in $DRD_{2/3}$ levels at the short term, but possibly at the long term after bariatric surgery.

Most imaging studies on the dopaminergic system in obesity have concentrated their attention on the $DRD_{2/3}$, of which the majority is located postsynaptically (Levey et al. 1993). However, the presynaptic dopamine transporter (DAT) could be equally important, because it regulates the synaptic dopamine levels, in particular for the tonic dopamine levels (Zhang et al. 2009). Therefore, the DAT may also play a role in reward processing of food. Three studies have investigated DAT availability in relation to BMI, so far. Chen et al. reported a negative correlation between BMI and striatal DAT availability, as measured with [^{99m}Tc]TRODAT-1 SPECT in healthy subjects (BMI range: 18.7–30.6 kg/m^2) (Chen et al. 2008). However, in a monozygotic twin study that applied the more specific ligand [^{123}I]nor-β-CIT SPECT, Koskela et al. (2008) were not able to show a difference in striatal DAT

availability between the heavier twin (BMI mean ± SD: 26.8 ± 3.6 kg/m^2) and its leaner twin sibling (BMI mean ± SD: 24.5 ± 3.1 kg/m^2). Both these studies included only a limited range of BMIs, and neither included severely obese subjects. However, a recent study using [^{123}I]FP-CIT SPECT included a large sample with a wider BMI range. In 123 healthy European subjects (BMI range: 18.2–41.4 kg/m^2), van de Giessen et al. (2012) found no association between BMI and striatal DAT availability. Furthermore, Thomsen et al. (2013) studied a sample that also included severely obese subjects (BMI range: 21.0–49.5 kg/m^2) and used the specific DAT radioligand [^{123}I]PE21 and SPECT. They found no correlation between BMI and DAT availability nor a difference in DAT availability between obese and normal weight subjects. Recently, Nam et al. (2018) also found no correlation between BMI and striatal DAT binding in a sample of 182 subjects using ^{123}I-FP-CIT SPECT. Overall, four out of five studies found no association between BMI and striatal DAT availability, which suggests that striatal DAT levels are not different in high BMI subjects.

Looking at the dopamine system from a slightly different angle, Wilcox et al. (2010) conducted a PET study in 15 healthy subjects (BMI mean: 25.3 kg/m^2) and 3 obese subjects (BMI > 30 kg/m^2) using the ligand 6-[^{18}F]fluoro-L-*m*-tyrosine (FMT) as a tracer to analyze the capacity of striatal neurons to convert levodopa (L-dopa) to dopamine. The results of this study showed that in obese and overweight subjects, the capacity to synthesize dopamine tended to be lower than in normal weight controls (although not significant after correction for age and gender). The study also found that the frequency of unsuccessful attempts of dieting and weight loss was negatively associated with the synthesis capacity of dopamine in the dorsal putamen. These findings point toward a downregulation mechanism that limits the available striatal dopamine production in response to overeating.

26.2.2 The Serotonergic System

Two (sub)types of serotonin (5-hydroxytryptamine) receptors (5-HT$_{2A}$ and 5-HT$_4$) and the serotonin transporter (SERT) have been studied in obesity with PET and SPECT in humans. In a study among 52 healthy subjects (BMI mean ± SD: 24.8 ± 3.7 kg/m^2) using [^{18}F]altanserin PET, Adams et al. (2004) found a positive correlation between BMI and (postsynaptic) 5-HT$_{2A}$ receptor binding in all cortical regions except the occipital cortex. They replicated this finding in a larger sample (n = 136) of healthy subjects with a broader BMI range (18.2–42.8 kg/m^2), including 14 obese subjects (Erritzoe et al. 2009). In this later study, the correlation was found for the complete neocortex, including the occipital cortex. The authors interpreted this finding as a compensatory upregulation of the cortical 5-HT$_{2A}$ receptor availability due to lower brain serotonin levels in the overweight and obese subjects (Lam et al. 2010; Bjorntorp 1995). Later, the same group again replicated the finding that obese subjects have higher cerebral 5-HT$_{2A}$ receptor binding than normal weight subjects (Haahr et al. 2015) and showed that 5-HT$_{2A}$ receptor binding predicted weight loss after gastric bypass surgery.

In a sample of 28 healthy subjects (BMI range: 20.5–40.0 kg/m^2) using [^{11}C]SB207145 PET, a positive correlation between BMI and (postsynaptic) 5-HT$_4$ receptor binding in the nucleus accumbens, globus pallidus, orbitofrontal cortex, and left temporal pole was found (Haahr et al. 2012). It is of particular interest that the positive correlations were mainly found in brain regions involved in the brain reward and salience circuitry, which plays an important role in overeating behavior.

There are several studies investigating the association between BMI and the SERT, which regulates synaptic serotonin levels. The first study to report an association was performed by Erritzoe et al. (Erritzoe et al. 2010), who showed in a [^{11}C]DASB PET study with 60 healthy volunteers ranging in BMI from 20.6 to 32.4 kg/m^2 (including 7 obese subjects) that BMI was negatively correlated with SERT binding in the global neocortex and in some subcortical regions (caudate nucleus, putamen, thalamus, and midbrain). This finding contrasts with results reported by Koskela et al. (2008). In this previously mentioned study among monozygotic twins, both DAT and SERT levels were investigated. Although SERT binding was not correlated with BMI on an individual level, heavier twins overall had higher SERT binding in the hypothalamus/thalamus region than their leaner twin siblings. Another study showed that obese women with binge eating disorder have decreased SERT availability in the midbrain compared to obese non-binge eating women (Kuikka et al. 2001). In a subsample of these women, successful treatment of the binge eating disorder was associated with an increase in SERT availability in the midbrain (Tammela et al. 2003). Recently, Nam et al. (2018) also found no correlation between BMI and SERT binding in the thalamus and midbrain in a sample of 182 subjects using ^{123}I-FP-CIT SPECT, but there was a positive correlation between SERT availability and BMI in the nonobese subjects (n = 142, mean BMI 25.1 ± 2.8 kg/m^2) and a negative correlation in the obese group (n = 40, mean BMI 32.9 ± 3.0 kg/m^2). Hesse et al. (2014) also reported a positive correlation between BMI and midbrain SERT availability (measured with ^{123}I-FP-CIT SPECT) in a sample of 127 healthy subjects (BMI range 18.2–41.1 kg/m^2). However, this was only demonstrated with a voxel-based analysis and was not significant in a region of interest analysis, and no association was found for the thalamus. Later, Hesse et al. (2016) performed a cross-sectional study with [^{11}C]DASB PET comparing a highly obese group (BMI range: 35–55 kg/m^2) with a nonobese group (BMI range 19–27 kg/m^2) and showed no difference between the groups. Versteeg et al. (2017) also showed no difference in thalamus and midbrain SERT binding (measured with ^{123}I-FP-CIT SPECT) between lean and obese subjects, but showed that obese insulin-resistant subjects have lower thalamus SERT compared to insulin-sensitive obese subjects. Haahr et al. (2015) also reported no difference between lean and obese subjects for SERT binding (measured with [^{11}C]DASB PET), but showed that the change in SERT binding correlated negatively with weight loss after gastric bypass surgery. Interestingly, they demonstrated an inverted U relationship between SERT binding and 5-HT$_{2A}$ receptor binding and suggested that the balance between 5-HT$_{2A}$ receptors and SERTs is important in weight regulation. Together, the reviewed studies on SERT binding indicate that there is no direct association between obesity or BMI and SERT binding in the midbrain or thalamus. However,

in subgroups of obese subjects, i.e., insulin resistance and binge eating disorder, SERT availability may be lower. More importantly, the 5-HT_{2A} receptor appears to have a more prominent role in obesity than SERT, but it is the balance between these two that seems most directly related to weight regulation.

26.2.3 The Noradrenergic System

The noradrenaline transporter (NAT) has the highest expression in the locus coeruleus, hypothalamus, and thalamus. Noradrenaline in the hypothalamus has direct effects on food intake. Hesse et al. (2017) studied NAT binding with [^{11}C]O-methylreboxetine PET in morbidly obese subjects compared to nonobese subjects. They found no difference in NAT binding, neither in the hypothalamus nor in the thalamus, locus coeruleus, or other regions. The same group also reported that NAT binding was associated with strengthened connectivity (measured with resting-state fMRI) with the insula/frontal operculum, which in turn correlated positively with BMI and impact of weight on quality of life (IWQOL-Lite) scores (Melasch et al. 2016). According to the authors, this may suggest a role of noradrenaline in emotional well-being related to weight, although this is still speculative.

26.2.4 The Opioid System

Whereas dopamine has been linked to the incentive motivation ("wanting") for food, endogenous opioids have been linked to the hedonic impact ("liking") when food is consumed (Berridge et al. 2010). Mu opioid receptors (MOR) modulate the effects of endogenous opioids. Karlsson et al. (2015) were the first to demonstrate that MOR binding is lower in both striatal and extra-striatal regions (including insula, amygdala, orbitofrontal cortex, and thalamus) in morbidly obese subjects compared to lean controls. Moreover, MOR binding correlated negatively with BMI, self-reported food addiction, and restrained eating patterns. This low level of MOR binding normalized after weight loss due to bariatric surgery in the previously mentioned brain regions (Karlsson et al. 2016). Interestingly, striatal $DRD_{2/3}$ binding (measured with ^{11}C-raclopride PET) in the morbidly obese subjects was similar to the lean subjects at baseline, and this remained unaltered after bariatric surgery. In the lean subjects, there was a clear positive correlation between MOR binding and $DRD_{2/3}$ binding in the ventral striatum and dorsal caudate nucleus, but this correlation was much weaker or nonexistent in these areas in the morbidly obese subjects, suggestive of an aberrant dopamine-opioid interaction in obesity (Tuominen et al. 2015). Furthermore, the same group showed that not only morbidly obese subjects have lower MOR binding but also subjects with binge eating disorder (BED), again in both striatal and extra-striatal regions (Joutsa et al. 2018). Although this work is all performed by one group and needs replication, it demonstrates the potential importance of the opioid system in obesity and eating disorders and shows that MOR binding might be a better marker than dopaminergic imaging of pathology in the reward system in obesity.

26.2.5 The Cannabinoid System

Cannabinoid 1 receptors (CB_1R) are widely expressed in the brain. Stimulation of CB_1R increases appetite and food intake, whereas pharmacological blockade reduces hunger, food intake, and body weight (Koch 2017). In a study including a range of food intake disorders (anorexia nervosa, bulimia nervosa, functional dyspepsia with weight loss, and obesity) with a wide range of BMI, there was a negative correlation between BMI and CB_1R availability in patients with food intake disorders and in healthy controls in the hypothalamus and brainstem (Ceccarini et al. 2016). However, in the patients with food intake disorders, the negative correlation was also found in brain regions of the mesolimbic reward system (midbrain, striatum, insula, amygdala, and orbitofrontal cortex). Although there is a large variety of food intake disorders, this may suggest that the CB_1R is indeed linked to food reward with an aberrant regulation in food intake disorders.

26.3 Discussion

This review of the literature shows that the dopaminergic, serotonergic, and opioid systems are involved in obesity, highlighting the importance of dysregulated molecular processes in the brain in obesity. The main findings that were replicated at least once are that 5-HT_{2A} receptor binding in cortical regions correlates positively with BMI and that striatal DAT availability and SERT availability in midbrain and striatum are not altered in obesity. The literature on the striatal $DRD_{2/3}$ availability has become more inconsistent, suggesting no or only a minor decrease of striatal $DRD_{2/3}$ availability in obesity. Further, the mu opioid system seems an important element in obesity and eating behavior, although this still needs replication. Finally, the few available studies show that the CB_1 receptor is linked to food reward with a possible aberrant regulation in food intake disorders.

26.3.1 Discussion of Findings on the Dopaminergic System

Whereas initial studies suggested a decrease in striatal $DRD_{2/3}$ availability in obesity, new studies show inconsistent findings. Van Galen et al. (2018) have sought to explain this discrepancy and suggested that there might be an inverted U-shaped relationship with an initial increase in striatal $DRD_{2/3}$ availability at moderately high BMI, in particular of high-affinity D_2 receptors and D_3 receptors, followed by a decrease of striatal $DRD_{2/3}$ availability at very high BMI. Given the more complex relationship between striatal $DRD_{2/3}$ availability and obesity that arises from the literature, the evidence appears limited for the original hypothesis that lower striatal $DRD_{2/3}$ availability is related to reward deficiency in obesity, which may lead to overeating (Volkow et al. 2011). Also, the initial comparison to substance abuse, in which lower striatal $DRD_{2/3}$ availability has repeatedly been reported (Volkow et al. 1996a, 2001a; Wang et al. 1997), is less obvious. This hypothesis is probably only

interesting for the morbidly obese subgroup. Animal research still provides some support for this model (van de Giessen et al. 2012, 2013a, b; Hamdi et al. 1992; Hajnal et al. 2008; Davis et al. 2009; Thanos et al. 2008; Johnson and Kenny 2010). For example, Johnson and Kenny (2010) demonstrated that a downregulation of striatal $DRD_{2/3}$ can be induced by a cafeteria-style diet and that a $DRD_{2/3}$ downregulation increases the susceptibility for reward deficits and compulsive eating behavior in rats. Also, interactions between $DRD_{2/3}$ receptor binding and insulin may exist, which may further complicate the interpretation of results concerning $DRD_{2/3}$ binding in obesity since many obese subjects may suffer from diabetes type 2 (de Weijer et al. 2014).

There is no evidence for a change in striatal dopamine release in obesity, whether induced by amphetamine or by food-related stimuli, although there might be a tendency to a decrease at (very) high BMI. It has been hypothesized that obese people have a blunted reactivity of the dopaminergic system, similar to what has been shown in cases of substance use disorders (Martinez et al. 2005, 2007). A blunted dopamine release in obesity would also fit in the reward deficiency theory. A dopamine release after food intake in healthy humans has been demonstrated after a meal (Small et al. 2003) and after amplification of dopamine release by methylphenidate (Volkow et al. 2002). Interestingly, the studies using glucose injection to mimic high-energy intake could not find any differences in dopamine release between lean and obese subjects. This might be explained by the fact that the intravenous glucose injection did not activate all the processes involved in eating, because it lacks important aspects like the sight, taste, texture and smell of food, as well as the actual action of eating (chewing, swallowing, etc.). Therefore, the reward experience after glucose injection might have been incomplete and too small to detect. A difference in the level of dopamine release between obese and normal weight subjects after real food intake might be very difficult to detect with the currently available techniques because of the naturally limited size of the dopamine release after food intake (about 10 times lower than after amphetamine administration (Bassareo and Di Chiara 1999)). Nevertheless, in one animal study, researchers managed to show with microdialysis (which is many times more sensitive than SPECT or PET imaging) that obese rats release less dopamine in the nucleus accumbens, both after food intake and after amphetamine stimulation (Geiger et al. 2009). In addition, it was shown that an amphetamine-induced striatal dopamine release is lower in obese subjects without binge eating disorder compared to obese subjects with binge eating disorder(Wang et al. 2011), which may be interpreted as increased craving, similar to the correlation with food craving score found by van de Giessen et al. (2014). Finally, we recently showed that striatal DA release may be involved in systemic glucose metabolism which may further complicate the interpretation of results on DA release in obesity (Ter Horst et al. 2018).

With regard to the presynaptic side of the dopaminergic system, imaging results quite consistently show that there is no relationship between BMI and DAT availability. This is in contrast to the results in rodent studies showing a decrease in DAT density on the cell surface in the striatum in animals on a high-fat diet for obesity induction (Speed et al. 2011; South and Huang 2008). However, one rodent study

showed that this effect only occurs in obesity-resistant mice on a high-fat diet and not in the obesity-prone mice on the same high-fat diet (Huang et al. 2006). The literature on substance use disorders shows variable results regarding DAT levels in drug abusers, but overall these studies suggest decreased levels of DAT in drug abusers (Volkow et al. 1996a, 2001b; Sekine et al. 2001; Yang et al. 2008; Newberg et al. 2007; Laine et al. 1999) and no change or an increase in DAT levels for users of cocaine (where the increase is possibly related to the short period of abstinence after cocaine intake (Malison et al. 1998; Volkow et al. 1996b)). Taken together, these findings do not support a similar mechanism in obesity and substance use disorders, as was previously hypothesized.

Concerning the role of dopamine in obesity, many important questions have been addressed, although the emerging literature is still not conclusive. One aspect that has not been studied yet is whether endogenous synaptic dopamine levels are altered in obesity. A dopamine depletion study (e.g., using alpha-methyl-para-tyrosine to decrease the synthesis of dopamine (Boot et al. 2008)) comparing obese and control subjects would be a possibility to address this question. However, additional studies on the role of striatal $DRD_{2/3}$ availability and the emerging role of other neurotransmitter systems (in particular serotonergic and opioid) and the interactions with changes in insulin levels/glucose metabolism may have a higher priority.

26.3.2 Discussion of Findings on the Serotonergic System

Regarding the serotonergic system, the positive correlation of BMI and cortical 5-HT_{2A} receptor binding in humans has been replicated (although by the same group) and seems a robust finding (Erritzoe et al. 2009; Adams et al. 2004; Haahr et al. 2015). It is (partly) supported by animal work, which also shows that there are significantly higher 5-HT_{2A} levels in the anterior olfactory nucleus and ventromedial hypothalamic nucleus (VMH) in obesity-prone mice compared to the obesity-resistant and control mice (Huang et al. 2004a, b). The positive association suggests that there is an upregulation of cortical 5-HT_{2A} receptors, which might be compensatory to decreased serotonin levels (Reneman et al. 2002). In a SPECT study comparing 10 bulimia patients to 11 healthy controls (all within a normal BMI range), no difference was found in cortical 5-HT_{2A} binding between the groups (Goethals et al. 2004). This suggests that it is not the pathologic eating behavior but the obese state that affects the 5-HT_{2A} receptor availability.

Furthermore, the (non-replicated) finding of a positive correlation between BMI and 5-HT_4 receptor availability shows that also subcortical, reward-related parts of the serotonergic system may be involved in obesity (Haahr et al. 2012). Indeed, the 5-HT_4 receptor has been implicated in food intake regulation and rood-related reward (Ratner et al. 2012; Francis et al. 2011). Possibly, this positive correlation is also a reflection of an upregulation of 5-HT_4 receptors due to a widespread decrease in serotonin levels throughout the brain, as previously described for the 5-HT_{2A} receptors.

The growing literature on SERT in obesity has demonstrated that there are no significant changes in SERT availability in obesity, but that it is the balance between 5-HT_{2A} receptor binding and SERT that is most important, in which 5-HT_{2A} receptor binding has a more prominent role. However, some preliminary data suggest a role for SERT in insulin resistance (Versteeg et al. 2017). Also, the role of SERT in (pathologic) eating behavior still remains unclear. Whereas obese subjects with binge eating had lower midbrain SERT than obese subjects without binge eating (Kuikka et al. 2001), a study in a subject sample with night eating syndrome found increased SERT availability in the midbrain (Lundgren et al. 2008, 2009). On the other hand, in bulimia nervosa patients, SERT availability was decreased in the thalamus and hypothalamus (Tauscher et al. 2001). So, binge eating might well lead to lower SERT availability, but the relation between SERT and eating behavior is complex and not yet disentangled.

26.3.3 Conclusion

In conclusion, the results of the imaging studies on neurotransmitter systems in obesity have clearly shown that the dopaminergic, serotonergic, opioid, and possibly the cannabinoid systems are affected. However, the previously hypothesized lower striatal $DRD_{2/3}$ availability in obesity has become a more complex relationship, and previously hypothesized similarities with substance use disorders appear to be less plausible. The disturbances in the serotonergic (5-HT_{2A} receptor) and opioid system (mu opioid receptor) tend to be larger than in the dopaminergic system and more responsive to surgery-induced weight loss. Finally, some studies indicated that obese subjects with eating binges and with insulin resistance are important subgroups within the obese population with different pathophysiological mechanisms that warrant further study.

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Neuroimaging Studies of Psychopathy

27

Philip Deming and Michael Koenigs

Contents

Abstract

In recent years, an increasing number of neuroimaging studies have sought to identify the brain anomalies associated with psychopathy. The results of such studies could have significant implications for the clinical and legal management of psychopaths, as well as for neurobiological models of human social behavior. In this chapter we provide a critical review of structural and functional neuroimaging studies of psychopathy. In particular, we emphasize the considerable variability in results across studies and focus our discussion on three methodological issues that could contribute to the observed heterogeneity in study data: (1) the use of between-group analyses (i.e., psychopaths vs. non-psychopaths) as well as correlational analyses (i.e., normal variation in "psychopathic" traits), (2) discrepancies in the criteria used to classify subjects as psychopaths, and (3) consideration of psychopathic subtypes. The available evidence suggests that each of these issues could have a substantial effect on the reliability of imaging data. We propose several strategies for resolving these methodological issues in future studies, with the goal of fostering further progress in the identification of the neural correlates of psychopathy.

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Human brain imaging techniques, such as magnetic resonance imaging (MRI), have become an indispensable means for investigating the neurobiological substrates of psychiatric and psychological disorders. In recent years, the use of neuroimaging in psychopathy research has become increasingly common. The potential implications of characterizing the neural correlates of psychopathy are far-reaching. Clinically, such knowledge could be used to aid in the diagnosis of the disorder and perhaps the identification of neural targets for treatment. In the legal domain, neuroimaging data could possibly inform questions of culpability, likelihood of future offense, and prospects for rehabilitation. However, structural and functional imaging studies have not yet revealed consistent neural correlates of psychopathy. The goal of this chapter is threefold: (1) to briefly summarize the extant neuroimaging data on psychopathy, (2) to identify a number of methodological inconsistencies that may contribute to the observed heterogeneity in the data, and (3) to make constructive suggestions regarding potential strategies for remediation of methodological inconsistencies in future studies.

Before summarizing the neuroimaging results, we first outline the scope of the studies we evaluated for this article. We specifically examined original published reports of human neuroimaging data wherein the authors make direct conclusions about the neural correlates of psychopathy in adults (in particular, neuroimaging reports with "psychopathy," "psychopaths," or "psychopathic" in the title; see Table 27.1). This approach omits two important related lines of research, which we briefly mention here. One is the study of the neural correlates of antisocial traits commonly associated with, but not limited to, psychopathy. Examples include violence (Raine et al. 1997; Volkow et al. 1995), antisocial personality disorder (Volkow et al. 1995; Barkataki et al. 2006), aggressive/impulsive behavior (Dolan et al. 2002), and pathological lying (Yang et al. 2005a). Although these traits may commonly overlap with psychopathy, none are unique to psychopathy. Accordingly, neuroimaging findings associated with these traits may not specifically inform the neural basis of psychopathy, and so we omit further mention of such studies in this review. (For a review on neuroimaging of antisocial behavior, see (Yang and Raine 2009)). The other line of research omitted here is the neuroimaging of children and adolescents with psychopathic tendencies (Dalwani et al. 2011; De Brito et al. 2009; Fairchild et al. 2013; Finger et al. 2012; Jones et al. 2009; Marsh et al. 2008). Research in children and adolescents is of course critical for understanding the development of antisocial behavior. However, the comparison of imaging data from adult and child/adolescent studies can be challenging for a number of reasons. One reason is that the diagnostic criteria for antisocial behavior in children/adolescents (such as conduct disorder) are necessarily somewhat different than the criteria for adult psychopathy, reflecting the considerable differences in life circumstances for children, adolescents, and adults. A second reason is that the brain undergoes substantial structural development throughout childhood and adolescence, such that neuroimaging findings vary significantly across preadult age groups, even among neurologically and psychologically healthy individuals (Giedd et al. 2009). Given these important differences, we believe the child/adolescent literature warrants its own review and evaluation. (For a review on neuroimaging findings related to antisocial behavior in children, see (Crowe and Blair 2008)).

Table 27.1 Neuroimaging studies of "psychopathy"

First author	Year	Title	Type of imaging	Type of analysis	PCL-R cutoff for P	Mean PCL-R for Ps	P sample size
Abe	2018	Reduced engagement of the anterior cingulate cortex in the dishonest decision-making of incarcerated **psychopaths**	F	C/R	n/a	n/a	n/a
Anderson	2017	Differentiating emotional processing and attention in **psychopathy** with functional neuroimaging	F	C/R	n/a	n/a	n/a
Anderson	2018	**Psychopathic** traits associated with abnormal hemodynamic activity in salience and default mode networks during auditory oddball task	F	C/R	n/a	n/a	n/a
Beckwith	2018	Reduced regional volumes associated with total **psychopathy** scores in an adult population with childhood lead exposure	S	C/R	n/a	n/a	n/a
Birbaumer	2005	Deficient fear conditioning in **psychopathy**: a functional magnetic resonance imaging study	F	BG	15	24.9	10
Bjork	2011	**Psychopathic** tendencies and mesolimbic recruitment by cues for instrumental and passively obtained rewards	F	C/R	n/a	n/a	n/a
Boccardi	2011	Cortex and amygdala morphology in **psychopathy**	S	BG	21	29.9	26
Boccardi	2010	Abnormal hippocampal shape in offenders with **psychopathy**	S	BG	30	34.6	12
Boccardi	2013	Atypical nucleus accumbens morphology in **psychopathy**: another limbic piece in the puzzle	S	BG	30	34.6	12
Buckholtz	2010	Mesolimbic dopamine reward system hypersensitivity in individuals with **psychopathic** traits	F	C/R	n/a	n/a	n/a
Carré	2013	The neural signatures of distinct **psychopathic** traits	F	C/R	n/a	n/a	n/a
Contreras-Rodriguez	2014	Disrupted neural processing of emotional faces in **psychopathy**	F	BG	20	27.8	22
Contreras-Rodriguez	2015	Functional connectivity bias in the prefrontal cortex of **psychopaths**	F, S	BG	20	27.8	22

(continued)

Table 27.1 (continued)

First author	Year	Title	Type of imaging	Type of analysis	PCL-R cutoff for P	Mean PCL-R for Ps	P sample size
Cope	2014	**Psychopathic** traits modulate brain responses to drug cues in incarcerated offenders	F	C/R	n/a	n/a	n/a
Craig	2009	Altered connections on the road to **psychopathy**	S	BG, C/R	25	28.4	9
Crooks	2018	The relationship between cavum septum pellucidum and **psychopathic** traits in a large forensic sample	S	C/R	n/a	n/a	n/a
de Oliveira-Souza	2008	**Psychopathy** as a disorder of the moral brain: fronto-temporo-limbic grey matter reductions demonstrated by voxel-based morphometry	S	BG, C/R	n/a	n/a	15
Decety	2013a	Brain response to empathy-eliciting scenarios involving pain in incarcerated individuals with **psychopathy**	F	BG, C/R	30	n/a	27
Decety	2013b	An fMRI study of affective perspective taking in individuals with **psychopathy**: imagining another in pain does not evoke empathy	F	BG, C/R	30	n/a	37
Decety	2014	Neural processing of dynamic emotional facial expressions in **psychopaths**	F	BG, C/R	30	n/a	27
Decety	2015	Socioemotional processing of morally-laden behavior and their consequences on others in forensic **psychopaths**	F	BG, C/R	30	n/a	38
Deeley	2006	Facial emotion processing in criminal **psychopathy**. Preliminary functional magnetic resonance imaging study	F	BG	25	29.3	6
Deming	2018	**Psychopathic** traits linked to alterations in neural activity during personality judgments of self and others	F	C/R	n/a	n/a	n/a
Denomme	2018	Neuroimaging metrics of drug and food processing in cocaine-dependence, as a function of **psychopathic** traits and substance use severity	F	C/R	n/a	n/a	n/a
Dolan	2009	**Psychopathy** and functional magnetic resonance imaging blood oxygenation level-dependent responses to emotional faces in violent patients with schizophrenia	F	BG, C/R	n/a	n/a	12

Ermer	2012	Aberrant paralimbic gray matter in criminal **psychopathy**	S	C/R	n/a	n/a	n/a
Espinoza	2018	Aberrant functional network connectivity in **psychopathy** from a large ($N = 985$) forensic sample	F	C/R	n/a	n/a	n/a
Espinoza	2019	Resting-state fMRI dynamic functional network connectivity and associations with **psychopathy** traits	F	C/R	n/a	n/a	n/a
Fede	2016	Distinct neuronal patterns of positive and negative moral processing in **psychopathy**	F	C/R	n/a	n/a	n/a
Freeman	2015	The posteromedial region of the default mode network shows attenuated task-induced deactivation in **psychopathic** prisoners	F	BG	28	31.3	22
Glenn	2009	The neural correlates of moral decision-making in **psychopathy**	F	C/R	n/a	n/a	n/a
Glenn	2010	No volumetric difference in the anterior cingulate of **psychopathic** individuals	S	BG, C/R	23	28.0	24
Glenn	2010	Increased volume of the striatum in **psychopathic** individuals	S	BG	23	27.2	22
Gordon	2004	Functional differences among those high and low on a trait measure of **psychopathy**	F	BG	n/a	n/a	n/a
Gregory	2012	The antisocial brain: **psychopathy** matters	S	BG	25	28.1	17
Gregory	2015	Punishment and **psychopathy**: a case-control functional MRI investigation of reinforcement learning in violent antisocial personality disordered men	F	BG	25	28.2	12
Harenski	2009	Neuroticism and **psychopathy** predict brain activation during moral and nonmoral emotion regulation	F	C/R	n/a	n/a	n/a
Harenski	2010	Aberrant neural processing of moral violations in criminal **psychopaths**	F	BG, C/R	30	31.8	16
Harenski	2014	Neural correlates of moral and non-moral emotion in female **psychopathy**	F	C/R	n/a	n/a	n/a

(continued)

Table 27.1 (continued)

First author	Year	Title	Type of imaging	Type of analysis	PCL-R cutoff for P	Mean PCL-R for Ps	P sample size
Hosking	2017	Disrupted prefrontal regulation of striatal subjective value signals in **psychopathy**	F	C/R	n/a	n/a	n/a
Intrator	1997	A brain imaging (single photon emission computerized tomography) study of semantic and affective processing in **psychopaths**	F	BG	25	29.9	8
Juárez	2013	Intrinsic limbic and paralimbic networks are associated with criminal **psychopathy**	F	BG, C/R	30	32.5	17
Kiehl	2001	Limbic abnormalities in affective processing by criminal **psychopaths** as revealed by functional magnetic resonance imaging	F	BG	24	32.8	8
Kiehl	2004	Temporal lobe abnormalities in semantic processing by criminal **psychopaths** as revealed by functional magnetic resonance imaging	F	BG	29	32.8	8
Kolla	2014	Disentangling possible effects of childhood physical abuse on gray matter changes in violent offenders with **psychopathy**	S	BG	25	27.7	9
Korponay	2016	Impulsive-antisocial dimension of **psychopathy** linked to enlargement and abnormal functional connectivity of the striatum	F, S	C/R	n/a	n/a	n/a
Korponay	2017	Impulsive-antisocial **psychopathic** traits linked to increased volume and functional connectivity within prefrontal cortex	F, S	C/R	n/a	n/a	n/a
Laakso	2001	**Psychopathy** and the posterior hippocampus	S	C/R	n/a	n/a	n/a
Larson	2013	The interplay of attention and emotion: top-down attention modulates amygdala activation in **psychopathy**	F	BG	30	31.3	24
Laurens	2001	Abnormal response inhibition in criminal **psychopaths**: Evidence from event-related fMRI	F	BG	n/a	n/a	14
Leutgeb	2015	Brain abnormalities in high-risk violent offenders and their association with **psychopathic** traits and criminal recidivism	S	C/R	n/a	n/a	n/a
Lindner	2018	Associations of **psychopathic** traits with local and global brain network topology in young adult women	F	C/R	n/a	n/a	n/a

Ly	2012	Cortical thinning in **psychopathy**	F, S	BG	30	31.8	21
Marsh	2014	When **psychopathy** impairs moral judgments: neural responses during judgments about causing fear	F	BG	n/a	n/a	n/a
Meffert	2013	Reduced spontaneous but relatively normal deliberate vicarious representations in **psychopathy**	F	BG	26	32.3	18
Mier	2014	Reduced embodied simulation in **psychopathy**	F	BG	25	26.7	11
Miskovich	2018	Abnormal cortical gyrification in criminal **psychopathy**	S	C/R	n/a	n/a	n/a
Molenberghs	2014	The influence of group membership and individual differences in **psychopathy** and perspective taking on neural responses when punishing and rewarding others	F	C/R	n/a	n/a	n/a
Motzkin	2011	Reduced prefrontal connectivity in **psychopathy**	F,S	BG	30	31.9	20
Müller	2003	Abnormalities in emotion processing within cortical and subcortical regions in criminal **psychopaths**: evidence from a functional magnetic resonance imaging study using pictures with emotional content	F	BG	31	36.8	6
Müller	2008a	Gray matter changes in right superior temporal gyrus in criminal **psychopaths**. Evidence from voxel-based morphometry	S	BG	28	33.4	17
Müller	2008b	Disturbed prefrontal and temporal brain function during emotion and cognition interaction in criminal **psychopathy**	F	BG	28	30.5	10
Osumi	2012	Amygdala dysfunction attenuates frustration-induced aggression in **psychopathic** individuals in a non-criminal population	F	C/R	n/a	n/a	n/a
Pardini	2013	Lower amygdala volume in men is associated with childhood aggression, early **psychopathic** traits, and future violence	S	C/R	n/a	n/a	n/a
Pujara	2014	Neural correlates of reward and loss sensitivity in **psychopathy**	F, S	BG, C/R	30	31.7	18
Pujol	2012	Breakdown in the brain network subserving moral judgment in criminal **psychopathy**	F	BG, C/R	20	27.8	22

(continued)

Table 27.1 (continued)

First author	Year	Title	Type of imaging	Type of analysis	PCL-R cutoff for P	Mean PCL-R for Ps	P sample size
Raine	2003	Corpus callosum abnormalities in **psychopathic** antisocial individuals	S	BG, C/R	23	30.3	15
Raine	2004	Hippocampal structural asymmetry in unsuccessful **psychopaths**	S	BG	23	29.9	28
Raine	2010	Neurodevelopmental marker for limbic maldevelopment in antisocial personality disorder and **psychopathy**	S	BG	23	28.7	18
Rilling	2007	Neural correlates of social cooperation and non-cooperation as a function of **psychopathy**	F	C/R	n/a	n/a	n/a
Rodman	2016	Selective mapping of **psychopathy** and externalizing to dissociable circuits for inhibitory self-control	F	C/R	n/a	n/a	n/a
Sadeh	2013	Emotion disrupts neural activity during selective attention in **psychopathy**	F	C/R	n/a	n/a	n/a
Sato	2011	Identification of **psychopathic** individuals using pattern classification of MRI images	S	C/R	n/a	n/a	n/a
Schultz	2016	**Psychopaths** show enhanced amygdala activation during fear conditioning	F	BG	30	32.1	31
Sethi	2018	Primary and secondary variants of **psychopathy** in a volunteer sample are associated with different neurocognitive mechanisms	F	BG	n/a	n/a	150
Shane	2018	Capacity for upregulation of emotional processing in **psychopathy**: all you have to do is ask	F	BG	30	32.0	15
Sheng	2010	Default network deactivations are correlated with **psychopathic** personality traits	F	C/R	n/a	n/a	n/a
Sommer	2010	In **psychopathic** patients emotion attribution modulates activity in outcome-related brain areas	F	BG	28	28.6	14
Tillem	2019	**Psychopathy** is associated with shifts in the organization of neural networks in a large incarcerated male sample	F	C/R	n/a	n/a	n/a
Veit	2010	Aberrant social and cerebral responding in a competitive reaction time paradigm in criminal **psychopaths**	F	C/R	n/a	n/a	n/a
Vermeij	2018	Affective traits of **psychopathy** are linked to white-matter abnormalities in impulsive male offenders	S	C/R	n/a	n/a	n/a

Vieira	2014	Distinct neural activation patterns underlie economic decisions in high and low **psychopathy** scorers	F	BG	n/a	n/a	18
Waller	2019	Weakened functional connectivity between the amygdala and the ventromedial prefrontal cortex is longitudinally related to **psychopathic** traits in low-income males during early adulthood	F	C/R	n/a	n/a	n/a
Yang	2005b	Volume reduction in prefrontal gray matter in unsuccessful criminal **psychopaths**	S	BG, C/R	23	28.4	29
Yang	2009	Localization of deformations within the amygdala in individuals with **psychopathy**	S	BG, C/R	23	28.0	27
Yang	2010	Morphological alterations in the prefrontal cortex and the amygdala in unsuccessful **psychopaths**	S	BG	23	n/a	26
Yang	2011	Abnormal structural correlates of response perseveration in individuals with **psychopathy**	S	BG, C/R	23	n/a	27
Yang	2012	Frontal information flow and connectivity in **psychopathy**	S	BG	n/a	n/a	55
Yoder	2015	Neural networks underlying implicit and explicit moral evaluations in **psychopathy**	F	C/R	n/a	n/a	n/a
Yoder	2015	Amygdala subnuclei connectivity in response to violence reveals unique influences of individual differences in **psychopathic** traits in a nonforensic sample	F	C/R	n/a	n/a	n/a
Zijlmans	2018	Neural correlates of moral evaluation and **psychopathic** traits in male multi-problem young adults	F	C/R	n/a	n/a	n/a

P psychopathy, *S* structural, *F* functional, *C/R* correlation or regression analysis, *BG* between-group analysis, *n/a* not applicable or data not available

27.1 Neuroimaging Data on Psychopathy: Summary of Results

Neuroimaging studies to date have highlighted brain regions that may be the most theoretically meaningful to psychopathy. However, reliance on primarily theory-driven analyses may obscure the significance of other relevant brain circuits. To this end, recent meta-analyses have attempted to specify brain regions consistently associated with psychopathy across studies. We present first the regions commonly highlighted by individual neuroimaging studies of psychopathy, followed by the results of the recent meta-analyses.

The neuroimaging studies of psychopathy can be divided into "structural" studies, which assess brain morphology, and "functional" studies, which assess brain activity (Table 27.1). Structural neuroimaging studies associate psychopathy with a host of morphological brain abnormalities: reduced volume of the amygdala (Boccardi et al. 2011; Ermer et al. 2012; Yang et al. 2009, 2010; Contreras-Rodríguez et al. 2015); reduced volume of the basolateral nucleus of the amygdala and increased volume of the central and lateral nuclei of the amygdala (Boccardi et al. 2011); reduced gray matter volume in the frontal cortex, especially the orbitofrontal cortex, the frontopolar cortex, the anterior rostral prefrontal cortex, and the right inferior frontal gyrus (Boccardi et al. 2011; Ermer et al. 2012; Yang et al. 2005b, 2010, 2011; de Oliveira-Souza et al. 2008; Gregory et al. 2012; Ly et al. 2012; Müller et al. 2008a); reduced volume of the dorsal anterior cingulate cortex and bilateral precentral gyri (Ly et al. 2012); reduced volume of the temporal cortex, especially the right superior temporal gyrus, anterior temporal cortices, superior temporal sulcus, and bilateral temporal pole (Ermer et al. 2012; de Oliveira-Souza et al. 2008; Gregory et al. 2012; Ly et al. 2012; Müller et al. 2008a; Yang et al. 2011; Kolla et al. 2014); reduced volume of midline cortical structures (Boccardi et al. 2011); reduced volume of the posterior cingulate cortex (Ermer et al. 2012); increased volume of the striatum, particularly the nucleus accumbens (Glenn et al. 2010; Korponay et al. 2016; Pujara et al. 2014; Leutgeb et al. 2015); increased volume of the corpus callosum (Raine et al. 2003); reduced volume of the posterior hippocampus (Laakso et al. 2001); normal volume but abnormal shape of the hippocampus (Boccardi et al. 2010); reduced volume of the parahippocampal regions (Ermer et al. 2012); reduced volume of the insula (de Oliveira-Souza et al. 2008; Gregory et al. 2012; Ly et al. 2012); presence of cavum septum pellucidum (Raine et al. 2010; Crooks et al. 2018); and reduced structural integrity of the uncinate fasciculus (Craig et al. 2009; Motzkin et al. 2011). Overall these studies link psychopathy with a variety of structural abnormalities within frontal and temporal areas, involving cortical and subcortical gray matter structures as well as white matter pathways. The identified structures play important roles in emotion and social cognition (amygdala, superior temporal cortex, uncinate fasciculus) as well as learning and memory (striatum, hippocampus). But within this broad functional/anatomical grouping of the study results, the available structural imaging data have not yet demonstrated reliable, replicated structural abnormalities in many of the identified brain regions.

Functional imaging studies measure brain activity, either at "rest" or during a particular cognitive task. In psychopathy research, functional imaging studies have typically featured tasks involving social and/or emotional processing, such as fear conditioning (Birbaumer et al. 2005; Schultz et al. 2016; Larson et al. 2013), viewing facial expressions of emotion (Carré et al. 2013; Deeley et al. 2006; Gordon et al. 2004; Contreras-Rodríguez et al. 2014; Decety et al. 2013a, 2014; Mier et al. 2014; Sethi et al. 2018), emotion attribution (Mier et al. 2014; Sommer et al. 2010; Meffert et al. 2013), moral judgment (Glenn et al. 2009; Harenski et al. 2009, 2010, 2014; Pujol et al. 2012; Decety et al. 2015; Fede et al. 2016; Yoder et al. 2015; Zijlmans et al. 2018), identification of emotionally salient words (Intrator et al. 1997), memory for emotionally salient words (Kiehl et al. 2001), selective attention and emotional processing during an emotion-word Stroop task (Sadeh et al. 2013), viewing emotionally salient scenes (Müller et al. 2003, 2008b; Shane and Groat 2018), social cooperation (Rilling et al. 2007), anticipation and/or receipt of reward (Pujara et al. 2014; Carré et al. 2013; Bjork et al. 2011; Buckholtz et al. 2010; Gregory et al. 2015; Hosking et al. 2017), punishment administration (Veit et al. 2010; Molenberghs et al. 2014), economic decision-making (Vieira et al. 2014), reversal learning (Gregory et al. 2015) response inhibition during a go/no-go task (Freeman et al. 2015; Rodman et al. 2016), viewing images of others in pain (Decety et al. 2013a, b), salience processing during an auditory oddball task (Anderson et al. 2018), viewing drug-related images (Cope et al. 2014; Denomme et al. 2018), and dishonest decision-making (Abe et al. 2018). Accordingly, many of these studies focus their analyses on emotion-related regions of interest, such as the amygdala (Birbaumer et al. 2005; Carré et al. 2013; Gordon et al. 2004; Mier et al. 2014; Sethi et al. 2018; Glenn et al. 2009; Fede et al. 2016; Harenski et al. 2014; Zijlmans et al. 2018; Kiehl et al. 2001; Rilling et al. 2007; Decety et al. 2013b; Cope et al. 2014). However, the imaging results indicate that psychopathy is associated with abnormal activity in widespread areas of the brain, not just those associated with emotional processing. Reduced activity has been observed in limbic and paralimbic areas, including the amygdala (Birbaumer et al. 2005; Carré et al. 2013; Mier et al. 2014; Sethi et al. 2018; Glenn et al. 2009; Harenski et al. 2014; Yoder et al. 2015; Kiehl et al. 2001; Shane and Groat 2018; Rilling et al. 2007), hippocampus and parahippocampal gyri (Kiehl et al. 2001; Müller et al. 2003; Shane and Groat 2018), anterior and posterior cingulate cortex (Birbaumer et al. 2005; Sethi et al. 2018; Decety et al. 2015; Fede et al. 2016; Harenski et al. 2014; Yoder et al. 2015; Kiehl et al. 2001; Müller et al. 2003; Rilling et al. 2007; Abe et al. 2018), ventral striatum (Kiehl et al. 2001), and insula (Birbaumer et al. 2005; Sethi et al. 2018; Meffert et al. 2013; Decety et al. 2013b, 2015; Shane and Groat 2018; Molenberghs et al. 2014). On the other hand, reduced activity has also been observed in association areas within frontal and temporal cortices (Birbaumer et al. 2005; Gordon et al. 2004; Mier et al. 2014; Müller et al. 2003, 2008b; Rilling et al. 2007; Molenberghs et al. 2014), as well as sensory areas such as posterior visual cortices (Deeley et al. 2006; Decety et al. 2014; Harenski et al. 2014; Müller et al. 2003) and parietal somatosensory cortex (Birbaumer et al. 2005; Deeley et al. 2006; Meffert et al. 2013), and motor structures such as the cerebellum (Deeley et al. 2006) and primary

motor cortex (Deeley et al. 2006). Increased activity has been observed in the frontal and temporal cortices (Decety et al. 2013a, b, 2015; Intrator et al. 1997; Kiehl et al. 2001; Müller et al. 2003), nucleus accumbens (Bjork et al. 2011; Buckholtz et al. 2010; Hosking et al. 2017; Decety et al. 2013b), as well as areas of the parietal lobe, occipital lobe, cerebellum, cingulate cortex, and amygdala (Müller et al. 2003). Functional imaging studies may also assess the correlated activity, or "functional connectivity," between various brain regions at rest or during a task. Psychopathy was associated with connectivity among brain regions known as the "default mode network," which includes the medial prefrontal cortex, posterior cingulate, and the inferior parietal lobule; frontoparietal connectivity; and a visual/posterior cingulate connectivity during an auditory "oddball" task (Juarez et al. 2013). Further, amygdala dysfunction in psychopaths during a task of moral decision-making was associated with reduced functional connectivity between the amygdala and the striatum (Osumi et al. 2012). At rest, psychopaths exhibit a reduction in functional connectivity between the left insula and dorsal ACC, the vmPFC and the amygdala, the vmPFC and medial parietal cortex, and the posterior cingulate cortex and anterior frontal cortical areas (Ly et al. 2012; Motzkin et al. 2011; Pujol et al. 2012; Waller et al. 2019). Taken together, these functional imaging data associate psychopathy with abnormal activity in limbic, subcortical, and cortical structures. As such, it is difficult to group the findings in any particular functional domain.

An intriguing observation is that, depending on the experimental context, the same brain area could be reported as either hypo- or hyperactive. For example, ventral striatum activity was abnormally low during memory for emotionally salient words (Kiehl et al. 2001), but abnormally high during reward anticipation (Bjork et al. 2011; Buckholtz et al. 2010). Similarly, amygdala activity was abnormally low during moral decision-making (Glenn et al. 2009), social cooperation (Rilling et al. 2007), viewing facial expressions of fear (Carré et al. 2013; Dolan and Fullam 2009), and memory for emotionally salient words (Kiehl et al. 2001), but abnormally high during the viewing of certain emotionally salient scenes (Müller et al. 2003) and facial expressions of anger (Carré et al. 2013). Furthermore, two studies employing ostensibly the same task, fear conditioning, though with different stimuli and definitions of psychopathy, found opposing results: abnormally low (Birbaumer et al. 2005) and abnormally high amygdala activity (Schultz et al. 2016). These results suggest that neural processing abnormalities in psychopathy may be significantly context-dependent. In other words, there is not yet clear evidence for a particular area being persistently hypo- or hyperactive; the functional activation data associated with psychopathy seem to depend critically on the experimenters' selection of tasks and stimuli. Recent evidence that neural structures such as the amygdala may switch affective mode (i.e., positive or negative, appetitive or avoidant) across situations could guide future investigations of the context-dependent nature of neural dysfunction in psychopathy (Berridge 2019).

Meta-analysis of whole-brain fMRI studies can identify regions consistently hypo- or hyperactive in psychopathy. Of the regions described above, only one was consistently related to psychopathy in one meta-analysis (Poeppl et al. 2018): right

amygdala activity was abnormally low. This meta-analysis also found abnormally low activity in the bilateral dorsolateral prefrontal cortex and left dorsomedial prefrontal cortex and abnormally high activity in the bilateral fronto-insular cortex. However, caution should be used when interpreting these findings, as the meta-analysis grouped studies of the construct of psychopathy with studies of distinct subsets of psychopathic traits (Latzman et al. 2019), a methodological issue that we discuss in further detail below. In fact, a more recent meta-analysis, which avoided this methodological issue, failed to replicate these findings and even observed relationships in the opposite direction to the prior meta-analytic findings (Deming and Koenigs 2020). For example, the recent meta-analysis found abnormally high activity in right amygdala, in direct contrast to the previous meta-analytic findings of abnormally low activity in the right amygdala. The recent meta-analysis further found hyperactivity in medial regions of the default mode network (including dorsomedial prefrontal cortex, posterior cingulate, and precuneus) and hypoactivity in a key node of the salience network (dorsal anterior cingulate) across a variety of experimental tasks. Future studies characterizing the complex nature of amygdala function and studies further exploring the dynamic interactions between intrinsic brain networks (including default mode network and salience network) will make substantial contributions to our understanding of the neural correlates of psychopathy.

In sum, the structural and functional abnormalities associated with psychopathy are widespread and rather variable, although regions within frontal and temporal lobe appear to be the most commonly identified in both types of study. Given the broad array of imaging results, it is reasonable to ask whether differences in methodology could account for some of the variability in the findings. In the following sections we highlight three methodological issues that could potentially limit the consistency and generalizability of results across the imaging studies.

27.2 Methodological Issues

27.2.1 Two Different Uses of the Term "Psychopathy"

One issue that could contribute to heterogeneity in the psychopathy imaging data concerns the use of the term "psychopathy." In the neuroimaging literature, the term "psychopathy" is commonly used at least two ways. In one usage, "psychopathy" denotes the condition of being a psychopath, implying a categorical designation that corresponds to the early predominant usage of the term in the clinical literature (Cleckley 1941; Lykken 1957; Karpman 1946). In studies employing this usage, the data analysis strategy typically involves between-group comparisons of neuroimaging data (i.e., psychopaths versus non-psychopaths; see Table 27.1). In the second usage, "psychopathy" denotes the degree of psychopathy. This usage can pertain to a "normal" sample of individuals, such as a community or university student sample, of which few, if any, would actually be diagnosed as psychopaths. In studies employing this usage, the data analysis strategy typically involves correlation or

regression analyses between a psychopathy score[1] and one or more neuroimaging measures (see Table 27.1). Importantly, the reported brain-behavior associations in this type of correlational analysis may depend substantially (if not entirely) on individuals within the normal range of social behavior. The implicit assumption of this correlational approach is that normal variation in certain social/affective/behavioral traits (as indexed by normal subjects' self-report scores on psychopathy questionnaires) is associated with variation in the activity of the same brain areas that are dysfunctional in severely psychopathic individuals. Although there are ample clinical and behavioral data suggesting that psychopathic traits do in fact fall along a continuum—with psychopaths representing a quantitatively greater manifestation of the traits rather than a qualitatively distinct category (Edens et al. 2006; Marcus et al. 2004; Walters et al. 2007, 2008)—there is not yet strong evidence to support the assumption that the neurobiological data are similarly continuous.

By analogy, consider the use of neuroimaging to identify the neural correlates of depression. Studies that compare the brain activity of clinically depressed patients with psychiatrically healthy individuals have associated depression with abnormal activity in several areas of the brain, including the subgenual cingulate cortex, dorsolateral prefrontal cortex, and dorsal anterior cingulate (Greicius et al. 2007; Johnstone et al. 2007; Mayberg et al. 2005). A separate study that correlated individual variation in the experience of negative affect with brain activity among psychiatrically healthy individuals identified an area of the ventromedial prefrontal cortex (adjacent to the subgenual cingulate), but did not identify the more dorsal frontal areas (Zald et al. 2002). These data indicate that normal variation in a particular trait is not necessarily associated with the same brain areas that are dysfunctional in the extreme pathological manifestation of the trait. The application of this logic to psychopathy research prescribes that the identification of brain areas associated with normal variation in certain social/affective/behavioral traits should not necessarily be used as evidence for the dysfunction of these areas in severely psychopathic individuals.

As a specific example of how this issue may complicate the interpretation of psychopathy neuroimaging data, consider findings on activity in the ventral striatum, a critical brain area in processing reward and positive emotion. Comparing a group of criminal psychopaths with a group of criminal non-psychopaths, Kiehl et al. found reduced activity in the ventral striatum among the psychopaths (Kiehl et al. 2001). Conducting a correlational analysis across a community sample of psychologically healthy individuals, Buckholtz et al. found that greater levels of "psychopathic" traits (impulsive-antisocial) were associated with increased activity in the ventral striatum in the anticipation of reward (Buckholtz et al. 2010). Another study found a similar association between "psychopathic" traits and ventral striatum

[1] Note that the data entered into such correlational analyses may be overall psychopathy scores (Glenn et al. 2009) or scores on a particular dimension or "factor" of psychopathy, such as antisocial impulsivity (Buckholtz et al. 2010) or the interpersonal factor (Glenn et al. 2009). Differences in the exact "psychopathic" traits being analyzed may also contribute to the heterogeneity of results regarding the neural correlates of psychopathy.

activity in response to the anticipation of reward (Bjork et al. 2011). One possibility is that the difference in findings could be due to the different task demands in each study (memory for emotionally salient words vs. reward anticipation). A second possibility is that the ventral striatum may respond differently in psychopaths than it does within the continuum of psychologically normal individuals. The Buckholtz et al. data seem to predict that a group of psychopaths would exhibit increased activity in the ventral striatum (relative to non-psychopaths) during reward anticipation (Buckholtz et al. 2010). However, one study comparing a group of criminal psychopaths to non-psychopaths on a task involving the passive receipt of reward found that psychopaths and non-psychopaths did *not* differ in ventral striatal response to monetary reward (Pujara et al. 2014). Instead, PCL-R score was positively correlated with ventral striatal response to reward only in the psychopathic group but not the non-psychopathic group. This finding clearly does not support the rationale for inferring neural correlates of psychopathy through the study of psychologically normal individuals.

To conclude our discussion of this point, we offer a suggestion that researchers be mindful of the characteristics of their subject sample and specify in their conclusions whether the neuroimaging data pertain to psychopaths, per se, or to normal variation in certain social/affective/behavioral traits.

27.2.2 Inconsistent Criteria for Identifying Psychopaths

A second issue that may contribute to heterogeneity in psychopathy imaging data is inconsistency in the procedures for evaluating and identifying psychopaths. Most neuroimaging investigations of psychopathy rely on the Hare Psychopathy Checklist-Revised (PCL-R) (Hare 2003) to define psychopathy. The PCL-R is a list of 20 psychopathic traits/behaviors that are scored from 0 to 2 based on the degree to which the subject exhibits the item, and thus total scores range from 0 to 40. PCL-R scores are ideally determined on the basis of a semi-structured interview and review of file information such as criminal records, employment records, school records, and collateral reports. However, studies involving non-incarcerated samples may lack access to detailed file information (e.g., Glenn et al. 2010; Raine et al. 2003; Yang et al. 2009). The PCL-R manual advises cutoff scores for grouping subjects: total scores of 30 or greater indicate psychopathy, scores of 20 or less indicate non-psychopathy, and scores of 21–29 are considered intermediate[2] (Hare 2003). In reviewing the methods of the published imaging studies on "psychopaths" (see Table 27.1), we found that this recommendation was followed in approximately one-third of categorical studies of psychopathy (Boccardi et al. 2011, 2013; Pujara et al. 2014; Motzkin et al. 2011; Schultz et al. 2016; Larson et al. 2013; Decety et al. 2013a, b, 2014, 2015; Harenski et al. 2010; Müller et al. 2003; Shane and Groat

[2] These PCL-R cutoff scores were developed with North American subject samples. A slightly lower psychopathy cutoff score (e.g., 28) may be appropriate for European samples (Hare et al. 2000).

2018; Juarez et al. 2013). Instead, researchers have routinely employed a variety of minimum PCL-R total scores, often in the mid-20s, to define psychopathy. Because the proportion of individuals with PCL-R scores in the mid- to upper 20s is much higher than the proportion of individuals with PCL-R scores above 30, using a cut-off score in the mid-20s could potentially result in a group of "psychopaths" among which the majority would have PCL-R scores below 30. This supposition is borne out by the data from the imaging studies. For the groups of "psychopaths" reported in the aforementioned imaging studies, 19 had mean PCL-R scores below 30 (see Table 27.1).

These inconsistent and relatively lenient criteria could substantially impact the variability and reproducibility of the imaging study results. A previous psychophysiological study found that subjects with intermediate PCL-R scores (21–29, mean = 25.8) exhibit significantly different patterns of emotion-modulated startle from subjects with PCL-R scores above the suggested cutoff (≥30, mean = 33.3) but very similar patterns of emotion-modulated startle to non-psychopaths (PCL-R scores ≤20, mean = 13.4) (Patrick et al. 1993). These data suggest that individuals with intermediate PCL-R scores (in the 20s) are more similar, at least in terms of affective psychophysiological responses, to non-psychopaths (PCL-R ≤ 20) than to psychopaths (PCL-R ≥ 30). If the neuroimaging data mirror these psychophysiological data, then the routine use of PCL-R cutoff scores in the 20s to define "psychopathic" subject groups has likely resulted in seriously obscured results.

As a specific example, consider the results of two functional imaging studies in which subjects viewed pictures with negative emotional content—fearful faces (Deeley et al. 2006) or a set of negatively valenced pictures that included faces (Müller et al. 2003). Müller et al. classified subjects as psychopaths if their PCL-R scores were greater than 30 (Müller et al. 2003); Deeley et al. used a more liberal threshold of 25 or greater (Deeley et al. 2006). The imaging results differed considerably. Deeley et al. found between-group differences in the cerebellum, fusiform gyrus, and postcentral gyrus (Deeley et al. 2006). For each of these areas, activity was greater in the non-psychopathic group than the psychopathic group; there were no brain areas where psychopaths exhibited greater levels of activity. By contrast, Müller et al. found that psychopaths had greater levels of activity in widespread areas of the brain, including the medial temporal lobe, occipital and parietal cortex, precentral gyrus, superior temporal gyrus, inferior and medial frontal gyri, anterior cingulate, and amygdala (Müller et al. 2003). The vast differences in imaging results could be due to a number of differences in study design; however, as we describe above, the difference in psychopathic subject classification may contribute substantially to the divergent results.

Judicious subject classification is particularly germane to this field given the small sizes of psychopathic samples. Of the 51 imaging studies that define a group of psychopaths (regardless of inclusion criteria), 19 have samples of $n = 15$ psychopaths or less (Table 27.1). The 15 imaging studies that use the advised PCL-R cutoff score (30 or greater) have psychopathic sample sizes ranging from $n = 6$ to $n = 38$, respectively. Thus, at present there are insufficient data available to evaluate whether the use of more stringent PCL-R cutoff scores yields more consistent results. Given

the small number of studies that actually used a PCL-R cutoff of 30 and the relatively small sample sizes within those studies, there is clearly a pressing need for imaging studies featuring larger samples of individuals with exceptionally high PCL-R scores. The recruitment of subjects with exceptionally high PCL-R scores may be costly and time-consuming, but in the long run, the field of psychopathy research will benefit from more uniform standards for subject classification. In our view, a more rigorous collective effort in this regard will facilitate the integration of reliable neuroimaging results with each other as well as with the clinical and psychological literatures on psychopathy.

27.2.3 Consideration of Psychopathic Subtypes

A third issue that may be contributing to the inconsistent imaging results in psychopathy is that psychopathy may consist of multiple distinct subtypes. The question of whether and how to subtype in psychopathy is nearly as old as the field of psychopathy research itself. Early work in this area described a theoretical distinction between "primary" and "secondary" psychopathy, based on the presumed etiology of the disorder as an innate versus an acquired disturbance of social-affective behavior (Karpman 1946, 1948). More recent empirical research demonstrates that subdividing psychopaths on certain personality characteristics reveals significant behavioral and psychophysiological differences between psychopathic subgroups. Perhaps the most widely published means of subdividing psychopaths is on the basis of trait levels of anxiety and negative affectivity. Low-anxious, but not necessarily high-anxious, psychopaths have been documented to show abnormalities (relative to non-psychopaths) on a variety of laboratory measures, including tests of approach or avoidance learning (Lykken 1957; Arnett et al. 1993, 1997; Newman et al. 1990; Schmauk 1970), delay of gratification (Newman et al. 1992), executive function (Smith et al. 1992), cued attention (Zeier et al. 2009), and economic decision-making (Koenigs et al. 2010). Taken together, these studies suggest that low-anxious psychopaths and high-anxious psychopaths have certain distinct behavioral and psychophysiological characteristics, despite similar overall levels of psychopathy. If these subgroups also have distinct neurobiological characteristics, and if the samples of psychopathic subjects in neuroimaging studies regularly contain a significant proportion of each subtype, then one might expect that the data would fail to show a consistent neurobiological defect. It seems that this has indeed been the case; as detailed above, there are few replicated neuroimaging findings in psychopathy. To date, only three neuroimaging studies of psychopathy have employed this subtyping strategy (Motzkin et al. 2011; Schultz et al. 2016; Sethi et al. 2018).

The potential importance of considering subgroups within a psychopathological disorder, with respect to understanding the neuroimaging correlates of the disorder, is illustrated by studies of frontal lobe dysfunction in schizophrenia. The initial neuroimaging research on this topic generated inconsistent and ostensibly conflicting results. Several studies reported PFC hypoactivation among individuals with schizophrenia (e.g., Barch et al. 2001; Carter et al. 1998; Perlstein et al. 2001),

whereas other studies reported no difference (Honey et al. 2002) or even PFC hyperactivation (e.g., Callicott et al. 2000; Manoach et al. 2000; Manoach et al. 1999). This apparent discrepancy has been addressed through the consideration of key differences *within* the schizophrenia patient group. For example, schizophrenia patients with significant working memory impairments typically exhibit PFC hypoactivity relative to controls, whereas patients with less impairment exhibit PFC hyperactivity (Manoach 2003). Moreover, PFC hypoactivity has been specifically associated with symptoms of "disorganization" (one of the three main symptom clusters of schizophrenia) (Perlstein et al. 2001). Thus, even though all patients with schizophrenia share the same diagnosis and a certain degree of overlapping symptoms, the subdivision of patients based on important differences in their neuropsychological test performance and their specific symptom profiles has proven to be a pivotal step in clarifying the neural correlates of the disorder. By analogy, the clarification of the neural correlates of psychopathy may similarly depend on the identification of one or more key variables that distinguish psychopathic subtypes.

To summarize this point, across many psychopathologies, the decision of whether and how to subtype is an issue. It is not always easy or necessary (depending on the research question) to examine disorders at this level. However, given the existing evidence that indicates significant behavioral and psychophysiological differences between certain psychopathic subgroups, it is perhaps worthwhile to consider subtyping in the neurobiological study of psychopathy. Employing this approach in future imaging studies may reduce the heterogeneity of the results and provide a more refined understanding of the disorder.

27.3 Conclusion

The elucidation of the neural correlates of psychopathy could have profound implications for the clinical and legal management of psychopaths, as well as for our basic understanding of the biological substrates underlying human social behavior. In this article we sought to provide a critical review of structural and functional imaging studies aimed at identifying the neurobiological abnormalities associated with psychopathy. To date, the results are highly variable. Within the broad array of data, one can find qualified support for theories highlighting the importance of emotion-related circuits in the brain, such as the ventromedial prefrontal cortex and amygdala (Blair 2007, 2008) or a wider "paralimbic" system[3] (Kiehl 2006). Alternatively one may view the heterogeneous collection of neuroimaging abnormalities, many of which are outside the canonical emotion circuits, as evidence for widespread, context-dependent neural deficits in information processing or integration (Newman et al. 2010).

[3] In addition to proposing dysfunction in areas preferentially involved in affective processing, Kiehl's "paralimbic hypothesis" also proposes a dysfunction in spatially distributed areas involved in language and attentional orienting.

Given the remarkable heterogeneity of imaging results, it is perhaps premature to interpret certain findings as support for any particular theoretical viewpoint. Instead, it may be instructive to first evaluate whether differences in study methodology could account for some of the variability in the findings. To this end we have raised a number of methodological considerations that may help explain some of the heterogeneity of data. For example, we noted that psychopathy imaging studies have employed a variety of design and analysis strategies. Among the structural imaging studies, some have measured regional volumes, whereas others have measured the integrity of white matter pathways. Among functional imaging studies, some have used complex decision-making tasks whereas others have used simple passive viewing tasks. Among both structural and functional imaging studies, some have focused their analyses on predetermined regions-of-interest whereas others have reported effects throughout the brain. In addition, sample size (and hence statistical power) varies significantly among studies. These differences in study methodology could certainly contribute to some degree of heterogeneity in the psychopathy imaging data; indeed, these issues are relevant for interpreting neuroimaging results for any type of psychopathology. The focus of the present chapter is to identify issues that are especially germane to neuroimaging studies of psychopathy. We have described three such issues in this review. One issue is whether the study identifies neurobiological differences between groups (psychopaths vs. non-psychopaths), or instead identifies brain areas associated with normal variation in social or affective traits among psychologically healthy individuals. The available evidence suggests that findings from these two different types of study may not be equally informative with respect to the neurobiology of psychopathy. A second issue is the consistency of criteria for classifying subjects as psychopaths—varying stringency in PCL-R cutoff scores between studies means varying levels of psychopathic behavior between study groups and, quite possibly, varying imaging findings. The use of more uniform standards for subject classification will facilitate a more straightforward comparison of results across studies. A third issue is the consideration of psychopathic subtypes. It could be that psychopaths consist of multiple subtypes (e.g., low-anxious vs. high anxious) that have distinct neurobiological profiles. Neuroimaging data could provide key evidence to support or refute this hypothesis.

Neuroimaging research on psychopathy is a burgeoning field with immense promise but also significant methodological challenges. We are optimistic that as future imaging studies of psychopathy employ more rigorous and judicious standards for evaluating and classifying subjects, the brain anomalies characterizing psychopathy will become more clear. In turn, the more precise imaging results will illuminate the psychobiological mechanisms underlying psychopathy.

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Mapping and Imaging the Aggressive Brain in Animals and Humans

28

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Abstract

Inappropriate interpersonal aggression and disruptive violent outbursts are common problematic symptoms of multiple psychiatric disorders and represent a significant global health issue. Current therapeutic strategies are limited due to a lack of understanding about the neural and molecular mechanisms underlying the "vicious" shift of normal adaptive aggression into violence. However, the advent of new neuroimaging tools for measuring human brain function, structure, chemistry, and connectivity together with the rapidly emerging preclinical tools for mapping, measuring, and manipulating discrete neuronal activity in the animal brain significantly advances our understanding of the precise neural microcircuitry and its dynamic neurochemical functioning underlying the initiation, execution, and termination of aggressive behavior. This chapter presents our current knowledge of the brain regions/circuits and neuromolecular signaling mechanisms underlying the regulation of aggressive behaviors, obtained from both animal research and clinical studies with special attention for the contribution of PET/SPECT neuroimaging tools. The highly detailed picture of the neural and molecular underpinnings of aggression obtained from preclinical animal studies is compared with the more global neuroimaging data from clinical studies, underscoring similarities, reconciling inconsistencies, and addressing putative gaps between the two fields of research.

28.1 General Introduction Aggressive and Violent Behavior

Across the animal kingdom, aggression is the behavioral weapon of choice for individuals to gain and maintain access to desired resources (food, territory, mating partners), defend themselves and their progeny from rivals and predators, and establish and secure social status/hierarchical relationships. Obviously, engaging in aggressive behaviors is risky for an individual, as it must weigh the potential benefits of winning (greater access to mates, territory, resources) against the potential costs of fighting (injury, death, loss of social status). Clearly from a biological point of view, aggressive behavior is considered a highly functional form of social communication leading to active control of resources and the social environment, and thus essential for individual and population survival explaining its evolutionary preservation. It is characterized by a ritualized set of species-specific stereotypical motor patterns performed in close interaction with another individual (Tinbergen 1951). In rodents, offensive aggressive behavior usually progresses from a variable preparatory or appetitive phase that involves approach/investigatory actions and diverse threatening displays signaling aggressive intentions to the more rigid consummatory phase that involves intense physical attack behaviors like kicking, biting, lunging, and chasing.

28.1.1 Different forms of agression in animals and humans

Importantly, two major types of aggression are recognized in both animals (offense and defense) and humans (proactive and reactive) that differ in motor patterns,

eliciting factors, neural pathways, development, and function. While animal *offensive* aggressiveness is a form of agonistic behavior initiated by an aggressor and displayed in the context of competition for resources, *defensive* aggression is elicited in response to threat or attack by an offensive conspecific or predator. For example, an offensive male may compete with other males for food, status, or females. An animal that is attacked by either a dominant male or a predator performs defensive aggression. For offense, the motor patterns are approach, offensive upright/sideways posture, attacks (simple bites or bite and kick), chase, piloerection, and tooth chattering (mainly in rats) or tail rattling (mostly in mice). In the minutes leading up to intense attack bites, the resident animal emits brief pulses of ultrasonic vocalizations in the 50 kHz ranges that may reflect high excitement (affiliative function). The bite targets are primarily the hindquarters of the flanks, back, and base of the tail (less-vulnerable body regions). The function is to obtain and retain resources like space, food, and mates. For defense, the motor patterns are avoidance/freezing, defensive upright and sideways posture (keep away), flight, and attacks (lunge and bite). These defensive motor acts are usually accompanied with urination/defecation and emittance of 22 kHz ultrasonic vocalizations indicative of fearful or adverse experiences (alarming function). The lunge and attack bite targets are primarily the face (snout), neck, and belly (vulnerable body regions). The function is to defend one's self, mates, and progeny from attacks of another animal of the same or different species. Besides offense and defense, additional subforms of aggressive behavior in animal research are distinguished as well, such as infant-directed aggression or infanticide, predatory aggression, play-fighting (in juvenile animals), and maternal aggression. The latter can be observed in females during the late stages of pregnancy and the early phases of nursing. Predatory aggression is known as quiet-biting attack observed as the swift killing of a mouse or a cricket by a rat.

The most basic acts of physical aggression in humans are hitting, kicking, biting, pushing, grabbing, pulling, shoving, beating, twisting, and choking. Threatening (verbal or otherwise) and using objects (weapons) to aggress are also included into this definition (Tremblay and Szyf 2010). However, two main forms of aggression are also recognized in humans (Vitiello and Stoff 1997; Wrangham 2018; Elbert et al. 2018), and the offensive pattern of aggression in animals generally relates to the "hot-tempered" *impulsive-reactive-hostile-affective* aggression subtype in humans. This form of aggression has its strong emotional engagement and autonomic/neuroendocrine arousal in common with offensive aggression in animals. Moreover, both in animals and humans, this form of aggressive behavior is usually initiated in response to a perceived threat such as the intrusion of an unfamiliar conspecific into the territory or in response to fear and frustration (omission of expected rewards). The second type of human aggression is described as the "cold-blooded" *premeditated-proactive-instrumental* aggression. This latter form of human callous-unemotional aggression seems to resemble more the quiet-biting attack or predatory and infanticide forms of aggressive behavior in rodents. Whereas the *reactive* form of aggression is predominantly seen in patients suffering from depression, drug addiction, schizophrenia, PTSD, Alzheimer, or intermittent

explosive disorder (IED), the *proactive* type of aggression is commonly expressed in habitually violent offenders with personality disorders (conduct, antisocial, or borderline) or psychopathic traits. A lack of differentiation of these two main types of aggression often leads to conflicting results in the literature. Recently, a third form of aggression is being distinguished that may derive from the positive reinforcing effects of repeatedly winning social conflicts and/or dominating social targets. This so-called **appetitive** aggression is characterized by a persistent motivation to seek out and compulsively engage in aggressive interactions for reasons of pleasure, i.e., "lust for violence" (Elbert et al. 2018). Finally, it should be noted that aggression in both animals and humans has to be conceptualized into two components, state-like aggressive behavior and trait-like aggressiveness. Whereas the latter refers to an individual's proneness or history to engage in persistently aggressive displays in various different contexts, state-like aggression refers to the actual execution of aggressive behaviors. This temporal distinction appears to be of crucial importance when linking certain physiological or neurobiological parameters to different mechanisms of aggression (Haller 2017). In particular, the preponderance of PET/SPECT brain imaging studies in humans assesses various ligand binding properties within brain regions of normal or personality-disordered individuals that differ in trait-like forms of aggressiveness. Brain imaging studies during the overt execution of some laboratory tasks that provoke at best mild aggressive-like tendencies (e.g., Taylor aggression paradigm, ultimatum game, point subtraction paradigm, etc.) to assess alterations in the executive neural mechanisms that control aggression are scarce.

28.1.2 Violence Is the Pathology of Functional Aggressive Behavior

Although most individuals engage in social conflicts with appropriate and well-controlled (functional) forms of aggressive behavior, a relatively small proportion of individuals escalates their aggression inappropriately and persistently and/or become extremely violent (maladaptive aggression). This small percentage (ranging from 3 to 7% in humans) of aggressive, antisocial, and violent individuals is a major source of death, social stress, and ensuing disability in the victims, thereby constituting one of the most significant problems for the public health, medical institutions, and criminal justice systems worldwide. Actually, interpersonal violence/aggression is among the leading causes of death worldwide for people aged 15–44 and contributes to 21.7 million disability-adjusted life years (WHO, Global Health Observatory Depository). Violent and pathological forms of aggression are not only observed in our general human society but in particular also clinically, co-morbid across a wide spectrum of DSM-V-defined psychiatric and neurological disorders, and are one of the most distressing and disabling sources of impairment (WHO world report on Violence and Health; DSM-V, American Psychiatric Association). Inappropriate aggressive outbursts and/or the inability to control violent impulses are frequently occurring behavioral symptoms that cut trans diagnostically across a spectrum of mental disorders (e.g., schizophrenia, autism, depression, drug

addiction) and aging-associated neurodegenerative diseases (dementia, Alzheimer, Parkinson), perhaps reflecting a shared underlying component at the level of specific neurons, circuits, and/or genes, as conceptually put forth by the NIH's RDoC (Research Domain Criteria; "units of analysis"). Indeed, a large share of homicides (up to 75%) are committed by people with responsibility diminished to a certain extent by mental illness (Vinkers et al. 2011). These clinical observations have motivated much of the scientific interest in aggressive behavior in animals. However, until a decade ago, most ethological animal studies of aggression have focused mainly on the ultimate and proximate mechanisms of normal adaptive aggressive behavior, while clinically the focus is predominantly on violent individuals and excessive or escalated forms of human aggressiveness. Although long considered to be a typical human proclivity, lethal violent-like forms of aggressive behavior are also expressed in 40% of mammalian species and have significant phylogenetic roots (Gómez et al. 2016). Therefore, translational animal models can be developed that capture the essential features of human violence (Miczek et al. 2013). Pathological aggressive and violent-like behaviors in rats and mice are characterized by operational criteria that include elements that are impulsive (absence of any introductory and exploratory social behavior), excessive (high and persistent levels of attacks), and socially atypical (injurious attack topography, disregard for submissive and appeasement signals, and indiscriminate social targeting). Violence can thus be defined as a pathological form of aggressive behavior that is not subjected to inhibitory control mechanisms and that has lost its function in social communication (i.e., aggression out of control and out of context) (Miczek et al. 2007, 2013; De Boer et al. 2017). Several of these signs and symptoms of violent-like aggressive display are reliably engendered in several novel animal models that have achieved, at least to a variable extent, similarity with human violent aggression in terms of symptomatology and phenomenology (face validity), phylogenetic and ontogenetic origins (construct validity), and response to clinically established treatments (predictive validity) (for review of the various animal models, see De Boer et al. 2009, 2017; Haller 2017; Miczek et al. 2013; Covington 3rd et al. 2019). These animal models of more pathological or violent-like aggressive behavior are aimed at identifying the neural processes that motivate an individual to fight excessively under conditions that would not typically produce intense or prolonged attacks.

28.2 Brain Regions and Neural Circuit Mechanisms Underlying the Regulation of Aggressive Behavior

For well over a century, neuroscientists have sought to understand the neural roots of aggression and violence by perturbing and monitoring brain activity through a variety of methods and in a wide variety of experimental animals such as monkeys, dogs, cats, rats, mice, voles, and hamsters. By employing increasingly sophisticated tools of functional neuroanatomy (i.e., from the classic electrical/chemical lesion and stimulation techniques to neurochemical mapping and manipulations), many important strides have been made in understanding the functional brain circuit

organization of different social (aggression, sex, parental care) behaviors, i.e., the structurally and functionally highly interconnected "social behavior neural network" (SBN) (Newman 1999; Chen and Hong 2018). To more comprehensively delineate this SBN, and particularly the specific neural circuitry involved in aggressive behaviors, determining the pattern of immediate early gene (IEG) expression has been employed successfully over the last two decades. Fos is the protein product of an IEG, *c-fos*, which is rapidly expressed in neurons shortly after their depolarization (activation), and consequent elevation of intracellular free calcium. Fos expression can be visualized using histochemical antibody staining or in situ hybridization techniques, and the number of Fos-positive neurons in each brain area is used to quantify the activation of the area, i.e., Fos as a surrogate marker of neuronal activation. Advantages of IEG mapping are that it has single-cell resolution and can be used to systematically map patterns of activity associated with a particular behavior across the entire brain. In addition, the neurochemical identity of the activated cells can be visualized as well by combining it with antibody staining of cytoplasmic or membrane-bound components of neurotransmitters. The disadvantage is obviously the low temporal resolution (30–60 min); the pattern of *c-fos* activation integrates all of the activity that occurred over a behavioral experiment, making it difficult to assign activity to specific actions or elements of aggressive behavior (i.e., social investigation, sniffing, or fighting per se). Nevertheless, application of this technique in aggression paradigms in rats, mice, and hamsters has revealed in great detail the SBN aggression circuitry that encompasses the intimately interconnected forebrain (limbic) structures: medial amygdala (MeA), bed nucleus of the stria terminalis (BNST), lateral septum (LS), mediodorsal and anterior thalamus, several hypothalamic nuclei including the anterior hypothalamic (AHA)/medial preoptic (MPOA) area, ventromedial hypothalamus (VMH), lateral hypothalamus (LH), the ventral portion of the premammillary nucleus (PMv), and anteroventral periventricular nucleus (AVPV). Evidence suggests that these limbic areas collectively encompass a hierarchical role in the sensory processing and generation of the preparatory/appetitive aspects prior to aggression and the final execution of the consummatory aggressive display sequences (Hashikawa et al. 2018; Anderson 2016). In addition, important "top-down" modulatory control is provided by cortical structures like the orbitofrontal (OFC), medial prefrontal (mPFC), and anterior cingulate cortex (ACC), as well as the ascending midbrain monoaminergic nuclei like the dorsal/medial raphe nucleus (DRN/MRN; serotonin), locus coeruleus (LC; noradrenaline), and ventral tegmental area (VTA; dopamine). The production of the autonomic and somatic motor output aspects of the various aggressive behavioral elements are to a large extent coordinated by the periaqueductal gray area (PAG) (see Fig. 28.1 and de Boer et al. (2015) for a more detailed review of the neuroanatomy of offensive aggression). Application of functional magnetic resonance imaging (fMRI) in awake rats that were provoked to be aggressively aroused in the bore of the MRI magnet, the global brain BOLD activation patterns generally overlapped with this neuroanatomically mapped social aggressive behavioral network (Ferris et al. 2008). Extensive comparative research demonstrated that this highly interconnected neural network for aggressive behavior is remarkably similar

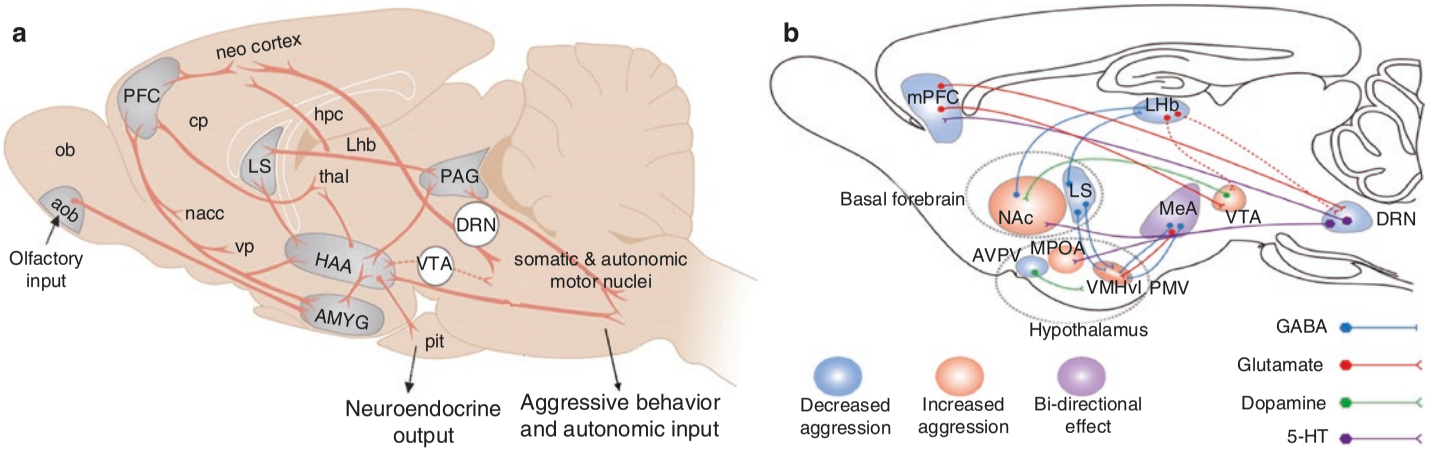

Fig. 28.1 (**a**) Schematic map of the brain areas involved in aggressive behavior. (**b**) Specific neurotransmitter connections that are involved in controlling aggressive behavior (effects on aggression are color coded) in rodents as reviewed in this paper. (Adapted from Aleyasin et al. 2018). *Abbreviations*: *aob* accessory olfactory bulb, *AMYG* amygdala, *cp* caudate putamen, *DRN* dorsal raphe nucleus, *HAA* hypothalamic attack area, which encompasses the *AVPV* anteroventral periventricular nucleus, *SPZ* subparaventricular zone, *MPOA* medial preoptic nucleus, *VMHvl* ventrolateral portion of the ventromedial hypothalamus, *PMV* ventral premammillary nucleus, *hpc* hippocampus, *Lhb* lateral habenula, *LS* lateral septum, *nacc* nucleus accumbens, *ob* main olfactory bulb, *PAG* periaqueductal gray, *PFC* prefrontal cortex, *pit* pituitary, *thal* thalamus, *vp* ventral pallidum, *VTA* ventral tegmental area

in many vertebrate species including human beings, indicating that it is evolutionary ancient and phylogenetically conserved (Goodson 2005; O'Connell and Hofmann 2012). Indeed, this basic brain aggression circuitry (at region level) is generally confirmed in humans by modern brain imaging techniques that allow the in vivo functional/structural (fMRI) analysis of the neuronal nodes/networks and of its associated neurochemistry (PET/SPECT) that are involved in certain types of aggressive behaviors. The brain areas and neural networks that are commonly activated during emotional processing, as well as the structural and functional alterations characterizing subjects with aggressive and antisocial behaviors, can be identified by using a variety of noninvasive imaging techniques (Raine and Yang 2006). For example, molecular imaging techniques used in nuclear medicine, namely, the positron emission tomography (PET) and single-photon emission computed tomography (SPECT), reveal the presence of specific radioactive tracers (injected in the bloodstream) in different brain regions depending on their specific uptake, thus showing the rate of metabolic/functional processes in specific brain regions. In addition, functional magnetic resonance imaging (fMRI) is a generally used tool to investigate the brain function, depending on the cellular oxygen consumption in different brain areas during resting or task-activated states. Below, based on both these preclinical and clinical studies, we further outline the various circuit nodes as well as the numerous neurotransmitter components therein that collectively make up the aggressive brain.

28.3 The Main Nodes/Network Components of the Aggressive Brain

28.3.1 Hypothalamus

Ever since the pioneering knife-cut lesion work of Philip Bard (1928) and the intracranial electrical stimulation experiments of Walter Hess and Bruegger (1943) showing suppression and provoking, respectively, of raging aggressive acts in cats, an extensive series of increasingly sophisticated lesion and electrical stimulation studies delineated the attack area in the medio-basal hypothalamus, hence called the "hypothalamic attack area" (HAA). This HAA consists of a region extending between the caudomedial LH and the ventrolateral VMH rostrally into the anterior hypothalamic/preoptic area (see Kruk (2014) for detailed recent review). While electrical stimulation of the HAA has been reported to induce fierce rivalry attack, stimulating the LH area (lateral to the fornix) promotes more the predatory-like "quiet-biting" attack forms of aggression (Chi and Flynn 1971; Haller 2018). However, despite its anatomical precision, wire electrodes still affect a rather ill-defined population of neurons and fibers of passage that do not allow definite conclusions on the precise causal neuronal and circuit-level mechanisms underlying offensive attack. The brain packs roughly 100,000 neurons and a billion synaptic connections in every cubic millimeter of gray matter tissue, and electrically stimulating or lesioning even a tiny location in the brain will excite/silence a very large

number of intermeshed cells of different kinds. Recently, newly emerging techniques for mapping, measuring, and manipulating neural activity based on genetic targeting of specific neuronal subtypes have solved many of these problems. In particular optogenetic and pharmacogenetic tools have made it possible to rapidly and reversibly activate or inhibit small molecularly distinct populations of neurons (anatomical and genetic precision) at any moment in time (temporal precision). In these methods, a gene that encodes an engineered microbial light-sensitive ion channel (optogenetic effector), or an engineered drug receptor (pharmacogenetic effector), is expressed in a desired subclass of neurons using viral vectors or a heritable transgene. Depending on the type of effector used, the neurons can be activated or inhibited at will in freely behaving animals. Optogenetic effectors are actuated using light of a particular wavelength, delivered into the brain region of interest via an implanted optic fiber (Anderson 2012; Deisseroth 2014). Pharmacogenetic effectors, called DREADDS, are actuated by administration of a designer drug that binds to the engineered receptor; this designer drug does not activate any endogenous receptors, nor do any endogenous ligands activate the synthetic receptor (Rogan and Roth 2011). These revolutionary techniques offer the ability to selectively manipulate distinct neural circuit elements that underlie aggression-relevant behaviors. The first experiments dissecting the microcircuitry of the hypothalamus involved in the regulation of aggression using these new neuronal manipulation tools focused on the ventrolateral subdivision of the VMH, a microscopic area comprised of roughly 10,000 cells. Optogenetic stimulation of these cells in male mice initiated immediate robust offensive attacks directed toward males, castrated males, females, and even inanimate objects (Lin et al. 2011). Accordingly, pharmacogenetic inhibition of these neurons suppressed normal attacks. Subsequent studies have capitalized on the fact that the neurons of the VMHvl are primarily glutaminergic (Choi et al. 2005) and are enriched with estrogen receptors of the alpha subtype (Esr1) and progesterone receptors (PR). Both Esr1/PR-knockout mice and RNAi knockdown of Esr1 in the VMHvl resulted in a dramatic decrease of natural intermale aggression (Sano et al. 2013). Furthermore, optogenetic stimulation of Esr1-expressing VMHvl neurons triggered attack behavior, while optogenetic inhibition suppressed natural fighting, demonstrating that Esr1/PR neurons in this small hypothalamic area are both necessary and sufficient to initiate and terminate bouts of aggression in both male (Lee et al. 2014; Yang et al. 2017) and female mice (Hashikawa et al. 2017). The involvement of Esr1/PR neurons is likely specific, as stimulation of non-Esr1 neurons within the VMHvl is not sufficient to drive aggression (Lee et al. 2014). The essential role of the VMHvl in aggression was further highlighted by in vivo electrophysiological single-unit recording techniques that revealed a prompt and robust increase in VMHvl neuronal activity during natural aggressive behavior (Lin et al. 2011; Falkner et al. 2014, 2016; Hashikawa et al. 2017). To further check whether the VMHvl neurons are also involved in the motivational/preparatory aspects of aggression (appetitive phase) in addition to the established role in initiation/execution of attacks (consummatory phase of aggression), Lin and coworkers adopted an operant responding task to temporally separate the seeking and action phases of aggression (Falkner et al.

2016). Employing in vivo calcium imaging, Lin and colleagues showed that the activity of VMHvl neurons is also increased during aggression-seeking behavior. Furthermore, optogenetic activation/inactivation of these neurons promoted/decreased, respectively, operant responding for access to an intruder that can be attacked (Falkner et al. 2016). These results clearly demonstrated that the role of the VMHvl in aggression extends beyond purely encoding the acute motor commands of fighting and is also involved in the motivational, aggression-seeking aspects. Obviously, the VMHvl is embedded within a larger (extra)-hypothalamic neuronal circuit whose nodes have distinct roles in modulating aggression. The multiple neuronal afferents and efferents of the HAA/VMHvl have been extensively mapped in rats using conventional anterograde and retrograde tracer techniques, thereby already demonstrating its crucial crossroad function to process and organize a wide variety of input and output information (see de Boer et al. (2015) for review). Very recently, the connectional architecture of specifically the Ers1-expressing VMHvl neurons was systematically mapped using six different viral-genetic tracing methods, confirming and extending the early classic track-tracing studies. The data revealed a high level of input convergence and output divergence from and to over 30 distinct brain regions with a high degree of bidirectionality (Lo et al. 2019). Prominent interconnected regions are several other hypothalamic (MPOA, AHA, AVPV, and PMV) and limbic (BNST, MEA, LS, mPFC, SUBv) areas that are well-known to be involved in controlling aggressive behavior, as well as some brain stem "aggression hotspots" (PAGvl, VTA, MRN). Below, we shortly summarize the roles of these other nodes within this extended neural circuit that project to the VMHvl. The MPOA, AHA, and PMV are three other important hypothalamic subareas of the global HAA that, already based on classic lesion/stimulation studies, have been implicated in regulating aggressive behaviors (Adams 2006; Ferris et al. 1997; Kruk 2014 for review; Motta et al. 2013). Recent optogenetic interrogations confirmed and extended their involvement and more precisely dissected the specific neuronal populations that modulate aggressive behavior, i.e., estrogen receptor beta (ER2)-expressing (Nakata et al. 2016) and galanin-containing neurons in the MPOA (Wu et al. 2014), tyrosine hydroxylase (TH)-expressing neurons in the AVPV (Scott et al. 2015), dopamine transporter (DAT)-expressing excitatory neurons in the PMV (Soden et al. 2016; Stagkourakis et al. 2018), and GABAergic neurons in the subparaventricular (SPZ) zone (Todd et al. 2018). This latter projection to the VMHvl seems essential for controlling the daily rhythm of aggression.

Although considerable understudied, there is clear evidence from several lesion and electrical stimulation studies in humans that the hypothalamus is also involved in mediating aggressive behavior similar to that seen in laboratory animals. For example, lesioning the posteromedial hypothalamic area successfully reduced or abolished excessive aggressiveness in violent patients (Sano and Mayanagi 1988; Dieckmann et al. 1988; Ramamurthi 1988; Pedrosa-Sanchez and Sola 2003; Weissenberger et al. 2001; De Almeida et al. 2008; Franzini et al. 2010), while a case study reported that electrical stimulation of this same hypothalamic area induces aggressive outbursts (Bejjani et al. 2002). Only two neuroimaging studies are available that present opposite results: One study shows that the hypothalamus

is more activated in individuals with aggressive features, while the second demonstrates that domestic violence offenders present lower metabolism in this region (George et al. 2004; Van den Stock et al. 2015). Unfortunately, the preponderance of human neuroimaging studies does not include the hypothalamic area and/or subareas as their region of interest, but rather are mainly focusing on temporal (amygdala) and cortical (prefrontal/cingulate) regions.

28.3.2 Amygdala/BNST

The amygdala is an important medial temporal lobe structure that consists of a range of interconnected nuclei having a common output through the central nucleus and the bed nucleus of the stria terminalis (BNST). Generally, it plays an essential role in the processing of a wide range of salient sensory stimuli and mediating autonomic, neuroendocrine, and behavioral responses that enable an organism to adapt to social and environmental challenges (LeDoux 2007). The amygdala, together with the frontal lobe (see below), is one of the brain regions that is consistently identified as showing altered activity in brain imaging studies of pathological aggressive and antisocial individuals. Human amygdala stimulation increases aggression (Vaernet and Madsen 1970), while numerous older studies have reported reductions in the severity and frequency of aggressive behavior after amygdalotomy (see Gouveia et al. (2019) for recent review). More recent MRI imaging studies revealed that adults and youths with psychopathic traits (i.e., premeditated aggressiveness) have reduced amygdala volume (Yang et al. 2009; Pardini et al. 2014) and functioning (Birbaumer et al. 2005; Glenn and Raine 2009), whereas individuals with more impulsive, reactive forms of aggression demonstrate exaggerated amygdala reactivity (Coccaro et al. 2007; Raine 2018; Da Cunha-Bang et al. 2017b). In a study conducted by Schiffer et al. (2011), non-offenders and violent offenders were examined in the forensic setting through MRI imaging. Interestingly, violent offenders presented a larger gray matter volume in the amygdala bilaterally, left nucleus accumbens, and right caudate head and decreased gray matter volume in the left insula. Additionally, regression analysis demonstrated that alterations in gray matter volume that discriminated violent offenders from non-offenders were correlated with psychopathy scores and lifelong aggressive behavior scores Schiffer et al. (2011).

Animal experiments, already at the end of the nineteenth century, showed that large electrolytic lesions of the amygdala had a strong taming effect in feral animals; even the most aggressive animal became docile and submissive by a bilateral amygdala lesion (Goltz 1884; Kluver and Bucy 1937; Rosvold et al. 1954). Particularly the medial amygdala (MeA) and the BNST have been implicated in regulating conspecific rivalry aggression, while the central amygdala (CeA) is more specifically involved in hunting and predatory aggressive attacks (Han et al. 2017). MeA neurons are active during fighting and in response to male/female conspecific chemosensory cues, as evidenced by the induction of c-fos and electrophysiological recordings (Veening et al. 2005; Hong et al. 2014). In addition, early lesion studies

have clearly implicated the MeA and BNST in mating, aggression, and rage-like behavior (Rosvold et al. 1954; Miczek et al. 1974; Kemble et al. 1984; Vochteloo and Koolhaas 1987; Wang et al. 2013). Electrical stimulation studies support the notion that the medial amygdalar area generally promotes aggression (Potegal et al. 1996; Siegel et al. 1999). While the MeA has stimulatory effects, the BNST has inhibitory effects on aggression as electrical stimulation of the BNST suppressed aggression in cats (Shaikh et al. 1986). Both the medial amygdala and BNST receive direct input from the accessory olfactory bulb, which in turn is the main relay station of olfactory information originating from the vomeronasal organ (Luiten et al. 1985). This part of the olfactory system is specialized in the detection of species-specific chemosensory signals. Hence, olfactory information that is crucial for proper social behavior in rodents has a dedicated entrance into the brain, reaching the medial amygdala and BNST almost directly, which in turn project intensively to the PMV and VMHvl, respectively. Unsurprisingly, the medial amygdala has an important function in the modulation of social behaviors on the basis of social experience and social recognition. Recently, it was demonstrated that the majority of c-fos-positive MeA neurons induced by attack are GABAergic. Optogenetic activation of these GABAergic neurons elicits male aggression, whereas stimulation of neighboring MeA glutaminergic neurons suppresses aggressive behavior (Hong et al. 2014). Optogenetic inactivation of MeA GABAergic neurons or permanent ablation of a subpopulation of GABAergic neurons expressing aromatase reduces normal intermale aggression (Hong et al. 2014; Unger et al. 2015). Although the MeA is characterized by a high density of both ER1 and androgen receptors (AR), it is not known whether these are located on these GABAergic cells. Likewise, whether and how these distinct sets of MeA neurons are precisely interconnected with the "attack" neurons in the VMHvl is not known yet, but it seems highly feasible that this is accomplished via its main downstream projection targets, the posterior portion of the BNST; stimulation of MeA-BNST projections results in increased aggression (Padilla et al. 2016). Interestingly, ER1 and AR receptors are also located on MeA neurons that produce the neuropeptide vasopressin (AVP). Interestingly, the synthesis of AVP in these neurons is potently enhanced by testosterone, the male gonadal steroid hormone that is intimately linked to aggressiveness (see below). This testosterone-dependent vasopressinergic system is sexually dimorphic and projects to the lateral septal area.

28.3.3 Septum/Hippocampus

Electrolytic lesioning or chemical inactivation of the lateral septum (LS) in birds and rodents dramatically increases the number of attacks towards conspecifics (Zeman and King 1958; Goodson et al. 1999; Potegal et al. 1981; Wong et al. 2016). Conversely, electrical or optogenetic stimulation of the LS suppresses natural and artificially evoked aggression (Potegal et al. 1981; Wong et al. 2016). Thus, the LS appears to be an essential gatekeeper for the expression of aggressive behavior. The

lateral septum is reciprocally and monosynaptically connected to both the aggression hotspots in the medial hypothalamus and medial amygdala. A recent study by Wong et al. (2016) indeed demonstrated that optogenetically activating GABAergic cells of the LS, which specifically project to the glutaminergic VHMvl "attack" neurons, can effectively suppress natural intermale attack and septal rage but had little effect on male-female mounting or nonsocial anxiety-like behavior. Given that the LS receives dense inputs from the hippocampus, and that some LS neurons show place fields, this pathway may modulate aggression by conveying spatial/contextual information. Furthermore, a recent study showed that the dorsal CA2 region of the hippocampus, which is characterized by expressing vasopressin AVP1B receptors, provides excitatory tone over the dorsal LS (Leroy et al. 2018). The LS is also characterized by a sexual dimorphic density of vasopressinergic fibers originating from the medial amygdala. Males have a higher AVP fiber density than females, and within the male gender, the density is negatively correlated with offensive aggressiveness. Both in rats and mice, highly aggressive males have a less dense vasopressinergic innervation of the lateral septum than low aggressive males.

Human patients with septal forebrain tumors exhibit elevated levels of anger, irritability, and aggressiveness. In addition, two recent structural MRI studies by Raine and colleagues demonstrated that adults with a large cavum septum pellucidum (CSP) showed higher levels of psychopathy and antisocial personality disorder (Raine et al. 2010; White et al. 2013). The septum pellucidum is one component of the septum that forms part of the septo-hippocampal system, and a large CSP is an early marker of abnormal fetal brain development during gestation until approximately 6 months post-birth (Sarwar 1989).

28.3.4 Prefrontal Cortex (PFC), Orbitofrontal Cortex (OFC), and Anterior Cingulate Cortex (ACC)

Frontal lobe impairments are one of the best-replicated factors for enhancing the intentions to behave aggressively in both animals and man (Kolb and Nonneman 1974; Siegel et al. 1999; De Bruin et al. 1983). Patients with damage to the frontal cortex exhibit more aggressive behavior (Anderson et al. 1999). The volume of the PFC gray matter in monkeys and humans correlates with social success and status (Sallet et al. 2011; Lewis et al. 2011). The frontal lobe consists of a number of subregions defined on the basis of their connections with thalamic nuclei and neuronal cytoarchitecture. Although the degree of complexity increases in higher vertebrates, there is a clear homology of frontal structures across a wide variety of vertebrate species. In particular the medial infralimbic (PFCvm), orbitofrontal (OFC), and anterior cingulate cortical areas have been associated with the inhibitory control of offensive aggression in a number of species. A meta-analysis of 43 structural and functional imaging studies found that the largest reductions in structure and function within the frontal lobe of aggressive and antisocial disordered individuals were observed in the orbitofrontal cortex, anterior cingulate cortex, and prefrontal cortex

(Yang and Raine 2009). This brain area is more generally involved in behavioral inhibition or impulsivity and the executive planning of motor output. Indeed, measures of impulsivity in male hamsters and rats are positively correlated with offensive aggression and prefrontal cortex activity measured by c-fos expression (Cervantes and Delville 2007; Coppens et al. 2014). Moreover, reduced prefrontal cortex serotonergic input and functioning has been associated with impulsive and violent forms of aggression in animals and humans (see below). Recently, Takahashi et al. (2014) demonstrated by employing optogenetic techniques that photostimulation of the principal pyramidal excitatory neurons in the mPFC, but not in the OFC, potently suppressed the initiation and execution of intermale aggression in mice, while optogenetic silencing of mPFC neurons caused an intensification of aggressive behavior. Hence, it is very plausible that the mPFC inhibits activity of a neural circuit that is tightly controlling the execution of aggressive attacks (i.e., VMHvl or MeA). In contrast, however, recent studies from Haller and colleagues have shown that postweaning socially isolated rats that demonstrate abnormal aggression exhibit structural deficits (reduced thickness), but higher activity in mPFC cells compared to control rats (Biro et al. 2017). Furthermore, they demonstrated that optogenetic stimulation of mPFC terminals in the mediobasal hypothalamus increased attack bite frequency, whereas the stimulation of similar terminals in the LH specifically resulted in violent-like (predatory) bites (Biro et al. 2018). These results indicate a direct prefrontal control over qualitatively different forms (rivalry vs. predatory) of aggression mediated by distinct hypothalamic circuitries. A recent human study, employing noninvasive transcranial direct current stimulation techniques to activate the dorsolateral prefrontal cortex, provided evidence that increasing prefrontal cortical activity can reduce intent to commit aggressive acts (Choy et al. 2018).

The anterior cingulate cortex (ACC) is another cortical limbic structure that has bidirectional connections with the prefrontal cortex, hypothalamus, amygdala, and hippocampus. In particular the rostral section of the ACC seems to be involved in emotional information processing and regulation of emotional responses (Bush et al. 2000). The cingulate cortex is activated by a variety of situations such as pain, motor function, conflict monitoring, error detection, reward, and during emotion and working memory tasks (Beckmann et al. 2009). The connections between ACC and amygdala through modulation by prefrontal cortex are fundamental for emotional behavior and in particular during anger control (Blair 2010; Davidson et al. 2000). Faulty regulation of emotion could result in impulsive aggression (Davidson et al. 2000). Indeed, several studies have demonstrated that patients with damage to the ACC show lack of empathy, response inhibition, and aggression control (Swick and Jovanovic 2002; Devinsky et al. 1995), while antisocial and violently aggressive individuals show structural ACC abnormalities (Boes et al. 2008; Meyer-Lindenberg et al. 2006; Rogers and De Brito 2016) or impairments in ACC functioning (Kiehl et al. 2001; New et al. 2002; Blair 2013). In contrast however, hyperactivation of anterior cingulate cortex was found in aggressive patients with schizophrenia and antisocial personality disorders if compared with nonaggressive

ones (Joyal et al. 2007). Another study has shown that reduced ACC functioning during a go-no-go task in prisoners doubled the likelihood of rearrest 3 years later, thereby indicating the potential for neuroimaging to provide predictive power for re-offending (Aharoni et al. 2014).

Although considerably less well studied in animals, a recent MRI study demonstrated increased ACC volumes in aggressive BALB/cJ mice, and this was associated with a 40% reduction of 1H-MRS GABA levels and a 20-fold increase of the GABA-degrading enzyme Abat in the ventral ACC (Van Heukelum et al. 2019; Jager and Amiri 2015).

28.3.5 Periaqueductal Gray (PAG)

The periaqueductal gray (PAG) represents one of the most important relays between the prefrontal, amygdala, and hypothalamic aggression nodes and the autonomic and somatic motor neurons in the medulla and spinal cord. The VMHvl, including the subpopulation expressing Esr1/PR, projects heavily to the dorsolateral and ventromedial parts of the PAG (Hashikawa et al. 2017; Lo et al. 2019), supporting older tracing studies that have indeed identified descending glutaminergic PAG projections to the pontine nucleus, raphe magnus and pallidus, medullary reticular formation, and directly to the spinal cord (Shaikh et al. 1986; Cameron et al. 1995). C-fos studies in several species consistently show that the (dorsolateral) periaqueductal gray is activated during offensive aggression (Kollack-Walker and Newman 1995; Haller et al. 2006; Veening et al. 2005). In vivo electrophysiological recording in cats showed that neurons in the dorsal and lateral parts of the PAG responded during agonistic encounters (Adams 1968). Electrical stimulation of the PAG induced aggression in male rats (Mos et al. 1982; Siegel et al. 1999), while PAG lesions may suppress aggressiveness in some (Mos et al. 1983) but not all studies (Lonstein et al. 1998). Collectively, the PAG is therefore generally considered to be the emotional motor output system for offensive aggression, orchestrating the involuntary autonomic physiological and somatic motor patterns of different forms of aggressive behaviors. To date, functional and structural imaging results of the PAG in violent aggressive or antisocial human individuals are not available.

28.3.6 Lateral Habenula (LHb)

A recently uncovered brain area involved in the motivational aspects of aggression is the lateral habenula. The habenula comprise a small group of nuclei that are located just above the thalamus and is divided into two asymmetric halves: the medial habenula (MHb) and the lateral habenula (LHb). The lateral habenula receives afferents from the hypothalamus, lateral septum, amygdala, BNST, nucleus accumbens, ventral pallidum, diagonal band of Broca, and anterior cingulate and prefrontal cortex and in turn sends dense glutaminergic projections

throughout the midbrain aminergic nuclei (Lammel et al. 2012) involved in reward and motivation such as the dopaminergic VTA and serotonergic DRN (see next section). The LHb is pivotal in processing aversive and rewarding information. Aversive stimuli, cues that predict its onset, or even the omission of an expected reward, lead to a strong increase in the activity of LHb neurons. Overactivity in the LHb is seen in both stress-induced learned helplessness (Li et al. 2011) and in depressive patients (Roisier et al. 2009). Conversely, unexpected delivery of rewards and cues predicting a reward decreases LHb neuron firing. The LHb is inhibited more strongly as expected reward probability or magnitude increases (Matsumoto and Hikosaka 2009). Hence, the LHB is generally considered the brain's "anti-reward" control center. A recent study utilizing optogenetics found that stimulation of GABAergic terminals that suppresses LHb firing increases the intensity of aggressive behavior in mice. The reverse was observed after optogenetic inhibition of these GABAergic terminals in the LHb (Golden et al. 2016). Hence, an emerging role for this brain region in controlling aggressive behavior based on emotional valence was recently suggested (Flanigan et al. 2017). To date, functional and structural imaging results of the LHb in violent aggressive or antisocial human individuals are not yet available.

28.4 Neurochemical and Hormonal Modulation of the Aggressive Neural Network

Obviously, the functional activity of this social behavior neural network, and thereby the selection of the appropriate behavioral response to social challenges and opportunities, is determined by a wide variety of molecular substrates (i.e., neurotransmitters, hormones, cytokines, and their respective metabolic enzymes, receptors, and intraneuronal signaling molecules). Undisputedly, among the neurochemical systems that are considered key signaling molecules in this neurocircuitry controlling aggression are the main inhibitory/excitatory amino acids (GABA/glutamate), canonical monoamines serotonin (5-HT) and dopamine (DA), the "social" nonapeptides oxytocin (OXT) and vasopressin (AVP), the "stress" neuropeptide corticotropin-releasing factor (CRF), the "stress" HPA and "sex" HPG axis's steroid hormones (corticosterone, testosterone, estrogen), and their cognate receptors. Indeed, the "aggression" neurons in the hypothalamus and other regions as outlined above receive these neurotransmitter projections and express a variety of their membrane-bound receptors, including serotoninergic 1A/1B and 2A/2C, dopaminergic DRD1/DRD2, and vasopressin/oxytocin AVP1A/AVP1B/OTR receptors, as well as the intracellular steroid hormone AR and EsR1/EsR2, PR, mineralocorticoid (MR), and glucocorticoid (GR) receptors. Since many of these neuromodulators change their levels rapidly and dynamically before, during, and after the execution of aggressive behaviors (see below), they may influence the various nodal neuron excitabilities and hence the initiation, maintenance, termination, and consequent social experiences of aggressive intercourse.

28.5 Serotonin

All major nodes of the neuronal network controlling offensive aggression are substantially innervated by serotonergic (5-HT) fibers originating from neurons in the dorsal and median raphé nuclei in the brain stem. More than any other neurochemical systems, this evolutionary ancient and very well-conserved neurotransmitter system is considered the primary molecular modulator of aggressiveness in a wide variety of animal species, including man (Siever 2008; Nelson and Trainor 2007; De Boer et al. 2015). However, the direction and exact causal linkage of this association is very complex, and it has proven notoriously difficult to unravel the precise role of this amine (and every facet of its synthesis and metabolic pathways, uptake and storage processes, and dynamic receptor signaling mechanisms) in the predisposition for and execution of aggressive behavior. For decades, high levels of aggressive behavior are believed to be associated with low brain 5-HT neurotransmission activity. This frequently reiterated and seductively simple serotonin deficiency hypothesis seems consistent with the fact that serotonergic receptor agonist drugs used to mimic higher serotonergic activity, generally reducing aggressive behavior (see de Boer and Koolhaas (2005) and Takahashi et al. (2012) for reviews). However, recent studies of the functional status of the 5-HT system before, during, and after the execution of normal adaptive and abnormal pathological forms of aggression have led to a somewhat different view. Display of normal adaptive offensive/defensive aggressive behavior aimed at securing territorial control, social dominance, or other resources is associated with enhanced 5-HT neuronal activity (see de Boer et al. (2015) for relevant references). A negative correlation between aggression and 5-HT as captured in the deficiency hypothesis seems to be a trait-like characteristic of pathological and abnormal forms of aggression (e.g., violence). For example, a clear positive correlation was found between the level of normal adaptive expressions of offensive aggression and basal cerebrospinal fluid (CSF) concentrations of 5-HT and/or its metabolite 5-HIAA. A significant negative correlation between aggression and 5-HT levels was found only upon inclusion of samples from abnormally and excessively aggressive trained fighter animals (de Boer et al. 2009). A critical evaluation of the csf 5-HIAA data in aggressive humans confirms this idea that the serotonergic deficiency appears to hold in particular for specific groups of individuals who persistently engage in more aberrant, impulsive, and violent forms of aggressive behavior rather than in individuals with instrumental (functional) forms of offensive aggression.

Treatment with 5-HT_{1A} or 5-HT_{1B} receptor agonists is one of the most potent pharmacological interventions to selectively suppress aggressive behavior in a variety of animal species and experimental paradigms (see Olivier and van Oorschot (2005) and de Boer and Koolhaas (2005) for reviews). However, apart from acting on receptors at postsynaptic sites, these two distinct receptor agonists also affect the two main serotonergic autoreceptors involved in the negative feedback control of the 5-HT neuron at the level of the synapse (5-HT_{1B}) and at the level of the cell soma (5-HT_{1A}). Activation of these receptors by agonists will potently activate the

negative feedback mechanisms and thereby reduce 5-HT neurotransmission. It appears that the anti-aggressive effects of these compounds are largely expressed via their action on the inhibitory autoreceptors located at the cell soma and the nerve terminal, presumably by attenuating intruder-activated 5-HT neurotransmission (De Boer and Newman-Tancredi 2016). Interestingly, highly aggressive animals are characterized by upregulated somatodendritic 5-HT_{1A} and terminal 5-HT_{1B} autoreceptor functionality (Caramaschi et al. 2008; De Boer et al. 2015). This considerably (approximately 20-fold) enhanced tonic inhibitory control of serotonergic neurons in aggressive males may explain the negative correlation between baseline levels of 5-HT and escalated aggression found in many species. Furthermore, to signify the causality of this correlation, 5-HT_{1A} autoreceptor sensitivity increased or decreased upon enhancing (by repeated victorious experiences) or attenuating (by repeated defeat experiences) aggressiveness, respectively. Notably, animals that escalated their aggressiveness and started to engage in violent-like aggressive behavior demonstrated 5-HT_{1A} autoreceptor supersensitivity (de Boer et al., in prep). More persuasively, recent molecular genetic studies have shown that transgenic mice with conditional (at adult age) overexpression of somatodendritic 5-HT_{1A} autoceptors demonstrate suppressed 5-HT neural firing that was associated with a profound hyperaggressive behavioral phenotype (Audero et al. 2013). These animal data confirm the causal role of tonic 5-HT activity in setting a trait-like threshold for executing overt aggressive behavior.

Similar to the findings in animals, agents with significant 5-$HT_{1A/1B}$ receptor agonism (i.e., buspirone, eltoprazine) have been found to be effective, although to variable degrees, in reducing aggressiveness in humans (Ratey et al. 1991; Mak et al. 1995; Santa-Cruz et al. 2017). Furthermore, a consistent finding has been an inverse relationship between 5-HT_{1A} receptor-provoked increases in plasma cortisol and trait aggressiveness in personality-disordered patients (Coccaro et al. 1995; Cleare and Bond 2000), indicative of impaired 5-HT_{1A} heteroreceptor functionality. Only 2 PET studies using the same 5-HT_{1A} receptor radioligand ([^{11}C]WAY100635) have been published: one reporting a positive relation between frontal 5-HT_{1A} receptor availability and trait aggressiveness (Witte et al. 2009), while the second showed an inverse correlation (Parsey et al. 2002). To date, only one recent PET imaging study has been performed examining 5-HT1B receptor availability in pathological aggression; 5-HT1B binding in the ventral striatum, anterior cingulate cortex, and orbitofrontal cortex was positively correlated with trait anger in the violent offender patient group but not in healthy controls (Da Cunha-Bang et al. 2017a). This clinical study reinforces preclinical data suggesting the involvement of 5-HT1B receptors in pathological aggression.

In addition to 5-HT_{1A} and 5-HT_{1B} receptors, another intrinsic feedback control mechanism of serotonin release is mediated by the serotonin transporter (SERT). SERT is distributed along the axons and synaptic terminals of 5-HT neurons and plays an essential role in the clearance of released extracellular 5-HT. In humans and nonhuman primates, polymorphisms in the promoter region of the gene coding for SERT is associated with aggression. Surprisingly, and generally in contrast to

the 5-HT deficiency hypothesis, the short-allele (loss-of-function) variant has been associated with increased levels of aggression both in males and females, presumably due to a disturbed serotonin reuptake (Hallikainen et al. 1999; Retz et al. 2004; Beitchman et al. 2006). In contrast however, gain-of-function polymorphisms in the SERT gene (either long 5-HTTLPR allele or the STin2VNTR12 variant) also has been shown to confer risk for aggression and violence in children (Beitchman et al. 2006; Davidge et al. 2004) and adults (Aluja et al. 2009; Hemmings et al. 2018). In line with this latter clinical finding, rats and mice that have genetically induced SERT deficiency, which consequently demonstrate high tonic extracellular 5-HT levels, generally exhibit a low-aggressive phenotype (Holmes et al. 2002; Homberg et al. 2007). This seems also in line with the observation that highly aggressive dogs exhibit enhanced SERT functionality (Rosado et al. 2010).

When the SERT binding radiopharmaceutical probes [^{11}C]McN 5652 and [^{11}C]DASB became available, SERT binding distribution patterns were quantified in brains of impulsive aggressive individuals and/or personality-disordered populations. One early study found lower 5-HTT binding in the ACC in impulsive aggressive personality-disordered patients (Frankle et al. 2005), indicative of attenuated 5-HT innervation of fronto-limbic regions and is generally in line with the hypo-serotonergic model of impulsive aggression. Another study of the same research group however was not able to extend this finding in a much larger cohort of IED patients but noticed that a measure of psychopathy, callousness, positively correlated with ACC SERT binding (van de Giessen et al. 2014). This again underscores the importance of stratifying personality-disordered patients into reactive or proactive forms of aggressiveness. In a third study, SERT availability was found to be significantly higher in high-impulsive aggressive subjects as compared to low-IA. Post hoc analysis demonstrated that the difference was mainly driven by increased SERT availability in the brain stem, pons, and midbrain. Interestingly, there was a positive correlation between SERT BP_{ND} (binding potential non-displaceable) in the high-IA and measures of childhood trauma. The authors propose that early-life adversity impaired 5-HT function, mainly through epigenetic alterations, leading to high-IA (Rylands et al. 2012).

Another serotonergic receptor implicated in aggression is the 5-$HT_{2A/C}$ heteroreceptor (5-$HT_{2A/C}$R) postsynaptically located on non-serotonergic neurons. Various clinical studies have shown differences of 5-HT_{2A}R binding in human subpopulations, but literature findings are not consistent. Cerebral 5-HT_{2A}R binding has been investigated most frequently in relation to aggressiveness. Violent aggression in humans was reported to be related to a decreased BP_{ND} of the PET tracer [^{18}F]setoperone in prefrontal cortex, especially at young age (Meyer et al. 2008). Using another PET tracer, [^{11}C]MDL 100907, reduced 5-HT_{2A}R availability was also observed across cortical regions in males with extreme levels of impulsive aggression without callous unemotional traits as compared to males with low levels of impulsivity (Rylands et al. 2012). In contrast to these findings, two other PET studies reported that 5-HT_{2A} receptor binding in the prefrontal cortex is increased in physically aggressive patients with impulsive aggressive personality disorder

(Rosell et al. 2010) and in patients with borderline personality disorder (Soloff et al. 2007) as compared to healthy controls. In addition, a postmortem study indicated that 5-HT_{2A} receptor expression in the prefrontal cortex is positively correlated with lifetime aggression in subjects who committed suicide, but not in subjects who died from non-neurological causes (Oquendo et al. 2006). However, a recent study using a large sample of healthy individuals did not find a consistent relationship between 5-HT_{2A}R binding in frontal cortex and the personality traits aggression or impulsivity (da Cunha-Bang et al. 2013).

The putative relationship between 5-HT_{2A}R binding and aggression has also been studied in experimental animals (Popova et al. 2010; Morrison et al. 2011). No change in the functional sensitivity of 5-HT_{2A}R was found in Norway rats bred for high defensive fear-induced aggression towards man, compared to rats with normal aggression, and 5-HT_{2A}R expression was also similar (Popova et al. 2010). 5-HT_{2A}R expression in the hamster brain did not change after social defeat, either in subordinate or dominant animals, as tested by immunohistochemistry (Morrison et al. 2011). Single-photon emission computed tomography (SPECT) studies observed differences in 5-HT_{2A}R binding of impulsive aggressive dogs compared to normal dogs. These dogs showed increased 5-HT_{2A}R binding in cortical areas, which could be ameliorated by administration of the antidepressant citalopram (Peremans et al. 2003, 2005). Finally, a recent rat study using the radiolabeled 5-HT_{2A} antagonist ([3H]MDL 100907) and agonist ([3H]Cimbi-36), no differences in 5-HT_{2A}R binding were observed between high- and low-aggressive WTG rats (Visser et al. 2015). Overall these findings suggest that 5-HT_{2A}R binding is not an important molecular marker of trait aggressiveness.

Ever since Brunner's landmark finding of a single, rare, missense mutation in the MAO-A gene being associated with antisocial and excessive aggressive behavior in a large Dutch family (Brunner et al. 1993), this main catabolic enzyme of monoamines has been the focus of interest in the neurogenetic architecture of human and animal aggression. Carriers of another low-expressing MAOA-VNTR allele similarly exhibit enhanced aggressiveness (Sabol et al. 1998; Manuck et al. 2000) or occur more commonly in violent compared to nonviolent incarcerated males (Stetler et al. 2014). Accordingly, hyper-methylation in the promoter of the MAOA gene is associated with antisocial personality disorder, and this epigenetic modification likely contributes to downregulation of MAO expression and dysregulation of 5-HT system, leading to impulsive aggressiveness and antisocial criminality (Checknita et al. 2015). Additionally, numerous studies have demonstrated gene-environment interaction effects such that greater early-life adversity increases the risk for impulsive aggressiveness in males with the low-expressing MAOA allele (Caspi et al. 2002; see for review Buckholtz and Meyer-Lindenberg (2008)). Similar gene-environment interactions as risk factor for violent traits have been reported for several other serotonin gene polymorphisms such that individuals with a certain allele are particularly prone to engage in violent behavior when they have a history of early-life maltreatment, but the effect disappeared when they are reared in an environment with low stress. Using PET imaging employing the radioligands [^{11}C]

clorgyline or [^{11}C]Harmine to measure MAOA availability, trait aggression in either a healthy population (Alia-Klein et al. 2008) or population of ASPD offenders (Kolla et al. 2015) was negatively associated with MAOA availability in several cortical and subcortical brain regions.

These clinical results linking MAOA dysfunction with enhanced aggressiveness are generally supported by mouse genetic and pharmacological studies. Increased aggression have been observed in both MAOA knockout mice (Cases et al. 1995) and mice with a naturally occurring mutation (Scott et al. 2008). Nonselective inhibitors of MAOA (e.g., phenelzine, tranylcypromine) produce acute anti-aggressive effects only at doses that also induce sedation and alter other nonaggressive behaviors (Valzelli et al. 1967). Intriguingly, and at variance with the serotonin deficiency hypothesis, these findings suggest that chronically increased 5-HT levels that result from reduced MAO function may promote or intensify escalated aggressive displays. However, the findings are consistent with a large body of work across species that links dysregulation (too much or too little) during ontogeny to impulsive aggressive behavior (Buckholtz and Meyer-Lindenberg 2008).

28.6 Dopamine

Dopamine has several important functions in the general control of behavior. The nigrostriatal dopaminergic system originating in the substantia nigra (SNR) has a central function in the control of motor output, which is obviously important for the execution of aggressive behaviors. The mesolimbic dopaminergic system, originating in the ventral tegmental area (VTA) and projecting to the ventral striatum/nucleus accumbens (NAc), is believed to be important for the motivational and rewarding aspects of behavior. Several imaging studies indeed show activation of the NAc during aggression-provoking tasks in human subjects (Buckholtz et al. 2010; Moran et al. 2014; Chester et al. 2016; Gan et al. 2016, 2017). Yet, clinical PET imaging studies assessing the link between dopaminergic synthesis function and aggression are still scarce. One study evaluated aggressive behavior and dopaminergic synthesis capacity employing [^{18}F]F-FDOPA PET imaging in 21 healthy males. A negative correlation between aggressive actions and dopaminergic synthesis capacity was found in the midbrain, caudate nucleus, and putamen (Schluter et al. 2013). Other studies focusing on dopamine receptors imaging (mainly D1-R) have been contradictory. In 2014, Plavén-Sigray and colleagues (Plavén-Sigray 2014) reported a negative correlation between D1-R levels in the limbic striatum and aggressive personality traits, using the PET tracer [^{11}C]SCH23390. In a replication study conducted by the same group, no significant correlations between D1-R in the limbic striatum and aggression were found. The authors argued that these discrepancies might be due to high sample homogeneity or that the previous findings were false positive (Plavén-Sigray 2018).

Studies in animals using c-fos mapping studies and/or in vivo microdialysis have demonstrated increased dopaminergic neuronal activity in VTA and release of

dopamine in the NAc following aggressive social interactions in mice, hamsters, and rats (Veening et al. 2005; Nehrenberg et al. 2013; Beiderbeck et al. 2012; van Erp and Miczek 2000; Ferrari et al. 2003). Furthermore, direct optogenetic activation of VTA dopamine neurons increases aggressive bout severity in mice (Yu et al. 2014). Pharmacological studies have shown that dopamine agonists increase aggressive behavior in rodents (Miczek and Haney 1994; Yu et al. 2014), while systemic injections of DRD1 or DRD2 family antagonists decrease it (Kudryavtseva et al. 1999; Fragoso et al. 2016). However, there is a general lack of behavioral specificity of this effect when the compounds are applied systemically. This is one of the main clinical problems with all the commonly prescribed neuroleptic dopamine antagonists (i.e., haloperidol, risperidone, clozapine, olanzapine) to curb excessive aggression in patients (Campbell et al. 1984; Ostinelli et al. 2017; Calver et al. 2015). While these studies confirmed a functional role for the dopaminergic VTA-NAc system in mediating aggression, they do not specifically address its role in the rewarding properties of, or the motivation for performing, aggressive behavior. Under laboratory conditions, acts of aggression and winning fights are shown to be rewarding, such that animals will strengthen future fighting (de Boer et al. 2009), demonstrate operant (nose-poking, lever-pressing) learning for the opportunity to attack another conspecific as a positive reinforcement (Fish et al. 2002; May and Kennedy 2009; Golden et al. 2017a, b; Falkner et al. 2016), or will exhibit conditioned place preference for a location associated with previously successful aggressive encounters (Martínez et al. 1995; Golden et al. 2016). Actually, individuals seeking out the opportunity to fight, even in the absence of overt threat-provoking cues, appear to engage in aggressive behavior as a source of pleasure. Actually, a significant proportion of individuals may even become "addicted to aggression" (Golden et al. 2017a, b). The term "appetitive aggression" has been used to describe these forms of aggression as a positive reinforcer (Elbert et al. 2018). Earlier microdialysis experiments in aggression-experienced rats have clearly revealed that DA levels in the NAc rise in anticipation of an aggressive social interaction (Ferrari et al. 2003), while another study demonstrated that blocking dopaminergic activity in this brain nucleus using D1 and D2 receptor antagonists reduces operant responding for access to an intruder (Couppis and Kennedy 2008). Similarly, if male California mice are given a DA receptor antagonist after they win a fight, then they fail to develop a strong winner effect (Becker and Marler 2015). In male Syrian hamsters, the accumulation of multiple winning experiences that lead to a strong winner effect is positively associated with substantial increases in TH-positive cells in NAc, BNST, and LS (Schwartzer et al. 2013). Recently, Golden and colleagues (Golden et al. 2017a, b, 2019) provided more direct evidence for the causal involvement of dopaminergic VTA-NAc projections in aggression-seeking behavior and aggression-addiction. They demonstrated that chemogenetically silencing D1-expressing medium spiny GABAergic neurons in the NAc decreased aggression self-administration (Golden et al. 2019). Thus, a growing body of evidence shows that aggression activates dopaminergic reward centers in the brain to promote positive valence and reinforce the motivation to act aggressively.

28.7 Glutamate/GABA

Glutamate and GABA are the main excitatory and inhibitory amino acid neurotransmitters, respectively, in the mammalian brain. Several kinds of mental disorders such as anxiety disorders, depression, autism, and also aggression are attributed to an imbalance between glutaminergic excitation and GABAergic inhibition in limbic areas (Miczek et al. 2007). It is not surprising therefore that many compounds that act as an agonist or antagonist on their cognate receptors can potently alter these disorders as well as aggressive behaviors. Initial preclinical data demonstrated pro-aggressive effects of microinjection of L-glutamate or kainite in the hypothalamic attack area (Brody et al. 1969; Haller et al. 1998). Subsequent pharmacological and genetic studies have shown that almost all subtypes of glutamate (NMDA, AMPA, kainate receptors, and metabotropic glutamate receptors) are involved in aggression, but the nature and extent of the response are highly variable (see Takahashi and Miczek (2014) for review) and behaviorally not specific. For example, antagonists of NMDA receptors may cause enhancement of aggression as well as suppression, together with abnormal locomotor activation or ataxia. Similarly, genetic ablation of subunits of NMDA receptors (Duncan et al. 2014), AMPA receptors(Vekovischeva et al. 2004; Shimshek et al. 2006; Adamczyk et al. 2012), and kainate receptors (Shaltiel et al. 2008) induces a range of abnormal behaviors including diminished aggressiveness in mice.

The inhibitory neurotransmitter GABA stands out as an important modulator of aggressive behaviors. An abundance of preclinical data shows that increasing GABAergic transmission through several pharmacological manipulations often inhibits aggressive behavior in mice (Krsiak et al. 1981; Puglisi-Allegra et al. 1981), rats (Molina et al. 1986) and cats (Cheu and Siegel 1998). Lower levels of GABA and the activity of the glutamic acid decarboxylase (GAD) enzyme are observed in highly aggressive individual rats, mice, and hamsters as well as more aggressive inbred strains of mice (Potegal et al. 1981; Haug et al. 1984; Guillot and Chapoutier 1996). Likewise, in human subjects lower plasma GABA levels (Bjork et al. 2001) and mitochondrial benzodiazepine receptor binding (Soreni et al. 1999) have been found in patients with high ratings of aggression. The aggression suppressing effects of GABA involve both the $GABA_A$ and the $GABA_B$ receptors; muscimol and baclofen, GABA agonists at the $GABA_A$ and the $GABA_B$ receptors, respectively, are effective inhibitors of aggression but in a behaviorally nonselective manner. The most intriguing evidence on the role of GABA in aggressive behavior comes from studies involving positive allosteric modulators such as benzodiazepines, alcohol, and the neurosteroid allopregnanolone. In contrast to the direct GABA agonists, these positive allosteric modulators of the $GABA_A$ receptor were shown to have biphasic effects on aggressive behavior, with low anxiolytic dosages increasing and high sedative dosages decreasing aggressive behaviors (Miczek et al. 2003; Fish et al. 2001; Gourley et al. 2005). The aggression-heightening and aggression-suppressing effects of benzodiazepines can be modified by previous social experiences (Ferrari et al. 1997). Alcohol reliably escalates aggression in approximately 30% of

male mice and rats, whereas the level of aggression in the other 70% either did not change or decreased relative to their basal level after an administration of a moderate dose (Miczek et al. 1998). This individual variation seems to be comparable to the human condition, and differences in the propensity for escalated aggression by alcohol may arise from functional and compositional differences in the $GABA_A$ receptor. Recent evidence in mice has demonstrated that the modulation of 5-HT impulse flow by GABA, acting via distinct receptor subtypes in the dorsal raphe nucleus, is of critical importance in the suppression and escalation of aggressive behavior (Miczek et al. 2015a, b). To date, no clinical PET imaging studies related to GABA/glutamate are available.

28.8 Hormones of the HPA (Cortisol/Corticosterone) and HPG Axis (Testosterone)

The steroid hormones cortisol/corticosterone and testosterone have been the most intensively studied hormones in relation to aggressive behavior. Disruptions of the hypothalamus-pituitary-adrenal (HPA) axis, the body's stress response system that regulates the release of corticosterone/cortisol, are frequently observed in aggressive and antisocial people. Similar to humans, animal studies have shown that low to moderate acute changes are associated with increased aggression in rats, whereas higher or longer-lasting changes are associated with decreased aggressiveness in mice. Recently, Kruk (2014) proposed an interesting concept that the anticipation of an impending conflict rapidly activates the HPA axis, producing an adrenocortical response that promotes an increased sensitivity for aggression, releasing and directing stimuli by a rapid feedforward to appraisal mechanisms in the brain. This stress-aggressive conflict feedforward mechanism seems to depend on the mineralocorticoid receptor (MR) as pretreatment with the MR antagonist spironolactone robustly inhibits resident's offensive aggression towards an intruder (Kruk et al. 2013). On the other hand, sustained glucocorticoid deficiency observed in a number of psychiatric disorders such as antisocial personality disorder and posttraumatic stress disorder is associated with abnormal aggressive behavior in these patients (McBurnett et al. 2000). The causal involvement of glucocorticoid deficiency in aggression and violence has been demonstrated in male rats (Haller and Kruk 2006). Glucocorticoid deficiency created by surgical removal of the adrenal gland and low corticosterone replacement induced violent-like forms of aggressiveness in male rats. These animals direct their attacks to vulnerable parts of the body, an effect that is normalized by corticosterone injections. Further analysis of the abnormal aggressive behavior suggests that the effects of chronic glucocorticoid deficiency on aggression and violence are somehow related to anxiety and/or physiological hypo-arousal.

Testosterone is the main gonadal steroid hormone that has traditionally been tightly associated with male offensive aggressiveness. This link between testosterone and aggression originated from the classic ablation-replacement studies using domestic fowl (Allee et al. 1939), mice (Beeman 1947; Barkley and Goldman 1977), and rats (DeBold and Miczek 1981; Koolhaas et al. 1980), showing a direct

causal relationship. Furthermore, baseline testosterone concentrations are positively correlated with aggressiveness and social dominance status (Schuurman 1980; Gesquiere et al. 2011). While testosterone levels rise rapidly in species ranging from rodents to humans after social competition, this response is generally higher and longer lasting in winners than in losers (Schuurman 1980; Oyegbile and Marler 2005; Fry et al. 2011).

Yet, the relationship between aggression and baseline levels of testosterone in humans is, even if statistically significant, rather small in magnitude. A meta-analysis of over 40 studies in humans found an overall correlation of $r = 0.08$ between testosterone and a variety of measures of aggression (Archer 2006). However, a growing body of evidence suggests that acute changes in testosterone within the context of competition and/or social provocation may be more relevant for the putative testosterone-aggression link. In both humans and animals, winning an aggressive interaction leads to a transient testosterone spike that enhances the chance of winning subsequent interactions (Carré et al. 2013; Trainor et al. 2004; Schuurman 1980). Losing a fight will reduce plasma testosterone levels for a long period of time and renders the defeated individual less motivated or able to aggress (Schuurman 1980). The behavioral effects of testosterone are partly due to its action on peripheral secondary sex characteristics, thereby changing the stimulus characteristics of the animal. More important however is its action on the brain. Exogenous testosterone administrations increased amygdala and hypothalamic reactivity (Hermans et al. 2008; Goetz et al. 2014), reduced orbitofrontal activity (Mehta and Beer 2010), and reduced amygdala-orbitofrontal connectivity (van Wingen et al. 2011) in response to angry facial expressions, which is what is observed in individuals with recurrent problematic impulsive aggressive behavior (Coccaro et al. 2007). During development, testosterone plays an important role organizing brain and behavior into a more masculine direction. Characteristic of the neuronal network for offensive behavior is that several of the subcortical brain structures are very sensitive to gonadal steroids. Social behavior-select neurons in the hypothalamus, medial amygdala, bed nucleus of the stria terminalis, and preoptic area are characterized by a high density of estrogen and androgen receptors (Wood and Newman 1999; Roselli and Resko 2001). Moreover, these neuronal nodes contain high amounts of aromatase and 5α-reductase, enzymes that convert testosterone into estradiol and the androgen dihydrotestosterone, respectively. Both metabolites of testosterone play a distinct role in the modulation of offensive aggression through their respective action on estrogen and androgen receptors. In particular the ER1 receptor has been implicated in the modulation of offensive aggression. Deleting this receptor through genetic modification completely abolishes aggression in male mice (Ogawa et al. 1997). Circulating levels of testosterone can be controlled experimentally through gonadectomy; however, even castrated males generate estrogen from testosterone produced in the adrenals. Therefore, only genetic deletion of aromatase in male mice eliminates estrogen action, resulting in a complete loss of aggressive behavior. Hence, individual variation in offensive aggressiveness may depend on the density of ER1 and/or the amount of aromatase present in various brain areas. Indeed, aggressive males show higher numbers of ER1-expressing cells in the

lateral septal area, the BNST, and the preoptic area. Moreover, the number of ER1 receptors increases with aggression in seasonally reproducing animals. However, also the androgen receptor is involved. Evidence in mice suggests that the androgen receptor increases in various limbic brain areas after winning experience (Fuxjager et al. 2010). One can conclude that the effects of testosterone on aggressive behavior depend on the complex interaction between the balance between the two converting enzymes, the density of ERα and androgen receptors, as well as experiential and contextual factors. The prominent link between gonadal steroids and enhanced aggression is further clearly demonstrated in animals and humans that are exposed to anabolic/androgenic steroids (AAS) during adolescence (Morrison et al. 2015). Several studies have shown that AAS exposure during this developmental period consistently increased aggressive behavior via alterations in several neurotransmitter systems (i.e., 5-HT, DA, and AVP) implicated in the control of aggression within the hypothalamic attack area.

28.9 Vasopressin and Oxytocin

Besides their important peripheral physiological functions as neurohypophysial-released hormones, the neuropeptides arginine vasopressin (AVP) and oxytocin (OXT) are also implicated in interneuronal communication within various nodes of the social brain network to modulate emotional and social behavioral and physiological responding (Lee et al. 2009a). These nonapeptides are arguably the most commonly studied neuropeptides in the modulation of social behavioral functions. AVP is generally known to increase anxiety-like behaviors, stress responsivity, and aggressiveness, whereas OXT has the opposite effects and facilitates social attachment, care, and affiliation (Heinrichs et al. 2009). Existing data from early pioneering work on these neuropeptides convincingly demonstrated opposite roles for AVP and OXT in fear learning processes (Bohus and de Wied 1998). More recent studies in feral wild-type rats and/or artificially selected aggressive and nonaggressive mice have demonstrated that high-aggressive animals exhibit higher levels of AVP release when compared to their nonaggressive counterparts (Koolhaas et al. 2010). In addition, there is abundant experimental evidence to support a causal function of vasopressin in proactive aggressive behavior and OXT in passive affiliative behavior. Direct micro-infusion of AVP or OXT into the cerebral ventricles or in selected brain regions facilitates or suppresses, respectively, offensive aggression (Calcagnoli et al. 2015). In addition, a positive correlation between levels of CSF vasopressin and life history of general aggression as well as aggression towards individuals (Lee et al. 2009a, b) has been reported, whereas impaired brain OXT-ergic signaling has been implicated in several human neuropsychiatric disorders associated with social deficits, impulsivity, and excessive aggression (Lee et al. 2009a, b). Furthermore, mutant mice with the vasopressin receptor V1A/V1B gene deleted showed virtually no offensive aggressive behavior anymore, whereas elevated aggressiveness was found in mice with deletions of the OXT receptor gene. Consistent with the aggression-promoting role of brain AVP, systemic as well as intra-hypothalamic

administration of AVP V1A/V1B receptor antagonists effectively block offensive aggressive behavior in male hamsters and WTG rats (Blanchard et al. 2005; Koolhaas et al. 2010). Basically, an opposite picture seems to emerge for brain OXT signaling. Recent ethopharmacological studies have clearly demonstrated that enhancement of brain OXT-ergic function, using either intraventricular, intra-amygdalar, or even intranasal administration routes, produced marked anti-aggressive and pro-social affiliative effects that are dose-dependent, behavior- and receptor-selective, and long-lasting (Calcagnoli et al. 2013, 2015). To date, no clinical PET imaging studies related to the nonapeptidergic system are available.

28.10 Concluding Remarks and Future Directions

The human and animal neurobiological research findings convincingly demonstrate that abnormal expressions of aggressive behaviors principally find their origin in a dysregulation of the deeply rooted neuronal circuits and/or neurochemical pathways in the brain that mediate normal social affiliative-aggressive behaviors. This highly conserved neural and gene expression brain network includes the intimately interconnected forebrain (limbic) structures amygdala, bed nucleus of the stria terminalis, lateral septum, mediodorsal and anterior thalamus, and several hypothalamic nuclei. Evidence suggests that these limbic areas collectively encompass a hierarchical role in the sensory processing and generation of the aggression aggressive display sequences. In addition, important "top-down" modulatory control is provided by cortical structures like the orbitofrontal (OFC), medial prefrontal (mPFC), and anterior cingulate cortex (ACC), as well as the ascending midbrain monoaminergic dorsal/medial raphe nucleus (DRN/MRN; serotonin) and ventral tegmental area (VTA; dopamine). The structural and functional properties of this social aggressive behavior brain network are established and constantly shaped by a dynamic interplay of genetic and environmental factors (stress, maltreatment, vicarious experiences, substance abuse) in particular during certain sensitive (i.e., perinatal and adolescent) developmental periods. Comparison of the animal and human data regarding the neuroanatomical and neurochemical organization of aggression, as outlined extensively in the previous sections, shows considerable similarities but also several inconsistencies and important omissions. Brain PET/SPECT/fMRI imaging studies largely substantiate that the neural circuitries that mediate aggressiveness in humans overlap with the network of brain regions controlling aggression in animals. However, it is quite surprising that virtually all of the human neuroimaging studies are predominantly concentrating on the cortical (i.e., prefrontal orbitofrontal and cingulate) and temporal lobe (amygdala) brain structures, while nodes like the hypothalamus and associated limbic midbrain (septum, hippocampus) and hindbrain (periaqueductal gray) structures that are significantly involved in the direct causal control of animal fighting and attack usually do not show up in the region of interest analyses. Furthermore, in human neuroimaging studies, the cortical brain nuclei are typically assessed as a large unitary structure, while animal studies clearly demonstrate the finely grained functional subdivision of these

regions, even to the level of distinct neurons. The reasons for this discrepancy likely have to do with the rather poor spatial resolution of the current neuroimaging techniques (1–1.5 mm^3) with respect to neuroanatomical functional subdivision. Another gap between clinical and preclinical studies is the fact that the majority of conducted PET/SPECT studies have focused mainly on the classic serotonergic and dopaminergic systems, whereas preclinical studies clearly demonstrate that several other neurotransmitters and peptides play an important role in aggression. Hence, developing appropriate radiopharmaceutical probes for these systems should advance our understanding of neurotransmitter dysfunctions in excessive and violent aggressiveness. Additionally, various therapeutic targets that deserve further characterization, such as the 5-$HT1_{A/B}$ (auto)receptors, Dad1/Dad2 receptors, and OXT and $AVPV1_{A/B}$ receptors, have been described. PET/SPECT imaging studies of these receptors may help to clarify their role in the pathophysiology of aggression. Obviously, the current emerging circuit-level knowledge of the neuromolecular underpinnings of aggression in both its normal and excessive forms has great potential to guide the rational development of effective therapeutic interventions for pathological social and aggressive behavior. Finally, the potential predictive utility of neuroimaging techniques (i.e., neuroprediction) for medical diagnosis, treatment, and perhaps even legal punishment of violence and other forms of serious antisocial behavior may provide substantial benefits for society.

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Part VI

Miscellaneous Subjects

Application of PET and SPECT to the Study of Autism Spectrum Disorders

29

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Contents

Abstract

Autism spectrum disorders (ASD) are a heterogeneous group of neurodevelopmental disorders involving deficits in social communication and stereotyped behaviors. It has been estimated that over 100 genes may be involved in the risk

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for autism, many of them involving brain synaptic transmission or brain development and growth. Neuroimaging studies with PET and SPECT have been used to assess metabolic and blood flow changes, as well as protein synthesis and inflammation in the brain associated with ASD. In addition, PET and SPECT have been used to target a number of neurotransmitter systems, including serotonin, dopamine, GABA, and acetylcholine. These studies have employed tracers that are neurotransmitter precursors and ligands for receptors and transporters. These studies have provided clues about how differences in development of these systems play a role in altered brain function in ASD and provide information leading to new intervention approaches. Increasingly, these molecular imaging approaches are being applied as biomarkers and for assessment of treatment response.

29.1 Introduction

Autism spectrum disorders are defined by behavioral impairments involving social communication and restrictive repetitive stereotyped behaviors (DSM-5) (American Psychiatric Association 2013). Underlying the spectrum of autistic behaviors are multiple etiologies, only a small fraction of which have been thus far identified. The reliance upon this behavioral definition results from the lack of biological markers for the majority of individuals with autistic behavior and is a source of difficulty in the design and reproducibility of imaging studies of brain neurochemistry. In spite of the fact that there are various etiologies for autistic behavior, the possibility of alteration in common signaling pathways, shared by multiple causes of autism, appears be supported by genetic studies (Bill and Geschwind 2009). This chapter will include studies of cerebral blood flow, glucose metabolism, protein synthesis, and inflammation, as well as studies providing evidence for a role of altered neurotransmission in autism measured through molecular imaging techniques. The role of these neurotransmitters during different periods of brain development will be discussed. Understanding the roles of each neurotransmitter in the brain across the lifespan and how those functions might be altered in autism will offer new routes for pharmacological intervention in autism and biomarkers of drug response.

29.2 Focal and Global Brain Alterations in Glucose Metabolism

29.2.1 Increased Global Brain Glucose Metabolism in Autism

The measurement of 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) with positron emission tomography (PET) has proved to be a valuable tool in identifying regional and global abnormalities in many neurological and psychiatric conditions. In the first study of glucose metabolism in autism, Rumsey et al. (1985) reported diffusely increased glucose metabolism by approximately 20% in a group of 10 autistic men compared to 15 healthy gender- and age-matched control subjects. The finding of globally increased glucose metabolism has not been replicated in subsequent FDG PET studies reported

(Herold et al. 1988; De Volder et al. 1987; Siegel Jr et al. 1992). However, there are methodological differences in subsequent studies, and therefore, differences in global glucose metabolism in autistic adults cannot be discounted. For example, Herold et al. (1988) compared six male autistic subjects to six healthy males and two females. Similarly, Siegel Jr et al. (1992) compared autistic adults (12 males, 4 females; 17–38 years) and normal controls (19 males, 7 females; mean age 27 years) mixed for gender and found no difference in global glucose metabolism. Since there are gender differences in glucose metabolism on the same order of magnitude of those Rumsey et al. reported between autistic and normal men (Baxter et al. 1987), the inclusion of females in control groups could mask a true global increase in glucose metabolism. De Volder et al. (1987) reported no differences in global glucose metabolism in 18 autistic children (11 males, 7 females, aged 2–18 years) compared to a control group which was comprised of children (3 normal children aged 7, 14, and 15 years; 3 children with unilateral pathology aged 9, 12, and 12.5 years) with various brain pathologies, as well as 15 adults (mean age 22 years). Few conclusions can be drawn from the De Volder study, since glucose metabolism shows marked changes with age (Chugani et al. 1987).

29.2.2 Regional Brain Glucose Metabolism Alterations in Autism and Related Disorders

29.2.2.1 Brain Glucose Metabolism in Autism

Horwitz et al. (1988) added four male autistic subjects to the series reported by Rumsey et al. (1985) and showed that the global brain glucose metabolic rate was 12% higher in the autistic group, a difference which was statistically significant. In addition, Horwitz et al. (1988) performed a correlation analysis, which showed significantly fewer positive correlations between frontal and parietal cortices, with the most notable discrepancy found between the left and right inferior frontal regions. Furthermore, the thalamus and basal ganglia also showed less correlation with frontal and parietal cortices in the autistic group compared to the controls.

Focal abnormalities of glucose metabolism have been reported in a number of other studies in which global brain glucose metabolism was not addressed. Heh et al. (1989) studied glucose metabolism in the cerebellum based upon neuropathological data showing fewer Purkinje and granule cells in the cerebellum (Bauman and Kemper 1994) and vermal cerebellar hypoplasia measured on MRI (Courchesne et al. 1988). However, Heh et al. showed no significant difference in mean glucose metabolic rates for cerebellar hemispheres or vermal lobes VI and VII in autistic subjects (5 males and 2 females; 19–36 years) compared to control subjects (7 males, 1 females; 20–35 years). Schifter et al. (1994) studied a heterogeneous group of children (9 males, 4 females; 4–11 years) with autistic behavior coexisting with seizures, mental retardation, and neurological abnormalities. Visual analysis of the FDG PET scans revealed that 5 of the 13 subjects had focal abnormalities located in different brain regions for each patient. Regions showing hypometabolism included the right cerebellum and left temporal/parietal/occipital cortices; right parietal cortex, bilateral thalamus, and left occipital cortex; right parietal and left temporal/parietal cortices; right parietal/occipital and left occipital cortices; and bilateral temporal lobes.

Buchsbaum et al. (1992) applied a visual continuous performance task, which was associated with greater right hemisphere than left hemisphere metabolism in autistic subjects (5 males, 2 females; 19–36 years) than in their normal control subjects (13 males; mean age 24 years). Siegel Jr et al. (1992) studied 16 high-functioning autistic adults (12 males, 4 females; 17–38 years) and 26 normal controls (19 males, 7 females, mean age 27 years) and reported that autistic subjects had a left > right anterior rectal gyrus asymmetry, as opposed to the normal right > left asymmetry in that region. The autistic group also showed low glucose metabolism in the left posterior putamen and high glucose metabolism in the right posterior calcarine cortex. The same group (Siegel et al. 1995) studied glucose metabolism in 14 adults with a history of infantile autism (12 men, 3 women, aged 17–38 years, mean 24 years; 15 of 16 subjects previously reported by Siegel Jr et al. 1992) and reported that autistic subjects showed abnormal thalamic glucose metabolism and that correlations of task performance with pallidal metabolism suggested subcortical dysfunction during the attentional task in autism. Haznedar et al. (1997) performed MRI and glucose PET scans on seven high-functioning autistic patients (5 males, 2 females; mean age 24.3 years) and seven sex- and age-matched normal adults. The right anterior cingulate was significantly smaller in relative volume and was metabolically less active in the autistic patients than in the normal subjects. However, this data was not corrected for partial volume effects, and the apparent decrease in glucose metabolism may be secondary to the reported volume decrease.

The same group more recently compared regional glucose metabolism in adults with ASD (21 males, 4 females; mean age 31.48 years) to those with schizophrenia (29 females; mean age 33.36 years). There was higher glucose metabolism across white matter regions, including the internal capsule, corpus callosum, and white matter in the frontal and temporal lobes, in the autism group (Mitelman et al. 2018a, b), while in the posterior cingulate, occipital cortex, hippocampus, basal ganglia parietal lobe, frontal premotor and eye fields, and amygdala, glucose metabolism was lower (Mitelman et al. 2018b).

Finally, there is an emerging group of pre- and posttreatment FDG PET studies in ASD. Park et al. (2017) employed deep brain stimulation (DBS) in the amygdala in a 14-year-old boy with ASD and self-injury. They reported high glucose metabolism in bilateral frontal cortices pre-DBS, whereas metabolism in the frontal cortices decreased to normal 2 years post-DBS. Żarnowska et al. (2018) studied a 6-year-old boy with ASD before and after treatment with the ketogenic diet. Pre-diet, there was glucose hypometabolism bilaterally in the mesial temporal lobes, basal ganglia, and cerebellum. After 12 months post-diet, there was markedly lower glucose metabolism diffusely in the whole cerebral cortex, with a relatively smaller reduction in the basal ganglia compared to pre-diet.

29.2.2.2 Glucose Metabolism in Autism and Infantile Spasms

An association of autism in children with a history of infantile spasms has been long recognized (Riikonen and Amnell 1981). Chugani et al. (1996) reported that 18 children (7 males, 11 females; 10 months to 5 years of age) from a total of 110

children with a history of infantile spasms showed bilateral temporal lobe glucose hypometabolism on PET, with normal MRI scans. Long-term outcome data was obtained for 14 of the 18 children; 10 of the 14 children met DSM-IV criteria for autism. All 14 children had continued seizures and cognitive impairment. Two temporal lobe regions, superior temporal gyrus and hippocampus, showed significant hypometabolism compared to age-matched controls. These observations are relevant not only because histological studies of postmortem brain tissue from autistic subjects show abnormalities in the hippocampus (Bauman and Kemper 1994), but also because recent studies using volumetric MRI in patients with fragile X syndrome have found abnormalities in the hippocampus (increased volume) and superior temporal gyrus (decreased volume) (Reiss et al. 1994). More recently, Dilber et al. (2013) studied a series of 90 patients with infantile spasms. Of the 90 patients with infantile spasms, 15 patients were diagnosed with autism using the Autism Behavior Checklist and the Childhood Autism Rating Scale. Compared to a group of nine patients with infantile spasms but no autism, the group with autism and infantile spasms (3–16 years) showed decreased metabolic activity in the temporal lobe as previously reported. In addition, 9/15 children with autism and infantile spasms showed decreased glucose metabolism in the frontal lobe, and 7/15 showed decreases in the parietal lobe. It is not clear whether the frontal and parietal lobe changes are specifically related to autism or whether these regions represent dysfunction related to their seizures.

29.2.2.3 Glucose Metabolism and Tryptophan Metabolism in Children with Autism and Tuberous Sclerosis

Asano et al. (2001) examined the relationship between autism and epilepsy in relation to structural and functional brain abnormalities in children with tuberous sclerosis complex (TSC). Children with TSC and intractable epilepsy underwent MRI and PET scans with FDG and alpha-[^{11}C]methyl-L-tryptophan (AMT). Based on the results of Autism Diagnostic Interview-Revised, Gilliam Autism Rating Scale, and overall adaptive behavioral composite (OABC) from Vineland Adaptive Behavior Scale, subjects were divided into three groups: autistic (OABC <70; $n = 9$), mentally retarded nonautistic (OABC <70; $n = 9$), and relatively normal intelligence (OABC > or =70; $n = 8$). PET studies showed that the autistic group had decreased glucose metabolism in the lateral temporal gyri bilaterally, increased glucose metabolism in the deep cerebellar nuclei bilaterally, and increased AMT uptake in the caudate nuclei bilaterally, compared to the mentally retarded nonautistic group. In addition, a history of infantile spasms and glucose hypometabolism in the lateral temporal gyri were both significantly associated with communication disturbance. Glucose hypermetabolism in the deep cerebellar nuclei and increased AMT uptake in the caudate nuclei were both related to stereotyped behaviors and impaired social interaction, as well as communication disturbance. These results suggested that generalized epilepsy in early life and functional deficits in the temporal neocortices may be associated with communication delays and that functional imbalance in subcortical circuits may be associated with stereotyped behaviors and impaired social interaction in children with TSC.

The same group assessed the structural and functional imaging features of cerebellar lesions and their neurobehavioral correlates in a large cohort of patients with tuberous sclerosis complex (Eluvathingal et al. 2006). A consecutive series of 78 patients with tuberous sclerosis complex underwent MRI and PET studies with FDG and AMT as part of their evaluation for epilepsy surgery. Neurobehavioral assessment included the Gilliam Autism Rating Scales (GARS) and the Vineland Adaptive Behavior Scales (VABS). Twenty-one patients (27%) had cerebellar lesions (10 boys; mean age 9 ± 8 years; 9 had right-sided, 10 had left-sided, and 2 had bilateral cerebellar lesions). The lesions showed decreased glucose metabolism (0.79 ± 0.10) and increased (1.04 ± 0.10) AMT uptake compared with the normal (nonlesional) cerebellar cortex. Comparisons between patients with (n = 20) and without (n = 57) a cerebellar lesion on neurobehavioral functioning, controlling for the number and location of cortical tubers, revealed that the cerebellar lesion group had higher overall autistic symptomatology. Within-group analyses of the cerebellar lesion group revealed that children with right-sided cerebellar lesions had higher social isolation and communicative and developmental disturbance compared to children with left-sided cerebellar lesions. The side of the cerebellar lesion was not related to adaptive behavior functioning. These findings provide additional empiric support for a role of the cerebellum in autistic symptomatology.

29.3 Focal and Global Brain Alterations Cerebral Blood Flow

29.3.1 Resting Cerebral Blood Flow

A number of studies of autistic subjects measuring cerebral blood flow with single-photon emission computed tomography (SPECT) can be found in the literature reporting a variety of global and focal abnormalities. George et al. (1992) reported global hypoperfusion in the resting state in adult autistic men with seizures (4 males, 22–34 years) compared to control subjects (2 males, 2 females; 25–32 years). George et al. (1992) further observed pronounced hypoperfusion in the frontotemporal cortices, whereas McKelvey et al. (1995) localized most consistent hypoperfusion to the vermis and the right cerebellar hemisphere in 3 adolescent autistic subjects (2 males, 1 female; 14–17 years). Mountz et al. (1995) also reported hypoperfusion in autistic subjects (5 males, 1 female; 9–21 years) compared to the control group (5 males, 2 females; 6–20 years) but localized it primarily to the left temporoparietal and the right anterior temporal region. In a study of cerebral perfusion using 99TCm-HMPAO in ten children (4–8 years) with autism and mental retardation, Gupta and Ratnam (2009) found generalized hypoperfusion in all ten cases compared to five age-matched controls.

Zilbovicius et al. (1992) measured regional cerebral blood flow with SPECT and ^{133}Xenon in 21 children (12 boys, 9 girls; aged 5–11 years, mean 7.4) with autism according to DSM-III-R criteria. Five cortical brain areas including the

frontal, temporal, and sensory association cortices were examined. The group with autism showed no cortical regional abnormalities compared to an age-matched group of 14 nonautistic children with slight to moderate language disorders. While the autistic subjects in this study were sedated, the control group (those with language disorders) was not. Zilbovicius et al. (1995) also studied cerebral blood flow in preschool autistic children in a longitudinal study. Five autistic children (three males, two females) were studied at the age of 3–4 years, and 3 years later were compared to two age-matched comparison groups of nonautistic children (5 children ages 3–4 years and 7 aged 6–12 years) with normal development. These investigators reported frontal hypoperfusion in autistic children at ages 3–4 years, but not at the ages of 6–7, and concluded that these results indicated a delayed frontal maturation in childhood autism. Chiron et al. (1995) compared blood flow in 18 autistic children (14 males, 4 females; 4–14 years) to 10 control subjects (5 males, 5 females; 4–16 years) and found that blood flow was greater in the left hemisphere in control subjects but greater in the right in autistic patients. All but one of the autistic subjects were sedated with intrarectal pentobarbitone and, in some cases, intramuscular droperidol, while only two of the ten control subjects were sedated. While barbiturates have been reported to decrease cerebral metabolism in adults (Theodore et al. 1986), Chiron et al. (1992) showed that cerebral blood flow induced by pentobarbitone was not statistically significant in children using ^{133}Xenon SPECT. Burroni et al. (2008) replicated a significant difference in right-left asymmetry in a study of 11 children with autism (6 boys, 5 girls, mean age 11.2 years) compared to an age-matched group of eigh normal children. Quantitative analysis was performed using a perfusion index and an asymmetry index. There was a global reduction of cerebral blood flow in the autism group and a significant difference in asymmetry with the right side showing higher blood flow in the autism group. Ito et al. (2005) compared 16 children with high-functioning autism (all male, 9–14 years, IQ 76–126) to 5 children with epilepsy (1 male, 4 females; 7–15 years) using ^{99m}Tc-ECD, and they reported significantly low relative cerebral blood flow in the left temporal region in the autism group based on a three-dimensional stereotactic region of interest template analysis. Sasaki et al. (2010) studied brain perfusion in 15 children (aged 4–16 years) with medically intractable epilepsy who also met the DSM-IV criteria for autism using ^{99m}Tc-ethyl cysteinate dimer SPECT, the easy Z-score imaging system (eZIS) program. For all of the children, the eZIS analysis showed a mixed hypoperfusion pattern, including the prefrontal cortex, medial frontal cortex, anterior cingulated cortex, medial parietal cortex, and anterior temporal cortex. There were two subgroups recognized based upon the pattern of hypoperfusion, the medial-cingulate type, and the temporal type, but these groups did not show any relationship with clinical symptoms. Also using ^{99m}Tc-ethyl cysteinate dimer SPECT evaluated using statistical parametric imaging, Yang et al. (2011) studied 23 children with ASD (mean age 7.3 ± 3 years), which included 14 with autism (11 males, 3 females) and 9 with Asperger's syndrome (9 male) compared to a control group (7 males, 1 females; mean age 5.5 + 2.4 years). The autism group showed significantly decreased cerebral blood

flow bilaterally in the frontal lobe and basal ganglia, while the Asperger group showed reductions bilaterally in the frontal, temporal, and parietal cortex and in the cerebellum. Wilcox et al. (2002) suggested that brain perfusion in autism varies with age in a study of 14 subjects with autism compared to age-matched control subjects ranging in age from 3 to 37 years. They reported prefrontal hypometabolism in all cases with autism, with further decreased metabolism in the frontal and left temporal lobe with increasing age.

Degirmenci et al. (2008) studied brain perfusion in children with autism (9 males, 1 females; mean age 6.9 ± 1.7 years), as well as their parents (8 fathers, mean age 39 years; 8 mothers, mean age 36 years) and siblings (7, mean age 13 + 5 years) and five age-matched children (three boys, two girls) as a control group using ^{99m}Tc-HMPAO brain SPECT. Visual and semiquantitative evaluations revealed hypoperfusion in the right posterior parietal cortex in three children with autism, in bilateral parietal cortex in one, bilateral frontal cortex in two, left parietal and temporal cortex in one, and right parietal and temporal cortex in one. Asymmetric perfusion was observed in the caudate nucleus in four children with autism. Semiquantitative analyses showed statistically significant hypoperfusion in the right inferior and superior frontal, left superior frontal, right parietal, right mesial temporal, and right caudate nucleus. Significant hypoperfusion was reported in the right parietal and bilateral inferior frontal cortex in the parent group and in the right frontal cortex, right caudate, and left parietal cortex in the sibling group. Thus, this study found hypoperfusion not only in the children with autism but also in their first-degree family members.

Most recently, resting blood flow was measured with PET/CT using the tracer [1-^{11}C] butanol, in adults with autism spectrum disorder (ASD) and normal IQ (Pagani et al. 2012). The ASD group (7 males, 6 females; 20–48 years) showed significant increases in cerebral blood flow in the right parahippocampal, posterior cingulated, primary visual and temporal cortex, putamen, caudate, substantia nigra, and cerebellum, compared to healthy controls (5 males, 5 females; 20–42 years). These results differ from earlier studies, which mainly reported hypoperfusion. However, these results are partially consistent with the studies of Chiron et al. (1995) and Burroni et al. (2008) that reported higher blood flow in the right hemisphere in the autism group.

Two newer aspects to blood flow imaging studies include examining effects of pharmacological agents on blood flow and use of blood flow patterns as a biomarker of autism. For example, Ozdemir et al. (2009) studied 11 children with autism (7 males, 4 females; 6–7 years) before and 3 months after treatment with risperidone with ^{99m}Tc-HMPAO SPECT. There was a significant increase in cerebral perfusion following risperidone treatment bilaterally in the prefrontal and frontal cortex. With regard to attempts to use imaging as a biomarker, Duchesnay et al. (2011) compared a dataset of 45 low-functioning children with ASD (37 males, 8 females; 5–12 years) to 13 non-ASD low-functioning children (9 males, 4 females; 5–15 years). Using the [O-15]-water PET rest functional brain abnormalities, including hypoperfusion in the right superior temporal sulcus and hyperperfusion in the left postcentral area, they were able to identify the ASD subjects with an accuracy of 88%, sensitivity of 91%, and specificity of 77%.

29.3.2 Blood Flow Changes During the Performance of Tasks

In a functional mapping study using [^{15}O]-water PET, Happe et al. (1996) applied a "theory of mind" task that required attributing mental states to the characters of a narrative. The statistical parametric mapping analysis showed that the Asperger's group (5 males, 20–27 years) showed a slightly different location of activation in the inferior prefrontal cortex (Brodmann area 9 instead of 8) compared to the normal control group (6 males, 24–65 years).

Müller et al. (1999) studied auditory perception and receptive and expressive language in five high-functioning autistic adults (4 men, 1 woman; 18–31 years) compared to five normal men (23–30 years) using an [^{15}O]water activation paradigm. Scans were performed at rest, while subjects listened to tones, short sentences, repeated short sentences, and generated sentences. Analyses of peak activations revealed reduced or reversed dominance for language perception in the temporal cortex and reduced activation of auditory cortex and the cerebellum during acoustic stimulation in the autistic group. Data from the four autistic men and five normal men were reanalyzed (Müller et al. 1998) to examine three predetermined regions of interest—dentate nucleus of the cerebellum, thalamus, and Brodmann area 46—based upon serotonin synthesis studies showing abnormalities in these three regions in autistic boys (Chugani et al. 1997, see below). The results of this study showed that the dorsolateral prefrontal cortex (area 46) and the thalamus in the left hemisphere and the right dentate nucleus showed less activation in the autistic men than in the control group for sentence generation. In contrast, with sentence repetition, increases in blood flow were significantly larger in the left frontal cortex and right dentate nucleus in the autistic subjects than the control group. These data suggest that the left frontal cortex, left thalamus, and right dentate nucleus showed atypical functional changes with language tasks in high-functioning autistic men.

Due to the small numbers of subjects, all of the functional mapping studies thus far performed should be considered pilot studies. However, this technique has been largely replaced by fMRI.

29.4 Protein Synthesis in Pervasive Developmental Disorder

Shandal et al. (2011) evaluated the cerebral protein synthesis rate of language brain regions in children with developmental delay with and without pervasive developmental disorder. Using L-[1-^{11}C]-leucine positron emission tomography (PET), eight children with developmental delay and pervasive developmental disorder (mean age, 76.25 months) were compared to eight children with developmental delay without pervasive developmental disorder (mean age, 77.63 months). There was a higher protein synthesis rate in developmental delay children with pervasive developmental disorder in the left posterior middle temporal region (P = .014). Furthermore, there was a significant correlation of the Gilliam Autism Rating Scale autism index score with the protein synthesis rate of the left posterior middle temporal region (r = .496, P = .05). In addition, significant asymmetric protein synthesis (right > left) was observed in the developmental delay group without pervasive

developmental disorder in the middle frontal and posterior middle temporal regions (P = .03 and P = .04, respectively). This study suggested that abnormal language area protein synthesis in developmentally delayed children may be related to pervasive developmental delay.

29.5 Neuroinflammation in ASD

There have been a number of neuropathology reports linking neuroinflammation to ASD (Vargas et al. 2005; Morgan et al. 2010). Neuroinflammation can be assessed in vivo using tracers aimed at the translocator protein (TSPO) that is upregulated in neuroinflammation in the mitochondria in microglia and astrocytes (Werry et al. 2019). Suzuki et al. (2013) studied microglial activation in young adults with ASD using the tracer [^{11}C](R)-PK11195. They reported significantly higher binding potential in the cerebellum, midbrain, pons, fusiform gyri, anterior cingulate, and orbital frontal cortex in men with ASD (n = 20, mean age 18.3) compared to 20 age- and IQ-matched adults. Using the second-generation TSPO tracer [^{11}C]PRB and PET-MR, Zürcher et al. (2020) failed to replicate this result. They found no brain regions showing higher TSPO binding in the ASD group (n = 15, mean age 24.1) compared to 18 matched controls. Further, there was lower [^{11}C]PRB binding in the bilateral insular cortex, bilateral precuneus/posterior cingulate cortex, and bilateral temporal, angular, and supramarginal gyri. While Suzuki et al. (2013) concluded there was microglial activation in ASD, Zürcher et al. (2020) suggested that lower TSPO binding reflected altered neuroimmune response or mitochondrial dysfunction in ASD.

While α-[^{11}C]methyl-tryptophan (AMT) was originally developed to measured serotonin synthesis in the brain (see section on serotonin synthesis below), it also measures the kynurenine pathway (Chugani and Muzik 2000). The kynurenine pathway is activated with neuroinflammation, and thus AMT PET studies may provide information about neuroinflammation in ASD. Chugani et al. (2016) employed AMT as a biomarker of drug response to buspirone in children aged 2–6 years with ASD. For the entire sample having a PET scan (N = 119), 65 showed at least 1 focal region with increased AMT uptake. Focal abnormalities were present in the basal ganglia (N = 27), thalamus (N = 24), cerebellum (N = 27), and brainstem (N = 26). Theses brain regions showing focally increased AMT may represent tryptophan metabolism by the kynurenine pathway and brain inflammation. In that study, the number of focal increases of AMT was significantly related to improvement in repetitive behavior, with fewer focal abnormalities associated with more improvement.

29.6 Studies of Neurotransmitter Function with PET and SPECT in Autism

Given the number of radiolabeled probes available for the study of neurotransmission with PET and SPECT, it is surprising that relatively few have been employed in the study of autism. Studies investigating alterations in neurotransmitters with PET in autism have focused on dopamine, serotonin, GABA, acetylcholine, and glutamate.

29.6.1 Dopamine Precursor and Transporter Studies

Ernst et al. (1997) studied 14 medication-free autistic children (8 boys, 6 girls, mean age 13 years) and 10 healthy children (7 boys, 3 girls, mean age 14 years) with [^{18}F]-labeled fluorodopa (FDOPA) using PET. FDOPA is a precursor of dopamine, which is taken up, metabolized, and stored by dopaminergic terminals. Ernst and colleagues calculated the ratio of activity measured between 90 and 120 min following tracer administration in the caudate, putamen, midbrain, and lateral and medial anterior prefrontal regions (regions rich in dopaminergic terminals) to that in the occipital cortex (a region poor in dopaminergic terminals). They reported a 39% reduction of the anterior medial prefrontal cortex/occipital cortex ratio in the autistic group, but there were no significant differences in any other region measured. These authors suggest that decreased dopaminergic function in the prefrontal cortex may contribute to the cognitive impairment seen in autism. More recently, the dopamine transporter was studied in children with autism (10 boys, 3–10 years) and 10 age- and gender-matched healthy children with the tracer ^{99m}Tc-TRODAT-1 imaged by SPECT (Xiao-Mian et al. 2005). This study reported a whole-brain increase in dopamine transporter binding in the autism group, whereas the striatum/cerebellum ratio showed no differences between the groups. Nakamura et al. (2010) measured dopamine transporter binding in adults with autism (20 men, 18–26 years) using [^{11}C]WIN-35,428 imaged with PET. Dopamine transporter binding was significantly higher in the orbital frontal cortex in the autism group compared to 20 age- and IQ-matched control subjects. Finally, Makkonen et al. (2008) reported no difference in striatal dopamine transporter binding in 15 children with autism (14 boys, 1 girl; 5–16 years) compared to 10 nonautistic children using the tracer [^{123}I]nor-b-CIT, which labels both the dopamine and serotonin transporter, imaged by SPECT. Subsequently, this group reported that clinical responders to fluoxetine showed a decrease in DAT binding, while nonresponders showed a trend for an increase in binding (Makkonen et al. 2011). Together these studies suggest altered dopaminergic function in frontal cortical regions but not in striatum in children and adults with autism.

29.6.2 Serotonin Precursor, Transporter, and Receptor Studies

Although there is an evidence for the potential involvement of several neurotransmitters in autism, the most consistent abnormal neurotransmitter findings involve serotonin. Schain and Freedman (1961) first reported increased blood serotonin in approximately one-third of autistic patients in 1961. Chugani et al. (1997) applied AMT as a PET tracer in children with autism. AMT, which was developed as a tracer for serotonin synthesis with PET (Diksic et al. 1990), is an analogue of tryptophan, the precursor for serotonin synthesis. Two fundamentally different types of serotonergic abnormality were found in children with autism (Chugani et al. 1997, 1999, Chandana et al. 2005). The first is a difference in whole-brain serotonin synthesis capacity in autistic children compared to age-matched nonautistic children. Serotonin synthesis capacity was greater than 200% of adult values until the age of

5 years and then declined toward adult values in nonautistic children. In contrast, serotonin synthesis capacity in autistic children increased gradually between the ages of 2 years and 15 years to values 1.5 times the adult normal values (Chugani et al. 1999). These data suggested that humans undergo a period of high brain serotonin synthesis capacity during early childhood and that this developmental process is disrupted in autistic children. The second type of abnormality reported relates to focal abnormalities in brain serotonin synthesis. Asymmetries of AMT uptake in the frontal cortex, thalamus, and cerebellum were visualized in children with autism, suggesting a role of the dentato-thalamo-cortical pathway in autism (Chugani et al. 1997). Subsequently, the same group measured brain serotonin synthesis in a large group of autistic children (n = 117) with AMT PET and related these data to handedness and language function (Chandana et al. 2005). Cortical AMT uptake abnormalities were objectively derived from small homotopic cortical regions using a predefined cutoff asymmetry threshold (>2 SD of normal asymmetry). Autistic children demonstrated several patterns of abnormal cortical involvement, including the right cortical, left cortical, and absence of abnormal asymmetry. Groups of autistic children, defined by the presence or absence and side of cortical asymmetry, differed on a measure of language as well as handedness. Autistic children with left cortical AMT decreases showed a higher prevalence of severe language impairment, whereas those with right cortical decreases showed a higher prevalence of left and mixed handedness. These results suggest that global as well as focal abnormally asymmetric development in the serotonergic system could lead to miswiring of the neural circuits specifying hemispheric specialization.

Decreased serotonin transporter binding has been reported in both children and adults with autism. Makkonen et al. (2008) using the SPECT tracer [^{123}I]nor-ß-CIT, labeling both the dopamine and serotonin transporter described above, reported reduced serotonin transporter binding capacity in the medial frontal cortex, midbrain, and temporal lobes. Similarly, Nakamura et al. (2010) reported decreased serotonin transporter binding throughout the brain in adults with autism (20 men, 18–26 years) using [^{11}C]McN-5652 imaged with PET. Furthermore, the reduction in binding in the anterior and posterior cingulate cortices was correlated with impairment in social cognition, while the reduction in serotonin transporter binding in the thalamus was correlated with repetitive and/or obsessive behavior. In contrast, Girgis et al. (2011) reported no significant difference in brain serotonin transporter binding, measured with [^{11}C]DASB and PET, in a group of eight adults with Asperger's disorder (mean age 29.7 years) and eight healthy control subjects matched for age, gender, and ethnicity. All subjects in this study had normal intelligence, while this was not the case for the other studies reporting changes in serotonin transporter binding. Hirosawa et al. (2017) performed a pilot study of [^{11}C]DASB PET as a biomarker of response to oxytocin in ten men with ASD, but [^{11}C]DASB binding potential was not related to drug response.

Serotonergic neurotransmission was also studied using tracers for receptor binding. Murphy et al. (2006) measured $5HT_{2A}$ receptors in eight men with Asperger's syndrome (mean age 26 years) using the SPECT tracer [^{123}I]5-I-R91150, compared to ten healthy age-matched men. The group with Asperger's syndrome

has significantly reduced serotonin receptor binding in total, anterior, and posterior cingulate cortex, bilaterally in frontal and superior temporal lobes and in the left parietal lobe. Interestingly, there were significant correlations with qualitative abnormalities in social interaction with binding reductions in the anterior and posterior cortices, as well as the right frontal cortex. More recently, 5-HT2 receptor distribution was measured with the PET tracer [^{18} F]setoperone in six high-functioning autistic adults compared to ten matched control subjects (Beversdorf et al. 2012). In this study, reduced serotonin receptor binding was found in the thalamus, and there was a negative relationship between thalamic binding and history of language impairment. Goldberg et al. (2009) compared the parents of children with autism (19 parents from 11 families, 8 females, 11 males) compared to adults who do not have children with autism (9 females, 8 males). The cortical 5HT2 binding potential, using [^{18}F]setoperone, to measure cortical serotonin type-2 receptor (5-HT$_2$) using PET, was significantly lower in the autism parent group compared to the control group. Furthermore, the 5HT$_2$ binding potential was inversely correlated with platelet serotonin levels in the parent group. These results are interesting in light of family members having what has been described as the broader phenotype of autism. Finally, Girgis et al. (2011) reported no difference in 5-HT$_{2A}$ receptor binding in a PET study using the tracer [^{11}C]MDL 100907 in a group of 17 adults with Asperger's disorder (mean age 34.3) compared to 17 healthy matched adults.

In order to assess the role of serotonin signaling at the 5HT1$_A$ receptor with oxytocin treatment, Lefevre et al. (2018) measured [^{18}F]MPPF binding with PET before and after intranasal administration of oxytocin. ASD subjects (n = 18, mean age 34.3 years) and controls (n = 24, mean age 26.3 years) did not differ on binding at baseline. Following oxytocin treatment, there was increased [^{18}F]MPPF binding in the healthy controls but not in the ASD group. These results demonstrate altered serotonin signaling in response to oxytocin in ASD and may limit efficacy of this treatment.

In summary, molecular imaging studies provide convincing evidence of altered serotonergic neurotransmission in both children and adults with autism, as well as in parents of autistic individuals. Altered serotonin synthesis, serotonin transporter, and serotonin receptors have been measured using PET and SPECT and different tracers in small groups of children and adults with autism compared to age-matched controls. These probes are increasingly being used as biomarkers to assess drug response to treatment.

29.6.3 GABA$_A$ Receptor Binding Studies

Cytogenetic studies reported the abnormalities in chromosome 15 in autism, specifically 15q11-13, the region encoding several GABA$_A$ receptor subunit genes (GABRB3, GABRA5, and GABRG3) (Silva et al. 2002; Menold et al. 2001; Buxbaum et al. 2002). Menold et al. reported two single-nucleotide polymorphisms located within the GABRB3 gene in autism. Moreover, symptoms of

autism can be associated with both Prader-Willi and Angelman syndromes, both of which involve alterations in the chromosome 15q11-13 region (for review see Soejima and Wagstaff 2005). Deletion of the maternal chromosome in this region results in Angelman syndrome, which is characterized by severe mental retardation, epilepsy, a puppetlike gait, and lack of speech. Deletion of the paternal chromosome 15q11-q13 results in Prader-Willi syndrome, which is characterized by mild or moderate mental retardation, hypotonia, obesity, and genital abnormalities. This region of chromosome 15 encodes $GABA_A$ receptor subunit genes GABRB3, GABRA5, and GABRG3 (Menold et al. 2001; Buxbaum et al. 2002; Wagstaff et al. 1991). [^{11}C]Flumazenil PET has been used to examine whether there are $GABA_A$ receptor binding abnormalities in patients with Angelman syndrome and Prader-Willi syndrome. Angelman patients with a maternal deletion of 15q11-13 leading to the loss of β3 subunit of the GABA receptor showed significantly decreased binding of [^{11}C]flumazenil in the frontal, parietal, hippocampal, and cerebellar regions compared to a patient whose deletion did not include the GABRB3 gene (Holopainen et al. 2001). Lucignani et al. (2004) studied six adults with Prader-Willi syndrome and found decreased [^{11}C]flumazenil binding in the insula and cingulate, frontal, and temporal neocortices compared to normal control subjects. Finally, Pearl et al. (2009) studied seven patients with succinic semialdehyde dehydrogenase deficiency with [^{11}C]flumazenil, compared to ten unaffected parents and eight healthy controls. Autistic behaviors, seizures, intellectual impairment, hypotonia, and hyporeflexia are found in patients with succinic semialdehyde dehydrogenase deficiency. Decreased $GABA_A$ receptor binding was lower in the amygdala, cerebellar vermis, and frontal, parietal, and occipital cortices in patients compared to both control groups. Thus, these imaging studies demonstrate decreased $GABA_A$ receptor binding in all of these genetic disorders in which autistic behavior is present. These studies demonstrate the utility of PET in elucidating the functional consequence of specific genetic abnormalities.

A study of GABA receptors in children with autism was performed using SPECT and the tracer [^{123}I]-iomazenil (Mori et al. 2012). In this study, 9 children with autistic disorder (mean age 7.3 years) and 15 children with Asperger's disorder (mean age 7.0 years) were compared to an age-matched group of 10 children with partial epilepsy (mean age 7.8 years), using stereotactic extraction estimation analysis. When comparing the ASD group to the focal epilepsy group, there were significant decreases in binding in the left superior frontal gyrus (29.4%), the right superior frontal gyrus (23.9%), and the left medial frontal gyrus (28.7%). When the comparison was done dividing the ASD group based upon intellectual impairment, only the group with intellectual impairment showed significantly decreased binding. In addition, they divided the ASD group based upon the presence (n = 6) and absence (n = 12) of focal epileptiform discharges. Both EEG-based groups showed the decreased frontal lobe binding, although the decreases were larger in the group with focal epileptiform discharges. Likewise, decreased GABA-benzodiazepine receptor binding has been reported in three adult males with high-functioning ASD compared to three healthy matched control subjects (Mendez et al. 2013). In a PET pilot

study with the tracer [^{11}C]Ro15-4513, which binds to α1 and α5 subunits of the $GABA_A$ receptor, there was significantly lower distribution volume in the group with ASD in 83 brain regions studied. Post hoc analyses with Bonferroni correction showed significant reductions only in the right and left nucleus accumbens and right and left subcallosal area. Using kinetic analyses, the authors report that the decreased binding was largely due to decreased α5 receptor binding site. These in vivo binding studies in both children and adults are consistent with studies in postmortem tissue showing decreased $GABA_A$ receptors (Blatt et al. 2001; Oblak et al. 2009, 2010, 2011) and GAD expression in ASD (Yip et al. 2008, 2009). In contrast, Horder et al. (2018) reported no difference in [^{11}C]flumazenil or [^{11}C]Ro15-4513 binding in adults with ASD compared with matched controls. These authors suggested that decreases in binding shown in previous studies might be confounded by the effect of medication use.

29.6.4 Acetylcholine

A number of fMRI studies have shown altered responses to face stimuli in fusiform gyrus and subjects with ASD. Suzuki et al. (2011) measure acetylcholinesterase activity in 20 adults with ASD using the tracer *N*-[^{11}C]methyl-4-piperidyl acetate. Acetylcholinesterase activity expressed in terms of the rate constant k_3 was lower bilaterally in the fusiform gyri in the group of adults with ASD compared to 20 matched control subjects. Furthermore, k3 values were negatively correlated with measures of social interaction.

29.7 Glutamate

Based upon studies of postmortem brain showing increased metabotropic glutamate receptor 5 in ASD, Fatemi et al. (2018) employed the tracer [^{18}F]-FPEB to measure mGluR5 binding in vivo. In this pilot study, there was significantly higher binding in the postcentral gyrus and cerebellum in the group with ASD (n = 6, mean age 20 years) compared to controls (n = 3, mean age 27 years).

29.8 Conclusions and Future Directions

These studies outlined here have only just begun to tap the surface of neurochemical and molecular measures possible. Future directions will be aided by the identification of the genetic causes of autism, decreasing the heterogeneity in the samples of people with ASD in the study. In addition, advances may be made by the combining imaging modalities that have been made possible by new software and hardware. For example, the implementation of PET/MR is an important advancement particularly for pediatric applications. This will allow both structural and neurochemical studies to be acquired in the same imaging session. PET/MR could provide both

presynaptic and postsynaptic measures of GABA function—MRS allows the measurement of GABA concentration in tissue, and [^{11}C]flumazenil allows the measurement of the $GABA_A$ receptor. Importantly for pediatrics, this PET/MR will eliminate the need for two sedations, co-registration, and arterial blood sampling for modeling and will facilitate advanced image analysis procedures. Finally, assessment of neurochemistry in vivo with neuroimaging has the potential, like no other imaging modality, to directly guide new pharmacological interventions and provide biomarkers for predicting drug response.

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PET and SPECT Imaging in ADHD

30

Gilles N. Stormezand

Contents

Abstract

ADHD is a clinically heterogeneous neuropsychiatric disorder with a childhood onset and is often accompanied by comorbidities. Symptoms consisting of inattention with or without hyperactivity or impulsivity may result from disturbances of higher cognitive control, involving multiple regions of the brain which are functionally connected. Although the value of PET and SPECT in establishing diagnosis is limited, it has added to understanding the neurobiological basis of

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ADHD. Investigations of cerebral perfusion and glucose metabolism during resting conditions and specific tasks have led ADHD to be associated with reduced functionality of the prefrontal cortex and the anterior cingulate cortex, as well as the basal ganglia, cerebellum and parietal lobe. In addition, there is a growing body of literature assessing the dopamine transporter, endogenous levels of dopamine, response to treatment with methylphenidate and the relationship with genotypes in ADHD with few studies having assessed serotonergic and noradrenergic functioning.

30.1 Introduction

In this chapter, an overview of the insights gained from PET and SPECT imaging in attention deficit hyperactivity disorder (ADHD) will be provided. Most research has focused on the detection of functional deficits in resting or fixed conditions, task-related disturbances and alterations in neurotransmitter systems, predominantly the dopaminergic system. More recently, studies have aimed to relate functional imaging findings to genotypes and specific behavioural characteristics, such as measurements of inattention, hyperimpulsivity and motivation.

ADHD is defined as a developmentally inappropriate disorder characterized by a combination of symptoms of inattention and hyperactivity/impulsivity (American Psychiatric Association 2013). The symptoms must be present for at least 6 months, and individuals must express several symptoms before the age of 12. In addition, the symptoms must be exhibited in at least two settings. ADHD can phenotypically be subdivided into the combined type, a predominantly inattentive type and a predominantly hyperactive/impulsive type. ADHD is the most prevalent as well as the most commonly treated neuropsychiatric condition in school-aged children (Goldman et al. 1998). In the USA, the prevalence is estimated between 5 and 8% (Dulcan 1997) and is similar to estimates worldwide (Faraone et al. 2003). The syndrome is much more common in boys than in girls (Wolraich et al. 1996). The symptoms persist into adulthood in up to 65% of cases, although only 16% of children with ADHD fulfil DSM criteria for ADHD at the age of 20 (Faraone et al. 2006). Typically, symptoms of inattention (40%) disappear at a lower rate than symptoms of hyperactivity (70%) and impulsivity (70%), which tend more to fade from childhood into adulthood (Biederman et al. 2000).

The symptoms of ADHD have often been ascribed to some sort of self-dysregulation. A growing emphasis has been placed on deficits of higher cognitive control, e.g. the ability to suppress inappropriate actions in favour of more appropriate ones (Casey and Durston 2006). These include motivational deficits (Johansen et al. 2009) and disturbances of executive functioning (Walshaw et al. 2010). ADHD patients often do not express symptoms of ADHD alone. Comorbidities are frequently encountered in ADHD patients, who have been reported to be at increased risk of developing delinquency, mood, anxiety and substance use disorders (Biederman et al. 1991). Oppositional defiant disorder, conduct disorder and

learning disorders are most prevalent in children, whereas antisocial disorder and alcohol/drug dependency are often observed in adults (Biederman 2005).

30.2 Aetiology

Both environmental and genetic aspects are likely to be involved in the aetiology of ADHD. Strong support for a genetic aetiology has been provided by studies of familial ADHD and studies establishing linkages between genotypes and an increased probability of developing ADHD. Based on numerous twin studies, heritability of ADHD is estimated 77% (Spencer et al. 2007a). Molecular genetic studies have associated polymorphisms at the dopamine transporter (DAT) gene (Cook Jr et al. 1995) and dopamine receptor D4 gene (DRD4) (Faraone et al. 2001) with ADHD, in particular the ten-repeat allele at the DAT1 gene and the seven-repeat allele at the DRD4 gene. However, given the prevalence of these alleles in the Caucasian population (10R DAT 1 allele $p \sim 0.75$ (Cook Jr et al. 1995), 7R DRD4 allele $p \sim 0.12$ (LaHoste et al. 1996)), it has to be stressed that the individual contribution of these genes to developing ADHD is modest. Environmental factors contributing to the onset of ADHD symptoms have been identified in the perinatal period, including prenatal exposure to teratogens and low birth weight (Mick et al. 2002a, b). Current models assume an interplay between both genetic and environmental aspects in developing clinical ADHD (Swanson et al. 2007). More recently, the focus of research has shifted towards inflammatory conditions in utero and a potential role of neuroinflammation in the development of ADHD (Dunn et al. 2019).

30.3 Neuroanatomy

In studies using nuclear imaging techniques, frontal and striatal structures have often been implicated in the brain localization of ADHD-related deficits (Table 30.1). Increasing evidence has come to suggest an involvement of the cerebellum, giving rise to a proposed disorder of the cerebello-striato-frontal cortical network. A theoretical framework has been developed in order to facilitate interpretation of functional deficits in ADHD. Nigg et al. conceptualized ADHD as a disorder of cognitive control, in which individuals with ADHD are unable to adjust behaviour appropriately when something unexpected occurs (Casey and Durston 2006; Nigg and Casey 2005). Key brain regions implicated in cognitive control are, first, the frontostriatal circuitry in predicting *what* will happen in a given context and, second, the frontoneocerebellar circuitry in predicting *when* the event may occur. Third, the frontoamygdalar circuitry is recruited in affect regulation, motivation and reactive response (Nigg and Casey 2005). The prefrontal cortex has been linked with several aspects thought to be affected in ADHD, including attention, inhibition, planning and working memory (Fassbender and Schweitzer 2006). It is interconnected with neocortical sensory and motor systems as well as subcortical structures, allowing to exert a top-down modulation of a wide variety of brain functions (Miller 2000). The striatum

Table 30.1 PET and SPECT studies of glucose metabolism and perfusion in ADHD during resting or fixed conditions

Series	*N* and clinical diagnosis	Technique and radiotracer	Study design	Findings	Specifications
Kim et al. (2010)	21 ADHD 11 NC	SPECT and ^{99m}Tc-HMPAO	Cross-sectional	Significant hypoperfusion in the right orbitofrontal, right medial gyri, the bilateral putamen and cerebellum of ADHD patients	All participants were Korean boys All participants were stimulant naïve Voxel-based analysis ($p < 0.0005$ uncorrected)
Oner et al. (2005)	29 ADHD 12 Epilepsy	SPECT and ^{99m}Tc-HMPAO	Cross-sectional	Significant reduction of prefrontal asymmetry indices in ADHD with age	All subjects were children between 7 and 14 years old ROI analysis ($p < 0.05$)
Lee et al. (2005)	40 ADHD 17 NC	SPECT and ^{99m}Tc-HMPAO	Longitudinal and cross-sectional	Decreased rCBF in the middle prefrontal region, middle temporal region and bilateral posterior cerebellar cortices in ADHD patients. Increased rCBF in the superior parietal region and in occipitoparietal junctions. MPH treatment reduced differences	All participants were children Patients were stimulant naïve at baseline Voxel-based analysis ($p < 0.01$ uncorrected)
Schweitzer et al. (2003)	10 ADHD	PET and [^{15}O]-H_2O	Longitudinal	Higher rCBF in the posterior cerebellum on MPH treatment. Off MPH treatment patterns were associated with higher rCBF in the bilateral precentral gyrus and left caudate nucleus	All participants were men 'Off' condition: 8 days without MPH treatment Voxel-based analysis ($p < 0.001$ uncorrected and $p < 0.05$ corrected)
Ernst et al. (1998a)	39 ADHD 56 NC	PET and [^{18}F]-FDG	Cross-sectional	No difference in rCMRglc between groups. Age was significantly negatively correlated with rCMRglc in women with ADHD	Participants were adults between 18 and 56 years old Prior stimulant treatment not specified ROI-based analysis ($p < 0.05$ corrected)

Table 30.1 (continued)

Series	*N* and clinical diagnosis	Technique and radiotracer	Study design	Findings	Specifications
Ernst et al. (1997)	10 ADHD	PET and [^{18}F]-FDG	Cross-sectional	Higher rCMRglc in the right anterior putamen and in the limbic region in ADHD. Lower rCMRglc in the left anterior putamen and left Sylvian region in ADHD	All participants were girls
	11 NC				8/10 ADHD patients received prior MPH treatment
					ROI-based analysis
Sieg et al. (1995)	10 ADHD	SPECT and [^{123}I] IMP	Cross-sectional	Relatively reduced left-to-right ROI count in global, frontal and parietal regions in ADHD	Participants were between 6 and 16 years old
	6 MC				Controls were a mixed psychiatry group
					Control group tended to be older
					Prior stimulant treatment not specified
					ROI-based analysis
Zametkin et al. (1990)	25 ADHD	PET and [^{18}F]-FDG	Cross-sectional	Lower global absolute CMRglc in ADHD and in 30 of 60 ROIS	Participants were adults
	50 NC				Patients were stimulant naïve
					ROI-based analysis ($p < 0.05$ uncorrected)
Lou et al. (1990)	9 ADHD	SPECT and ^{133}Xe	Cross-sectional	Reduced rCBF in striatal and posterior periventricular regions in ADHD. Increased rCBF in the occipital cortex in ADHD	Patients were between 6 and 15 years old
	15 NC				Prior stimulant use not specified
					ROI-based analysis ($p < 0.05$ uncorrected)

NC normal controls, *MC* mixed control group

receives input from limbic, associative and motor areas of the prefrontal cortex (Haber et al. 2000). It can be functionally subdivided into the ventral striatum, involved in emotion, motivation and reward-guided behaviours; the associative striatum, related to cognition; and the sensorimotor striatum, modulating motor function (Haber 2003). Impulsivity in ADHD might be a consequence of impaired integration of reinforcing or avoidance stimuli from the ventral striatum and ventral amygdala, respectively, with the current behaviour of the child (Nigg and Casey 2005).

30.4 Structural Imaging

Structural imaging has revealed differences between ADHD patients and healthy controls in multiple regions of the brain, the most consistent finding being smaller sizes of particular brain structures in ADHD patients. Controversy exists as to whether this is more prominent on the left side or on the right side. In a review by Seidman et al., a decrease of 3–5% in total cerebral volume was reported in 7 of 12 included imaging studies, mostly in the right hemisphere (Seidman et al. 2005). The most commonly reported structural abnormalities include a smaller volume of the prefrontal cortex, corpus callosum (particularly posterior regions), caudate nucleus (either right or left) and cerebellum (mostly posterior and inferior lobes) (Seidman et al. 2005). Most studies have been performed in a paediatric population, and it is highly questionable whether these findings can be extrapolated to the adult population. One study by Castellanos et al. addressed this issue. In this case-control study, structural differences between ADHD patients and healthy controls in childhood persisted into adolescence, except for the caudate nucleus, in which a normalization effect with age was present (Castellanos et al. 2002). More recently, the efforts of the Enhanced Neuroimaging Genetics through Meta-Analysis Study Group, employing data of a much larger number of subjects (ADHD $n = 2246$ and controls $n = 1934$), have firmly confirmed the presence of structural differences in patients with ADHD (Hoogman et al. 2017). These changes were more apparent when multimodal imaging and graph-theoretical analyses were used. Despite the statistical significance, it was still noted that the relatively small effect sizes do not allow the use of MRI for diagnosis.

30.5 Functional Imaging: Cerebral Blood Flow and Glucose Metabolism

Rather than being described in terms of structural abnormalities, ADHD research may benefit more from a functional imaging approach. As clinical evaluation is considered the mainstay for establishing the diagnosis of ADHD, the role of functional imaging for establishing diagnosis may be limited. However, functional imaging may have great value in defining ‘endophenotypes’ in ADHD, correlating behavioural characteristics and genotypes with specific functional deficits. The role of functional imaging is further enhanced by a lack of histopathological studies of ADHD, which renders functional imaging essential to develop insight into the neural basis of ADHD. Methods for assessing functionality in ADHD include fMRI, PET, SPECT, QEEG and MRS. In children, fMRI may be the most suitable method to investigate activational neural circuitries, because of radiation dosimetry issues with nuclear imaging techniques. PET and SPECT studies in ADHD have mostly focused on adults, except for the majority of studies assessing cerebral perfusion. PET and SPECT imaging has been performed both at resting or fixed conditions and during tasks. Table 30.1 summarizes the findings on cerebral perfusion (CBF) and glucose metabolism (CMRglc) in ADHD during resting or fixed conditions. The

table serves to highlight brain regions which may be functionally impaired in ADHD as well as to illustrate differences among studies in sample sizes, group characteristics, statistics and radiotracers used. Limitations, particularly of the earlier studies, include prior use of stimulant medication, small sample sizes, mixed or lacking control groups, demographic differences among groups and a region-of-interest (ROI)-based approach.

Analogous to structural imaging results, functional imaging reports investigating lateralization have yielded inconsistent results. Langleben et al. found an elevated left-to-right perfusion ratio in the frontal and temporal regions using voxel-based ^{99}mTc-ECD SPECT in prepubescent boys with ADHD who had the most severe symptoms (Langleben et al. 2001). In addition, Oner et al. reported relative right-sided hypoperfusion in the prefrontal lobes during resting conditions in 29 drug-naïve ADHD children (age 7–13), which tended to normalize with age (Oner et al. 2005). However, the opposite (right > left perfusion asymmetry) was observed by Spaletta et al. in the dorsolateral prefrontal cortex (Spalletta et al. 2001).

30.6 Task-Related Functional Imaging

It can be seen from Table 30.1 that studies performed under resting or fixed conditions tend to show disparate results with multiple brain regions affected across studies. Although these findings could be indicative of a more widespread area in the brain with altered functionality in ADHD, it might also be related to individual differences which are not ADHD specific. Therefore, it can be hypothesized that functional imaging would benefit from the integration of tasks, during which functional deficits related to ADHD become apparent. During task execution, ADHD patients may demonstrate both regions of hypoactivity and hyperactivity in comparison to controls. The former can be viewed of as a reduced capability to recruit a certain brain region which is necessarily activated in the healthy subject, whereas the latter can be seen as inefficient, requiring extra energy to perform a task. Alternatively, activation of regions which are not normally activated could reflect the usage of a compensatory mechanism. Discriminative tasks across (paediatric) ADHD literature typically allow assessment of components of executive functioning, such as inhibition, working memory, planning, set shifting and fluency (Walshaw et al. 2010). The studies referred to in the following paragraph make use of a specific task to identify dysfunctions related to ADHD.

Amen et al. applied perfusion SPECT both during resting conditions and a concentration task to assess functional differences between adults with ADHD ($n = 27$) and healthy controls ($n = 20$). The most significant differences were observed in the prefrontal orbits and poles. Reduced activation of these regions was associated with a post hoc sensitivity and specificity of above 74% for discriminating ADHD from controls (Amen et al. 2008a). Ernst et al., using [^{15}O]-H_2O PET and a decision task, found that normal controls ($n = 12$) were more likely to activate the right anterior cingulate cortex and the left hippocampus than subjects with ADHD ($n = 10$) (Ernst et al. 2003). It can be hypothesized that impaired functioning of the prefrontal

cortex and anterior cingulate cortex may lead to the compensatory usage of different brain regions. In correspondence, Schweitzer et al. reported increases in cerebral perfusion predominantly in the occipital areas in men with ADHD during the Paced Auditory Serial Addition Task, which is used to assess working memory, whereas non-ADHD men showed increased perfusion in the anterior cingulate and frontal regions. Interestingly, the ADHD patients confirmed to have used visual strategies, consistent with activation of the occipital cortex. This finding might thus be reflective of the compensatory use of visuospatial skills in ADHD (Schweitzer et al. 2000).

In order to increase statistical power, some researchers have aimed to combine results from studies to create ADHD versus control contrasts. An activation-likelihood estimation (ALE) meta-analysis performed by Dickstein et al., combining data from 16 neuroimaging studies (13 fMRI and 3 PET), revealed that healthy controls were more likely than ADHD subjects to activate the left ventral prefrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, bilateral parietal lobe, right thalamus, left middle occipital cortex and right claustrum, extending from the insula to striatum. ADHD patients tended to activate the insula within the frontal lobe and portions of the middle frontal cortex, left thalamus and the right paracentral lobule more than controls (Dickstein et al. 2006). Another very recent review combining 55 task-based fMRI studies showed specific patterns of altered activity in children and in adults with ADHD. In children with ADHD, significant hypoactivity was reported in the frontal regions and putamen bilaterally, as well as the right parietal and right temporal regions, whereas hyperactivity was seen in the right angular gyrus, middle occipital cortex, posterior cingulate cortex and midcingulate cortex. Adults with ADHD displayed a less widespread pattern of altered activity in relation to controls. Hypoactivity relative to controls was observed in the right central sulcus, precentral sulcus and middle frontal gyrus in subjects with ADHD. Relative hyperactivity was seen in a region with a peak in the right angular and middle occipital gyri (Cortese et al. 2012). Thus, the results from task-based functional imaging implicate that ADHD pathophysiology may involve different functionally interconnected neuronal networks (Yeo et al. 2011), e.g. reduced recruitment of the ventral and somatomotor networks in children and the frontoparietal system in adults, which may be compensated for by other neuronal systems.

30.7 Response to Pharmacological Treatment

In addition to functional imaging during resting or fixed conditions or tasks, investigating the response to pharmacological treatment may offer further insights into the neurobiological basis of ADHD. Although treatment with stimulant therapy such as methylphenidate (MPH) has been shown to improve symptoms in a majority of ADHD patients, at least on the short term, it is not yet fully clear how it affects neural mechanisms. Functional MRI studies have yielded inconsistent results, with one report mentioning upregulatory effects of MPH on frontostriatal regions (Rubia et al. 2011), whereas another study described decreased perfusion resulting from MPH treatment in these regions (O'Gorman et al. 2008). These studies were

however performed in different groups (ADHD boys vs. ADHD men). One of the proposed mechanisms of MPH is that it alters more widespread patterns of activation in ADHD patients to more localized patterns similar to those activated in attention processes in normal subjects. In fact, in healthy adults, MPH has been shown to reduce the required increase in global brain metabolism to accomplish a cognitive performance task, indicating that MPH improves efficiency and allows to 'focus' more. Also, MPH does not seem to increase global brain metabolism when no cognitive task is performed (Volkow et al. 2008). Early PET and SPECT studies have failed to report significant influences of stimulant treatment on glucose metabolism or perfusion in subjects with ADHD, probably because a cognitive task was missing (Matochik et al. 1994; Ernst et al. 1994). Schweitzer et al. failed to observe normalization of brain perfusion after 3 weeks of MPH treatment in ADHD men ($n = 10$), despite normalization of behaviour during a test of executive functioning (PASAT). Instead, it was reported that MPH reduced perfusion in the prefrontal cortex (Schweitzer et al. 2004). Langleben et al. reported areas of increased perfusion of the motor, premotor and anterior cingulate cortex 36 h after MPH cessation in prepubescent boys with ADHD ($n = 20$) during a 'go/no-go task'. This finding suggests that discontinuing MPH treatment may disrupt the normalization effect on cerebral perfusion, probably resulting from the absence of inhibitory striatal signals (Langleben et al. 2002). Alternatively, this finding might be reflective of a withdrawal effect (Castellanos 2002). Differences in assessing the effect of MPH might be related to differences in groups, type of task (e.g. working memory requirements) or imaging techniques used.

Functional imaging has revealed several characteristics that separate responders from nonresponders to MPH treatment, offering another possibility to elucidate the effects of MPH on neuronal systems. Cho et al. reported that nonresponders showed higher rCBF at baseline in the left anterior cingulate cortex, the left claustrum, the right anterior cingulate cortex and the right putamen in comparison to responders. Only one area of decreased perfusion in the right superior parietal lobe was seen in nonresponders (Cho et al. 2007). These observations indicate that MPH treatment may be beneficial only when a perfusion deficit is present in areas on which MPH acts to increase perfusion, such as in the anterior cingulate and the prefrontal cortex. This hypothesis is supported by the findings from a study by Kim et al., who showed increased perfusion in the bilateral prefrontal cortex, caudate nucleus and thalamus in responders (20/32), regions typically involved in ADHD pathophysiology, after 8 weeks of MPH treatment (Kim et al. 2001). Amen et al. reported a superior response to MPH in ADHD patients who showed relatively small increases in rCBF in the left and right prefrontal poles during a concentration task at baseline as opposed to those who had larger increases in these regions (Amen et al. 2008b). In this case, the larger increases in prefrontal perfusion at baseline during a concentration task might indicate an already sufficient reaction of the brain to the task, without the potential of MPH to further enhance it. Rather than describing a direct effect on perfusion of MPH, these findings might reflect resolution of a hypodopaminergic state with MPH treatment, given the correlation between increased dopamine transporter (DAT) density and cerebral blood flow in the subcortical and cortical

attention network (da Silva et al. 2011). In the following paragraphs, this, among other issues, will be further addressed.

30.8 Neurotransmitter Systems

Frontal and striatal structures receive large projections from the dopaminergic, noradrenergic and serotonergic system. Dopaminergic neurons are predominant in the prefrontal cortex and the striatum. The parietal lobe, part of the posterior attention centre, is predominantly modulated by noradrenaline (Levy and Farrow 2001). Treatment with drugs targeting both dopaminergic and noradrenergic systems has been demonstrated to improve symptoms of inattentiveness, executive function and working memory, whereas serotonergic treatment is generally considered to have poor effectiveness (Biederman and Spencer 1999).

30.9 Dopaminergic System

The dopamine system has been extensively investigated in ADHD. The most compelling evidence for its involvement in ADHD is the clinical benefit a substantial part of ADHD patients experience during methylphenidate (MPH) treatment, although MPH mediates its effects through the noradrenergic system as well (Arnsten 2006). Oral MPH is the most commonly used pharmacologic treatment of ADHD. It acts as an inhibitor of the DAT, which functions to reuptake dopamine from the synaptic cleft. This has been demonstrated in vivo using [^{99m}TC]-TRODAT SPECT (Krause et al. 2000; Dresel et al. 2000). At therapeutical levels of 0.3–0.6 mg/kg, oral MPH is likely to occupy more than 50% of DAT (Volkow et al. 1998). As a consequence, dopamine uptake by the presynaptic neuron is blocked, and the release of dopamine in the extraneuronal space is increased (Elia et al. 1990). Correspondingly, PET imaging with [^{11}C]-raclopride has shown that MPH treatment results in increased levels of endogenous dopamine in the striatum, both in ADHD patients and healthy controls (Volkow et al. 2007a; Rosa-Neto et al. 2005). This is reflected by a *decrease* in binding potential (B_{max}/K_d) of [^{11}C]-raclopride, resulting from increased competition from endogenous dopamine (Laruelle 2000). Measurements of DAT availability, D2/D3 (postsynaptic) receptor availability and [^{11}C]-raclopride binding potential have been correlated with symptoms of inattentiveness and hyperactivity (Table 30.2), suggesting the involvement of the dopamine reward pathway in the pathophysiology of ADHD (Volkow et al. 2009).

One of the most widely accepted theories concerning ADHD is the dopamine-deficit theory (Levy 1991). According to this theory, there is a reduced level of striatal extrasynaptic dopamine in ADHD. This, in turn, could be either due to high DAT activity or low dopamine release. Indeed, early studies assessing the DAT with SPECT have shown significantly increased striatal DAT density in ADHD patients when compared to controls (Krause et al. 2000; Dresel et al. 2000; Dougherty et al. 1999; Cheon et al. 2003; Larisch et al. 2006; Spencer et al. 2007b). Increased DAT

Table 30.2 Correlations between PET and SPECT findings and clinical symptoms of ADHD

Series	*N* and clinical diagnosis	Technique and radiotracer	Study design	Findings	Specifications
Volkow et al. (2011)	45 ADHD 41NC	PET and [^{11}C]-cocaine and [^{11}C]-raclopride	Cross-sectional	Positive correlation between markers of motivation (MPQ) and D2/D3 and DAT availability in the nucleus accumbens and DAT availability in the nucleus accumbens in ADHD	Patient group was a selection of the group in (Volkow et al. 2009) ROI analysis of nucleus accumbens and midbrain
Volkow et al. (2009)	53 ADHD 32 NC	PET and [^{11}C]-cocaine and [^{11}C]-raclopride	Cross-sectional	Negative correlation between symptoms of inattentiveness (SWAN) and D2/D3 receptor availability in the left accumbens region, left caudate, left midbrain and left hypothalamic area and with DAT availability in the left midbrain in ADHD	All participants were adults Patients were stimulant naïve Voxel-based analysis
Volkow et al. (2007b)	20 ADHD 25 NC	PET and [^{11}C]-cocaine	Cross-sectional	Significant positive correlation between DAT availability at the putamen and scores of inattentiveness (CAARS A) in both ADHD patients and controls, with CAARS A scores being approximately five times higher in patients for a given DAT availability	All participants were adults Patients were stimulant naïve ROI-based analysis of caudate nuclei and putamina

(continued)

Table 30.2 (continued)

Series	*N* and clinical diagnosis	Technique and radiotracer	Study design	Findings	Specifications
Jucaite et al. (2005)	12 ADHD	PET and [^{11}C]-PE2I and [^{11}C]-raclopride	Cross-sectional	Positive correlation between the degree of hyperactivity and striatal DAT binding in the striatum ($r = 0.66$) in subjects with ADHD	Subjects were not age matched: ADHD patients were boys (age 13.8 ± 1.2 years), controls were men (29.5 ± 5.8 years)
	10 NC				3/12 patients were not stimulant naïve
Ernst et al. (2003)	10 ADHD	PET and [^{15}O]-H_2O	Cross-sectional	Performance on a decision task was positively correlated with activation of the right ventral prefrontal cortex, right middle frontal cortex and right hippocampus and negatively correlated with activation of the right orbitofrontal gyrus and left dorsal prefrontal gyrus in ADHD	All participants were adults
	12 NC				2/10 received prior stimulant treatment
					Voxel-based analysis of a priori set ROIs
Kaya et al. (2002)	13 ADHD	SPECT and ^{99m}Tc-HMPAO	Cross-sectional	Negative correlation ($r = -0.071$) between teachers Du Paul rating scale and perfusion of the right medial temporal cortex in ADHD	All participants were children
	17 NC				Patients were stimulant naïve
					Analysis of ROI uptake vs. cerebellum
Gustafsson et al. (2000)	28 ADHD	SPECT and ^{99m}Tc-HMPAO	Cross-sectional	Rutter scale of behaviour symptoms was significantly higher in children with visual abnormalities	All participants were children
					Participants were not stimulant naïve
					7/28 had abnormalities on visual inspection

CAARS Conners adult ADHD rating scale, *SWAN* strengths and weaknesses of ADHD symptoms and normal behaviour, *MPQ* multidimensionality personality questionnaire

binding was also observed in the right caudate nucleus using [^{11}C]-altropane PET, a radiotracer with considerably higher specific DAT binding than [^{99m}Tc]-TRODAT-1 (Spencer et al. 2007b). Although increased striatal DAT density has supposedly been one of the characteristic ADHD-related neural dopaminergic abnormalities, there have been several reports finding no increased DAT density (van Dyck et al. 2002) or reduced striatal DAT density in ADHD patients (Volkow et al. 2007b, 2009; Hesse et al. 2009). A recent meta-analysis, combining results from nine studies, has shown an overall increase of 14% in DAT binding among ADHD patients (Fusar-Poli et al. 2012). However, the authors conclude that a confounding factor was present in the finding that drug-naïve ADHD patients expressed significantly lower DAT values than those who were previously treated. Accordingly, Feron et al. found that previous MPH treatment may result in higher than pretreatment DAT binding (Feron et al. 2005). Another report demonstrated, contrastingly, a lower DAT binding effect of previous MPH treatment (Vles et al. 2003). It has been hypothesized that DAT density may vary over time, functioning to maintain homeostatic tonic levels of synaptic or extrasynaptic dopamine, e.g. low levels of dopamine require low levels of DAT, whereas high levels of dopamine require high levels of DAT (Swanson et al. 2007). From this point of view, it can be seen that *low* levels of DAT, such as in drug-naïve ADHD patients, might indicate the presence of a dopamine deficit. Other factors besides prior use of stimulant medication that might influence DAT binding include age (7% decline per decade (Larisch et al. 2006)) and smoking (decrease of DAT binding (Krause et al. 2002)).

PET and SPECT imaging of the dopamine transmitter system have also been applied to discriminate responders from nonresponders to MPH treatment. Several studies have reported a significantly worse clinical response to MPH in ADHD patients who showed low striatal DAT binding at baseline (Krause et al. 2005; la Fougere et al. 2006). Krause et al. investigated a group of 18 non-smoking and non-medicated ADHD patients and classified 6/18 as 'nonresponders' to MPH treatment, defined as a score ≥4 on the Clinical Global Improvement Scale. Interestingly, 5/6 nonresponders had a baseline striatal DAT binding that was lower than that of the age-matched control group (Krause et al. 2005). Similar results were obtained by La Fougere, who reported no response in all five ADHD subjects with lower initial striatal DAT binding than group-matched controls (la Fougere et al. 2006). These observations have been challenged by Cheon et al., who reported patients with a good response to MPH to have lower DAT binding at baseline (Cheon et al. 2005).

Imaging of the dopaminergic system has not been limited to the striatum alone. Voxel-based studies have revealed additional brain regions with dopaminergic deficits in ADHD, including reduced DAT binding in the right midbrain (Jucaite et al. 2005) and both reduced DAT and D2/D3 receptor binding in the left midbrain (Volkow et al. 2009), the nucleus accumbens (Volkow et al. 2007b, 2009) and the left hypothalamus (Volkow et al. 2009). The finding of reduced D2/D3 receptor binding in the nucleus accumbens is notable, since the reward and motivational deficits in ADHD have been hypothesized to be due to the disturbances of the mesoaccumbens dopamine pathway (Sonuga-Barke 2005). However, alterations in extrastriatal D2/

D3 receptor binding have to be interpreted with caution since the amount of selective binding of the radiotracer ([^{11}C]-raclopride) is much lower in extrastriatal regions. Another tracer, [^{18}F]-DOPA, can be used to assess presynaptic dopaminergic integrity. The influx of tracer (K_i values) reflects dopamine transport into the neurons, dopamine decarboxylation and dopamine storage capacity (Leung 2004). Ernst et al. found reduced [^{18}F]-DOPA uptake in the prefrontal area, but not in the striatum and midbrain, in adults with ADHD (Ernst et al. 1998a). This contrasts with later findings of increased [^{18}F]-DOPA uptake in the right midbrain in children (Ernst et al. 1999). A more recent study revealed that the strongest reductions in in vivo presynaptic dopamine synthesis and dopamine release were present in the nucleus accumbens, putamen and midbrain in male adolescents with ADHD (Forssberg et al. 2006). Limitations of this study were the small sample size (eight patients vs. six controls) and that most patients were not drug naïve. In a subgroup of eight drug-naïve ADHD patients (adult men), Ludolph et al. reported lower K_i in the left putamen, right amygdala and right dorsal midbrain and relatively increased K_i in the left amygdala and right anterior cingulate in comparison to healthy controls, providing further evidence of dysregulated dopamine turnover in ADHD in extrastriatal regions (Ludolph et al. 2008).

30.10 Noradrenergic System

In addition to the dopaminergic system, there is accumulating evidence for central noradrenergic disruption in ADHD (Biederman and Spencer 1999; Pliszka et al. 1996). The noradrenergic system has been shown to be of great importance in attentional and motivational tasks associated with the prefrontal cortex (Arnsten and Li 2005). The norepinephrine transporter (NET) is involved in the reuptake of dopamine and mediating dopamine release in the prefrontal cortex (Carboni et al. 1990; Moron et al. 2002). The blockade of NET by MPH treatment may thus be an additional mechanism by which MPH acts to increase dopamine availability in the synaptic cleft, particularly in the frontal cortex, in which NET density is relatively high, whereas DAT density is relatively high in the striatum (Sesack et al. 1998a). A pharmacokinetic study performed on healthy adults demonstrated that MPH has a higher affinity for NET blockade than DAT blockade, with an ED50 of 0.14/mg/kg for NET and an ED50 0.25 mg/kg for DAT (Hannestad et al. 2010). A recent voxel-based analysis has shown increased dopamine release in prefrontal and temporal cortices after MPH administration (Volkow et al. 2012), which then might reflect a NET-mediated response to MPH, since prefrontal regions express low DAT density (Sesack et al. 1998b).

There is a paucity of PET and SPECT studies assessing the noradrenergic system in ADHD. One study by Kim et al. combined genotyping and perfusion SPECT to show a dependency between cerebral blood flow in the prefrontal cortex and carriership of the C allele at the α-2A-adrenergic receptor gene in a group of 21 Korean boys with ADHD. Although this finding might not be generalizable because of ethnic considerations and small sample sizes, it does provide further in vivo evidence of

NET involvement in ADHD. A more recent study assessed the norepinephrine system directly using (S,S)-[^{18}F]FMeNER-D2 [(S,S)-2-(α-(2-[^{18}F]fluoro[2H2]methoxyphenoxy)benzyl)morpholine] PET, reporting no significant differences between patients with ADHD ($n = 22$) and controls ($n = 22$) (Vanicek et al. 2014), although it was noted that potential frontal and lateral cortical differences may have remained undetected because of the low NET expression and thus low sensitivity of PET imaging in these regions. Another approach, correlating genotyping with NET imaging, did show genotype-dependent differences in NET binding potential between the groups, providing evidence for genetic influences on alterations in the norepinephrine system in ADHD (Sigurdardottir et al. 2016).

30.11 Serotonergic System

Alterations in serotonin levels have been linked with hyperactivity (Gainetdinov et al. 1999) and impulsivity/aggression (Krakowski 2003), attracting interest towards in vivo imaging of the central serotonin transporter (SERT) in ADHD. ^{131}I-beta-CIT and ^{123}I-FP-CIT, radiotracers used to assess the DAT in striatal structures, can also be used to assess the SERT in the midbrain and brainstem, as there is a specific binding of these tracers in these regions (van Dyck et al. 2002; Booij et al. 2007). However, no differences were observed in SERT availability between ADHD patients and healthy controls in these regions (van Dyck et al. 2002; Hesse et al. 2009). More recently, specific PET tracers became available for the evaluation of serotonergic transmission (SERT binding potential), providing the advantage of increased spatial resolution. Although an initial evaluation using [^{11}C]MADAM did not show a significant difference between patients and healthy controls (Karlsson et al. 2013), a later study employing larger sample sizes reported a significant difference in the interregional correlation between the precuneus and the hippocampus, pointing towards altered functional coupling in patients with ADHD. However, direct regional comparisons did not show significantly different SERT binding between the groups (Vanicek et al. 2017).

30.12 Linkage Between Neurotransmitter Systems and Genotypes

Identifying patients with genotypes has gained attraction in ADHD neuroimaging research, as it reduces group heterogeneity and may allow detection of more specific patterns of dysfunction. Among the genes thought to be involved in ADHD pathology are the ten-repeat allele polymorphism at the DAT1 gene and the seven-repeat allele polymorphism at the DRD4 gene. The DAT1 gene has structurally been related to a smaller caudate nucleus volume, whereas the DRD4 gene has been associated with reduced prefrontal grey matter volume (Durston et al. 2005). In vivo imaging of the DAT receptor with ^{123}I-IPT SPECT has linked homozygosity of the ten-repeat allele at the DAT1 gene (10/10) with higher values of DAT binding in the

basal ganglia and a poorer response to MPH treatment in drug-naïve children with ADHD (Cheon et al. 2005). A later report using a different radiotracer, [^{99}mTc]-TRODAT-1, did not find significant differences in DAT binding in ADHD patients with the 10/10 genotype and those without (Krause et al. 2006). Szobot et al. found a reduced striatal DAT response to MPH treatment in a specific group of male adolescents with ADHD and comorbid substance use disorder as well as the DRD4 seven-repeat allele and homozygosity for the ten-repeat allele at the DAT1 gene. This finding may implicate an additive effect of the combination of both DAT1-10/10 and DRD4-7R on the DAT (Szobot et al. 2011). With regard to the NET system, a negative correlation between NET methylation at a cytosine-phosphate-guanine (CpG) site and NET BP has been observed using PET, along with a negative correlation with ADHD severity scores (Sigurdardottir et al. 2019).

30.12.1 Correlation with Clinical Symptoms

Identification of neural substrates for attention, executive functioning and impulsivity may help in diagnosing ADHD subtypes, evaluating treatment response and identifying genes. Several rating scales, typically rated by patients, teachers, parents and clinicians, have been developed to assess ADHD severity and can be used to correlate PET and SPECT findings with specific symptoms or symptom severity. Table 30.2 provides an overview, including studies assessing perfusion and glucose metabolism as well as neurotransmitter systems.

30.13 Conclusions

The results of PET and SPECT imaging, despite considerable variability, point towards hypoactivation of the prefrontal cortex and the anterior cingulate cortex, as well as the basal ganglia, cerebellum and the parietal lobe. During tasks, ADHD patients may recruit compensatory brain regions, particularly motor and premotor areas, or use visual strategies, which are reflected by increased perfusion or glucose metabolism of the occipital cortex. Regional functional deficits that have become apparent in studies with PET and SPECT require integration with current knowledge of functional neuroanatomy. In this light, ADHD can be viewed of as a highly heterogeneous disorder which might affect one or more of the neuroanatomic regions involved in attention: mainly subcortically located networks of alertness and arousal, mixed cortical-subcortical-cortical orienting networks and a selective attentional network modulated by the anterior cingulate cortex.

Conflicting results have been reported concerning the levels of DAT in ADHD patients. It is likely that DAT is not the sole contributing factor to the dopamine disturbances in ADHD and that other neurotransmitter systems are involved, such as the serotonergic and noradrenergic system. PET imaging has revealed consistent evidence that MPH increases endogenous dopamine levels, although it is less clear how it affects the dopamine transporter.

30.14 Limitations

As a result of limitations to general application of PET and SPECT in a paediatric population, still relatively few studies have been conducted in ADHD, and sample sizes have typically been small. Furthermore, ADHD research, mostly earlier work, has been complicated by clinical heterogeneity of inclusion groups. Factors contributing to this heterogeneity include the effects of therapeutic interventions, comorbidities, age and gender. Furthermore, studies have also shown considerable variability in resting and task conditions. One major drawback of the current literature is that longitudinal studies are lacking, which may aid enormously in understanding how functional deficits in ADHD develop from childhood into adulthood.

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SPECT and PET Imaging of Apathy

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Abstract

Apathy is a frequent behavioural syndrome which is now characterised by precise criteria. It can be found in various neuropsychiatric diseases. In Alzheimer's disease (AD), in particular, it is present at all stages, and, in patients with minor/mild cognitive disorders, it is a risk factor for dementia conversion.

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An anterior cingulate-subcortical circuit which originates from the anterior cingulate cortex in Brodmann's area (BA) 24 and 32 and projects to the ventral striatum, is the main anatomical support of motivated behaviour. Lesions of this cortico-subcortical circuit are responsible for apathetic syndromes.

SPECT perfusion studies first demonstrated in vivo the relationships between apathy and lesions of this circuit. FDG PET studies confirmed these findings in particular in AD. In degenerative diseases, apathy is generally related to anterior cingulate hypoperfusion or hypometabolism. This is a recognisable pattern for image interpretation.

In post-stroke patients, the situation is different, apathy being mostly due to lesions located at the subcortical levels of the circuit.

In Parkinson disease, in particular under subthalamic nucleus deep brain stimulation which is known to increase apathy, the metabolic pattern is somehow different with an increased metabolism in the right frontal areas and a decrease in the posterior cingulate.

In many neuropsychiatric disorders, brain molecular imaging is helpful to show or confirm the possible anatomical correlates of apathy and its association with other local regional dysfunctions. This has to be taken into account in the image reporting since it can have therapeutic implications.

31.1 Introduction

Imaging findings in degenerative diseases such as Alzheimer's disease (AD) using single photon emission tomography (SPECT) brain perfusion studies or [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) positron emission tomography (PET) are mainly used in relation to cognitive symptoms. However neuropsychiatric disorders also include behavioural symptoms, and both cognitive and behavioural symptoms are consequences of brain dysfunction and therefore may impact the imaging results. Apathy is recognized as a frequently associated behavioural syndrome in many neuropsychiatric disorders, including several common neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease (AD) and focal lesion syndromes such as stroke. It is an important issue in many respects such as prevalence, clinical handicap, pathophysiology and treatment (van Reekum et al. 2005). Furthermore, this syndrome has been shown to be related to specific cortical and subcortical regions dysfunctions which can be detected on SPECT and PET imaging. Therefore, the goal of this chapter is to draw the attention of the nuclear medicine community to this syndrome and the related imaging findings.

31.2 What Is Apathy?

Apathy is prevalent across many neurodegenerative, neurological and psychiatric disorders. It represents the most common behavioural and psychological symptom in patients with AD and is often observed in Parkinson's disease (PD), vascular

dementia, traumatic brain injury, frontotemporal dementia, progressive supranuclear palsy, major depression and schizophrenia (Husain and Roiser 2018). The definition and the diagnostic criteria for apathy have evolved overtime, and the terminology employed to refer to apathy can vary in the context of different pathological conditions. In addition, the term apathy is employed to describe both a symptom and a syndrome (Brown and Pluck 2000). An international consensus group recently updated the diagnostic criteria for apathy in brain disease (Robert et al. 2018). Apathy is defined as a quantitative reduction of goal-directed activity in comparison to the patient's previous functioning level. Symptoms must persist for at least 4 weeks and affect at least two of the three apathy dimensions (behaviour/cognition; emotion; social interaction). The full criteria are presented in Table 31.1.

Table 31.1 The 2018 apathy diagnostic criteria

For a diagnosis of Apathy the patient should fulfill the criteria A, B, C and D
Criterion A: A quantitative reduction of goal-directed activity either in behavioural, cognitive, emotional or social dimensions in comparison to the patient's previous level of functioning in these areas. These changes may be reported by the patient himself/herself or by observation of others
Criterion B: The presence of at least 2 of the 3 following dimensions for a period of at least 4 weeks and present most of the time
B1. Behaviour and cognition
Loss of, or diminished, goal-directed behaviour or cognitive activity as evidenced by at least one of the following: • **General level of activity:** The patient has a reduced level of activity either at home or work, makes less effort to initiate or accomplish tasks spontaneously, or needs to be prompted to perform them • **Persistence of activity:** He/she is less persistent in maintaining an activity or conversation, finding solutions to problems or thinking of alternative ways to accomplish them if they become difficult • **Making choices:** He/she has less interest or takes longer to make choices when different alternatives exist (e.g. selecting TV programs, preparing meals, choosing from a menu, etc.) • **Interest in external issue:** He/she has less interest in or reacts less to news, either good or bad, or has less interest in doing new things • **Personal wellbeing:** He/she is less interested in his/her own health and wellbeing or personal image (general appearance, grooming, clothes, etc.)
B2. Emotion
Loss of, or diminished, emotion as evidenced by at least one of the following: • **Spontaneous emotions:** The patient shows less spontaneous (self-generated) emotions regarding their own affairs, or appears less interested in events that should matter to him/her or to people that he/she knows well • **Emotional reactions to environment:** He/she expresses less emotional reaction in response to positive or negative events in his/her environment that affect him/her or people he/she knows well (e.g. when things go well or bad, responding to jokes, or events on a TV program or a movie, or when disturbed or prompted to do things he/she would prefer not to do) • **Impact on others:** He/she is less concerned about the impact of his/her actions or feelings on the people around him/her • **Empathy:** He/she shows less empathy to the emotions or feelings of others (e.g. becoming happy or sad when someone is happy or sad, or being moved when others need help) • **Verbal or physical expressions:** He/she shows less verbal or physical reactions that reveal his/her emotional states

(continued)

Table 31.1 (continued)

B3. Social interaction
Loss of, or diminished engagement in social interaction as evidenced by at least one of the following:
• **Spontaneous social initiative:** The patient takes less initiative in spontaneously proposing social or leisure activities to family or others
• E**nvironmentally stimulated social interaction:** He/she participates less, or is less comfortable or more indifferent to social or leisure activities suggested by people around him/her • **Relationship with family members:** He/she shows less interest in family members (e.g. to know what is happening to them, to meet them or make arrangements to contact them) • **Verbal interaction:** He/she is less likely to initiate a conversation, or he/she withdraws soon from it • **Homebound**: He/she prefer to stays at home more frequently or longer than usual and shows less interest in getting out to meet people
Criterion C These symptoms (A–B) cause clinically significant impairment in personal, social, occupational or other important areas of functioning
Criterion D The symptoms (A–B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to a diminished level of consciousness, to the direct physiological effects of a substance (e.g. drug of abuse, medication), or to major changes in the patient's environment

These criteria have been used in a survey of the prevalence of apathy in elderly people referred to memory centres (Manera et al. 2019). The frequency of apathy varied significantly based on the diagnostic groups (0% of subjects with apathy in the subjective cognitive disorder group; 25% in the mild neurocognitive disorder group; 77% in the major the mild neurocognitive disorder group; and 57% in the depressive group). All subjects with apathy fulfilled the criteria for the behaviour/cognition dimension, 73.1% fulfilled the criteria for the emotion dimension, and 97.4% fulfilled the criteria for the social interaction dimension. Behaviour/cognition showed the highest sensitivity, the association of emotion and social dimension the highest specificity. The concordance between the 2009 (Robert et al. 2009) and the 2018 diagnostic criteria indicated an almost perfect agreement.

Apathy is also associated with loss of autonomy in daily life activities (Lechowski et al. 2009) and with worse function in mild dementia (Zhu et al. 2019).

Neuropsychiatric symptoms are present very early in AD and related disorders. Apathy and depressive symptoms are the most frequent neuropsychiatric symptoms in mild cognitive impairment (MCI) (Brown and Pluck 2000; Robert et al. 2018; Manera et al. 2019). In a prospective study on predictive factors for AD, Robert et al. (2006) reported that after 3 years, the risk of conversion to AD was significantly higher for patients with lack of interest, which is one of the core apathetic symptoms (Gonfrier et al. 2012). It was demonstrated that apathetic but not depressive symptoms are a major risk factor for conversion to dementia in MCI subjects (Zhu et al. 2019). A recent review (Ruthirakuhan et al. 2019) confirmed an increased risk of developing AD in mild neurocognitive disorders patients with apathy with or without depression. It has been suggested that rather than being a causal risk factor, apathy might be an early sign of AD (van Dalen et al. 2018).

Finally, it is important to underline that, since loss of interest is a central feature in apathy diagnosis as well as in depression diagnosis, it is not surprising that apathy and depression often co-occur in several psychiatric, neurological and neurodegenerative conditions (Benoit et al. 2012). However apathy and depression have different neurobiological correlates (Tagariello et al. 2009).

31.3 Apathy Theoretical Framework: What Is Known About Its Anatomical Bases?

Definition and criteria come from the clinical experience but also from core theoretical frameworks which are important to briefly describe. Firstly, apathy has been related to the motivation and reward systems involving mesolimbic and neostriatal cortex. Dopamine projections have been suggested to mediate reward. Berridge and Robinson (1998, 2003) argue that reward is a constellation of multiple processes many of which can be separately identified in behaviour. In animal studies, Berridge (1996) suggested that dopamine-related neural systems mediate more specifically the wanting or incentive salience component. The second important theoretical framework is that of goal directed behaviour (GDB). This model is related to goal-directed behaviour/activity defined as behaviour aimed toward a goal or toward completion of a task (Brown and Pluck 2000). The functional integration of motivational, cognitive and motor processes is central in this model.

These frameworks fit with the presumed underlying pathophysiological mechanisms indicating that apathy is the clinical consequence of various underlying dysfunctions of mental and biological processes required to elaborate, initiate and control intentional/goal-directed behaviour. They share a similar anatomical substratum known as the anterior cingulate cortex (ACC)-ventro-striatal loop.

Alexander (Cummings 1997) first described a series of parallel frontal-subcortical circuits that link the frontal cortex to striatum, globus pallidus and thalamus. Five circuits are described and share a common structure. They originate in the prefrontal cortex, project to the striatum, connect to the globus pallidus and substantia nigra and reach the thalamus. The complete circuit is a closed loop with projections from the thalamus back to the prefrontal cortex (Benoit et al. 1999).

Motivated behaviour is supported by the anterior cingulate-subcortical circuit, which originates from the ACC in Brodmann's area (BA) 24 and 32. The corresponding neurons project to ventral striatum called "limbic striatum", then to the ventral pallidum and the substantia nigra before reaching the anterior thalamus.

Lesions affecting this circuit produce a decrease in motivation also called anterior cingulate syndrome. Infarcts, tumours, hydrocephalus, haemorrhage, encephalitis, degeneration or trauma which involved part of this circuit have been reported in patients producing syndromes called akinetic mutism or abulia which can be considered as extreme forms of apathy. Post-stoke apathy in particular is observed roughly in 35% of the patients (van Reekum et al. 2005) and is difficult to separate from depression (Migneco et al. 2001). Except in rare cases of specific anterior cingulate infarction (Anderson et al. 2003), apathy seems to result more often from

subcortical damages such as thalamic or striatal involvement than from cortical lesions (Tagariello et al. 2009; Berridge and Robinson 1998). In general, the prevalence of apathy in diseases involving the basal ganglia is reported to be around 40%.

Summarizing the scientific evidences, Le Heron et al. (2018) consider that the clinical phenotype of apathy is associated with disruption of a ACC-ventro-striatal circuit and connected brain regions, including orbitofrontal cortex whatever the underlying pathology (neurodegenerative, vascular …). In AD, for example, this is due to cortical neurodegeneration, while after stroke it is more likely to be related to sub-cortical vascular lesions.

31.4 How Is Apathy Reflected in Molecular Imaging?

The first imaging results which strengthened the anterior cingulated circuit concept were obtained using regional cerebral blood flow (rCBF) SPECT studies. They were confirmed later using [^{18}F]fluorodeoxyglucose PET metabolic imaging. Important imaging data were also obtained in the particular case of Parkinson's disease neurostimulation, and there are recent findings regarding amyloid and tau imaging.

31.4.1 SPECT Perfusion Studies

The first study was published by Mena et al. (Craig 1996). They studied 31 AD patients using the Neuropsychiatric Inventory (NPI) (Cummings 1997) and perfusion SPECT. Perfusion SPECT data were obtained using a ^{133}Xe calibrated ^{99m}Tc-HMPAO method which combined the spatial resolution of HMPAO with the absolute quantification of regional cerebral blood flow provided by ^{133}Xe. With this method, rCBF could be expressed in millilitres per hundred grams and per minute (Onoda et al, 2011). Regional measurements were performed using regions of interest (ROI) automatically derived from an MRI template coregistered to SPECT images. They found a significant correlation between the NPI apathy score and the reduced regional cerebral blood flow in the antero-frontal regions—including the ACC—and in the thalami. These correlations survived taking into account the covariance of MMSE and dysphoria. Although the results did not specifically involve the anterior cingulated gyrus but several anterior areas including it, this work was the first in vivo imaging study demonstrating the relationship between ACC cerebral blood flow and apathy using region of interest analysis (ROI) and absolute quantification.

Benoit et al. studying the "behavioral and psychological signs and symptoms of dementia" in a population of 20 AD patients observed that apathy was the most frequent behavioural symptom. Using ROI analysis on ^{99m}Tc-ECD SPECT images, they demonstrated a negative correlation between the NPI apathy score and the perfusion of the right ACC.

The first work addressing this issue using voxel by voxel analysis was performed by Migneco et al. (2001) who confirmed the specific involvement of the ACC in

apathy. They included 41 patients; 21 were considered apathetic according to the NPI using a threshold of 2 on the apathy score. Twenty other non-apathetic patients were also included. SPECT studies were performed using ^{99m}Tc-ECD and a three-headed gamma camera (Prism 3000 XP, Philips) equipped with a LEUHR fan beam collimator. SPM96 was used to compare apathetic versus non-apathetic patients and showed a significantly decreased perfusion in apathetic patients in a very clearly defined zone corresponding to the ACC BA 24 (Fig. 31.1). The study which included 28 AD patients and 13 non-demented patients also showed that the results remained independent from the aetiology.

The same group (Benoit et al. 2004) using a dedicated Apathy Inventory scale (AI) (Robert et al. 2002) and SPM analysis of ^{99m}Tc-ECD SPECT data was able to refine the correlation analysis. In 30 AD patients, they correlated the behavioural and emotional dimensions of apathy measured using the AI with rCBF. Total AI score was negatively correlated with left and right superior orbitofrontal gyrus and with the left middle frontal gyrus (BA 10) perfusion. Concerning AI clinical dimensions, the lack of initiative score correlated negatively with ACC rCBF (BA 24 and 25). Lack of interest had an inverse correlation with orbitofrontal gyrus rCBF (BA 10) and emotional blunting with left superior dorsolateral prefrontal cortex (BA8). According to this work, the different dimensions of apathy are related to different orbitofrontal areas, and anterior cingulate involvement is more specifically related to the lack of initiative.

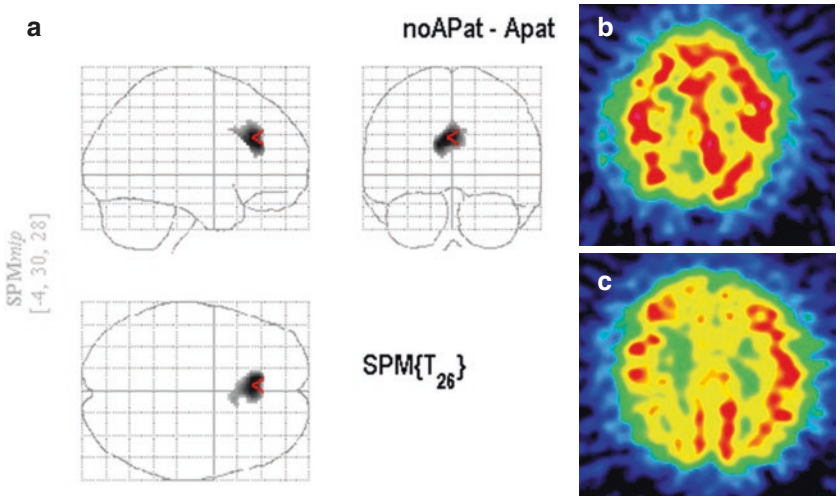

Fig. 31.1 ^{99m}Tc-SPECT demonstration of anterior cingulate involvement in apathy adapted from Migneco et al. (2001). (**a**) SPM analysis comparing apathetic and non-apathetic patients showing a very specific difference in anterior cingulated area (BA 24). (**b**) Transaxial cut involving the anterior cingulated cortex in a normal subject. (**c**) Same level of transaxial cut in an apathetic patient showing hypoperfusion in the anterior cingulate region

In studies addressing post-stroke apathy, the results are different. For example, Onoda et al. (2011) studied 102 post-stroke patients using ^{123}I-IMP rCBF SPECT and showed that apathy was present in 37% of the patients and related to basal ganglia hypo-perfusion.

31.4.2 [^{18}F]FDG-PET Studies

Marshall et al. (2007) investigated 41 patients with probable AD. Fourteen of them were considered as apathetic based on the Scale for Assessment for Negative Symptoms in Alzheimer's Disease (SANS-AD) (Reichman et al. 1996). Images were obtained using [^{18}F]FDG PET and analysed by SPM. This study also found significantly reduced metabolism in the ACC of apathetic versus non-apathetic AD patients. The reduced metabolism extended to the orbitofrontal area and to the thalamus bilaterally. The results remained the same after covarying for the effect of MMSE score, education, cognitive symptoms duration or mood depression. The relationship with thalamic metabolism was no longer significant when covarying for the effect of age. These findings confirmed with FDG PET the pattern of ACC involvement related to apathy (Fig. 31.2) described on perfusion SPECT.

More recently Schroeter et al. (2011) investigated 54 patients including 19 probable AD, 13 FLTD and 10 "other dementias". Fifty percent of the patients exhibited

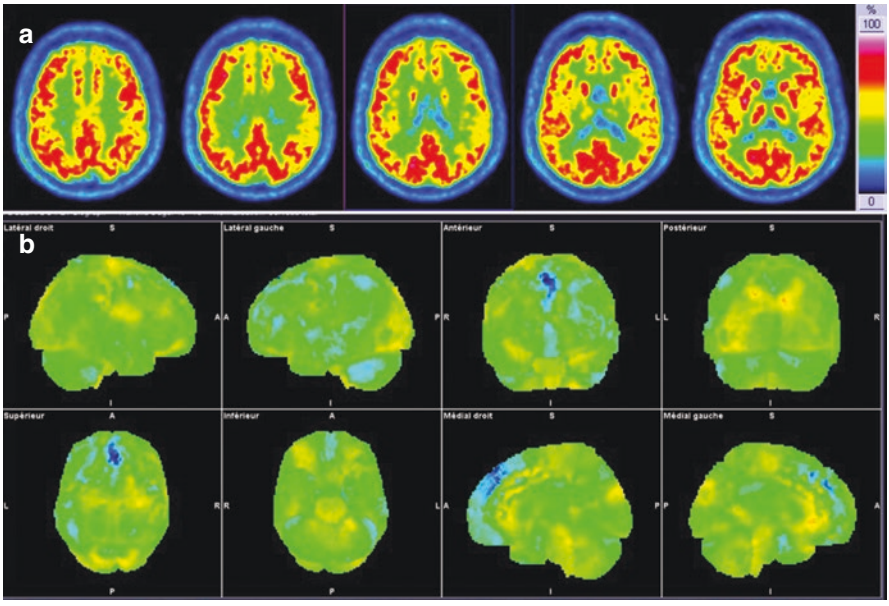

Fig. 31.2 Patient with apathy on [^{18}F]FDG-PET. (**a**) Transaxial cuts showing hypometabolism in the anterior cingulate cortex. (**b**) Comparison to a normal data base showing local anterior-cingulate hypometabolism (expressed as *z*-score)

apathy on the NPI. They were all studied using [^{18}F]FDG PET and data were analysed using SPM. Apathy correlated with hypometabolism in the ACC. Additional hypometabolism correlating with apathy was found in midcingulate, subcalosal area and ventral striatum. Combining the three behavioural symptoms tested, namely, apathy, disinhibition and eating disorder with age and severity of cognitive symptoms, a disjunction analysis showed additional hypometabolism in the ventral tegmental area related to apathy.

Eyre et al. (2017) studied the correlations between neuropsychiatric symptoms and [^{18}F]FDG brain metabolism in 53 AD patients. They used NPI for symptoms evaluation and SPM for [^{18}F]FDG PET image analysis. They found a significant inverse correlation of apathy and left inferior frontal cortex (BA 10 and 11) metabolism and an inverse correlation between depression and dorsolateral prefrontal (BA 45) metabolism. Areas related to apathy were slightly different from those previously described. They were located more interiorly and anteriorly. Nevertheless, they were also located in the medial anterior frontal cortex.

In the study of Schroeter et al. (2011) involving different types of dementias, the authors showed that apathy correlated with hypometabolism of the ACC but also with other areas such as inferior temporal pole and laterofrontal areas.

31.4.3 PET Imaging in Parkinson's Disease (Baseline and Stimulation)

Metabolic imaging with [^{18}F]FDG PET was used to identify apathy bases in PD. The most important cohort published included 45 PD patients well screened without dementia or depression and assessed for apathy with AES. The image analysis controlled for confounding factors as age, dopatherapy dose and depression (MDRS). The results confirmed the involvement of BA47, BA10, BA18 and insula with positive correlations (increased apathy scores with increased metabolism) and cerebellar metabolism with negative correlations (increased apathy scores with decreased metabolism) (Perin et al. 2018). All these areas are known to be involved in emotion and cognition. Several recent studies have highlighted the non-motor role of the cerebellum in cognition and emotion (Marshall et al. 2019). This role was first described by clinical observations and also by studying the anatomical connections between cerebellum, prefrontal cortex and thalamus (Stoodley and Schmahmann 2009).

However, the ACC involvement was not identified in PD's studies, whereas the posterior cingulate gyrus, belonging also to limbic circuits, appeared involved. These differences may be due to methodological issues: different scales used to evaluate apathy, different therapies for PD or AD patients. These results support the hypothesis that apathy is related to a general limbic network alteration and not only a single structure's (i.e., ACC) one.

Subthalamic nucleus (STN) deep brain stimulation (DBS) is a well-known therapy for severely disabled PD patients. Although this surgery improves motor performances, several clinical studies have reported emotional (Le Jeune et al. 2008),

behavioural (Sauleau et al. 2014; Temel et al. 2006) and cognitive (Houvenaghel et al. 2015; Parsons et al. 2006) disturbances.

Especially, apathy has been identified as a consequence of STN DBS (Saint-Cyr et al. 2000). Apathy scores worsened at 3 and 6 months after surgery in a consecutive series of 15 patients, without evidence of depression or dementia, and independently of L-DOPA therapy dose in pre and post-operative status (Drapier et al. 2006).

Metabolic neuroimaging with [^{18}F]FDG has been used to highlight the neural network involved in apathy.

In a series of 12 patients who underwent STN DBS and who had neither dementia nor depression, increased apathy scores after surgery were correlated with increased metabolism in right frontal middle gyrus (BA 10) and right inferior frontal gyrus (BA 46 and 47) and increased apathy scores after surgery are correlated with decreased metabolism in bilateral posterior cingulate gyrus (BA 31) and left medial frontal gyrus (BA 9). Equivalent DOPA dose, in pre and post-operative status, was included as a confounding factor in the statistical analysis. These results described apathy as a consequence of disruption of prefrontal cortex-basal ganglia loops, involved in generation and control of behaviour, responsive of metabolic changes as hyper or hypometabolism (Le Jeune et al. 2009).

Using more specific imaging with dopaminergic radio ligands, Thobois et al. characterized also apathy induced by STN DBS. PD patients with apathy show reduced dopamine receptor capacity in bilateral ventral striatum and after methylphenidate less important dopamine release particularly in prefrontal cortex and post cingulate gyrus. These results are consistent with dopaminergic denervation areas (Lawrence et al. 2011; Thobois et al. 2010).

Apathy is a complex disorder with three dimensions: emotional, behavioural and cognitive (Dujardin and Defebvre 2007). Metabolic neuroimaging confirms the key role of prefrontal cortex loops and dopaminergic system in PD patients at baseline or after STN DBS. It shows that apathy is mediated by brain structures involved in motivational and emotional processes, independently of reduction of dopamine therapy (Robert et al. 2012) and dopamine mesolimbic pathway degeneration (Thobois et al. 2010).

Identification of metabolic predictors of apathy on pre-operative images may help the clinician to avoid surgery or choose another target (i.e., GPi). Indeed, apathy impairs the quality of life after surgery (Langner-Lemercier et al. 2015) and pallidal stimulation did not induce apathy (Lozachmeur et al. 2014). In a large cohort of PD patients assessed before STN DBS, only metabolic activity in right ventral striatum was associated with apathy after surgery. This area could be a biomarker of the non-motor effects, such as apathy, of STN DBS (Robert et al. 2014).

31.4.4 Amyloid and Tau PET Imaging

A pilot study was published by Eyre et al. (2017) using [^{18}F]FDDNP that binds both to cerebral aggregates of amyloid-β (Aβ) plaques and tau neurofibrillary tangles.

They studied 16 depressed elderly volunteers and showed that [^{18}F]FDDNP binding in the ACC was negatively associated with the apathetic global score ($r = -0.62$, $p = -0.02$; where low score equals greater severity of apathy), suggesting that apathy in late life depression is associated with higher amyloid and/or tau levels in the ACC.

Perin et al. (2018)studied a large cohort of 585 cognitively normal subjects who underwent PET imaging with different amyloid tracers and evaluated their depressive symptoms. Their results suggest that, although the presence of a depressive disorder is unlikely to be a direct consequence of increasing Aβ, amyloid burden may increase the risk of apathy.

Kitamura et al. (2018) studied 11 clinically diagnosed AD and 15 MCI subjects using [^{11}C]PBB3 (tau) and [^{11}C]PiB (amyloid) PET comparing high and low apathy scores. AD patients with high apathy scores showed larger PBB3 SUVR values in the frontal cortex and orbitofrontal cortex than patients with low apathy scores ($p = 0.006$ and $p = 0.007$, respectively). None of the other regions showed significant differences in mean [^{11}C]PBB3 SUVR values between the two patient groups. There was no significant correlation between apathy scores and mean [^{11}C]PiB SUVR values in the orbitofrontal cortex.

Marshall et al. (2007) recently studied 16 patients with AD dementia and 24 MCI subjects who underwent [^{11}C]PiB (amyloid) and [^{18}F]AV-1451 (tau) PET. They found marginal associations between apathy and bilateral ACC and medial orbitofrontal tau burden.

More studies are needed to further clarify the relationships between amyloid/tau depositions and apathy. At this point, Aβ amyloid burden seems not to influence the apathetic status, whereas tau deposition occurring in ACC and orbitofrontal cortex is likely to be related to apathetic symptoms.

31.5 Conclusion

In clinical practice apathy is an easily recognizable clinical syndrome that is present in many neuropsychiatric diseases. Molecular imaging studies conducted across different disease types, provided evidences that apathy is mostly related to dysfunction of ACC-ventro-striatal circuitry and connected structures (Le Heron et al. 2018). In current practice, hypoperfusion or hypometabolism in the ACC related to apathy is a robust finding.

In this context, brain metabolic imaging is particularly helpful to show and/or confirm the possible anatomical correlates and the association with other local regional dysfunctions. The interest is not only at the diagnostic level but also at the therapeutic one, for the choice of a specific pharmacological drug or to select the optimal non pharmacological intervention.

In terms of research, brain imaging tools are essential for the understanding of motivation disorders which are at the crossroads between cognition and behaviour.

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PET/SPECT/MRI/fMRI Studies in the Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome

32

Yasuyoshi Watanabe

Contents

Abstract

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a serious, debilitating disorder with a wide spectrum of symptoms, including fatigue, pain, depression and neurocognitive deterioration. Over 17 million people around the world have ME/CFS, predominantly women with peak onset at 30–50 years. Given the wide spectrum of symptoms and unclear etiology, specific biomarkers for diagnosis and stratification of ME/CFS are lacking. Here the results from PET/SPECT/MRI/fMRI studies are reviewed to understand the pathophysiology and to develop therapies of this severe syndrome.

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32.1 Introduction

32.1.1 Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex, chronic medical condition characterized by symptom clusters that include: pathological fatigue and malaise that is worse after exertion, cognitive dysfunction, immune dysfunction, unrefreshing sleep, pain, autonomic dysfunction, neuroendocrine and immune symptoms. ME/CFS is common, often severely disabling and costly. Over 17 million people around the world have ME/CFS, predominantly women with peak onset at 30–50 years. The Institute of Medicine (IOM) in US reviewed the ME/CFS literature and estimates that between 836,000 and 2.5 million Americans have ME/CFS at a cost of between 17 and 24 billion dollars annually in the USA. The IOM suggested a new name for ME/CFS and called it Systemic Exertion Intolerance Disease (SEID) (Institute of Medicine of the National Academies 2015). SEID's diagnostic criteria are less specific and do not exclude psychiatric disorders. The 2010 Canadian Community Health Survey discovered that 29% of patients with ME/CFS had unmet health care needs and 20% had food insecurity—lack of access to sufficient healthy foods. ME/CFS can be severely disabling and cause patients to be bedridden. Yet most patients (80%) struggle to get a diagnosis because doctors have not been taught how to diagnose or treat ME/CFS in medical schools or in their post-graduate educational training. Consequently, the patients with ME/CFS suffer. They are not diagnosed with ME/CFS and are not treated accordingly. Instead of compassionate care from their doctors, they are often ridiculed by the very people from whom they seek help. The precise etiology of ME/CFS remains unknown, but recent advances and research discoveries are beginning to shed light on the enigma of this disease including the following contributors: infectious, genetic, immune, cognitive including sleep, metabolic and biochemical abnormalities. Management of patients with ME/CFS is supportive symptomatic treatment with a patient centered care approach that begins with the symptoms that are most troublesome for the patient. Pacing of activities with strategic rest periods is, in our opinion, the most important coping strategy patients can learn to better manage their illness and stop their post-exertional fatigue and malaise. Pacing allows patients to regain the ability to plan activities and begin to make slow incremental improvements in functionality (Review: Bested and Marshall 2015).

Symptoms in an individual person fluctuate in intensity and severity, and there is also great variability in the symptoms between different persons. Many different potential etiologies for ME/CFS have been investigated, including infectious, neurological, endocrine, immunologic, psychiatric, environmental and genetic etiologies. However, until now, the diverse nature of the symptoms cannot be fully explained. All this leads to controversies, between some patient advocacy groups on one side and researchers and physicians on the other side, about the condition itself, the name for the illness, the etiology and the effectiveness of the few available

treatment options. There are also still existing controversies among physicians. Some call the term ME inaccurate and misleading, because real encephalomyelitis, a specific and often lethal neuropathological process, does not occur (Wojcik et al. 2011). Others, however, mention that more recent research and clinical experience strongly point to widespread inflammation and multisystemic neuropathology, suggesting that the label ME/CFS is not appropriate anymore. One should use the term ME because it indicates an underlying pathophysiology (Carruthers et al. 2011). The debate is still ongoing.

32.1.2 Classification of ME/CFS

Several diagnostic criteria in ME/CFS were developed after the introduction of the label CFS in 1988 by CDC in USA. The problem between these different existing criteria is that they do not select homogeneous sets of patients. Prevalence estimates increased from 0.24% using the Fukuda criteria (Fukuda et al. 1994) to 2.54% using the Reeves criteria (Reeves et al. 2005). Some symptoms of the Fukuda criteria overlap with depression, whereas the Canadian Consensus criteria (Carruthers et al. 2003) differentiate patients with ME/CFS from those who are depressed and identify patients who are more physically debilitated and have greater physical and cognitive functional impairments (Jason et al. 2004). So, recently most of the clinicians and referees of major journals refer Fukuda + Canadian Consensus criteria. However here in this chapter, the labels with CFS, ME, CFS/ME and ME/CFS are really difficult to be judged and confused by the non-expert readers, so that just the disease name ME/CFS will be used throughout this chapter.

Consequently, an International Consensus Panel consisting of clinicians, researchers, teaching faculty, and an independent patient advocate was formed (together 13 countries and a wide range of specialties) to develop new criteria based on current knowledge. These criteria were recently published and should promote optimal recognition of ME/CFS by primary physicians and other healthcare providers, improve the consistency of diagnoses in patients internationally and facilitate clearer identification of patients for research studies (Carruthers et al. 2011). In Japan, we followed such an international consensus and revised the diagnostic criteria accepted by the Ministry of Health, Labor, and Welfare (MHLW), Japan, in 2014, the members of Fatigue Clinical Center in Osaka City University Hospital headed by Prof. Hirohiko Kuratsune, Japan, learned from the patients with different diagnostic criteria including SEID, Fukuda, Reeves, Canadian, and Japanese ones, and SEID's criteria covered almost 100% of the patients with other diagnostic criteria.

For the diagnosis ME/CFS, a patient has to meet the criteria for postexertional neuroimmune exhaustion (A), at least one symptom from three neurological impairment categories (B), at least one symptom from three immune/gastrointestinal/genitourinary impairment categories (C) and at least one symptom from energy

metabolism/transport impairments (D). The international consensus criteria are as follows (derived from Carruthers et al. 2011):

(A) Postexertional neuroimmune exhaustion
1. Marked, rapid physical and/or cognitive fatigability in response to exertion
2. Postexertional symptom exacerbation
3. Postexertional exhaustion
4. Prolonged recovery period
5. Low threshold of physical and mental fatigability resulting in a substantial reduction in pre-illness activity level

(B) Neurological impairments
1. Neurocognitive impairments: difficulties with processing information and short-term memory loss
2. Pain: headaches and significant pain in muscles, muscle-tendon junctions, joints, abdomen, or chest
3. Sleep disturbances: disturbed sleep patterns and unrefreshed sleep
4. Neurosensory, perceptual and motor disturbances

(C) Immune, gastrointestinal and genitourinary impairments
1. Flu-like symptoms may be recurrent or chronic and typically activate or worsen with exertion.
2. Susceptibility to viral infections with prolonged recovery periods.
3. Gastrointestinal tract problems: nausea, pain, bloating, irritable bowel syndrome.
4. Genitourinary tract problems: urinary urgency or frequency, nocturia.
5. Sensitivities to food, medications, odours or chemicals.

(D) Energy production/transportation impairments
1. Cardiovascular: orthostatic intolerance, palpitations, dizziness
2. Respiratory: air hunger, laboured breathing, fatigue of chest wall muscles
3. Loss of thermostatic stability: subnormal body temperature, sweating, feverishness, cold extremities
4. Intolerance of extremes of temperature

32.2 MRI Morphometry Studies in Patients with ME/CFS

Pioneering MRI studies showed mostly subcortical white matter abnormalities which corresponded to the foci (hotspots) of multiple sclerosis patients with severe fatigue sensation. However, some studies with MRI brain morphometry (Buchwald et al. 1992; Natelson et al. 2005; Schwartz et al. 1994a; Lange et al. 1999) reported an increased number of subcortical white matter abnormalities associated with ME/CFS, but other studies showed conflicting results (Cope et al. 1995; Cope and David 1996). Significant limitation of these morphological findings lies in a not adequate spatial resolution and the absence of an automated procedure of data analysis at that time.

Using a reliable fully automated observer-independent procedure: the voxel-based morphometry (Ashburner and Friston 2000) and high-resolution images acquired with 3.0 T MRI, our research group (Okada et al. 2004) conducted

voxel-based morphometry of 16 ME/CFS patients and 49 age-matched healthy control subjects and demonstrated a reduction of grey-matter volume in bilateral prefrontal cortices in the patients with ME/CFS. Furthermore, the severity of volume reduction in the right prefrontal cortex was proportional with the disability score of the patients. de Lange et al. (2005) also found a grey-matter volume reduction with MRI voxel-based morphometry in a total of 28 ME/CFS patients, and the extent of volume decline was well correlated with the reduction of their physical activity. Later, de Lange et al. (2008) demonstrated recovery from the cerebral atrophy in those ME/CFS patients who responded to cognitive behavioural therapy for 6 months, indicating that the atrophy might be due to a reduction of dendritic arch volume rather than neuronal cell death.

Recently, Barnden et al. (2018) recruited 43 ME/CFS subjects and 27 healthy controls and performed 3 T MRI T1- and T2-weighted spin-echo (T1wSE and T2wSE) scans. T1wSE signal follows T1 relaxation rate (1/T1 relaxation time) and corresponds to myelin and iron (ferritin) concentrations. They performed MRI signal level group comparisons with SPM12. Spatial normalization after segmentation was performed using T2wSE scans and applied to the coregistered T1wSE scans. After global signal-level normalization of individual scans, the T1wSE group comparison detected decreased signal-levels in ME/CFS in a brainstem region (cluster-based inference controlled for family wise error rate, PFWE = 0.002), and increased signal-levels in large bilateral clusters in sensorimotor cortex white matter (cluster PFWE < 0.0001). Moreover, the brainstem T1wSE values were negatively correlated with the sensorimotor values for both ME/CFS (R2 = 0.31, $P = 0.00007$) and healthy controls (R2 = 0.34, $P = 0.0009$), and the regressions were co-linear. This relationship, previously unreported in either healthy controls or ME/CFS, in view of known thalamic projection-fibre plasticity, suggests brainstem conduction deficits in ME/CFS may stimulate the upregulation of myelin in the sensorimotor cortex to maintain brainstem—sensorimotor connectivity. The authors also stated that voxel-based morphometry (VBM) did not find group differences in regional grey-matter or white-matter volumes. They argued that increased T1wSE observed in sensorimotor WM in ME/CFS indicates increased myelination which is a regulatory response to deficits in the brainstem although the causality cannot be tested in this study. Altered brainstem myelin may have broad consequences for cerebral function and should be a focus of future research. Our group in RIKEN, Japan, has been trying to confirm the changes in myelination in different neural circuits in the patients with ME/CFS.

32.3 fMRI Study in Patients with ME/CFS

de Lange et al. (2004) investigated neural correlates of ME/CFS using fMRI. They measured behavioural performance and cerebral activity using rapid event-related functional MRI in 16 ME/CFS patients and 16 matched healthy controls while they were engaged in a motor imagery task and a control visual imagery task. ME/CFS patients were considerably slower on performance of both tasks, but the increase in reaction time with increasing task load was similar between the groups. Both groups

used largely overlapping neural resources. However, during the motor imagery task, ME/CFS patients evoked stronger responses in visually related structures. Furthermore, there was a marked between-groups difference during erroneous performance. In both groups, dorsal anterior cingulate cortex was specifically activated during error trials. Conversely, ventral anterior cingulate cortex was active when healthy controls made an error but remained inactive when ME/CFS patients made an error. These results support the notion that ME/CFS may be associated with dysfunction of motor planning. Furthermore, the between-groups differences observed during erroneous performance point to motivational disturbances as a crucial component of ME/CFS.

Patients with ME/CFS often have difficulties with complex auditory information processing. In a series of two fMRI studies, Lange et al. (2005) compared BOLD signal changes between healthy controls and patients with ME/CFS who had documented difficulties in complex auditory information processing (Study 1) and those who did not (Study 2) in response to performance on a simple auditory monitoring and a complex auditory information processing task (mPASAT). They hypothesized that under conditions of cognitive challenge: (1) patients with ME/CFS who have auditory information processing difficulties will utilize frontal and parietal brain regions to a greater extent than healthy controls, and (2) these differences will be maintained even when objective difficulties in this domain are controlled for. Using blocked design fMRI paradigms in both studies, they first presented the auditory monitoring task followed by the mPASAT. Within and between regions of interest (ROI), group analyses were performed for both studies with statistical parametric mapping (SPM99). Findings showed that patients with ME/CFS are able to process challenging auditory information as accurately as healthy controls but utilize more extensive regions of the network associated with the verbal WM system. Patients with ME/CFS appear to have to exert greater effort to process auditory information as effectively as demographically similar healthy adults. These findings provide objective evidence for the subjective experience of cognitive difficulties in patients with ME/CFS.

In this context, our research group (Mizuno et al. 2015) found trans-hemispheric overactivation, less efficient and costly processes of frontal cortical activation in Childhood ME/CFS. The ability to divide one's attention deteriorates in patients with childhood chronic fatigue syndrome (CCFS). Mizuno et al. conducted a study using a dual verbal task to assess allocation of attentional resources to two simultaneous activities (picking out vowels and reading for story comprehension) and fMRI. Patients exhibited a much larger area of activation, recruiting additional frontal areas. The right middle frontal gyrus (MFG), which is included in the dorsolateral prefrontal cortex, of CCFS patients was specifically activated in both the single and dual tasks; this activation level was positively correlated with motivation scores for the tasks and accuracy of story comprehension. In addition, in patients, the dorsal anterior cingulate gyrus (dACC) and left MFG were activated only in the dual task, and activation levels of the dACC and left MFG were positively associated with the motivation and fatigue scores, respectively. Patients with CCFS exhibited a wider area of activated frontal regions related to attentional resources in order to

increase their poorer task performance with massive mental effort. This is likely to be less efficient and more costly in terms of energy requirements. It seems to be related to the pathophysiology of patients with CCFS and to cause a vicious cycle of further increases in fatigue.

Using fMRI, our group Tanaka et al. (2006) studied brain responsiveness in six male ME/CFS patients and in seven age-matched male healthy volunteers. Responsiveness of auditory cortices to transient, short-lived, noise reduction was measured, while subjects performed a fatigue-inducing continual visual search task. Responsiveness of the task-dependent brain regions was decreased after the fatigue-inducing task in the normal and ME/CFS subjects and the decrement of the responsiveness was equivalent between the two groups. In contrast, during the fatigue-inducing period, although responsiveness of auditory cortices remained constant in the normal subjects, it was attenuated in the chronic fatigue syndrome ME/CFS patients. In addition, the rate of this attenuation was positively correlated with the subjective sensation of fatigue as measured using a fatigue visual analogue scale, immediately before the magnetic resonance imaging session. ME/CFS may be characterised by attenuation of the responsiveness to stimuli not directly related to the fatigue-inducing task. We interpret these data as overactivation of defence mechanisms in the pathophysiology of ME/CFS, in order to avoid further exhaustion after the first-stage fatigue by the simple or single-channel fatigue-evoked task. The prefrontal, orbitofrontal cortices, and posterior cingulate network (or loop) may be involved in this kind of exaggerated defence.

Recently, abnormal resting-state functional connectivity in the brain has been reported by Gay et al. (2016). Their findings that the functional connectivity of the left anterior midcingulate with the sensory motor network and the connectivity of the left posterior cingulate cortex with the salience network were significantly decreased are in good agreement with our MEG studies on mental task-induced fatigue. Boissoneault et al. (2018) demonstrated disruptions in functional connectivity (FC) at rest in chronically fatigued patients including perturbations in static FC (sFC), that is, average FC at rest between several brain regions subserving neurocognitive, motor and affect-related networks. By using arterial spin labelling fMRI in 19 patients with ME/CFS and 15 healthy controls, they reported that healthy controls showed greater increases than ME/CFS in static FC between insula and temporo-occipital structures and between precuneus and thalamus/striatum. Furthermore, inferior frontal gyrus connectivity to cerebellum, occipital and temporal structures declined in healthy controls but increased in ME/CFS. The patients also showed lower dynamic FC between hippocampus and right superior parietal lobule. Both static FC and dynamic FC correlated with task-related fatigue increases. Shan et al. (2018) also studied the default mode network (DMN) in 45 ME/CFS patients and 27 healthy controls. They demonstrated that BOLD signals in the posterior cingulate cortex (PCC), the driving hub in the DMN, were more complex in ME/CFS in both resting state and during the performance of the task ($p < 0.05$). The FCs between medial prefrontal cortex (mPFC) and both inferior parietal lobules (IPLs) were weaker ($p < 0.05$) during resting state, whereas during task mPFC-left IPL and mPFC-PCC were weaker ($p < 0.05$). The dynamic FCs between the DMN

hubs were more complex in ME/CFS ($p < 0.05$) during the task. Each of these differences accounted for 7–11% variability of health scores. Through the study, they showed that DMN activity is more complex and less coordinated in ME/CFS, which suggested that brain network analysis could be potentially used as a diagnostic biomarker for ME/CFS.

As is apparent from other fMRI and MEG studies with healthy volunteers in fatigue-inducing tasks, defence mechanisms exist both in healthy state (Tanaka et al. 2009, 2013, 2015; Tanaka and Watanabe 2010) and ME/CFS pathological state to avoid ultimate exhaustion, but the sensitivity to the fatigue level may be much greater in patients with ME/CFS. This might be related to less repair energy in the metabolome analysis in ME/CFS patients (Yamano et al. 2016).

32.4 Hypoperfusion in Patients with ME/CFS Demonstrated by SPECT and PET

In 1992, the first study with ^{99m}Tc-HMPAO (^{99m}Tc-labelled hexamethylpropyleneamine oxime) in patients with ME/CFS was published. In this study, regional cerebral blood flow (rCBF) was assessed in 60 clinically defined (according to the Canadian consensus criteria) ME/CFS patients and 14 normal control subjects using ^{99m}Tc-HMPAO SPECT. The ME/CFS group showed significantly lower cortical/cerebellar rCBF ratios, throughout multiple brain regions. Forty-eight patients with ME/CFS (80%) showed at least one or more rCBF ratios significantly less than normal values. The major cerebral regions involved were frontal (38 cases, 63%), temporal (21 cases, 35%), parietal (32 cases, 53%) and occipital (23 cases, 38%). The rCBF ratios of the basal ganglia (24 cases, 40%) were also reduced. The authors concluded that ^{99m}Tc-HMPAO brain SPECT provided objective evidence for functional impairment of the brain in the majority of ME/CFS patients. These findings may not be diagnostic of ME/CFS but ^{99m}Tc-HMPAO SPECT may play an important role in clarifying the pathophysiological development of ME/CFS (Ichise et al. 1992).

In 1994, Schwartz et al. performed magnetic resonance imaging (MRI) and SPECT imaging with ^{99m}Tc-HMPAO in 16 patients with ME/CFS to compare the usefulness of functional and anatomic imaging in the detection of intracranial abnormalities. MRI and SPECT examinations were performed within a 10-week period. The results of both modalities were compared with age-matched control subjects. Patients with ME/CFS had significantly more abnormalities throughout the cerebral cortex and basal nuclei on SPECT scans compared to normal subjects (7.31 vs 0.43 abnormalities per subject, $p < 0.001$); most of these lesions were small (less than 1 cm), but 30 (27%) of 113 SPECT lesions were larger than 2 cm. The most common sites of involvement in patients with ME/CFS were the lateral frontal cortex, lateral temporal cortex and basal ganglia. SPECT abnormalities were present in 13 (81%) of 16 patients vs. 3 (21%) of 14 control subjects. Compared to MRI, SPECT scans showed significantly more abnormalities in patients with ME/CFS. Three patients had a follow-up SPECT scan after clinical improvement and

showed remission in 60% of the defects. One patient that was scanned twice without clinical improvement had a similar number of abnormalities in both studies. The authors concluded that SPECT abnormalities occur more frequently and in greater numbers than MRI abnormalities in patients with ME/CFS and that SPECT may prove to be useful in following the clinical progress of patients with this syndrome (Schwartz et al. 1994a).

The largest study was initiated by Costa et al. in 1995. ^{99m}Tc-HMPAO SPECT was performed in 146 subjects, of which 67 patients were diagnosed with ME/CFS, 10 patients with epilepsy, 20 young patients with a depression, 9 elderly patients with a depression and 40 normal volunteers. The brain perfusion ratios were generalised and reduced in patients with ME/CFS compared to normal volunteers. The lowest values (with a significant decrease) were found in the frontal cortex of both hemispheres and in the brainstem. The perfusion of the brainstem in patients with ME/CFS was correlated to the brainstem perfusion in the other patient groups and the healthy volunteers. The brainstem perfusion ratios of the ME/CFS patients were significantly lower than the controls and the patients with major depression. The authors stated that brainstem hypoperfusion appears to be the differentiating factor between patients with ME/CFS and those with major depression. Whether these findings are the cause of the patients' problems or a consequence of the disease process is not known. One explanation of the reduced brainstem perfusion is given by the authors. Sleep disorders can be one of the symptoms in patients with ME/CFS, and this may be related to abnormal physiology of the reticular formation, which is an important component of the brainstem structure, composed of midbrain, pons and medulla oblongata. This reticular formation contains systems concerned with activation and inhibition of sleep, consciousness and arousal, with activation and inhibition of movement and with control of behaviour and memory via connections with the limbic system. The reticular formation also includes groups of neurons which constitute respiratory and cardiovascular centres, as well as another less-defined centre controlling peristaltic and other motor and secretory activities in the gastrointestinal tract (Costa et al. 1995).

Since then, several SPECT studies have been performed with ^{99m}Tc-HMPAO (Schwartz et al. 1994b; Fischler et al. 1996; Peterson et al. 1994; Machale et al. 2000; Lewis et al. 2001; Schmaling et al. 2003) and with *N*-isopropyl-4-[^{123}I]iodoamphetamine (^{123}I-IMP) (Tomoda et al. 2000; Kanai et al. 2007). Unfortunately, no unequivocal observations were made. Studies in the early 1990s showed a global cerebral hypoperfusion. However, these studies made no difference between ME/CFS patients with or without associated psychiatric diseases. Subsequent studies were performed in more homogeneous groups of patients with ME/CFS but found controversial results. One study showed hypoperfusion of the brainstem; another study showed hyperperfusion of the thalamus. Three studies did not found any difference between ME/CFS patients and healthy volunteers. Data concerning this hypoperfusion (observed by using SPECT and in other cases PET) was well summarized by A.W.J.M. Glaudemans in the previous version of "PET and SPECT in Psychiatry" (2014).

In 2002, our research group (Kuratsune et al. 2002) also reported a decrease in rCBF in eight female ME/CFS patients as compared with eight normal controls by using ^{15}O-labelled water ($H_2{}^{15}O$) and PET. The rCBF was lower in the ME/CFS patient group than in the control group in a wide range of brain regions including frontal, prefrontal, orbitofrontal and insular cortices; middle occipital, middle temporal and anterior cingulate; parahippocampal, superior temporal, transverse temporal and precentral gyri; putamen; globus pallidus; hippocampus; mesencephalus; and cerebellum. When the global CBF was quantitatively estimated by averaging all pixels, it was 46.0 ± 5.8 and 40.1 ± 5.2 mL/min/100 mL in the control and ME/CFS groups, respectively; this difference was statistically significant ($p < 0.05$).

32.5 ^{18}F-FDG-PET Study

In 1998, Tirelli et al. investigated the brain metabolism of 18 patients with ME/CFS using [^{18}F]fluorodeoxyglucose (^{18}F-FDG). The results of the ME/CFS patients were compared with a group of six patients affected by depression and six age-matched healthy controls. The patients with ME/CFS were not taking any medication at the time of the PET scan, and depressed patients were drug-free for at least 1 week before the PET examination. The authors examined 22 cortical and subcortical brain regions. ME/CFS patients showed a significant hypometabolism in the right mediofrontal cortex and brainstem in comparison with the healthy controls. Moreover, when patients affected by ME/CFS and depression were compared, the latter group showed a significant and severe bilateral hypometabolism of the medial and upper frontal regions, whereas the metabolism of brain stem was normal. ^{18}F-FDG PET showed specific metabolism abnormalities in patients with ME/CFS in comparison with healthy and depressed patients. The most relevant finding was the brain stem hypometabolism, which was also reported in a perfusion SPECT study. This brain stem hypoperfusion seems to be a marker for in vivo diagnosis of ME/CFS (Tirelli et al. 1998).

One comparative study between ^{99m}Tc-HMPAO SPECT and ^{18}F-FDG PET was published. Eighteen patients, who fulfilled the diagnostic criteria for ME/CFS, were investigated. Thirteen patients had abnormal SPECT brain perfusion scans and five had normal scans. Fifteen patients had normal glucose brain metabolism scans and three had abnormal scans. Not any correlation was found between the two nuclear medicine modalities. It was possible to have brain perfusion abnormalities without corresponding changes in glucose uptake (Abu-Judeh et al. 1998).

Siessmeier et al. tried to identify in an observer independent analytical approach individual alterations of glucose metabolism in a carefully selected population of ME/CFS patients, in order to assess how often significant abnormalities occur among such patients and whether the abnormalities follow a specific pattern. In addition, a group analysis was performed to correlate regional functional impairment with different neuropsychological alterations occurring in ME/CFS patients. Brain ^{18}F-FDG PET was performed in 26 patients, with ages ranging from 26 to 61 years. Single-subject comparisons with an age- and sex-matched normal

database ($n = 18$) and a group comparison between the patients and normal controls were undertaken, along with additional correlation analyses between brain metabolism and psychometric test scores. Twelve of the 26 patients showed no significant decrease in FDG uptake compared with the controls. Of the remaining 14, 12 showed hypometabolism bilaterally in the cingulate gyrus and the adjacent mesial cortical areas. Five of these 12 patients also had decreased metabolism in the orbitofrontal cortex. The two remaining patients had hypometabolism in the cuneus/precuneus. Correlation analysis showed significant correlations between some test scores (anxiety, depression and health-related quality of life but not fatigue) and regional reductions in glucose metabolism. In total, abnormalities were only detectable in approximately half of the patients examined, and no specific pattern for ME/CFS could be identified. The authors state, however, that PET may provide valuable information in helping to stratify ME/CFS patients into subgroups with and without apparent alterations in the central nervous system (Siessmeier et al. 2003).

In our study, the same patients were recruited for three categories of PET studies within 2 days: neuroinflammation, serotonin transporter density and FDG PET. In 12 patients, as compared with 10 healthy control subjects, we could not detect any significant change of glucose utilization rate even in the brain stem (unpublished data). However, more recently, Sahbai et al. (2019) demonstrated severe posterior hypometabolism but normal perfusion in a patient with ME/CFS with PET/MRI.

32.6 Deterioration of the Serotonergic System

Still no particularly effective pharmaceuticals for ME/CFS are available. Various drugs have been proposed and antidepressants are commonly prescribed. Fluoxetine is an antidepressant of the selective serotonin reuptake inhibitor class. The use of fluoxetine was suggested because this drug has fewer sedative and autonomic nervous system side effects, and studies pointed out that fluoxetine is beneficial in patients with ME/CFS with at least 50% reduction in severity of depressive symptoms and between 25 and 50% reduction in symptom severity in another third of the patients (Lynch et al. 1991). In Japan, it proved effective for one third of the patients. Other studies, however, mention no beneficial effects of fluoxetine therapy on any characteristic of ME/CFS (Vercoulen et al. 1996).

Because of the mentioned beneficial results of fluoxetine therapy, there was a growing interest in the role of the serotonergic system in the development of ME/CFS. In patients with postviral fatigue syndrome, upregulation of hypothalamic 5-hydroxytryptamine receptors was found; the same study did not find upregulation in patients with primary depression. These findings suggest an increased role of the serotonergic system in postviral fatigue syndrome, which may lead to improved understanding of the pathogenesis of this disorder and also of the chronic fatigue syndrome (Bakheit et al. 1992). Our study Narita et al. (2003) showed a significant increase of variants in serotonin transporter gene promoter polymorphism, which emphasizes the ‘serotonergic system dysfunction hypothesis’ when considering the etiology of ME/CFS (Narita et al. 2003).

The hypothesis of a role of the serotonergic system in the pathophysiology of ME/CFS led to several studies that used serotonin PET tracers in patients with ME/CFS. [^{11}C](+)McN5652 binds specifically to the 5-hydroxytrytophan (5-HT) transporter molecule and was already used in brains of ecstasy abusers and patients with obsessive-compulsive disorder (McCann et al. 1998; Simpsom et al. 2003). Our research group Yamamoto et al. (2004) found a decrease of the density of serotonin reuptake sites (5-HT transporters) in the rostral subdivision of the anterior cingulate cortex of patients with ME/CFS by using [^{11}C](+)McN5652 as compared with age-matched normal volunteers (5). This subdivision is different from that in the dorsal anterior cingulate, in which binding potential values of individual patients showed a weak negative correlation with their self-reported pain scores. Therefore, we thought that the deterioration of serotonergic system in the rostral anterior cingulate plays a key role in the pathophysiology of ME/CFS. The deterioration of the serotonergic tone in this brain region is related to autonomic nerve dysfunction, since the autonomic centre is in the vicinity of the region.

Another group used the selective 5-HT receptor ligand [^{11}C]WAY-100635 in ten patients, who were completely medication-free and did not have current comorbid psychiatric illnesses, and in ten healthy control subjects. They found a widespread reduction in 5-HT receptor binding potential in patients with ME/CFS in comparison with the control subjects. The reduction was particularly marked in the hippocampus bilaterally, where a 23% reduction was observed. The authors of this study also found evidence of decreased 5-HT receptor number or affinity, which may be a primary feature of ME/CFS related to the underlying pathophysiology, or a finding secondary to other processes, such as previous depression, other biological changes or behavioural consequences of ME/CFS (Cleare et al. 2005).

32.7 Neuroinflammation Demonstrated by PET

Many researchers focused on immune insults in pathophysiology of ME/CFS (Review by Klimas et al. 2012). A variety of results showed elevation of cytokines, lymphokines and some growth factors in the plasma. Our research group (Nakatomi et al. 2014) recently found with [^{11}C](R)-PK11195 and PET that neuroinflammation was detected in widespread brain areas (in the cingulate cortex, hippocampus, amygdala, thalamus, midbrain and pons) in ME/CFS patients and was associated with the severity of their specific neuro-psychologic symptoms (Nakatomi et al. 2014). In ME/CFS patients, the $BP_{(ND)}$ values of [^{11}C](R)-PK11195 in the amygdala, thalamus and midbrain positively correlated with cognitive impairment score, the $BP_{(ND)}$ values in the cingulate cortex and thalamus positively correlated with pain score and the $BP_{(ND)}$ value in the hippocampus positively correlated with depression score. Neuroinflammation in different brain regions of ME/CFS patients could be the core pathophysiology, and this could be a good biomarker for development of objective diagnostic criteria and effective medical treatments. Preliminary study in

collaboration with Karolinska Institutet PET Centre using [^{11}C]PBR28 and PET on monozygotic twin pairs one of which was a patient with ME/CFS also showed the elevation of signals which could be interpreted as activation of microglia and astrocytes in their brain. [^{18}F]DPA-714, which detects 18-kD translocator protein specific for microglial and astrocytes activation with higher sensitivity than [^{11}C](R)-PK11195, is selected in our on-going study on the therapeutic effects of anti-neuroinflammatory drugs in patients with ME/CFS. So far, we have done [^{18}F]DPA-714 PET studies on 59 ME/CFS patients and 39 age-matched healthy controls, and approximately 40% of the patients showed an elevated value of [^{18}F]DPA-714 binding over the threshold (average + 2SD) of healthy subjects.

32.8 Integrated PET Studies with a Variety of Blood Biomarkers

In our ongoing research, we are performing an integrated study of autonomic nerve function and other fatigue biomarkers such as biological oxidation (Fukuda et al. 2016a), reduced repair energy (decrease of initial members of the TCA cycle) (Fukuda et al. 2016b; Yamano et al. 2016), inflammation biomarkers (highly sensitive C-reactive protein CRP, cytokines, lymphokines, etc.), metabolome analyses (Yamano et al. 2016), exosomes and inclusion proteins/microRNAs (Eguchi et al. 2020) with PET scans using [^{11}C]DASB instead of [^{11}C]McN5652 for serotonin transporter density and [^{11}C](R)-PK11195 and [^{18}F]DPA-714 for the extent of neuroinflammation. In 10 ME/CFS patients, we could preliminarily show a positive correlation between autonomic dysfunction and reduction of serotonergic presynaptic components in the anterior cingulate cortex and also a negative correlation between serotonin transporter density and the extent of neuroinflammation in some brain regions. We are still recruiting more patients for this study.

32.9 Discussion and Conclusions

Figure 32.1 shows our working hypothesis of the pathophysiology of ME/CFS, based not only on the study of ME/CFS but also on the study of mental/physical fatigue (Tanaka et al. 2015; Watanabe et al. 2008, 2012). Cumulative knowledge is obtained by great efforts of many researchers in this field including those of related diseases, mostly functional somatic syndromes such as fibromyalgia, functional dyspepsia, irritable bowel syndrome, multiple chemical sensitivity, sick building syndrome, gulf war syndrome and so on. A chronological order of pathophysiology in patients with ME/CFS should be proposed through a cohort study with longitudinal follow-up in patients with ME/CFS. Most important is the development of stage-dependent and molecular mechanism-based therapies/therapeutics for patients suffering daily from extremely low quality of life.

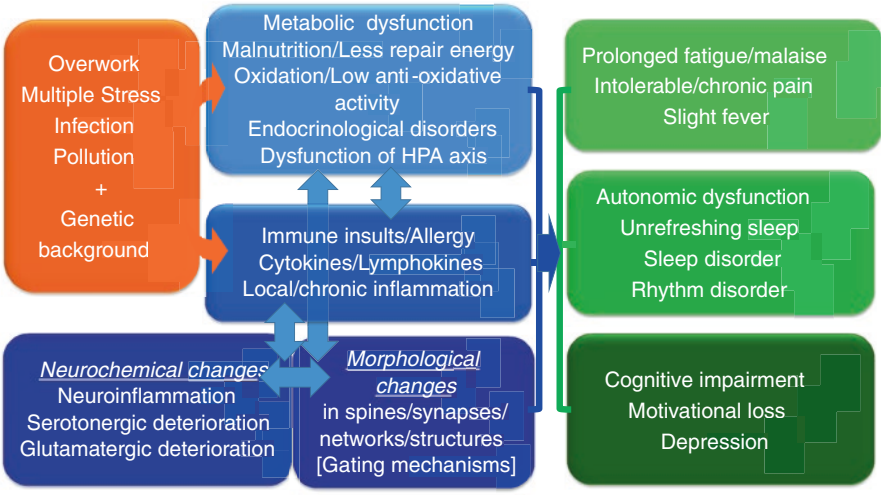

Fig. 32.1 Plausible mechanistic structure of ME/CFS through the studies including PET/SPECT/MRI/fMRI/MEG with a variety of biomarker studies

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Sleep Disorders

33

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Abstract

Sleep disorders have been the subject of a number of positron emission tomography and single-photon emission computed tomography studies. Narcoleptic patients with cataplexy displayed decreased hypothalamic and thalamic perfusion during resting wakefulness, which may be related to hypocretinergic deficiency and altered vigilance. However, nuclear imaging data on narcolepsy without cataplexy and idiopathic hypersomnia remain scarce. In restless legs syndrome and periodic limb movements, hypoactivity in pre- and postsynaptic dopaminergic transmission in the striatum and substantia nigra may underlie compulsive limb movements. Sleepwalking showed specific brain perfusion changes during slow wave sleep and wakefulness, possibly indicative of a dissociated state. Rapid eye movement sleep behavior disorder patients showed changes in blood flow in the pons, frontal lobes, striatum, and hippocampus, linking this disorder to later onset of neurodegenerative diseases (synucleinopathies). Localized brain metabolism increases during non-rapid eye movement sleep in insomnia and depression are in line with the "hyperarousal" hypothesis underlying sleep disturbances in these patients. Even with these insights, radioisotope imaging in sleep medicine is still in its infancy. Further research should aim to increase sample sizes, provide adequate control groups, and acquire additional timepoints for imaging, for instance, before, during, and after the onset of symptoms.

33.1 Introduction

The growing field of sleep medicine has seen an increase in the use of neuroimaging techniques to gain insight into the neurobiological bases of sleep disorders. Positron emission tomography (PET) is a functional brain imaging technique that requires the injection of positron-emitting isotopes into the bloodstream, in order to monitor the differential blood flow (regional cerebral blood flow, rCBF) or glucose consumption (cerebral metabolic rate for glucose, CMRglu) in metabolically active areas, or to observe the distribution of a neurotransmitter receptor ligand. Single-photon emission computed tomography (SPECT) also requires the injection of a radiolabeled compound. A gamma camera then detects the photons emitted

reflecting the distribution of the radioisotope according to the differential brain perfusion or neurotransmitter function. The use of PET and SPECT in sleep medicine has thus far been limited but is expanding rapidly.

These techniques were initially applied to the investigation of normal brain function across the sleep-wake cycle. Sleep can be separated into two stages: rapid eye movement (REM) sleep and non-REM (NREM) sleep. REM sleep in normal subjects exhibits sustained neural activity and cerebral blood flow (Jones 1991). Compared to wakefulness and NREM sleep, REM sleep showed increased blood flow and glucose metabolism in the amygdala, thalamus, hippocampus, anterior cingulate cortex, temporo-occipital areas, basal forebrain, and brainstem (Maquet et al. 1990). Deactivations were present in the dorsolateral prefrontal cortex, posterior cingulate gyrus, precuneus, and inferior parietal cortex (Maquet 1997, 2000; Maquet et al. 1990). In contrast to REM sleep, NREM sleep was mainly characterized by a decrease in cerebral blood flow, predominantly in the dorsal pons, mesencephalon, thalami, basal ganglia, basal forebrain, anterior hypothalamus, medial prefrontal cortex, anterior cingulate cortex, and precuneus (Andersson et al. 1998; Braun et al. 1997; Kajimura et al. 1999; Maquet and Franck 1997; Maquet et al. 1996, 2000).

In this chapter, PET and SPECT neuroimaging studies of sleep-related disorders will be discussed, namely, narcolepsy; restless legs syndrome (RLS), often associated with periodic limb movements (PLM); parasomnias, present during either REM sleep (e.g., REM sleep behavior disorder, RBD) or during NREM sleep (e.g., sleepwalking); and finally insomnia, often associated with depression. It is important to understand the differential limitations of PET and SPECT measures in imaging paroxysmal disorders such as disorders of sleep. Whereas metabolic measures (e.g., CMRglu, FDG PET) are suited to observing temporal changes between sleep states, measures of neurotransmission (e.g., dopamine) offer information about the integrity of these pathways, less likely to show variability across sleep state transitions. Other neuroimaging techniques were also used in sleep research and sleep medicine and included anatomical studies with magnetic resonance imaging (MRI) and functional brain responses with functional MRI (fMRI). Such studies exceed the scope of the present chapter and are reviewed elsewhere (Cross and Dang-Vu 2019; Dang-Vu et al. 2007, 2009; O'Byrne et al. 2014).

33.2 Central Hypersomnolence Disorders

Excessive daytime sleepiness, defined as episodes of irrepressible need to sleep during daytime, is a common experience that can be caused by several medical conditions, substance abuse, and more generally insufficient and/or disturbed sleep (Ohayon 2008). However, when not attributable to these conditions or to another sleep disorder such as sleep apnea, excessive daytime sleepiness is the main symptom of central hypersomnolence disorders (ICSD-3), (Sateia 2014) which include narcolepsy and idiopathic hypersomnia (IH). With an estimated prevalence of 0.03% (for narcolepsy) and 0.5% (for IH) (Hale et al. 2016), these

disabling neurological conditions can have severe complications ranging from increased risk of accidents to cognitive impairment and depression, leading to a poor quality of life (Ozaki et al. 2008).

33.2.1 Narcolepsy

Besides excessive daytime sleepiness, other frequent symptoms of narcolepsy include sleep paralysis, hypnagogic hallucinations, and sleep fragmentation, with frequent nighttime awakenings. Their sleep periods are also characterized by a premature entry into REM sleep (sleep-onset REM periods, SOREMPs). A common but unspecific biological marker that is found in narcolepsy is the human leukocyte antigen (HLA) subtype DQB1*0602. Narcolepsy is divided in two subtypes depending on the presence or not of cataplexy, which is defined by the sudden (partial or complete) loss of muscle tone triggered by emotional stimulation (Dauvilliers et al. 2014). Approximately 70% of patients with narcolepsy are diagnosed with *narcolepsy type 1* (*NT1*; previously called narcolepsy-cataplexy) characterized by a reduction in cerebral spinal fluid (CSF) hypocretin-1 levels (Thannickal et al. 2000). This deficit is thought to be caused by an autoimmune component damaging hypocretin (also termed orexin)-producing neurons in the lateral hypothalamus, which would produce these cataplexy attacks (Liblau et al. 2015). Hypocretinergic dysfunction is thought to underlie the unstable sleep-wake transitions and impaired vigilance in NT1 (Dauvilliers et al. 2007). Narcolepsy patients who do not report cataplexy are grouped into the *narcolepsy type 2 (NT2)* subtype, in which there is no consistent CSF hypocretin-1 deficit (Mignot et al. 2002).

Neuroimaging techniques have been mainly applied to NT1 in order to decipher the neurobiological bases of this disorder. SPECT and PET studies looked at neuromodulatory changes (dopamine, DA; acetylcholine, ACh; serotonin, 5-HT), as well as glucose metabolism and brain perfusion, during the sleep-wake cycle. Research has proven largely inconclusive, particularly with regard to neurotransmission. However, several neuroimaging studies on NT1 have consistently demonstrated both structural and functional alterations of the hypothalamus, which is in line with the pathophysiological concept that NT1 underlies a deficiency of the hypocretin system. Moreover, several functional studies point to disturbed limbic activity, consistent with reduced vigilance, hypocretinergic dysfunction, and abnormalities in emotional processing. A summary of these findings on NT1 is provided below and in Table 33.1 and Fig. 33.1. In contrast, NT2 did not receive much attention in the brain imaging field with only one study using nuclear imaging so far (see Sect. 33.2.1.5).

Table 33.1 SPECT and PET studies in narcolepsy-cataplexy

Study	Imaging technique employed	Target	Number of patients/ controls	Patients receiving treatment/ total number of patients	Results
Sudo et al. (1998)	PET ^{11}C-MPB	ACh	11/21	0/11	No change
Derry et al. (2006)	PET ^{18}F-MPPF	5HT-1A	14/0	12/14	Inconclusive in absence of control group
Eisensehr et al. (2003a, b)	SPECT 1PT	Presynaptic DA binding	7/7	0/7	No change
Rinne et al. (2004)	PET ^{11}C-CFT	Presynaptic DA binding	10/15	0/10	No change
Eisensehr et al. (2003a, b)	SPECT IBZM	Postsynaptic DA (D2) binding	7/7	0/7	Increased striatal DA
Hublin et al. (1994)	SPECT IBZM	Postsynaptic DA (D2) binding	6/8	0/6	No change
Staedt et al. (1996)	SPECT IBZM	Postsynaptic DA (D2) binding	10/10	0/10	No change
Rinne et al. (1995)	PET ^{11}C-raclopride	Postsynaptic DA (D2) binding	7/7	6/7	No change
Khan et al. (1994)	PET ^{11}C-raclopride	Postsynaptic DA (D2) binding	17/32	12/17	No change
MacFarlane et al. (1997)	PET ^{18}F-PSP	Postsynaptic DA (D2) binding	6/6	0/6	No change
Joo et al. (2004)	PET ^{18}F-FDG	CMRglu	24/24	0/24	Reduced CMRglu in hypothalami and thalamic nuclei
Dauvilliers et al. (2010)	PET ^{18}F-FDG	CMRglu	21/21	14/21	Increase of CMRglu in limbic cortex
Joo et al. (2004)	SPECT ^{99m}Tc-ECD	rCBF	25/25	0/25	Reduced cerebral perfusion in hypothalami

(continued)

Table 33.1 (continued)

Study	Imaging technique employed	Target	Number of patients/ controls	Patients receiving treatment/ total number of patients	Results
Hong et al. (2006)	SPECT ^{99m}Tc-ECD	rCBF during a cataplectic attack	2/0	0/2	Increased perfusion in limbic areas, basal ganglia, thalami, sensorimotor cortices and brainstem. Decreased perfusion in prefrontal cortex and occipital lobe
Chabas et al. (2007)	SPECT ^{99m}Tc-ECD	rCBF during a cataplectic attack	1/0	0/1	Increased perfusion in cingulate cortex, orbitofrontal cortex, and right putamen

PET and SPECT studies in narcolepsy-cataplexy, including citation, the specific imaging technique employed, targeted physiology, the number of patients and controls, the number of participants receiving treatment out of the total number of patients, and a summary of the results

33.2.1.1 Acetylcholine, Serotonin, and Dopamine Functions in Narcolepsy

Sudo et al. (1998) focused on ACh neurotransmission in narcolepsy-cataplexy. They used PET with the radioligand ^{11}C-*N*-methyl-4-piperidyl-benzilate (^{11}C-MPB) in order to target the muscarinic ACh receptor. When comparing 11 patients with narcolepsy-cataplexy to 21 controls, there was no difference in ^{11}C-MPB binding in the thalamus, pons, striatum, or cerebral cortex.

Derry et al. (2006) evaluated 5-HT neurotransmission in patients with narcolepsy-cataplexy. They used PET with 2′-methoxyphenyl-(*N*-2′-pyridinyl)-*p*-^{18}F-fluoro-benzamidoethylpiperazine (^{18}F-MPPF) in order to study 5-HT$_{1A}$ receptors. This study found an increase in ^{18}F-MPPF binding in the anterior cingulate, temporal, and mesio-temporal cortices in patients during sleep compared to wakefulness. However, this study is limited by the lack of a control group.

A few studies investigated presynaptic DA binding in narcolepsy-cataplexy using ^{123}I-(*N*)-(3-iodopropene-2-yl)-2b-carbomethoxy-3b-(4-chlorophenyl)tropane (^{123}I-IPT) SPECT (Eisensehr et al. 2003a, b) and ^{11}C-2b-carbomethoxy-3b-(4-fluorophenyl)tropane (^{11}C-CFT) PET (Rinne et al. 2004). However, there was no significant difference when comparing patients with narcolepsy-cataplexy and controls. When looking at postsynaptic D2 receptor binding, a study found a difference between patients and controls using SPECT and ^{123}I-(*S*)-2-hydroxy-3-iodo-6-methoxy-([1-ethyl-2-pyrrolidinyl] methyl)benzamide (^{123}I-IBZM). They found

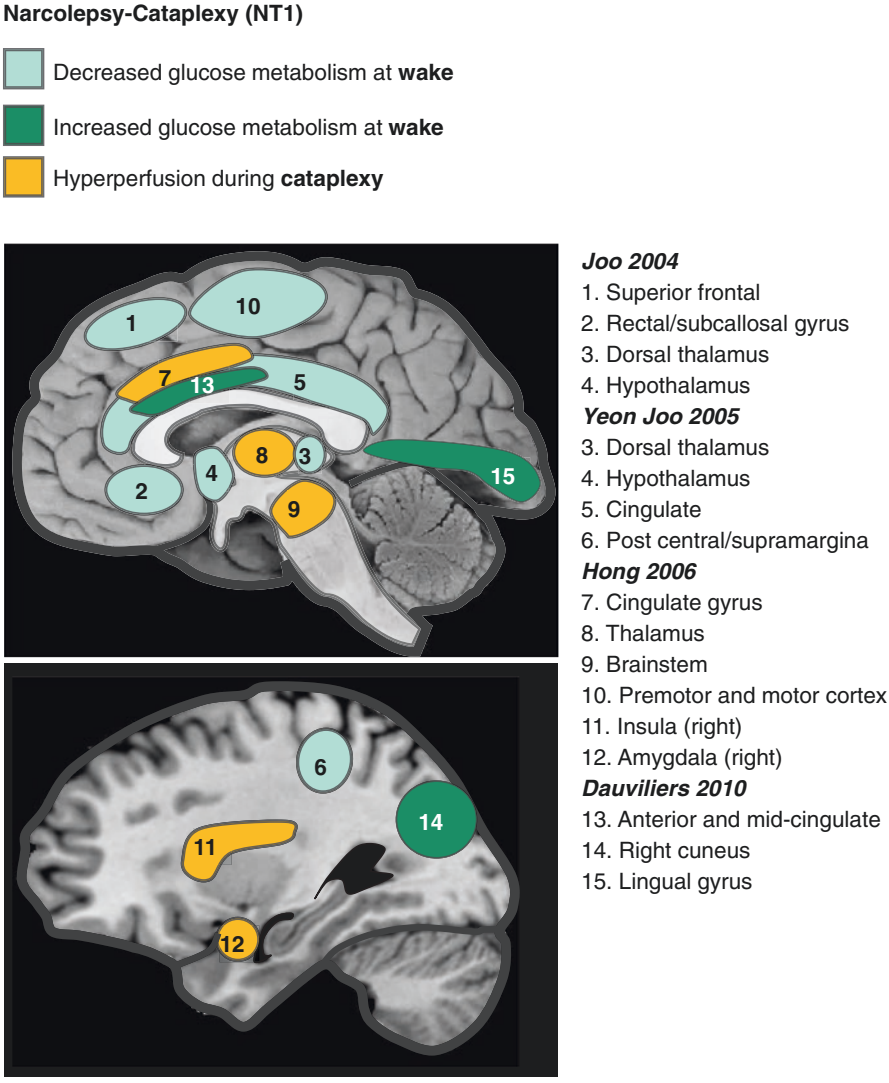


Fig. 33.1 Brain regions showing differences in CMRglu or rCBF during wakefulness in narcolepsy-cataplexy (NT1), as well as hyperperfusion (rCBF) during cataplectic attack. Adapted from Dang-Vu et al. (2014)

increased D2 binding in the striatum in seven patients with narcolepsy-cataplexy. There was also a positive correlation between IBZM binding to the striatum and the incidence of sleep attacks and cataplexy (Eisensehr et al. 2003b). However, other studies using SPECT scans with IBZM were not able to replicate these findings (Hublin et al. 1994; Staedt et al. 1996). Khan et al. (1994) and Rinne et al. (1995) examined the relationship between dopamine and narcolepsy-cataplexy using a

PET study with ^{11}C-raclopride, but their results were inconclusive. MacFarlane et al. (1997) conducted a study using PET with ^{18}F-fluoropropyl-spiperone (^{18}F-PSP) ligand and were not able to find a difference in the striatal binding of D2 in patients with narcolepsy-cataplexy.

33.2.1.2 Brain Glucose Metabolism and Perfusion in Narcoleptic Individuals

Another important aspect that several neuroimaging studies examined is the difference in narcoleptic brain activity during the day. Two studies concentrated on the assessment of CMRglu during resting wakefulness. One study assessed the CMRglu of 24 patients with narcolepsy (including 21 with cataplexy) and 24 normal individuals using PET with ^{18}F-fluorodeoxyglucose (^{18}F-FDG). They found that patients had reduced CMRglu in the bilateral posterior hypothalami and mediodorsal thalamic nuclei (Joo et al. 2004). However, this study did not include EEG measurements, which weakens the strength of the findings. Another study used SPECT with Technetium-^{99}m-ethylcysteinate dimer (^{99m}Tc-ECD) and found that there was hypoperfusion in the bilateral anterior hypothalami. This study also found decreased rCBF in the caudate, superior/middle frontal gyri, postcentral gyrus, parahippocampal gyrus, and cingulate cortex in patients with narcolepsy-cataplexy (Yeon Joo et al. 2005). Both studies concluded that altered hypothalamic activity could reflect hypocretin deficiency in patients with narcolepsy-cataplexy, while the other neuroimaging patterns could be related to dysfunctions in emotional and cognitive processes. In contrast, a study conducted by Dauvilliers et al. (2010) used PET with ^{18}F-FDG and found an increase in CMRglu in the limbic cortex (more precisely in the anterior and midcingulate cortex), as well as in the right cuneus and lingual gyrus. However, this last study included patients treated with psychostimulants and did not use an objective assessment of vigilance with EEG.

33.2.1.3 Neural Correlates of Cataplexy

Given the inherent difficulty in "catching" a patient with narcolepsy in the scanner during a cataplectic episode, few studies have examined brain activity during cataplexy (loss of muscle tone). A study was conducted using ^{99m}Tc-ECD SPECT on two individuals suffering from narcolepsy with cataplexy. Scans obtained *during* a cataplexy episode were compared to those recorded during wakefulness and REM sleep. Cataplexy was associated with increased perfusion in limbic areas (amygdala, cingulate gyrus), basal ganglia, thalami, sensorimotor cortices, and the brainstem. Conversely, perfusion decreased in the prefrontal cortex and the occipital lobe (Hong et al. 2006). Increased activity in the cingulate cortex and amygdala may underlie abnormalities in the neural processing of emotions (which typically trigger cataplectic episodes), but the small sample limits the interpretation of findings. A case study using SPECT with ^{99m}Tc-ECD found an increased perfusion in the cingulate cortex and basal ganglia during an episode of cataplexy, in agreement with the previous report (Chabas et al. 2007). Dauvilliers et al. (2010) finally scanned

two patients with narcolepsy-cataplexy with PET with ^{18}F-FDG during a cataplectic attack, but did not find any significant difference when cataplexy scans were compared to the corresponding baseline wakefulness scans of the same patients.

33.2.1.4 Pharmacological Treatment of Narcolepsy

Since the main symptom of narcolepsy is excessive sleepiness, medications that promote vigilance are vital in narcolepsy treatment. Psychostimulants are known to induce enhanced wakefulness as well as improvements in physical functioning; hence this class of drugs has seen much use in treating narcolepsy. Studies involving functional neuroimaging techniques such as SPECT and PET have investigated the neural effects of these drugs in patients with narcolepsy.

Methylphenidate

Methylphenidate, an amphetamine derivative, is commonly used for treating narcolepsy. One SPECT study used ^{133}Xe inhalation to examine rCBF in patients with narcolepsy before and after treatment with methylphenidate for about 2 weeks. Administration of the drug increased rCBF during the awake state in the brainstem and cerebellar region (Meyer et al. 1980). The specificity of this finding to narcolepsy cannot be assessed, because controls were omitted in this study. Moreover, whether the patients had a history of cataplexy was not mentioned.

Modafinil

Modafinil is another psychostimulant drug used to promote wakefulness in patients with sleep disorders. In one experiment, ^{99m}Tc-ECD SPECT was performed when patients with narcolepsy-cataplexy were in the awake state, both before and after a 4-week treatment with either modafinil or a placebo (Joo et al. 2008). Modafinil caused a significant reduction in subjective daytime sleepiness, while the placebo did not, and patients in the on-modafinil condition showed an increase in rCBF in the bilateral prefrontal cortices (Joo et al. 2008). Thirty-two narcolepsy patients took part in this experiment, but in the absence of controls, the findings cannot be specifically applied to narcolepsy. Another experiment employed ^{18}F-FDG PET to measure CMRglu in patients with narcolepsy-cataplexy (Dauvilliers et al. 2010). Some of the patients were given modafinil and/or antidepressants (for treating cataplexy). Narcoleptics who received the treatment had a higher CMRglu in the cerebellum and the primary sensorimotor cortex compared to untreated patients, which contrasts with the SPECT study by Joo et al. (2008), in which modafinil was associated with a decrease in rCBF in the cerebellum. Researchers conducted another study using ^{18}F-FDG PET to assess changes in CMRglu after the administration of modafinil (Kim et al. 2007). Eight patients with narcolepsy (including six with cataplexy) completed the experiment. After 2 weeks of treatment with modafinil, the left hippocampus of narcoleptics exhibited an increase in CMRglu compared to pretreatment scans. Given that similar neuroimaging pattern was found with modafinil treatment in healthy volunteers (Joo et al. 2008), the specificity of this finding to narcolepsy might be questioned.

33.2.1.5 Narcolepsy Type 2

So far, only one study investigated NT2 using nuclear imaging. Huang et al. (2018) compared 29 patients with NT2, 26 healthy sleepers, and 104 drug-free and newly diagnosed patients with NT1 using ^{18}F-FDG PET during wakefulness. They found increased metabolic rate in the fusiform, striatum, thalamus, hippocampus, basal ganglia, and cerebellum in NT1 compared to NT2. However, hypometabolism was more prominent in patients with type 2 in the Heschl's gyrus and paracentral lobule compared to NT1. Moreover, the hypo- and hypermetabolism seen in NT1 patients compared to healthy controls were not observed in patients with NT2. They found that in both types of narcoleptic patients, the alteration in brain metabolism was correlated with performance in neurocognitive tests (i.e., Continuous Performance Test and Wisconsin Card Sorting Test). This study concluded that NT2 patients exhibit less brain metabolism alterations and less severe cognitive impairment due to preserved hypothalamus integrity (Huang et al. 2018).

33.2.1.6 Summary

Generally, SPECT and PET studies did not demonstrate a consistent difference in ACh, DA, or 5-HT neurotransmission in narcolepsy-cataplexy. Patients had reduced activity in the bilateral, hypothalamic, and thalamic nuclei, in agreement with a dysfunction of the hypocretinergic system and an impairment of vigilance. Importantly, alterations of limbic structures were found and are in agreement with abnormalities in emotional processing. Furthermore, these imaging data are in agreement with neuropsychological studies finding symptoms of narcolepsy in patients with hypothalamic lesions (Dempsey et al. 2003; Muller 2010). Although studies showed functional brain changes in narcoleptic patients posttreatment with the drugs discussed above, the meaning and significance of these differences still remain unclear, especially given the general lack of control and/or placebo groups. Further studies are thus needed to provide information on the specificity of these drug effects to patients with narcolepsy. Moreover, given the recent clinical distinction between NT1 and NT2, further investigation on the neural mechanisms distinguishing these two disorders needs to be performed.

33.2.2 Idiopathic Hypersomnia

Idiopathic hypersomnia (IH) is characterized by excessive daytime sleepiness but, in contrast to narcolepsy, does not involve cataplexy, SOREM periods, or hypocretin-1 deficiency. Compared to NT1, IH has been less investigated, and the neural correlates of IH remain unclear. So far, only one study investigated IH using MRI (Pomares et al. 2019) and SPECT (Boucetta et al. 2017), and one study used PET (Dauvilliers et al. 2017). Boucetta and colleagues scanned 13 patients with IH and 16 healthy sleepers using ^{99m}Tc-ECD SPECT to assess cerebral blood flow during resting wakefulness. Patients with IH exhibited lower rCBF in the medial prefrontal and posterior cingulate cortices. The altered rCBF levels in the medial prefrontal cortex were correlated with higher self-reported daytime sleepiness (Boucetta et al. 2017). As these regions belong to the default mode network (DMN), which plays a

key role in the maintenance of conscious awareness (Greicius et al. 2003), their lower function in IH might contribute to the impaired vigilance of IH patients during the daytime. In addition, the altered rCBF in these regions was strikingly similar to the rCBF distribution found during NREM sleep in good sleepers (Dang-Vu et al. 2005) reflecting the possible intrusion of NREM sleeplike patterns into wakefulness in IH (See Fig. 33.2).

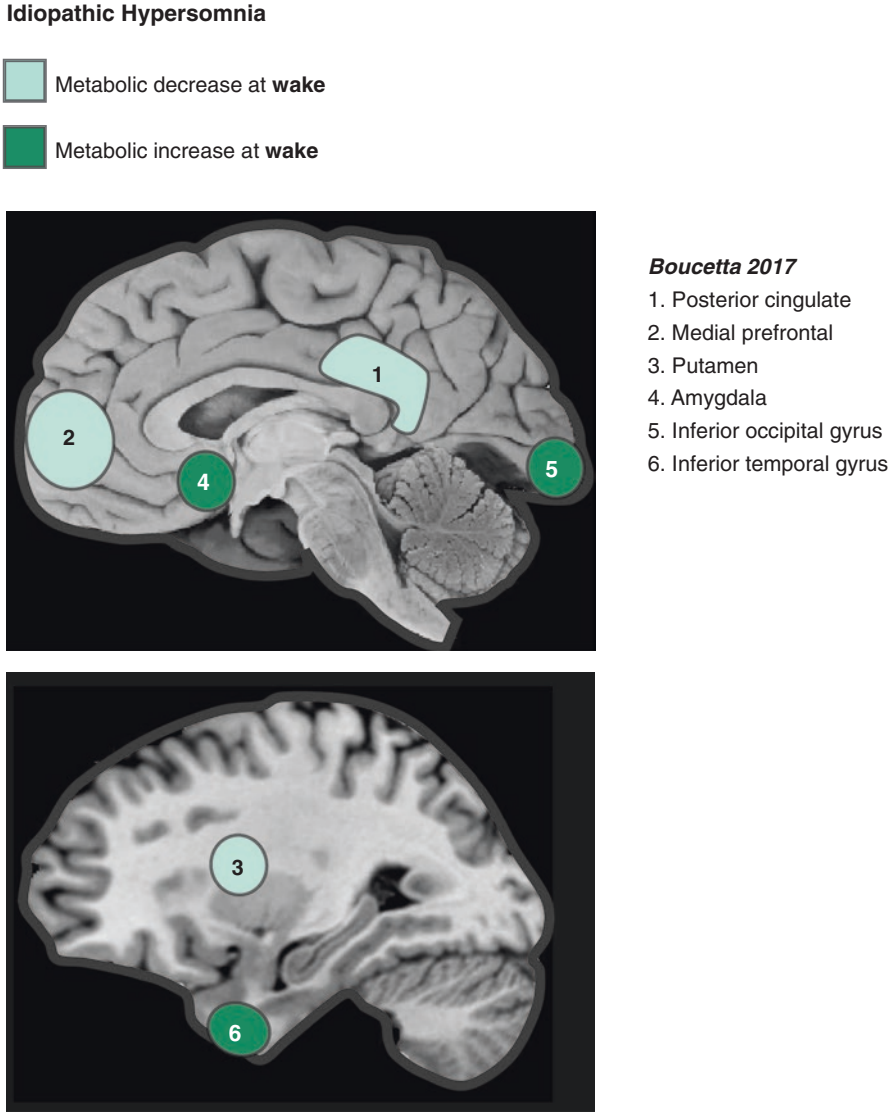


Fig. 33.2 Brain regions showing hyperperfusion or hypoperfusion in rCBF during wake in patients with idiopathic hypersomnia (IH). The rCBF decrease during wake in IH is strikingly similar to the decrease in rCBF observed during NREM sleep in good sleepers (Dang-Vu et al. 2005)

In contrast, using ^{18}F-FDG PET scanner in 9 IH, 16 NT1, and 19 healthy controls during wakefulness, Dauvilliers et al. (2017) revealed no hypometabolism in both IH and NT1 patients compared to healthy controls but hypermetabolism in similar regions in both disorders, including bilateral middle cingulate and fusiform regions, the Rolandic operculum, and the temporal and insula lobes. Given the similar alterations found in IH and NT1, they suggested that their results might reflect the neural correlates of excessive daytime sleepiness rather than specific features of each disorder (Dauvilliers et al. 2017).

The difference in sample characteristics and techniques used might contribute to these divergent findings. Further investigation needs to be performed between the different types of central hypersomnolence disorders, in order to understand the common and distinct alterations underlying each disorder.

33.3 Restless Legs Syndrome and Periodic Limb Movements

Restless legs syndrome (RLS) and periodic limb movements (PLM) are distinct yet overlapping sensorimotor disorders. RLS is characterized by an overwhelming urge to move the legs (and less often, the arms), especially when at rest and in the evening or at night. The compulsion is associated with persistent feelings of discomfort from deep inside the limbs (AASM 2005; Allen et al. 2003). PLM is distinguished by intermittent episodes of repeated and highly stereotyped limb movements when at rest, typically during NREM sleep (PLMS), but also occurring during wakefulness (PLMW). The same patient can exhibit both PLMS and PLMW. The movement typically consists of an extension of the big toe and partial flexion of the ankle, knee, and, less often, hip. While these movements disturb sleep and can result in arousal or awakening, patients are mostly unaware of the movements or even that their sleep has been disturbed. Diagnosis requires a polysomnographic recording in combination with a complaint such as "unrefreshing" sleep (AASM 2005; Pennestri et al. 2006).

Epidemiological studies estimate a 5–20% prevalence of RLS (Allen et al. 2003) and a 3.9% prevalence of PLMS in the general population (Ohayon and Roth 2002). RLS-related symptoms are responsible for sleep-onset insomnia and nocturnal awakenings in 94% of patients (Montplaisir et al. 1997). RLS can occur in an isolated form (idiopathic) or can be secondary to (or associated with) other medical conditions, such as iron deficiency anemia, neuropathy, and Parkinson's disease (PD) (AASM 2005; Allen et al. 2003; Pedroso et al. 2013). Depression and anxiety-related psychiatric illnesses are more prevalent in RLS and PLM patients than in healthy individuals (Pennestri et al. 2006; Picchietti 2006).

RLS and PLM frequently co-occur. However, PLM is nonspecific, occurring in isolation in healthy individuals, or comorbid with other sleep disorders such as narcolepsy, RBD, and sleep apnea (Pennestri et al. 2006). Since both disorders are so closely associated, few neuroimaging studies have examined PLM alone, and instead RLS and PLM are most often considered in concert. The following section will first describe neuroimaging studies centered on RLS and will end by covering the few studies of PLM alone.

33.3.1 Restless Legs Syndrome

There are few functional neuroimaging studies of RLS. A PET study by Trenkwalder et al. (1999) involving six RLS patients and six age-matched controls measured CMRglu with ^{18}F-FDG and found no significant differences. It is noteworthy that the patients were scanned outside of the symptomatic period.

Most PET and SPECT studies of RLS have looked for neurotransmission abnormalities using radioligands for DA and opioids. It has been shown that DA antagonists exacerbate RLS symptoms, whereas DA agonists and opioids are the major form of therapy for RLS (Stiasny-Kolster et al. 2005; Trenkwalder et al. 2008). DA studies focused mainly on the striatum, examining both presynaptic DA transporter (DAT) and postsynaptic D2 receptor binding. Striatal DAT can be taken as an indicator of DA neuron density in the substantia nigra (SN). Some PET studies showed decreased presynaptic DA function in the striatum of RLS patients versus controls, using either 6-[^{18}F]fluoro-L-dopa (^{18}F-dopa) (Ruottinen et al. 2000; Turjanski et al. 1999) or ^{11}C-methylphenidate (Earley et al. 2011). However, an early PET study using ^{18}F-dopa found no such difference, albeit with a limited sample of patients (Trenkwalder et al. 1999). Furthermore, a number of SPECT studies found no difference in DAT in RLS versus controls, using ^{123}I-2beta-carbomethoxy-3beta-(4-iodophenyl)tropane (^{123}I-β-CIT) (Michaud et al. 2002; Mrowka et al. 2005) or ^{123}I-IPT (Eisensehr et al. 2001; Linke et al. 2004). Recently, Lin and colleagues used ^{99}mTechnetium-[2-[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo(3,2,1)oct-2-yl] methyl](2mercapto-ethyl)amino]ethyl]amino]ethanethiolato(3-)-N2,N2,S2,S2]oxo-[1R-(exo-exo)] (^{99}mTc-TRODAT) SPECT and revealed significant decrease in DAT striatal binding in 22 early-stage RLS patients compared to 12 healthy controls. Specifically, they showed uptake deficits in both sides of the caudate nucleus and striatum (Lin et al. 2016).

The discrepancy in these findings may be attributable to particular pharmacokinetic properties of radioligands used in PET and SPECT. Earley et al. (2011), in the aforementioned study, scanned their patients in the morning (n = 20) and evening (n = 16) and found no difference in DA according to time of day. Hence, time of day does not seem to modulate DAT binding. There was also no significant correlation between severity of RLS symptoms and DAT. Kim et al. (2012) employed SPECT with ^{123}I-β-CIT and ^{123}I-IBZM and, in contrast with all previous presynaptic DA studies, found an increase in DAT density in the striatum, as well as the caudate and posterior putamen.

Postsynaptic D2 receptor binding studies are also rather equivocal. A few SPECT studies used ^{123}I-IBZM. Most found no difference (Eisensehr et al. 2001; Tribl et al. 2002, 2004), while one found a slight decrease in striatal D2 receptor binding in RLS patients versus controls (Michaud et al. 2002). Two PET studies using ^{11}C-raclopride found divergent results: Turjanski et al. (1999) found a decrease and Cervenka et al. (2006) an increase in striatal D2 receptor binding. This discrepancy may be explained by the inclusion of a sample of RLS patients previously exposed to DA drugs in the study by Turjanski et al. (1999), whereas patients in the other study were drug-naïve

(Cervenka et al. 2006). It has in fact been shown that D2 receptors can be downregulated by chronic drug treatment, hence decreasing ligand binding (Stanwood et al. 2000). Cervenka et al. (2006) measured D2 receptor binding in extrastriatal structures by scanning 16 RLS patients with ^{11}C-FLB457 and found increased binding potential in the striatum as well as in the insula, thalamus, and anterior cingulate cortex. The areas showing increased D2 receptor binding are part of the medial nociceptive system, which regulates the affective component of pain. If this system were to undergo endogenous DA depletion, one could expect upregulation of D2 receptors, just as the study showed. The authors also took measurements in the morning and the evening and found no diurnal changes in D2 binding potential. Furthermore, no significant correlation was found between RLS symptom rating and D2 binding potential. Hence diurnal changes in RLS symptom severity cannot be accounted for by presynaptic DA transmission (Earley et al. 2011) or postsynaptic D2 binding (Cervenka et al. 2006). In a later PET study using ^{11}C-raclopride, Earley et al. (2013) found that RLS patients had lower D2 receptor binding potential in the putamen, as well as the caudate but not ventral striatum. Interestingly, in light of the divergent results of previous PET and SPECT studies, the authors of the study deemed D2 receptor binding potential of questionable value to RLS research.

Since RLS seems to be a disorder of the nociceptive system, it follows that the opioid system, which modulates pain, may play a role in RLS. Indeed, opioid receptor agonists have been shown to improve RLS symptoms (Walters 2002). This effect may however be mediated by DA and may not necessarily reflect a deficiency in endogenous opioids (Barriere et al. 2005). In support of this, one PET study has examined opioids in RLS, using ^{11}C-diprenorphine (a nonselective opioid receptor ligand), and found no differences between patients and controls, although the authors did find some correlations between RLS severity or pain scores and opioid binding in several brain areas (von Spiczak et al. 2005).

In addition to nigrostriatal abnormalities in DA neurotransmission, descending dopaminergic projections to the lower brainstem and spinal cord, as well as opioid receptors in the spinal cord, are also thought to play an important role in RLS pathophysiology. In addition, spinal cord lesions and peripheral neuropathies are associated with RLS (Trenkwalder and Paulus 2010). However, limitations in the resolution of PET and SPECT in these areas preclude further investigation using these imaging techniques.

33.3.2 Periodic Limb Movements

Dopaminergic transmission has been studied in relation to PLM. At the presynaptic level, Happe et al. (2003) measured DA transmission in 11 patients with Parkinson's disease (PD) using SPECT with ^{123}I-β-CIT. Patients with PD showed a stark reduction in striatal binding compared to controls, as expected. By also measuring PLMS by polysomnography, the authors detected a negative correlation between the number of PLMS and striatal DA binding values. This suggests a possible role of presynaptic DA deficiency in PD-induced PLMS. Staedt and colleagues examined

postsynaptic D2 receptor binding in the striatum of PLMS patients in a few studies using SPECT and ^{123}I-IBZM (Staedt et al. 1993, 1995a, b) and found decreased D2 receptor occupancy (Staedt et al. 1993, 1995a). DA replacement therapy can reverse this pattern and restore sleep quality (Staedt et al. 1995b).

33.3.3 Summary

PET and SPECT studies on RLS and PLM seem to indicate a hypoactivity of DA neurotransmission underlying these disorders, both at the presynaptic and postsynaptic levels. DA deficiency, in concert with CNS iron depletion, may unbalance the sensorimotor control of pain. Further research into RLS and PLM brain activation during sleep is needed to confirm these findings and shed further light on these little explored disorders.

33.4 Parasomnias

Parasomnias are characterized by undesirable physical events and experiences occurring during entry into sleep, within sleep, or during arousals from sleep (AASM 2005). They are divided into two categories: REM and NREM parasomnias. Although some forms are benign, others may result in injury and sleep disruption, severely affecting one's life. PET and SPECT bring important contributions to the pathophysiology of parasomnias.

33.4.1 Sleepwalking

One common type of NREM parasomnia is sleepwalking, formally known as somnambulism. It "consists of a series of complex behaviors that are usually initiated during arousals and slow wave sleep (SWS; i.e., deep NREM sleep) and culminate in walking around with an altered state of consciousness and impaired judgment" (AASM 2005). Bassetti et al. (2000) hypothesized that sleepwalking is a dissociated state, consisting of both mental and motor arousal. Using SPECT, recordings were taken from a 16-year-old man in two conditions: one recording during SWS, the other 24 s after the occurrence of a sleepwalking episode arising from SWS. In both conditions, the patient was injected with ^{99m}Tc-ECD. Compared to undisturbed SWS, there was an increase in rCBF post-sleepwalking, particularly in the posterior cingulate cortex and the anterior cerebellum (Bassetti et al. 2000). Interestingly, these areas showed a decrease in activity in healthy volunteers during SWS compared to wakefulness (Maquet et al. 2000). Furthermore, Bassetti et al. compared their data to those of control subjects and observed that the patient demonstrated a decrease in perfusion in the frontoparietal associative cortices during the sleepwalking episode compared to wakefulness in controls. This hypoperfusion was interpreted as reflecting a lack of self-related awareness and the inability to recall the

events of the sleepwalking episode. In contrast, the hyperperfusion of the posterior cingulate and cerebellum were thought to reflect persistent arousal patterns, which is in line with the hypothesis of a dissociated state. These findings should be interpreted with caution as they were based on a single individual with sleepwalking.

More recent studies investigated brain function of sleepwalkers during wakefulness. Using ^{99m}Tc-ECD SPECT, Dang Vu et al. scanned 10 adult sleepwalkers during wakefulness in the morning as compared to 12 control subjects and found no difference in brain perfusion between groups (Dang-Vu et al. 2014). However, when scanning again a subsample of these individuals (eight sleepwalkers and nine controls) after a night of total sleep deprivation, they observed a hypoperfusion of the inferior temporal cortex compared to controls. While increased sleep propensity (i.e., sleep deprivation) is known to promote sleepwalking episodes in the following sleep period (Zadra et al. 2008), these SPECT findings revealed a pattern of neural dysfunction characterizing wakefulness in sleepwalkers after sleep deprivation (Dang-Vu et al. 2014). A few years later, the same team revealed that after total sleep deprivation, sleepwalkers (ten adults) showed reduced rCBF in left parietal and temporal regions and increased rCBF in right parahippocampal gyrus during resting-state wakefulness compared to ten control subjects (Desjardins et al. 2018). Moreover, during the SWS period following the total sleep deprivation, sleepwalkers displayed reduced perfusion in the left insula, postcentral gyrus, and superior temporal gyrus (Desjardins et al. 2018). Combined with the findings from 2015, these results are in line with the increased vulnerability of sleepwalkers to sleep deprivation.

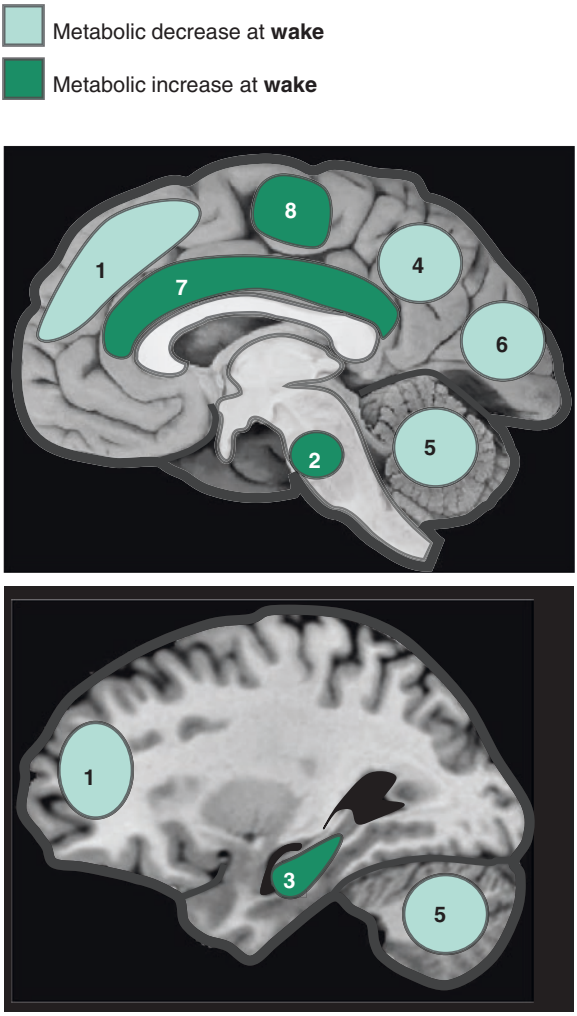
33.4.2 REM Sleep Behavior Disorder

Within REM parasomnias, RBD is accompanied by a loss of skeletal muscle atonia usually present during REM sleep and involves complex motor activity occurring specifically in association with dream mentation. The disorder is characterized by unpleasant dreams and dream enactment, which could be disturbing to the patient or the bed partner (AASM 2005). RBD can exist with or without a medical condition, respectively known as secondary RBD or idiopathic RBD (iRBD). Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) tend to develop in patients with RBD several years later (Postuma et al. 2009) with an estimate of 41% risk 5 years after RBD clinical manifestations (Postuma et al. 2015) and more than 90% after 14 years (Iranzo et al. 2014). SPECT and PET have played a significant role in highlighting the brain regions involved in RBD pathophysiology and clinical evolution. A summary of these findings on idiopathic RBD is provided in Fig. 33.3.

33.4.2.1 Hypo- and Hyperperfusions in RBD

A study performed by Shirakawa et al. (2002) compared 20 male iRBD patients to 7 healthy male subjects using *N*-isopropyl-*p*-^{123}I-iodoamphetamine (^{123}I-IMP) SPECT. Compared to the control group, a statistically significant decrease of rCBF

Idiopathic RBD



Mazza 2006
1. Superior frontal lobe
2. Pons
3. Right hippocampus
4. Parietal lobe

Vendette 2011
1. Superior frontal lobe
2. Pons
3. Hippocampus (bilaterally)
4. Precuneus

Hanyu 2011
4. Precuneus
5. Cerebellum

Dang-Vu 2012
2. Pons
3. Hippocampus (bilaterally)

Ge 2015
6. Occipital lobe
7. Cingulate
8. Supplementary motor area
2. Pons
3. Hippocampus (bilaterally)

Mayer 2015
1. Premotor area
2. Pons
5. Cerebellum

Fig. 33.3 Brain regions showing hyperperfusion or hypoperfusion in rCBF during wake in iRBD patients. Many of these changes in rCBF mirror those observed in several synucleinopathies. Adapted from Dang-Vu et al. (2014)

was found in the right and left upper portion of the frontal lobe and in the pons. The scans were performed at night, although it was not clear which state of vigilance the subjects were experiencing. A few years later, Mazza et al. (2006) conducted a study using ^{99m}Tc-ECD SPECT, which included eight iRBD patients and nine healthy control subjects. In contrast to Shirakawa et al. (2002), significant hyperperfusions were found in the pons, as well as in the putamen and the right hippocampus. Interestingly, increased rCBF is also present in the latter two regions during the

early stages of PD (Imon et al. 1999). In addition, decreased perfusion was found in the frontal lobe, particularly in motor cortices, and in the temporoparietal cortices. A larger study of 20 iRBD patients and 20 control subjects exhibited similar results (Vendette et al. 2011). Once again using ^{99m}Tc-ECD SPECT, hyperperfusion was displayed in the pons, the putamen, and bilaterally the hippocampus and hypoperfusion in frontal and medial parietal areas.

Hanyu et al. (2011) monitored rCBF using ^{123}I-IMP SPECT in 24 patients with iRBD. In contrast with previous studies, they did not find significant differences between patients and controls in the brainstem and frontal areas. Results did however display hypoperfusion in iRBD patients, in the precuneus, cerebellum, and uncus regions, also identified by Vendette et al. (2011).

In order to investigate longitudinal rCBF alterations, Sakurai et al. (2014) performed repeated ^{123}I-IMP SPECT sessions on nine iRBD patients with a mean interval of 22 ± 9 months between the two scans. Patients were taking medication to treat their symptoms during both scans. They found a decreased rCBF in medial parietooccipital lobe and in the right posterior cingulate during the follow-up SPECT session compared to baseline, in line with a progressing neurodegenerative process. However, they did not reveal any changes in neuropsychological tests (e.g., Geriatric Depression Scale-15, Frontal Assessment Battery Test, Wechsler Memory Scale-Revised: Logical Memory I and II) between the two sessions. It is important to note that most patients were taking medication (e.g., clonazepam) at both sessions to decrease RBD symptoms (Sakurai et al. 2014).

Two studies led by Caselli et al. (2006) and Fujishiro et al. (2010) assessed CMRglu with ^{18}F-FDG PET in subjects with dream enactment behavior. These subjects displayed decreased CMRglu in multiple cortical areas, such as occipital, frontal, parietal, temporal, and cingulate. No polysomnographic recording was performed to confirm a diagnosis of RBD; rather, patients were selected based on questionnaires and interviews only, hence diminishing the validity of the study. However, in 2015, Ge and colleagues confirmed the decreased metabolism in the occipital cortex and lingual gyrus using ^{18}F-FDG PET in 21 iRBD patients and 21 healthy controls. They also found increased metabolism in the supplementary motor area, cingulate, pons, and hippocampus/parahippocampus compared to controls, similarly to perfusion SPECT studies. Interestingly, change in metabolism correlated with clinical measures, including a negative correlation between RDB duration and metabolism in the medial frontal gyrus but a positive correlation between RBD duration and metabolism in the anterior vermis (Ge et al. 2015).

SPECT with ^{99m}Tc-ECD was used to predict the onset of PD and DLB in 20 iRBD patients (Dang-Vu et al. 2012). The average follow-up of 3 years revealed that PD or DLB emerged in ten of the patients; interestingly, only these ten patients showed an increase in hippocampal rCBF at baseline. It can thus be proposed that the progression of idiopathic RBD into PD or DLB can be predicted via abnormal perfusion in the hippocampus.

While the studies above described functional neuroimaging acquired in iRBD patients mainly during wakefulness, only two studies reported brain activations associated with RBD behavioral manifestations. The first one was conducted on a

single man, with multiple system atrophy and RBD, and compared to two healthy control subjects (Dauvilliers et al. 2011). After injecting ^{99m}Tc-ECD *during* a RBD episode, compared to wakefulness, the patient showed increased perfusion in the supplementary motor area, suggesting this area's involvement in the onset of dream enactment behaviors. The effect was not present in controls when contrasting REM sleep vs. wakefulness. Another study performed ictal SPECT with ^{99m}Tc-ECD tracer injected after 10 s of a RBD episode in four RBD patients, including one iRDB patient, one RBD patient with PD, and two RBD patients with narcolepsy. They found activations in the bilateral premotor areas, periaqueductal area, pons, and anterior lobe of the cerebellum in all patients (Mayer et al. 2015). No SPECT data has been obtained so far during REM sleep per se (outside motor manifestations) in RBD patients.

33.4.2.2 Dopaminergic Imaging

Due to the relationship between RBD and PD, multiple system atrophy, and other conditions associated with DA dysfunction (Gagnon et al. 2009), there have been numerous SPECT and PET ligand studies in the last decade analyzing the nigrostriatal DA system in RBD patients. It has been suggested that substantia nigra alteration and reduced DAT update in RBD would be predictive markers for conversion to synucleinopathy. After De Marzi and colleagues found that more than 65% of iRBD patients displayed loss of nigral hyperintensity similar to PD patients using 3.0-T susceptibility-weighted (SW) MRI (De Marzi et al. 2016), Bae et al. (2018) compared the loss of nigral hyperintensity with SW MRI and DAT uptake with iodine 123–2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl)nortropane (^{123}I-FP-CIT) SPECT to determine whether substantia nigra alteration could predict RBD patients at risk for conversion to PD in 18 patients with iRBD, 18 PD patients, and 18 healthy controls. They found that nigral hyperintensity and DAT uptake ratios were lower in 11 iRBD patients compared to controls but still higher than PD patients. Within these 11 iRBD patients with low nigral hyperintensity, 5 developed symptoms of synucleinopathy within 18 months, suggesting that SW imaging might be a useful tool to detect RBD patients with high risk for short-term conversion (Bae et al. 2018).

A group performed two SPECT studies with ^{123}I-IPT demonstrating a decrease in DAT at the presynaptic site of the striatum in iRBD patients compared to age- and sex-matched controls (Eisensehr et al. 2000, 2003a). Additionally, these two studies also included an assessment of postsynaptic D2 receptor binding using ^{123}I-IBZM SPECT and found no significant change in iRBD compared to controls and PD. This suggests that DA dysfunction in the striatum is restricted to the presynaptic level in RBD patients, in line with a loss of DA midbrain neurons, and similarly to findings in PD (Tatsch et al. 1997). Similar results were found when using ^{11}C-dihydrotetrabenazine (^{11}C-DTBZ) PET in 6 iRBD patients compared to 19 controls (Albin et al. 2000). Similarly, a PET study was performed using (+)-[^{11}C]dihydrotetrabenazine (^{11}C-DTBZ) tracer to measure presynaptic striatal binding and (-)-5-[^{123}I]iodobenzovesamicol ([^{123}I]IBVM) SPECT to assess thalamic cholinergic binding in 13 patients with probable MSA and presence of RBD. Compared to 27

healthy controls, the MSA-RBD patients showed a decrease in thalamic cholinergic binding as well as a decrease in striatal binding, which was negatively correlated with the severity of REM atonia (Gilman et al. 2003). Whether it is the degeneration of nigrostriatal DA neurons that contribute to RBD symptoms in MSA needs to be investigated with a comparison between MSA patients with and without RDB symptoms.

In agreement with the studies conducted by Eisensehr et al. (2000, 2003a, b), the density of striatal DAT was measured, and a decrease in presynaptic binding was found, most prominently in the posterior putamen. This was later confirmed by Li and colleagues who used ^{99}mTc-TRODAT-1 SPECT on 43 patients with iRBD. They found that the 18 patients with decrease DAT uptake in the left striatum and putamen at baseline converted to a full-blown synucleinopathy (i.e., 2 DLB, 3 MSA, 13 PD) after a median of 4.1 years of follow-up (median interval of 10.5 years from the estimated iRBD symptoms onset) (Li et al. 2017). Using ^{18}F-DOPA PET on 20 patients with iRBD and 19 healthy controls, Stokholm and colleagues investigated nigrostriatal dopaminergic function and also revealed reduced uptake bilaterally in the putamen but not in caudate (Stokholm et al. 2017). Moreover, using ^{11}C-(*R*)-(2-chlorophenyl)-*N*-methyl-*N*-(1-methylpropyl)-3-isoquinoline-carboxamide (^{11}C-PK11195) PET on the same patients, they investigated whether neuroinflammation (i.e., increase in peripheral benzodiazepine receptor translocator protein binding expressed by activated microglia) usually shown in synucleinopathies was also present in RBD. They found increased microglial activation in the left substantia nigra but not in the putamen and caudate. They did not find correlation between dopaminergic deficit and neuroinflammation. Because only a subset of patients actually revealed abnormally high level of microglial activation in the substantial nigra, they proposed that future studies should investigate whether the presence of neuroinflammation in RDB patients might represent a marker of conversion to synucleinopathies (Stokholm et al. 2017). Four studies examined DAT in RBD patients using SPECT with ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl)nortropane (^{123}I-FP-CIT). Two studies in particular concluded that an insignificant number of RBD patients demonstrated a decrease of striatal DAT (Stiasny-Kolster et al. 2005; Unger et al. 2008).

Another report compared 14 idiopathic RBD patients, 14 early-stage Parkinson's disease, and 12 controls (Kim et al. 2010). Further confirming the studies performed by Eisensehr and colleagues (2000, 2003a), the RBD patients showed lower binding in the striatum compared to control subjects, more specifically in the putamen. This binding was however higher compared to Parkinson's disease patients, suggesting a progressive DA impairment from RBD to Parkinson's disease. In a more recent ^{123}I-FP-CIT SPECT study, 43 idiopathic RBD and 18 controls were examined longitudinally for striatal DAT (Iranzo et al. 2010). It was found that there was reduced binding in 40% of the RBD patients. This study included a follow-up demonstrating that a neurodegenerative disorder developed in eight of the IRBD patients within 2.5 years after the imaging took place. Interestingly, six of these eight patients had reduced DAT at baseline, highlighting the significance of lowered DAT in the prediction of disease evolution.

A case study involving a 73-year-old man used ^{11}C-CFT to assess changes of nigrostriatal presynaptic DA 1 year and 3.5 years after the onset of RBD (Miyamoto et al. 2010). Compared to controls, the first year's results displayed only a minor decrease in the posterior putamen, yet after 3.5 years, there was a more pronounced decrease of 4–6% per year. Similarly, a recent 3-year study used ^{123}I-FP-CIT SPECT on 20 IRBD patients (Iranzo et al. 2011). Complementary to the case report, there was a reduction in binding over time (compared to controls) in all striatal regions with the exception of the right caudate nucleus, further demonstrating a progressive nigrostriatal dopaminergic dysfunction. Alteration in the substantia nigra over time has been reported with diverse neuroimaging techniques including MRI (De Marzi et al. 2016).

Overall, these data suggest that iRBD are in line with the concept of RBD as a "prodromal" phase of synucleinopathies. However, RDB can also occur after PD diagnosis or never at all, which lead to the question whether a distinct RBD phenotype of PD might exist. Arnaldi and colleagues (2015a, b) investigated dopaminergic deafferentation using ^{123}I-FP-CIT-SPECT in 12 patients with iRBD, 16 PD patients without RBD (at baseline and at clinical follow-up), and 24 PD patients with RBD (symptoms at baseline or present during follow-up). They found that PD patients with presence of RBD revealed lower DAT striatal binding and more severe motor impairment than PD patients without RBD. Moreover, by computing caudate specific binding ratio (caudate SBR; i.e., caudate DAT uptake minus background DAT uptake), they observed that PD patients without RBD showed preserved nigro-caudate functioning compared to iRBD patients and PD patients with RBD suggesting that nigro-caudate deafferentation could be the hallmark of RBD. In comparison, nigro-putamen deafferentation (i.e., putamen SBR) observed in PD patients with and without RBD would represent an hallmark of PD severity as it is relatively preserved in iRBD patients but progressively altered in PD along with progressive motor impairment (Arnaldi et al. 2015b). Future studies might take into consideration the presence or absence of RBD in PD patients as it might explain some of the divergent results found in studies comparing iRBD and PD patients.

Because of its relationship with synucleinopathies, iRBD has been extensively studied with a focus on DA dysfunction. However, only one study investigated possible alteration in the serotonergic system in iRBD. Indeed, it has been shown that antidepressants, especially serotonin reuptake inhibitors (SSRI), can lead to loss of atonia during REM (induced-RDB) suggesting possible abnormal serotonergic system integrity. Using ^{123}I-FP-CIT-SPECT in 20 iRBD patients and 23 healthy controls, they assessed DAT uptake in caudate and putamen as well as serotonin transporter (SERT) uptake in the midbrain, pons, and thalamus. As expected, they found lower striatal binding in iRBD compared to controls but found no difference in SERT uptake at the brainstem and thalamic levels (Arnaldi et al. 2015a).

33.4.2.3 Metabolic Brain Networks

Beyond single region alterations, recent studies focused on metabolic brain networks using ECD-SPECT and/or FDG PET imaging. More specifically PD exhibits stereotyped changes in brain structure and function that is associated with a highly

reproducible disease-related metabolic brain network called PD-related covariance pattern (PDRP) and includes increased metabolic activity in the internal globus pallidus, thalamus, pons, and cerebellum as well as reduction in premotor and parietal regions. This increased PDRP expression is associated with progressive motor impairment (Eidelberg 2009). Recent studies found that PDRP expression is increased in some patients with RBD suggesting higher risk for conversion to PD. More precisely, Holtbernd and colleagues used resting-state ^{18}F-FDG PET on a cohort of 10 iRBD patients and 10 healthy controls as well as resting-state ^{99m}Tc-ECD SPECT on a cohort of 17 iRBD patients and 17 healthy controls and performed annual follow-up clinical assessment for 4.6 (±2.5) years after baseline imaging. They found that PDRP expression (i.e., metabolic activities in pons, cerebellum, putamen/globus pallidus, thalamus, sensorimotor, lateral premotor, and parietal association cortex) was increased in iRBD patients compared to controls in both PET and SPECT imaging. Moreover, 8 iRBD patients (out of the 17 with follow-up) were diagnosed with PD or DLB, and 3 developed signs of probable MSA (Holtbernd et al. 2014). In another study also using ^{18}FDG PET, Meles et al. (2017) also found higher PDRP expression in 21 iRBD compared to 19 healthy controls but lower compared to 20 PD patients and 22 patients with DLB. Interestingly, more than half of the RBD subjects revealed PDRP expression in the range of PD patients. In the same study, they also used DAT-SPECT and olfactory testing to offer a more complete assessment of iRBD patients at risk for conversion. Indeed, both loss of DAT binding and hyposmia symptoms have been associated with high risk for developing synucleinopathies (Mahlknecht et al. 2015). PDRP and striatal DAT binding were not significantly correlated in iRBD patients, but they found that PDRP expression was higher in iRBD patients presenting hyposmia ($N = 9$) compared to iRDB without hyposmia (Meles et al. 2017). Whether the presence of high PDRP expression, low striatal DAT binding, and hyposmia might reflect higher risk for phenoconversion needs to be assessed.

Beyond PDRP expression, Wu et al. (2014) showed that RBD patients might also exhibit its own unique metabolic network as well. Indeed, using ^{18}FDG PET on 21 iRBD patients and 21 healthy controls, they found that iRBD-related metabolic network would be characterized by increased metabolic activity in pons, thalamus, medial frontal areas, hippocampus, supramarginal/inferior temporal gyri, and posterior cerebellum with reduced activity in occipital and superior temporal regions. When compared with 21 hemi-PD patients (i.e., early PD with only one clinically symptomatic side) and 16 patients with moderate PD, they found that the iRBD-related metabolic network was also increased in hemi-PD patients compared to controls and slightly lower compared to iRBD (although not significant). Compared to iRBD, moderate PD showed a decreased expression in iRBD-related metabolic network compared to iRBD but higher PDRP expression compared to iRBD and hemi-PD (Wu et al. 2014). Future studies need to assess whether this iRBD-related metabolic network might reflect a prodromal phase of PD and predict those with higher risk of phenoconversion.

33.4.3 Summary

Sleepwalking demonstrates brain patterns reminiscent of both SWS and wakefulness states, therefore appearing as a dissociated state. Moreover, alterations in brain perfusion during wakefulness and SWS after sleep deprivation might reflect the neural correlates underlying the increased propensity of sleepwalking episodes when lacking sleep. Additional studies are needed to further qualify the role of SWS alterations in somnambulism.

In iRBD patients, SPECT and PET have shown a presynaptic dysfunction of DA nigrostriatal pathways, further indicating that iRBD represents the early stages of PD, DLB, and multiple system atrophy. Moreover, the risk of progression from iRBD to other neurodegenerative disorders can be estimated using SPECT. Hypoperfusions found in the pons agree with human studies involving pontine lesions in RBD pathophysiology (Culebras and Moore 1989; Gomez-Choco et al. 2007; Kimura et al. 2000; Limousin et al. 2009; Plazzi and Montagna 2002; Provini et al. 2004; Schenck and Mahowald 2002; Tippmann-Peikert et al. 2006; Xi and Luning 2009; Zambelis et al. 2002). The role of structures such as the hippocampus and cognitive aspects of RBD should be further investigated. Finally, brain activity patterns during behavioral episodes and during sleep should be further examined to shed new light on the pathophysiology of RBD.

33.5 Insomnia

33.5.1 Primary Insomnia

Primary insomnia is defined by as a dissatisfaction with sleep quality and complaints of difficulties falling asleep and/or maintaining sleep and/or waking up early with the incapacity to fall back asleep occurring more than three times a week for over a month. Moreover, often accompanied by a feeling of fatigue and daytime functioning impairments, these difficulties cannot be attributed to any medical or psychiatric cause, drug abuse, or other sleep disorders (e.g., sleep apnea) (Sateia 2014). The diagnosis of primary chronic insomnia is applied when the patient complains of sleep difficulties at least three times a week for more than 3 months (ICSD-3). Sleep loss—especially when it becomes chronic—is impairing, as it can have consequences on physical and mental health (Bonnet and Arand 2007), including increased risk for depression (Tsuno et al. 2005). Insomnia affects about 40% of the population on a temporary basis and more than 10% of the population in a persistent/chronic manner (Chung et al. 2015) and thereby represents a major health issue.

Electroencephalography (EEG) and functional and structural imaging have contributed much to the current scientific knowledge of insomnia. Many studies have been conducted using functional and structural MRI, with various applications

(e.g., voxel-based morphometry (VBM) and proton magnetic resonance spectroscopy (^{1}H-MRS) (Cross and Dang-Vu 2019; Desseilles et al. 2011; O'Byrne et al. 2014)). In this section we will focus on the studies using PET and SPECT in primary insomnia (see Fig. 33.4) and then fatal familial insomnia.

Only a few studies have recorded brain activity during NREM sleep in order to assess the functional neuroanatomy of primary insomnia. In order to measure regional brain metabolism (indexed by CMRglu) during waking and NREM sleep, Nofzinger et al. (2004b) used ^{18}F-FDG PET in 7 patients with primary insomnia

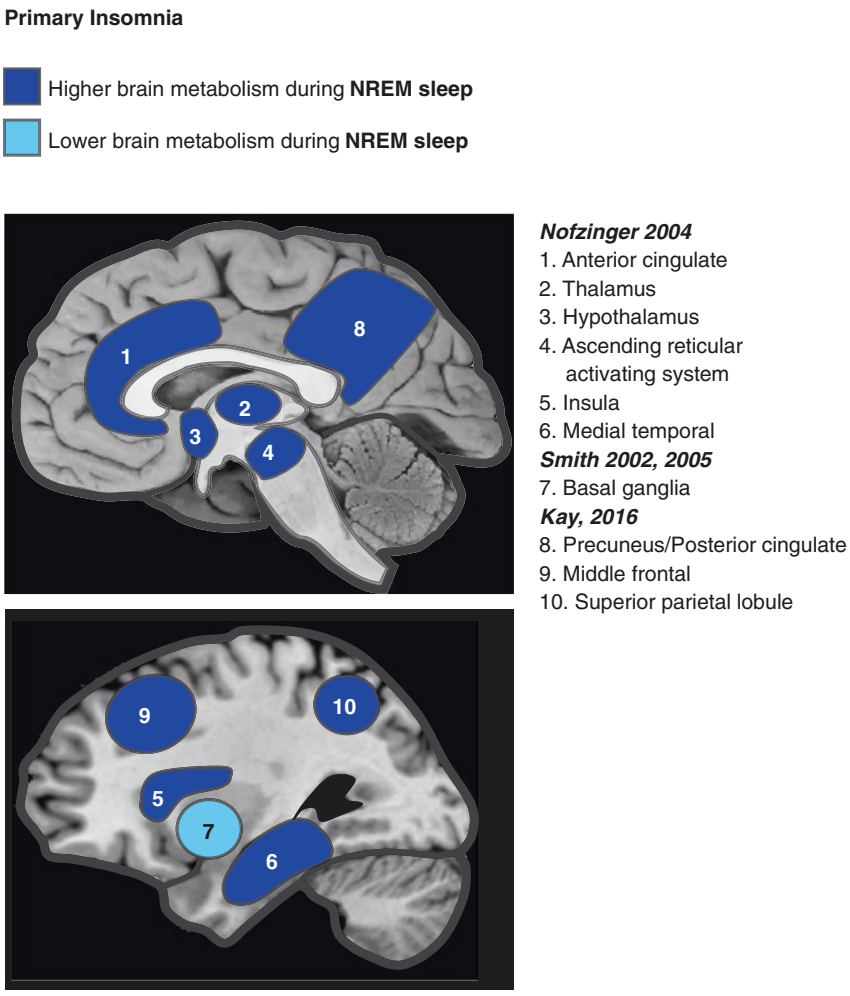


Fig. 33.4 Regional cerebral metabolism reduction and increase during NREM sleep in primary insomnia compared to good sleepers. Kay and colleagues suggested that the smaller decline in glucose metabolism from wake to NREM might represent an impaired disengagement during NREM sleep. Adapted from Dang-Vu et al. (2014)

(i.e., sleep difficulties for more than 1 month) and 20 healthy age-matched and gender-matched subjects. During the transition from waking to NREM sleep, insomnia patients showed (1) a global CMRglu increase as compared to healthy subjects, suggesting that there is an overall cortical hyperarousal in insomnia; (2) less reduction of relative CMRglu in the ascending reticular activating system, hypothalamus, insular cortex, amygdala, hippocampus, anterior cingulate, and medial prefrontal cortices; and (3) an increased metabolism in the thalamus, which might reflect persistent sensory processing and information processing as well as subsequent shallower sleep. In contrast, during wakefulness, patients with insomnia showed a decreased metabolism in subcortical (thalamus, hypothalamus, and brainstem reticular formation) as well as in cortical regions (prefrontal cortex bilaterally, left superior temporal, parietal, and occipital cortices).

In 2016, the same team used ^{18}F-FDG PET to scan a larger sample, including 44 patients with primary insomnia and 40 good sleepers, during both morning wakefulness and NREM sleep at night. They did not find any whole-brain glucose metabolism difference between groups, and both groups showed significantly lower whole-brain glucose metabolism during NREM sleep than during wake. However, they found group-by-state interactions in relative regional CMRglu in the precuneus/posterior cingulate cortex, left middle frontal gyrus, left inferior/superior parietal lobules, left lingual/fusiform/occipital gyri, and right lingual gyrus, suggesting that insomniacs have a smaller decline than healthy sleepers during NREM sleep compared to wake or a smaller increase during wake compared to NREM sleep in these clusters. They argue that such smaller decline from wake to NREM might represent an impaired disengagement during NREM and consequently a lack of regionally restorative sleep in these specific regions. Consequently, this could explain the daytime cognitive-affective symptoms of insomnia as these regions are involved in cognitive (i.e., left frontoparietal), self-referential (i.e., precuneus/posterior cingulate), and affective (i.e., left middle frontal, fusiform/lingual gyri) processes (Kay et al. 2016).

If we consider these findings together, they indicate that insomnia might involve elevated regional brain activity during sleep due to smaller differences in brain metabolism between NREM and wake. In both studies, the smaller increase in prefrontal cortex activity during wakefulness compared to controls is consistent with (1) reduced attentional abilities and impaired cognitive flexibility resulting from inefficient sleep and (2) a chronic state of sleep deprivation (Drummond et al. 2001; Durmer and Dinges 2005; Thomas et al. 2000).

In order to estimate rCBF during NREM sleep, another early study by Smith et al. (2002) compared five patients with chronic primary insomnia (in this study, defined by sleep difficulties for more than 6 months) with four normal sleepers using SPECT, employing technetium-^{99m}-hexamethylene-propyleneamine oxime (^{99m}Tc-HMPAO). No significant regional increase has been shown during this period, but a reduced rCBF was observed in frontal medial, occipital, and parietal cortices, as well as in the basal ganglia. This result suggests that primary insomnia is associated with an abnormal pattern of regional brain function during NREM sleep that particularly involves basal ganglia. It is interesting to notice that Nofzinger

et al. (2004b) had also found decreases in activity in these same regions in patients with primary insomnia, but during wakefulness. It is necessary to consider two methodological limitations in Smith's study. Both concern the timing of blood flow measurement: (1) it was only sampled during the first NREM cycle, and (2) it was measured after a longer duration of NREM sleep in insomniac patients than in healthy subjects. The consequence of the first limitation is that the decreased metabolism in insomniac patients might reflect a cortical hypoarousal during the initial phases of NREM sleep following sleep onset. However, it is still possible that the patients were more aroused over later NREM sleep cycles, which would be more consistent with higher beta activity later at night (Perlis et al. 2001). The second limitation leads to a possible underestimation of activity in the patients because blood flow decreases over long NREM periods. Because of such methodological limitations, these preliminary results cannot rule out the hyperarousal hypothesis of idiopathic insomnia. Cognitive behavioral therapy including sleep restriction and stimulus control was applied in the Smith's study, and four of the insomniac patients were rescanned after they had been treated by this therapy (Smith et al. 2005). After treatment, there was a reduction of at least 43% in the sleep latency, and a global 24% increase in CBF, with a significant increase in the basal ganglia. The authors proposed that such an increase in brain activity might reflect the normalization of sleep homeostatic processes. These promising results will certainly inspire further investigations on the effects of psychotherapy on brain functioning in insomnia.

33.5.2 Fatal Familial Insomnia

Fatal familial insomnia (FFI) is a hereditary or sporadic disease caused by a prion protein gene mutation. This illness is invariably lethal (Lugaresi et al. 1986). It is characterized by insomnia, autonomic hyperactivity, and motor abnormalities (Lugaresi et al. 1986; Montagna et al. 2003). The disrupted sleep pattern is characterized by a loss of sleep spindles and SWS and enacted dreams during REM sleep (Montagna et al. 2003).

In a study by Perani et al. (1993), four awake patients were investigated using PET and ^{18}F-FDG. The analysis revealed a prominent hypometabolism in the anterior part of the thalamus. There were two types of clinical presentation. Two patients exhibited symptoms restricted to insomnia and dysautonomia. Thalamic hypometabolism was found isolated in one subject, accompanied by a frontal, anterior cingulate and temporal polar hypometabolism in the other. In the two patients with a more complex clinical presentation, hypometabolism was more widespread and involved many cortical areas, the basal ganglia and the cerebellum. This widespread pattern was already present at an early stage of the disease and was found significantly aggravated as the disease progressed in one patient, examined twice several months apart. However, it is not known whether this widespread hypometabolism is indicative of the more advanced stages of the disease or whether it indicates two forms of this disorder, one thalamic and the other disseminated.

In another study by Cortelli et al. (1997), seven patients with FFI were investigated using ^{18}F-FDG and PET to examine regional cerebral glucose utilization. All FFI patients presented a severely reduced glucose utilization of the thalamus and a mild hypometabolism of the cingulate cortex. In six of these subjects, brain hypometabolism also affected the basal and lateral frontal cortex, the caudate nucleus, and the middle and inferior temporal cortex. Further comparison between homozygous ($n = 4$) or heterozygous ($n = 3$) patients at codon 129 showed that the hypometabolism was more widespread in the heterozygous group, which had a significantly longer symptom duration at the time of ^{18}F-FDG PET study. Comparison between neuropathological and ^{18}F-FDG PET findings in six patients showed that areas with neuronal loss were also hypometabolic. However, cerebral hypometabolism was more widespread than expected from histopathological changes and significantly correlated with the presence of protease-resistant prion protein. Neuroimaging results indicate that hypometabolism of the thalamus and cingulate cortex is a common feature of FFI, while the involvement of other brain regions depends on the duration of symptoms and some unknown factors specific to each patient (Cortelli et al. 1997). Even in a case of atypical FFI, thalamic hypometabolism was confirmed as an early marker, while cortical changes vary with clinical presentation and stage (Bar et al. 2002). More recently, serotonin transporters of two FFI patients were examined with ^{123}I-β-CIT SPECT as compared to age-expected control values (Kloppel et al. 2002). This study showed a reduced availability of serotonin transporters of 57% and 73%, respectively, in a diencephalic region of the two FFI patients. Although this finding suggests an involvement of serotonin neurotransmission, it is not clear whether it is causal in FFI pathogenesis (Kloppel et al. 2002).

In another study by Cortelli et al. (2006), 9 asymptomatic carriers of the D178N mutation, 10 noncarriers belonging to the same family, and 19 age-matched controls were studied over several years in order to examine how and when the degenerative process begins. The CMRglu was measured with ^{18}F-FDG PET in parallel with detailed clinical, neuropsychological examinations and polysomnography with EEG spectral analyses. All cases at the beginning of the study had a normal CMRglu as well as normal clinical and electrophysiological examinations. Concerning the mutation carriers, four of them developed typical FFI over the course of the study. On the other hand, their CMRglu and their clinical and electrophysiological examinations remained normal 63, 56, 32, and 21 months before disease onset. The carrier whose tests were normal 32 months before disease onset was reexamined 13 months before onset. A selective hypometabolism in the thalamus was shown at that time, while an abnormality in thalamic sleep spindle formation was detected by spectral EEG analysis. Following clinical disease onset, CMRglu was reduced in the thalamus in all three patients examined. The data of the study suggest that the neurodegenerative process associated with FFI begins in the thalamus between 13 and 21 months before clinical presentation of the disease.

33.5.3 Neuroimaging of Sleep in Depression

A pioneering study by Ho et al. (1996) examined the first NREM period in 10 unmedicated patients with unipolar depression and in 12 healthy controls. The depressed patients showed higher CMRglu during NREM sleep in the pons, posterior cingulate, amygdala, hippocampus, and occipital and temporal cortices. There was a significant reduction of relative CMRglu in medial orbital frontal and anterior cingulate cortices, caudate nucleus, and medial thalamus. These early findings support the hypothesis that hyperarousal in depression affects a network of limbic and posterior cortical regions, but also that the decreased medial frontal and striatal metabolism may be a hallmark of depression (Drevets et al. 1997).

In a first study by Nofzinger et al. (1999), six unipolar depressed subjects and eight healthy subjects underwent separate ^{18}F-FDG PET scans during waking and during their first REM period of sleep. Changes in CMRglu from waking to REM sleep were assessed in each group as well as interactions in patterns of change between groups. Compared to the control subjects, depressed patients in this study did not show increases in CMRglu in anterior paralimbic structures in REM sleep compared to waking. Depressed subjects did, however, show greater increases from waking to REM sleep in CMRglu in the tectal area and a series of left hemispheric areas including the sensorimotor cortex, inferior temporal cortex, uncal gyrus-amygdala, and subicular complex than did the control subjects. These observations suggest that changes in limbic and paralimbic function from waking to REM sleep differed significantly between normal and depressed patients.

The second Nofzinger et al. investigation (2000) focused on the association between EEG measures and ^{18}F-FDG PET measures in depressed patients. The study was undertaken in 9 healthy controls and 12 depressed subjects. The main findings were that beta power negatively correlated with subjective sleep quality for both healthy and depressed subjects. Beta frequency oscillations in EEG are high-frequency, low-amplitude neural oscillations associated with behavioral arousal and attentional processes, observed mostly in waking and REM sleep (Nofzinger et al. 2000). In both depressed and healthy subjects, beta EEG was positively associated with CMRglu in the ventromedial prefrontal and lateral inferior occipital cortices. There was a trend, in the depressed group, for beta power to correlate positively with relative whole-brain metabolism during NREM sleep (first NREM sleep cycle). For the depressed group only, beta EEG was also positively correlated with CMRglu in the left dorsolateral prefrontal cortex and amygdala/uncal gyrus regions.

More recent studies have confirmed that depressed patients have relatively persistent "elevated" activity measured by CMRglu across many brain regions during sleep compared to pre-sleep wakefulness (REM, 24 depressed patients compared to 14 controls; NREM, 12 depressed patients compared to 13 controls). As shown in Fig. 33.5, regions more activated during REM sleep included frontal, parietal, premotor, and sensorimotor cortices, as well as the insula, the ventral pallidum, and the midbrain reticular formation (Nofzinger et al. 2004a). Regions more activated during NREM sleep included the temporal and occipital cortices, as well as the insula, posterior cingulate, cerebellum, and thalamus (Germain et al. 2004). However,

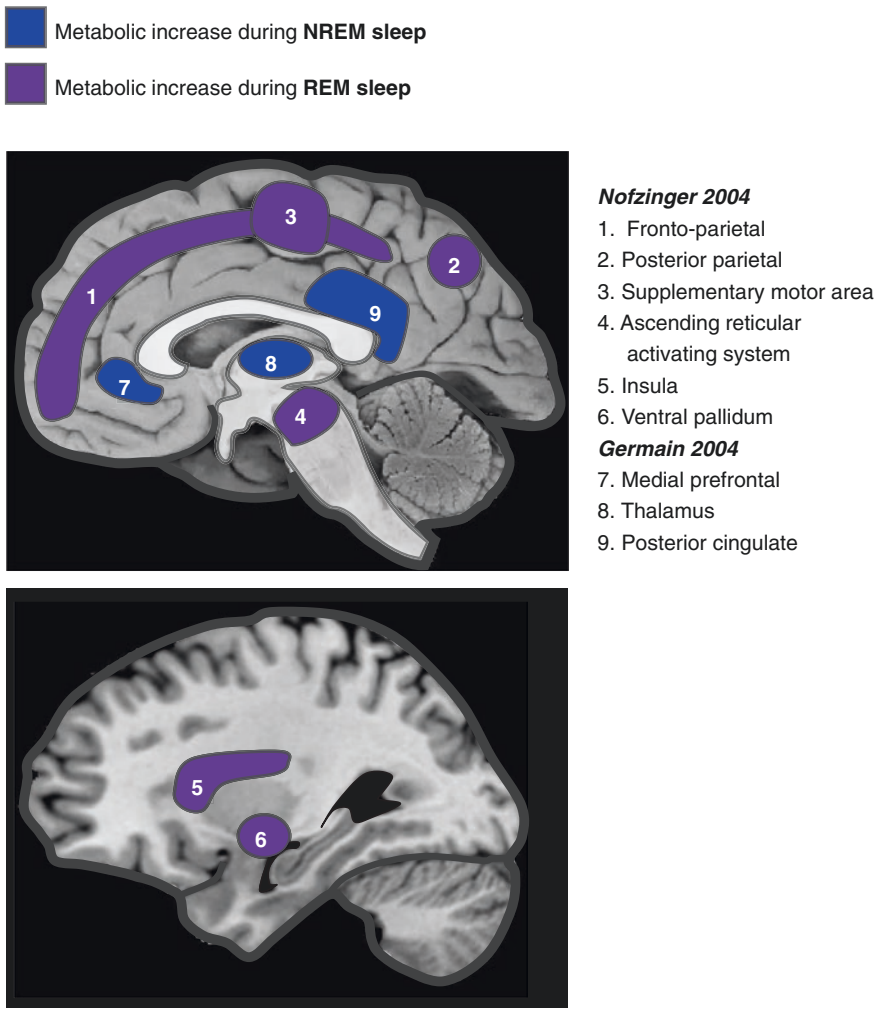


Fig. 33.5 Metabolic changes during REM and NREM sleep in depression. During NREM (Germain et al. 2004) and REM (Nofzinger et al. 2004a), depressed patients showed "elevated" activity measured by CMRglu across several cortical and subcortical regions in sleep compared to pre-sleep wakefulness. Adapted from Dang-Vu et al. (2014)

increased metabolism was also found in prefrontal cortex, unlike Ho et al. (1996). These results are again consistent with a general hyperactivation of arousal systems in depression that may underlie both sleep disturbances such as insomnia and non-restorative sleep complaints in depressed patients.

Increased rapid eye movement density (number of REMs per minute of REM sleep) was found to correlate with depression severity and clinical outcomes (Buysse

et al. 1999).In humans, REM bursts are classically thought to reflect ponto-geniculo-occipital (PGO) waves, possibly associated with orienting responses and arousal processes during sleep (Peigneux et al. 2001; Wehrle et al. 2005). An ^{18}F-FDG PET study assessed cerebral glucose consumption in a group of 13 medication-free depressed patients during REM sleep (Germain et al. 2004). The average REM count (an automated analog of REM density) was found to positively correlate with metabolism in a network of regions involved in emotional regulation and emotion-induced arousal (medial and ventrolateral prefrontal cortex) as well as in regions linking emotion and attention systems (striate cortex, precuneus, and posterior parietal cortex). Whether increased activity in these regions drives hyperarousal during REM sleep remains unclear. These results might not be specific to depression, because no control data were provided in that study and because the observed activation pattern overlapped with results of healthy controls from other studies (Braun et al. 1998; Peigneux et al. 2001).

33.5.4 Summary

Because currently available data are limited and not perfectly consistent, any conclusion about the cerebral correlates of insomnia during NREM sleep must remain tentative. While there is some evidence for decreased activity in cortical areas during early NREM sleep as well as during wakefulness, several subcortical regions involved in sleep/wake regulation, including limbic and paralimbic regions, were found to be more active during the transition from waking to sleep states. Current data generally support the hyperarousal theory of insomnia, with increased neuronal activity during NREM sleep as a possible key factor contributing to sleep misperception and disturbances occurring in insomnia.

Depression is often associated with insomnia, as well as with hyperarousal characterized by persistent "elevated" activity across many brain regions during NREM sleep, but also during REM sleep. Strong evidence for hyperarousal in both primary insomnia and depression, together with persistent alterations in sleep architecture in remitted depression, corroborate common neurophysiological mechanisms underlying sleep and mood regulation.

33.6 General Conclusions

Functional neuroimaging is a compelling tool that provides unprecedented possibilities to explore brain function during normal and pathological sleep. PET and SPECT studies have provided many insights into the neurobiological bases of sleep pathologies, which are strongly linked to the regulation of mood, emotion, and decision-making. Narcoleptic patients seem to have decreased hypothalamic and thalamic activity, in line with a hypocretin dysfunction and altered vigilance, with increased activity in the amygdala and cingulate cortex, which may be related to

abnormal emotional processing. Nuclear imaging in narcolepsy type 2 (i.e., without cataplexy) remains to be investigated. Recent findings in idiopathic hypersomnia suggested preserved hypocretinergic system but lower activity in medial prefrontal cortex and posterior cingulate cortices, suggesting possible intrusion of NREM-like features during wakefulness in idiopathic hypersomnia. For RLS and PLM, hypoactivity in pre- and postsynaptic DA transmission in the striatum and SN may underlie the compulsive limb movements. RBD patients show changes in activity in the pons, hippocampus, frontal lobes, and striatum, suggesting that an altered nigrostriatal dopaminergic activity in RBD might predict conversion to Parkinson's disease and Lewy body dementia. Hyperactivity throughout many brain regions during NREM sleep in insomnia is also observed in depression, suggesting common pathophysiological mechanisms underlying both disorders.

Even with these insights, functional neuroimaging in sleep medicine is still in its infancy. Methodological issues such as small sample sizes and omitted control groups limit the reliability of some studies, including case studies. Furthermore, technical issues involved in imaging patients during sleep, particularly in movement disorders, have impeded the progress of new studies. As the field matures, advanced multimodal neuroimaging and improved experimental designs will allow observations to be made at additional timepoints of these disorders, with larger sample sizes and control groups, and will therefore further characterize the pathophysiological mechanisms of sleep disorders and the functional consequences of long-term sleep disruption. PET and SPECT will finally be essential to examine and monitor the neural effects of current and future pharmacological compounds targeting sleep disorders.

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PET and SPECT Imaging of Non-pharmacological Interventions for Psychiatric Disorders

34

Andrej Doma

Contents

Abstract

In spite of developments in pharmacotherapy of psychiatric disorders, nonresponders and non-remitters remain a major problem. This chapter gives an overview of research using PET and SPECT concerning the treatment of psychiatric disorders with other interventions: electroconvulsive therapy, lesion surgery, psychotherapy, vagus nerve stimulation, transcranial magnetic stimulation, and deep brain stimulation.

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Abbreviations

5-HT_{1A}	Serotonin-1A receptor
5-HT_2	Serotonin-2 receptor
^{99m}Tc-ECD	Technetium [^{99m}Tc] bicisate
^{99m}Tc-HMPAO	Technetium [^{99m}Tc] exametazime
ACC	Anterior cingulate cortex
BD	Bipolar disorder
BT	Behavior therapy
CBT	Cognitive behavioral therapy
CMRGlu	Cerebral metabolic rate for glucose
CSTC	Cortico-striatal-thalamo-cortical circuit
DBS	Deep brain stimulation
DLPFC	Dorsolateral prefrontal cortex
DMPFC	Dorsomedial prefrontal cortex
ECT	Electroconvulsive therapy
FDG	^{18}F-2-Fluoro-2-deoxy-D-glucose
GABA	Gamma-aminobutyric acid
HDRS	Hamilton depression rating scale
IPT	Interpersonal therapy
MDD	Major depressive disorder
OCD	Obsessive–compulsive disorder
OFC	Orbitofrontal cortex
PET	Positron emission tomography
rCBF	Regional cerebral blood flow
sgACC	Subgenual anterior cingulate cortex
SPECT	Single-photon emission computed tomography
SSRI	Selective serotonin reuptake inhibitors
TMS	Transcranial magnetic stimulation
VLPFC	Ventrolateral prefrontal cortex
VMPFC	Ventromedial prefrontal cortex
VNS	Vagus nerve stimulation

34.1 Introduction

In spite of developments in pharmacotherapy of psychiatric disorders, nonresponders and non-remitters remain a major problem. Several non-pharmacological techniques like electroconvulsive therapy, lesion surgery, and psychotherapy have been in use for several decades, while numerous novel techniques of brain stimulation are under investigation.

Knowledge of pathophysiological processes in psychiatric disorders remains limited, and deeper understanding might be achieved through further investigation, resulting in the evolution of treatment techniques. Functional imaging, including PET and SPECT, can provide crucial information.

The present chapter aims to give an overview of research done using PET and SPECT in the treatment of psychiatric disorders beyond pharmacotherapy: electroconvulsive therapy, lesion surgery, psychotherapy, vagus nerve stimulation, transcranial magnetic stimulation, and deep brain stimulation.

34.2 Neuroimaging Findings in Depression and Obsessive–Compulsive Disorder

Depressive disorder is associated with several dysfunctional neural systems: subcortical systems involved in emotion and reward processing (amygdala, ventral striatum), medial prefrontal and anterior cingulate cortical regions involved in processing emotion and automatic or implicit regulation of emotion, and lateral prefrontal cortical systems—the VLPFC and DLPFC—involved in cognitive control and voluntary or effortful regulation of emotion (Kupfer et al. 2012).

Typical neuroimaging findings in treatment-naïve patients with depression include increase of regional cerebral blood flow (rCBF) in the VLPFC (Drevets et al. 1992) and reduction of rCBF in the DLPFC (Goethals et al. 2005). Normalization of rCBF or glucose metabolism was seen after pharmacotherapy (Brody et al. 1999, 2001; Kennedy et al. 2001; Mayberg et al. 2000). The subgenual anterior cingulate cortex (sgACC: Brodmann area 25) has consistently been shown to be hyperactive during depressive episodes in TRD patients (Drevets et al. 1997, 2008; Mayberg 2009). The sgACC is part of distributed corticolimbic neurocircuits implicated in "visceromotor" functions and in modulating affect, such as sadness and ruminative thought patterns. Clinical efficacy of pharmacotherapy and different non-pharmacological treatment strategies correlate with decreases in the sgACC metabolic activity (Baeken et al. 2015).

Obsessive–compulsive disorder (OCD) is a chronically debilitating anxiety disorder, characterized by two sets of symptoms: obsessions, which are impulsive recurrent thoughts usually concerning dirt or order of objects, and compulsions, repetitive behavior acts carried out in relation to obsessions, e.g., washing, counting, or rearrangement of objects in symmetrical array (Koran et al. 1996).

In OCD alone, several neuroimaging studies reported an increased cerebral activity of the orbitofrontal cortex and anterior cingulate cortex, angular gyrus in the parietal lobe, and thalamus and visual association cortex and a reduction of glucose metabolism and rCBF within bilateral parietal lobes (Baxter et al. 1987; Menzies et al. 2008; Nordahl et al. 1989; Perani et al. 1995; Rauch et al. 1994; Rauch 2003; Rubin et al. 1992; Swedo et al. 1989). Despite frequent comorbidity of OCD and major depressive disorder (MDD), Saxena et al. (2001) proved that depressive episodes occurring in OCD patients and primary MDD patients are mediated by different basal ganglia–thalamic pathways.

Elevated baseline rCBF and CMRGlu were observed in OCD patients in the orbitofrontal cortex, anterior cingulate cortex, basal ganglia, and thalami (Baxter et al. 1987; Nordahl et al. 1989; Perani et al. 1995; Nakatani et al. 2003; Yamanishi et al. 2009).

Several studies demonstrated an increased activity in OCD patients in the frontal cortex and subcortical structures, including the anterior cingulate cortex, orbitofrontal cortex, basal ganglia, and thalamus (Baxter et al. 1987; Swedo et al. 1989; Millet et al. 2013), while the most common finding in FDG-PET studies after treatment in patients with OCD is decreased CMRglc in the caudate nucleus, thalamus, anterior cingulate cortex, or orbitofrontal cortex (van der Straten et al. 2017).

Evidence of complexity of molecular mechanisms that cause OCD symptoms was given by Perani et al. (2008). In their study, the coexisting reduction of serotonin 5-HT(2A) and dopamine D2 receptor availability was seen in the frontal polar, dorsolateral, and medial frontal cortices, as well as in the parietal and temporal associative cortices of drug-naïve OCD patients in comparison with healthy controls.

34.3 PET and SPECT in Electrical Neurostimulation

Eighty years after two Italian psychiatrists, Cerletti and Bini, first used electroshock to induce convulsions in man as a treatment for mental illness, electroconvulsive therapy (ECT) remains an important tool in the treatment of psychiatric disorders. Despite its great clinical value, the mode of action remained unknown until recently, when functional neuroimaging enabled insight into the molecular basis of brain activity (reviewed in Petrides et al. (2011)). Functional neuroimaging vastly contributed to mapping of pathophysiological processes, study of neurotransmitters, and observation of various modes of therapy. Findings in deep brain stimulation (DBS), vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS), and ECT are discussed below.

34.3.1 Deep Brain Stimulation

Deep brain stimulation (DBS) is a nondestructive, adjustable, reversible neurosurgical technique involving the stereotactic implantation of electrodes that continuously emit short high-frequency electrical impulses (generally 120–160 Hz) in order to stimulate specific subcortical or deep cortical structures. Intracranial electrodes are connected to an implanted pulse generator/battery pack in the chest wall. Once implanted, the pulse generator can be finely tuned to maximize clinical benefit and avoid unwanted adverse effects (reviewed by Lozano and Lipsman (2013)). The technique was introduced in the late 1980s by a team of the neurosurgeon A. L. Benabid from Grenoble, who used it to treat movement disorders (Benabid et al. 1987).

DBS is approved by the Food and Drug Administration (FDA) in the United States for the treatment of PD, essential tremor, dystonia, epilepsy, and OCD. As of 2019 more than 160,000 patients worldwide have received DBS for different neurological and non-neurological conditions with an additional 12,000 patients treated every year (Lee et al. 2019a).

34.3.1.1 DBS in OCD

OCD is the only psychiatric indication for DBS, approved by the FDA. DBS for targeting ventral capsule/ventral striatum for medically refractory OCD was given human device exemption in 2009. Since then, other targets include the nucleus accumbens, bed nucleus of the stria terminalis, subthalamic nucleus, anterior limb of the internal capsule, and inferior thalamic peduncle (Lee et al. 2019a).

The exact mechanism of DBS is still unknown. Several hypotheses suggest a global inhibition of the cortico-striato-thalamo-cortical circuits as a main mechanism (Lozano and Lipsman 2013).

The inhibition hypothesis suggests that DBS therapy leads to local neuronal inhibition via several mechanisms, such as neurotransmitter depletion (glutamate), release of inhibitory neurotransmitter (GABA; adenosine), or nerve conduction block. The excitation hypothesis suggests that DBS directly excites neural activity via increased glutamatergic or dopaminergic pathways. The hypothesis of signal disruption suggests that DBS modulates the pathologic neuronal response in targeted areas and thus generates an information lesion. There is evidence that DBS stimulates neurogenesis and plasticity processes (reviewed by Lozano and Lipsman (2013)).

Several studies evaluated changes in rCBF and CMRGlu after DBS treatment. Chronic successful treatment has been associated with a decrease of metabolism in prefrontal and orbitofrontal cortices in several studies.

A therapeutic effect and decrease of off-stimulation-related hypermetabolism in the right frontal middle and superior gyri, right parietal lobe, postcentral gyrus, and bilateral putamen status were seen after high-frequency bilateral DBS of subthalamic nuclei in ten refractory OCD patients (Le Jeune et al. 2010). In a study by Van Laere et al. (2006), six refractory OCD patients received chronic DBS of anterior limb of the internal capsule. A significant decrease of metabolism was seen in anterior cingulate gyrus and nucleus caudatus, and changes in symptoms after treatment were inversely related to metabolic changes in the left ventral striatum, left amygdala, and left hippocampus. The same research group confirmed similar results in a following study on 16 OCD patients (Suetens et al. 2014). Lee et al. (2019b) evaluated the metabolic changes in five patients after bilateral inferior thalamic peduncle chronic DBS. A decrease of activity was observed in the caudate, putamen, and cingulum.

Rauch et al. (2006) measured changes in rCBF during high- and low-frequency stimulation and during off-condition using ^{15}O PET in six OCD patients undergoing ventral capsule-/ventral striatum-targeted DBS. No significant change in rCBF was seen comparing the DBS off-condition and low-frequency DBS. During acute high-frequency DBS, rCBF significantly increased in the orbitofrontal cortex, anterior cingulate cortex, putamen, and globus pallidus. Increase of activity in the dorsal anterior cingulate, thalamus, striatum, and globus pallidus was also reported by Dougherty et al. (2016) in DBS targeting VC/VS in six patients using ^{15}O PET. Similarly, increase of CMRGlu in the left-sided orbitofrontal cortex has been reported after DBS of inferior thalamic peduncle (Lee et al. 2019b).

Results are somewhat inconsistent with previous studies, where response to neurosurgery, pharmacotherapy, and psychotherapy of OCD resulted in a decrease of metabolism in bilateral caudate, the head of the right caudate, and bilateral thalamus (Baxter et al. 1992; Biver et al. 1995; Sachdev et al. 2001; Saxena et al. 2002, 2009; Schwartz et al. 1996). Differences in metabolic activity between acute and chronic DBS, medical therapy, psychotherapy, and surgical interventions suggest different underlying processes of symptomatic alleviation in OCD.

Figee et al. (2014) measured the dopamine D2/D3 receptor availability after acute and chronic DBS targeting nucleus accumbens in 15 OCD patients. Both acute and chronic DBS decreased binding potential of ^{123}I-IBZM in striatum, implying DBS-induced release of dopamine. This suggests a direct excitatory effect of DBS on putamen or, alternatively, the spread of stimulation from ventral to the dorsal striatum through striato-nigro-striatal pathways. Decreased binding potential was associated with clinical improvement after both acute and chronic DBS.

Further research is needed to improve the understanding of pathophysiological processes involved in OCD and mechanisms of treatment techniques.

34.3.1.2 DBS in Depression

Several studies evaluated the use of DBS as an antidepressant treatment, targeting subcallosal cingulate gyrus, nucleus accumbens, medial forebrain bundle, ventral capsule/ventral striatum, and inferior thalamic peduncle. The results of these studies were of mixed success. While uncontrolled trials found long-term clinical improvement in up to 60% of patients with refractory depression (Bewernick et al. 2010), and stable long-term antidepressant effect (Bewernick et al. 2012), two multicentre randomized sham-controlled trials failed to replicate these results (Holtzheimer et al. 2017; Dougherty et al. 2015).

Three studies evaluated the effect of DBS targeting nucleus accumbens using FDG-PET. A team by Schlaepfer et al. (2008) assessed metabolic differences in three depressed patients after acute 1 week DBS. Increased activity was observed in dorsolateral and dorsomedial prefrontal cortices, cingulate, amygdala, and nucleus accumbens, and decreased activity was observed in ventromedial and ventrolateral prefrontal cortices, thalamus, and dorsal nucleus caudatus.

The same research group conducted another study on 10 patients after chronic 12-month DBS of nucleus accumbens. They reported decrease of activity in cingulate region and prefrontal regions including orbital prefrontal cortex (Bewernick et al. 2010). In contrast to their previous study, no increase of activity was observed in the nucleus accumbens. This was attributed to short-lasting acute tissue reaction to the implantation of DBS device.

A French group of Millet et al. (2014) compared the effect of DBS on limbic and cognitive pathways by implanting two electrodes in the nucleus accumbens and caudatus in four treatment-resistant depressed patients. All four patients first received DBS of the nucleus accumbens, and in three nonresponders, the caudate region was stimulated. During an extended period of nucleus accumbens

stimulation, three of four patients responded only when voltage was increased. The clinical outcome of targeting nucleus accumbens was better than targeting caudate. A decrease of CMRGlu was observed after nucleus accumbens stimulation in the posterior cingulate gyrus, superior and medial gyrus, and frontal lobe, and an increase was observed in bilateral frontal lobe, left frontal lobe, and anterior cingulate gyrus. The results suggest that the nucleus accumbens, rather than the caudate, is a potential therapeutic neuroanatomic target for stimulation in treatment-resistant depressed patients.

DBS of the subcallosal cingulate white matter for the treatment of depression showed a decrease of CMRGlu in six major depressive disorder (MDD) patients in the subgenual cingulate, OFC, and medial frontal and insular cortices and increases in dorsolateral prefrontal cortex and dorsal cingulate (Mayberg et al. 2005). The same research group expanded initial cohort of patients to 20 and confirmed previous results, additionally showing a metabolic increase in the posterior and anterior midcingulate gyri (Lozano et al. 2008).

Other areas for DBS in limbic pathways are being considered, including habenula and medial forebrain bundle. Further investigations are required to identify the ideal deep brain stimulation target for the treatment of depression.

34.3.1.3 DBS in Anorexia Nervosa

Anorexia nervosa is a complex disease with one of the highest mortality rates among psychiatric disorders. There is evidence that the illness is associated with limbic dysfunctions, which manifests in several emotional pathways: self-awareness, visual and gustatory sensation, and reward pathway. Several research groups evaluated DBS for anorexia nervosa targeting the subcallosal cingulate cortex, nucleus accumbens, ventral capsule/ventral striatum, and bed nucleus of the stria terminalis. Three studies used PET to evaluate changes in cerebral activity after DBS in anorexia nervosa patients.

Lipsman and colleagues (2017) selected subcallosal cingulate as a target for DBS in anorexia nervosa in 2 studies involving 6 and 16 patients. A significant increase of body mass index, depression, anxiety, and affective regulation has been observed after 1 year. This study involved neuroimaging with FDG-PET at baseline and at 6 and 12 months after DBS placement and detected decreased subcallosal cingulate and medial frontal activity and increased parietal activity at both 6 and 12 months of ongoing brain stimulation.

Zhang et al. (2013) evaluated changes in glucose metabolism using PET after targeting the nucleus accumbens with DBS. Compared to healthy controls, significant baseline hypermetabolism was found in six anorexia nervosa patients in the right and left superior, medial, and inferior frontal gyri, hippocampus and amygdala, left subcallosal gyrus, bilateral lentiform nucleus left insula, and brainstem. Baseline hypometabolism was seen in the bilateral parietal lobe. The hypermetabolism in the frontal lobe, hippocampus, and lentiform nucleus decreased after DBS in four patients.

34.3.2 Vagus Nerve Stimulation

The vagus nerve is the longest cranial nerve, consisting of 80% afferent and 20% efferent fibers. Special visceral efferent fibers of the vagus nerve (VN) arise from the nucleus ambiguus and control the muscles of the palate, pharynx, upper esophagus, and larynx. General visceral efferent fibers arise from the dorsal motor nucleus and provide parasympathetic innervation primarily to the gastrointestinal, cardiovascular, and respiratory systems. Afferent fibers project from the sensory receptors in the pharynx, meninges, external auditory meatus, and chemoreceptors and baroreceptors of the aortic arch, cardiorespiratory system, and digestive organs and enter the nodose ganglia. Fibers from visceral organs and throat converge onto nucleus tractus solitarius and spinal trigeminal nucleus, respectively. Furthermore, there are synaptic connections to higher centers in the brain such as the hypothalamus, dorsal raphe, nucleus ambiguus, dorsal motor nucleus of the vagus nerve, amygdala, and thalamus, which in turn project to the insular cortex and the more rostral regions of orbital, ventrolateral, and medial prefrontal cortex (reviewed in Ben-Menachem (2002)).

While left vagus nerve stimulation (VNS) has become a well-established, safe, and effective FDA-approved treatment for refractory epilepsy, studies by Elger et al. (2000) and Harden et al. (2000) demonstrated an antidepressant effect assessing VNS in refractory seizures. Furthermore, surrogate markers of mood alteration such as improved psychosocial function, attention, temperament, and the ability to cooperate have been reported in association with VNS treatment. The FDA approved the use of VNS as an adjunctive long-term treatment for a treatment-resistant depression in 2005 (Groves and Brown 2005). In a prospective study of VNS use in 795 depressed patients over 5 years, Aaronson et al. (2017) demonstrated that VNS, combined with treatment as usual, was superior to treatment as usual without VNS with a significantly higher 5-year cumulative response rate and a significantly higher remission rate being reported in a VNS-treated group. By 2018, more than 100,000 patients worldwide have received VNS treatment.

In VNS, two helical bipolar stimulating electrodes are wrapped around the left vagus nerve and connected to the electronic stimulator, surgically implanted in the chest wall. Intermittent electrical stimulation is delivered to the vagus nerve (reviewed in Milby et al. (2008)). Due to technical challenges and surgical risk, a novel noninvasive transcutaneous vagus nerve stimulation (tVNS) method has been developed, applying stimulation either on the cervical nerve or areas of the ear, rich in afferent vagus nerve innervation (Trevizol et al. 2015).

The mechanism of action of VNS in major depression is poorly understood. Current models of depression hypothesize dysregulation in the areas of prefrontal, cingulate, and insular cortices, amygdala, hippocampus, striatum, dorsal thalamus, hypothalamus, and brainstem nuclei (Price and Drevets 2010). The afferent vagal fibers provide numerous intersections with these mood-associated regions.

The mood modulation effect of VNS is thought to be associated with alterations of norepinephrine and serotonin neural systems, elevated levels of inhibitory

neurotransmitter GABA, as well as inhibition of aberrant cortical activity by reticular system activation (reviewed in Milby et al. (2008)).

The association between pretreatment CMRGlu and antidepressant response over time was examined by Conway et al. (2012a) in 15 treatment-resistant MDD patients after 12 months of VNS. Response to treatment and the rate of HDRS change were associated with lower pretreatment CMRGlu in the anterior insular cortex and higher pretreatment CMRGlu in the orbitofrontal cortex in responders in comparison with nonresponders.

Differences between cortical activity after acute and chronic VNS were reported by several authors. Changes of CMRGlu regarding baseline activity after 12 months of chronic VNS included decreases in the right superior temporal gyrus, right posterior insular cortex, subgenual cingulate, and ventromedial prefrontal cortex (Pardo et al. 2008) and increases in the left inferior temporal gyrus and cerebellar hemisphere (Conway et al. 2013).

Acute changes of CMRGlu involved decreases from baseline in the right dorsolateral and dorsomedial prefrontal cortex, anterior cingulate cortex, and right superior temporal gyrus/right posterior insular cortex at 3 months (Conway et al. 2013), decreases in medial frontal and limbic activity at 4 weeks (Zobel et al. 2005), and decreases in insular and precuneus at 10 weeks of VNS (Kosel et al. 2011); significant rCBF decrease was found in response to acute VNS in a study of 13 subjects (Conway et al. 2012b) in the left and right lateral orbitofrontal cortex and left inferior temporal lobe. Increased rCBF was measured in the right dorsal anterior cingulate, the left posterior limb of the internal capsule, the right superior temporal gyrus, and the left cerebellar body.

Several research groups reported a pattern of right decrease and left increase hemispheric activity regardless of the duration of VNS (Conway et al. 2013; Pardo et al. 2008; Kosel et al. 2011). Conway et al. (2013) assessed acute and chronic effects of VNS in 13 depressed patients. Response to treatment at 12 months was associated with a significant trend of decreasing mean CMRGlu in the right DLPFC over time. Notable was a v-shaped pattern with a decreased activity in the right DLPFC CMRGlu at 3 months returning to baseline at 12 months. A significant decrease in the right but not the left DLPFC at 10 weeks of VNS in responders was also reported by Zobel et al. (2005) using HMPAO SPECT. Kosel et al. (2011) described the decrease in the right precuneus, cuneus, and lingual gyrus in HMPAO SPECT in 15 depressed patients. These findings resemble reported decreases of DLPFC activity associated with an antidepressant outcome in other treatment modalities, like CBT (Goldapple et al. 2004) or ECT (Nobler et al. 2001). The DLPFC is predicted to play a leading role in emotional control with activation of the left DLPFC being associated with processing positive emotions and activation of the right DLPFC being responsible for processing negative emotions (Mondino et al. 2015).

Due to small response rate (2/8) among patients in the Pardo study, no correlation between antidepressant outcome and changes in CMRGlu was established after 12 months of VNS (Pardo et al. 2008).

In conclusion, pronounced changes in cortical activity were observed after VNS that correspond to synaptic pathways, associated with depression. Changes after VNS resemble reported findings after other treatment modalities (ECT, CBT). Further neuroimaging studies are needed to identify the exact mechanism of VNS and to establish correct treatment framework.

34.3.3 Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a noninvasive tool based on an electromagnetic coil applied to the scalp producing an intense, localized magnetic field which either excites or inhibits a focal cortical area. It was first used in humans by Barker et al. (1985). TMS can be applied one stimulus at a time, single-pulse TMS; in pairs of stimuli separated by an interval, paired-pulse TMS; or periodic, in trains, repetitive TMS (rTMS).

Single-pulse TMS can be used for mapping motor cortical outputs and studying central motor conduction time. Paired-pulse TMS can provide measures of intracortical facilitation and inhibition and study cortico–cortical interactions. Periodic rTMS can be modified into slow, low-frequency (≤1 Hz) rTMS or fast, high-frequency (>1 Hz) rTMS. Low-frequency rTMS is likely to cause inhibition of neuronal firing in a localized area, whereas high-frequency rTMS inversely leads to activation. The effects induced are not limited to the targeted cortical region; changes can also occur at distant interconnected sites in the brain. The level of metabolic response is frequency dependent (Nahas et al. 2001; Speer et al. 2000).

The therapeutic use of TMS has been described for psychiatric disorders, such as depression, obsessions/compulsions, bipolar disorders, acute mania, hallucinations, schizophrenia, catatonia, and post-traumatic stress disorder, and for neurologic diseases such as Parkinson's disease, dystonia, tics, tinnitus, or epilepsy; in the rehabilitation of aphasia or of hand function after stroke; and for pain syndromes (reviewed in Guse et al. (2010); Rossi et al. (2009)).

TMS has been approved by the FDA for use in treatment-resistant depression. High-frequency TMS to the left dorsolateral prefrontal cortex (DLPFC) is recommended for the treatment in patients with depression (Fox et al. 2012).

34.3.3.1 Dorsolateral Prefrontal Cortex as a Target of rTMS Stimulation in Depression

The principal structures involved in depression are the hippocampus, subgenual anterior cingulate cortex, left DLPFC, and other parts of the limbic network. The subgenual ACC and DLPFC are known to have extensive functional connections. Subgenual ACC is located deep in the brain and cannot be stimulated by TMS. DLPFC is located on the cortical surface and can easily be modulated by TMS. The exact neurobiologic mechanism attributing to the antidepressant effect of rTMS over the left DLPFC has not yet been determined (Fox et al. 2012). Other brain regions associated with affective processing, including DMPFC, frontopolar

cortex, VMPFC, and VLPFC, have also been considered as potential targets for clinical application of rTMS (Junghofer et al. 2017).

Neuroimaging studies have clarified decreased blood flow and glucose metabolism in the left prefrontal cortex, accompanied by a right-sided hypermetabolism in patients with depression (Baxter Jr et al. 1989; Martinot et al. 1990; Sackeim et al. 1990).

Bench et al. (1995) reported changes in the rCBF with improvement of symptoms after drug treatment. rTMS stimulation of the hypofunctional left prefrontal cortex as a means of antidepressant therapy was proposed by George et al. (1995).

Acute effect of low-frequency 1 Hz rTMS over the left DLPFC in healthy subjects resulted in a decrease of CMRGlu in the contralateral prefrontal cortex, bilateral anterior cingulate, basal ganglia, hypothalamus, midbrain, and cerebellum (Kimbrell et al. 2002). These areas are known to have well-defined efferent projections of the lateral prefrontal cortex (Alexander et al. 1986) and could therefore play a role in the antidepressant effect of low-frequency stimulation of the left DLPFC.

Immediate rCBF changes of both high- and low-frequency rTMS within the same group of healthy subjects were examined by Knoch et al. (2006). Both slow and fast rTMS over the left DLPFC increased rCBF in the area of stimulation. Low-frequency rTMS also induced a significant increase in rCBF contralateral to the stimulation area and a decrease in the ipsilateral orbitofrontal cortex. Acute high-frequency rTMS applied over the right DLPFC was associated with an increase of activity at the stimulation site, in the bilateral orbitofrontal cortex, and in the left medial thalamus compared to low-frequency rTMS. The side- and frequency-dependent acute neurophysiological effects of rTMS were probably related to hemisphere-dependent circuits.

Opposite physiological effects of low versus high rTMS were demonstrated by Loo et al. (2003) in a group of 18 depressed patients. Acute low-frequency rTMS over the left DLPFC did not cause any significant changes in the frontal region. Relative decrease of rCBF was observed in the left DLPFC after low-frequency rTMS and increase after high-frequency rTMS.

Similarly, a course of high-frequency rTMS over the left or right DLPFC in depressed patients was associated with local increase of rCBF or CMRGlu and antidepressant effect in a number of studies (Nahas et al. 2001; George et al. 1995; Catafau et al. 2001; Feinsod et al. 1998; Fujita and Koga 2005; Kimbrell et al. 1999; Klein et al. 1999; Mottaghy et al. 2002; Zheng 2000). In contrast, long-term effect of a course of low-frequency rTMS stimulation over the right DLPFC decreased rCBF in the bilateral prefrontal, orbitofrontal cortices, anterior insula, right subgenual cingulate, and left parietal cortex in MDD patients, and no areas of increased rCBF were detected (Kito et al. 2008).

Two studies examined the therapeutic effect and changes in rCBF or rCMR of a course of high- versus low-frequency left DLPFC rTMS in depressed patients. Kimbrell et al. (1999) reported that global hypometabolism at baseline was associated with clinical improvement with 20 Hz rTMS whereas response to 1 Hz rTMS treatment was related to baseline global hypermetabolism. Speer et al. (2000)

demonstrated that high-frequency rTMS treatment was associated with a widespread increase of rCBF while low-frequency rTMS resulted in regional decreases.

In conclusion, a number of SPECT and PET studies focused at functional changes, associated with rTMS treatment of major depression. In most of these studies, such treatment resulted in an increase of perfusion or metabolism in the prefrontal cortex. Findings are consistent with the hypothesis that high- and low-frequency rTMS have opposite physiological effects, possibly by correcting hypo- and hypermetabolism, respectively. Studies examining the immediate effect of rTMS on rCBF and CMRGlu have reported differing results, with both local increases and decreases occurring with high- and low-frequency rTMS. Further studies will be needed to determine the precise mechanisms behind the antidepressant effect of rTMS.

34.3.3.2 Neuronavigated rTMS

The efficacy of TMS relies on the location of DLPFC stimulation. Inaccurate targeting of DLPFC affects the clinical outcome. As to the standard technique, DLPFC is positioned 5 cm anterior to the motor cortex across the curvature of the scalp. However, due to anatomical variations in skull size and brain size, this measurement may not be accurate. Functional neuroimaging or electroencephalography-guided DLPFC was designed to improve the accuracy of procedure and the clinical outcome (Fox et al. 2012). The efficacy of neuronavigated rTMS on hypofunctional areas in MDD was explored in several studies. Garcia-Toro et al. (2006) delivered high-frequency rTMS to an area of low baseline rCBF activity and low-frequency rTMS to an area showing high baseline activity. The comparison was made to either sham rTMS or the group receiving high-frequency rTMS to the left prefrontal cortex and low-frequency rTMS to the right prefrontal cortex. Enhanced selectivity of the rTMS did not result in enhanced efficacy.

Paillère Martinot et al. (2010) administered high-frequency rTMS over the most hypometabolic prefrontal area in 48 medication-resistant major depression patients. Standard rTMS and sham rTMS groups served as a comparison. The highest improvement according to Montgomery–Åsberg Depression Rating Scale (MADRS) scores was observed with left PET-guided stimulation, significantly superior to sham and right-guided stimulation, while the comparison between left PET-guided and standard rTMS was not significant. Targeting the left DLPFC was more effective than sham, but failed to be an effective target area for stimulation in half of the patients. These findings are in contrast to the study of Herwig et al. (2003), who found similar improvement after delivering rTMS to the site of hypometabolic DLPFC compared to the contralateral DLPFC in 25 MDD patients. The results of Herwig et al. support the hypothesis of increased effectiveness of applying high-frequency rTMS over hypometabolic prefrontal regions, irrespective of side of stimulation, as suggested by Kimbrell et al. (1999).

In contrast, Baeken et al. (2009) reported that better clinical outcome of high-frequency rTMS treatment was achieved in subjects, expressing higher pretreatment metabolic activities in the bilateral DLPFC and the anterior cingulate cortex. Their study was done on 21 antidepressant-free treatment-resistant depression patients of the melancholic subtype.

34.3.3.3 Pretreatment rCBF as an rTMS Response Predictor

Several authors reported pretreatment rCBF of specific brain regions as a strong predictor for response to rTMS in pharmacoresistant depressed patients.

Baseline Hypometabolism

Reduced blood flow in the orbitofrontal and anterior cingulate was associated with good response to high-frequency rTMS treatment over the left DLPFC in eight depressed patients. Responders also exhibited significantly lower pretreatment blood flow in the left amygdala compared to nonresponders (Nadeau et al. 2002).

Deeper abnormalities of rCBF in nonresponders to rTMS were reported in parahippocampal gyrus and thalamus (Mottaghy et al. 2002; Richieri et al. 2011), anterior cingulate (Mottaghy et al. 2002; Kito et al. 2008; Teneback et al. 1999), and the inferior frontal (Kito et al. 2008; Teneback et al. 1999), periinsular (Mottaghy et al. 2002; Kito et al. 2008), bilateral frontal, left uncus/parahippocampal cortices and left medial temporal cortices (Richieri et al. 2011). Heterogeneity of structures reflects the involvement of several neural systems, associated with depression (reviewed in Kupfer et al. (2012)).

Inconsistent findings were reported regarding response to rTMS and pretreatment activity in the anterior cingulate cortex. Greater rTMS response was associated with decreased (Mottaghy et al. 2002) or increased pretreatment rCBF (Speer et al. 2000; Kito et al. 2008; Baeken et al. 2009; Teneback et al. 1999), while no relationship between rCBF in rostral anterior cingulate and response to rTMS was observed by Loo et al. (2003). High pretreatment anterior cingulate cortex rCBF was also a positive predictor value for the response of high-frequency rTMS treatment in 24 depressed patients (Kito et al. 2012). Baeken et al. (2015) identified higher mean baseline CMRGlu in sgACC in responders to accelerated high-frequency (20 Hz) rTMS over the left DLPFC, compared to nonresponders.

A negative correlation between the treatment outcome and baseline activity in the limbic structures, namely, parahippocampal gyrus, and the thalamus was identified in two studies using a similar protocol of high-frequency rTMS stimulation of the left DLPFC in depressed patients (Mottaghy et al. 2002; Richieri et al. 2011).

Kito et al. (2012) measured baseline regional cerebral blood flow in frontal regions in 24 depressed patients. Lower regional cerebral blood flow ratio between DLPFC and VMPFC was associated with better response to treatment with high-frequency rTMS over the left DLPFC.

Using simultaneous dual-isotope technique of FDG and ^{99m}Tc-HMPAO, Conca and colleagues (2002) were able to detect statistically significant common changes in rCBF and CMRGlu patterns in four drug-resistant depressed patients after ten sessions of low-frequency rTMS. The uptake of both isotopes on pretreatment scans was increased in the upper frontal regions bilaterally and decreased in the left orbitofrontal cortex compared to controls. After rTMS treatment, a clear right-sided lateralization of rCBF also in areas remote from the stimulation site was seen although no relevant changes in lateralization of the glucose uptake were observed. On the contrary, no lateralization of both rCBF and CMRGlu was reported in a study of similar design by Peschina et al. (2001). This suggests that rTMS

therapeutic activation is probably region and illness dependent. Small sample size of both studies should also be taken into account.

Baseline Connectivity

Depression is associated with increased functional connectivity of the default mode network, a frontoparietal cortical network, which is active when an individual is at rest while his or her mind wanders freely. This state of hyperconnectivity correlates with scores of rumination and is thought to reflect abnormal negative self-referential thinking in the depressed state (Avissar et al. 2017). TMS has been shown to normalize elevated functional connectivity of the default mode network in depression.

According to fMRI studies, changes in connectivity of the stimulated region are predictive of the response after rTMS for depression (Ge et al. 2017). Baeken et al. (2015) provided evidence that at baseline, elevated functional connectivity of the sgACC with structures in the default mode network predicts TMS response.

In a ^{99m}Tc-ECD SPECT study by Richieri et al. (2018), a pretreatment predictive value of connectivity of the CLPFC on further rTMS response in 58 TRD patients was investigated. Their study has provided evidence that before rTMS, responders exhibited increased SPECT connectivity between the left DLPFC and the right cerebellum in comparison with nonresponders. This is consistent with high baseline CMRGlu in the cerebellum of rTMS responders, compared to nonresponders in a study by Wu and Baeken (2017).

In conclusion, the antidepressant mechanism of action of TMS may require connectivity from the site of stimulated cortex to deeper structures like the striatum and cerebellum. Patients with better pre-TMS functional connectivity respond better to TMS and show better reduction in depression severity. For patients with reduced baseline connectivity to deeper structures, direct stimulation of those structures with DBS may offer a better outcome.

34.3.3.4 TMS and Imaging of Dopamine Activity

Several studies explored the effect of acute rTMS on the release of endogenous dopamine in the striatum. Using acute 10 Hz rTMS over the left DLPFC, Pogarell et al. (2006) demonstrated the induction of the release of endogenous dopamine in bilateral striatum. The study was performed in four major depressive patients using ^{123}I-IBZM, a dopaminergic D2 receptor antagonist.

However, in a study by Strafella and colleagues (2001), rTMS of the left DLPFC was associated with unilateral reduced binding of ^{11}C-raclopride, a D2 dopamine receptor antagonist, to its main projection area in the striatum, namely, the ipsilateral head of the caudate nucleus in healthy subjects. No changes were observed in binding in the putamen, nucleus accumbens, or right caudate of the dorsolateral prefrontal cortex. In a later study by Strafella et al. (2003), rTMS of the left primary motor cortex in six healthy subjects caused a reduction in ^{11}C-raclopride binding in the left putamen compared with rTMS of the left occipital cortex. There were no changes in binding in the striatal projection contralateral to the stimulated area. Reduction of dopaminergic binding potential in areas of subgenual anterior cingulate as well as in pregenual anterior cingulate and

orbitofrontal cortices was seen acutely after rTMS of the left DLPFC in healthy volunteers (Cho and Strafella 2009) using ^{11}C-FLB457, a high-affinity dopamine D2/D3 agonist radioligand for extrastriatal dopamine receptors. No significant changes were observed after the rTMS over the right DLPFC. The difference between healthy subjects and patients in uni- and bilateral release of dopamine could be influenced by the underlying disease-related neurochemical changes. Hemispheric differences after stereotactic stimulation are also known from other studies (Knoch et al. 2006; Saijo et al. 2010a).

Kuroda et al. (2006) failed to demonstrate the release of endogenous dopamine in the basal ganglia after long-term high-frequency rTMS over the left DLPFC in depressive patients. No change in ^{11}C-raclopride binding in the caudate nucleus and putamen was detected despite clinical improvement of depression. In a later study using L-[β-^{11}C]DOPA, a ligand to access the rate of endogenous dopamine synthesis, Kuroda et al. (2010) also failed to demonstrate changes in the striatal dopamine synthesis rate following long-term high-frequency rTMS over the left DLPFC in eight major depressive patients. The results of both studies suggest that chronic rTMS, in contrast to acute rTMS, has a limited effect on the dopaminergic system.

34.3.3.5 TMS in Schizophrenia

In a study by Horacek et al. (2007), the effect of rTMS on brain metabolism changes and clinical improvement in schizophrenia patients with auditory hallucinations was evaluated. After long-term low-frequency rTMS applied to the left temporoparietal cortex, significant improvement in symptoms and hallucination scales was reported. rTMS decreased the brain metabolism in the left superior temporal gyrus and in the interconnected regions and increased the activity in the contralateral cortex and in the frontal lobes. On the contrary, no changes in rCBF were detected by Hajak et al. (2004), neither in schizophrenic patients treated with high-frequency rTMS over 10 days nor in sham-treated control group, despite clinical improvement of depressive symptoms after treatment.

High-frequency rTMS administered to the right DLPFC was used by Schreiber et al. (2002) to treat a single schizophrenic patient affected with refractory command hallucinations. Decreased perfusion in the left cerebellar and right temporal regions and slightly decreased perfusion in bilateral infero-frontal regions, more prominent on the right, as well as mild, nonhomogeneous uptake in the caudate nuclei were reported on a pretreatment scan. After treatment, an improvement in perfusion was seen in frontal, infero-frontal, and temporal regions, more prominent on the right, and an increased uptake in the left thalamus.

34.3.4 Electroconvulsive Therapy

ECT is the most effective somatic treatment in psychiatry, with unsurpassed efficacy and remarkable safety. ECT is effective for various conditions and is a viable treatment option when pharmacotherapy and psychotherapy have failed; when affective, psychotic, or catatonic symptoms are present; and when rapid relief of

symptoms is required because of suicide risk or deterioration of medical conditions (reviewed in Petrides et al. (2011)).

34.3.4.1 Glucose Metabolism Changes in ECT

Several studies evaluated the changes in rCBF and cerebral glucose metabolism before and after a series of ECT in depressed patients (Table 34.1). The results are somewhat inconsistent, ranging from an overall decrease to an increase of activity.

A decrease in rCBF or CMRGlu after ECT has been most commonly reported in frontal regions, the parietal regions, the left inferior and the left medial temporal lobes, and the posterior cingulate gyrus (Nobler et al. 1994, 2001; Suwa et al. 2012; Yatham et al. 2000; Henry et al. 2001; Volkow et al. 1988). A decrease of activity in the ventrolateral prefrontal and orbitofrontal cortex was also observed in responders to antidepressants (Brody et al. 1999; Nobler et al. 2001), which further implicates the involvement of the prefrontal cortex in the neuroanatomical pathway of depression. On the contrary, several studies also reported increases in rCBF or glucose metabolism in these cortical regions (Suwa et al. 2012; Mervaala et al. 2001; Awata et al. 2002; Blumenfeld et al. 2003; Milo et al. 2001; Takano et al. 2006; Vangu et al. 2003; Ota et al. 2003). Increase in rCBF or glucose metabolism in the basal ganglia, the occipital regions, the parietal regions, and the brainstem was also observed (Nobler et al. 2001; Suwa et al. 2012; Henry et al. 2001; Yuuki et al. 2005; Takano et al. 2007; Elizagarate et al. 2001). No statistical difference in glucose metabolism was reported by Yatham et al. (2000) and Reininghaus et al. (2012) on post-ECT scans in comparison with baseline despite clinical response.

Heterogeneous results could be due to small sample size of all studies, concomitant medicaments, different therapeutic protocols, and different indications for the treatment. Further studies with larger sample sizes are needed to clarify the mechanism of antidepressant action of ECT.

34.3.4.2 Long-Term Effect of ECT

The safety and long-term effects of ECT were evaluated by several authors (reviewed in Petrides et al. (2011)). Navarro and colleagues (2004a) found no differences in rCBF comparing healthy controls and patients 12 months after ECT treatment. Anghelescu presented a single MDD patient who received more than 60 ECT sessions in 5 years and later presented normal CMRGlu in comparison with the normal database. No clinical signs of progressive cognitive deterioration were reported in several patients, treated with ECT over many years, including a 74-year-old patient, who received more than 400 ECT treatments (reviewed in Petrides et al. (2011)).

Navarro et al. (2004b) compared the long-term effect of ECT or pharmacological treatment in MDD patients. After a 12-month follow-up period of euthymia, both treatment subgroups were associated with normalization of baseline hypoperfusion in frontal regions, and no significant differences were found in frontal brain perfusion either between patient subgroups and healthy controls or between ECT remitters and antidepressant drug remitters. Long-term ECT treatment is thus not associated with structural brain lesions.

Table 34.1 Summary of studies using PET and SPECT for assessing changes in cerebral glucose metabolism and rCBF after ECT treatment of psychiatric disorders

Author	Radiotracer used	Number of patients, type of disorder (responders)	Healthy controls	Timing of the second scan after completion of ECT	ECT: number of sessions, type of stimulation	Areas of decreased activity on posttreatment scan	Areas of increased activity on posttreatment scan	Areas of correlation with HDRS changes
Suwa et al. (2012)	FDG	13 MDD, 3 BD (12)	11	12 days	10, bilateral	Frontotemporal neocortex	Right medial temporal, amygdala, pons	None
Reininghaus et al. (2012)	FDG	12 MDD (3)	None	1–7 days	8; bitemporal (9 patients), right unilateral (3 patients)	None	Left temporal lobe (marginal increase)	None
Nobler et al. (2001)	FDG	6UP, 4BP (10)	None	5 days	6–25,bilateral	Bilateral superior frontal lobe, dorsolateral and medial prefrontal cortex, bilateral parietal regions, posterior cingulate gyrus, left inferior temporal lobe	Occipital	–
Yatham et al. (2000)	FDG	6UP (5)	None	7 days	8–12, uni-/bilateral	None	None	None

(continued)

Table 34.1 (continued)

Author	Radiotracer used	Number of patients, type of disorder (responders)	Healthy controls	Timing of the second scan after completion of ECT	ECT: number of sessions, type of stimulation	Areas of decreased activity on posttreatment scan	Areas of increased activity on posttreatment scan	Areas of correlation with HDRS changes
Henry et al. (2001)	FDG	6UP and BP (3)	None	2–7 days	6–10, bilateral	Frontal lobes, bilateral parietal regions	Right basal ganglia, occipital, brainstem	Decrease in the right parietal, right anterior, left posterior frontal
Volkow et al. (1988)	FDG, ^{15}O-H_2O	4UP (3)	None	24 h	6–11, bilateral	Bilateral frontal cortex (not statistically significant)	None	–
Guze et al. (1991)	FDG	4BP (4)	None	1 day, 3 patients; 112 days, 1 patient	6–11, bilateral	None	Day 1: none Day 112: middle frontal gyrus, parahippocampal gyrus	–
Yuuki et al. (2005)	FDG	4 MDD, 3 BP (7)	10	1 month	6–20, bilateral	Bilateral medial frontal cortex	Left occipital, parietal lobe	–
Sermet et al. (1998)	^{11}C-MET	8 MDD (4 underwent both pre- and post-ECS scan)	5	3 h	Single, bilateral	None	Global bilateral cortical cellular protein metabolism hyperactivation	–

Takano et al. (2007)	^{15}O-H_2O	6 MDD (6)	None	(1) Pre-ECT under anesthesia, (2) during ECT, (3) post-ECT 10–30 min	5–12, bilateral	Post-ECT: return of global CBF to the pre-ECT baseline after 10–30 min, increase in the thalamus, anterior cingulate, dorsolateral, medial frontal cortex compared to the pre-ECT baseline	During ECT Basal ganglia, midbrain, pontine tegmentum, thalamus, amygdala, hypothalamus, vermis, inferior frontal, parietal, and temporal cortex (compared to pre-ECT baseline)	–
Mervaala et al. (2001)	^{99m}Tc-ECD, ^{123}I-iomazenil	20 (ECD), 5(iomazenil) MDD (20)	None	1 week	6–11, bilateral	None	ECD: right temporal, bilateral, parietal cortices Iomazenil: bilateral frontal, parietal, occipital cortices, right prefrontal cortex	–

(continued)

Table 34.1 (continued)

Author	Radiotracer used	Number of patients, type of disorder (responders)	Healthy controls	Timing of the second scan after completion of ECT	ECT: number of sessions, type of stimulation	Areas of decreased activity on posttreatment scan	Areas of increased activity on posttreatment scan	Areas of correlation with HDRS changes
Segawa et al. (2006)	^{99m}Tc-ECD	8 MDD, 2 BD (6)	None	3–20 days	8–12, bilateral	Left medial prefrontal area, left limbic regions	None	No positive correlation Statistically significant negative correlation: left frontopolar gyrus, amygdala, nucleus accumbens, globus pallidus, superior temporal gyrus
Scott et al. (1994)	^{99m}Tc-ECD	15 MDD	None	After 45 min	Single, bilateral	Inferior anterior cingulate cortex	None	–

Awata et al. (2002)	^{99m}Tc-HMPAO	9 MDD (2 weeks: 9)	9	2, 12 weeks	6–9, bilateral	None	2 weeks: bilateral anterior cingulate, caudal orbitofrontal, right insular, right posterior middle frontal gyrus to the level of controls 12 weeks: increased compared to baseline	–
Kohn et al. (2007)	^{99m}Tc-HMPAO	8 MDD (7)	25	1 week	9.9 ± 1.9, bilateral	Responders: parietotemporal, cerebellar cortices Nonresponders: none	None	–
Elizagarate et al. (2001)	^{99m}Tc-HMPAO	10 MDD (10)	None	Intraictal during the third ECT session	6–12, bilateral	Occipital lobe (6 patients), parietal lobe (3 patients)	Temporal lobe, basal ganglia	–
Blumenfeld et al. (2003)	^{99m}Tc-HMPAO	10 MDD (10)	None	Ictal (within 30 s of the ECT stimulus)—interictal (2 min prior to ECT stimulus)	Bitemporal (8 patients), bifrontal (2 patients)	None	Bifrontal ECT: prefrontal, anterior cingulate Bitemporal ECT: lateral frontal cortex, anterior temporal lobes	–

(continued)

Table 34.1 (continued)

Author	Radiotracer used	Number of patients, type of disorder (responders)	Healthy controls	Timing of the second scan after completion of ECT	ECT: number of sessions, type of stimulation	Areas of decreased activity on posttreatment scan	Areas of increased activity on posttreatment scan	Areas of correlation with HDRS changes
Bonne et al. (1996)	^{99m}Tc-HMPAO	11 MDD, 9 bipolar (11)	None	5–8 days	7–14, bilateral frontotemporal	None	Responders: anterior, posterior cingulate, basal ganglia, right hemisphere Nonresponders: none	Inverse correlation between severity of depression and HMPAO uptake, positive correlation between improvement and increase in tracer uptake
Milo et al. (2001)	^{99m}Tc-HMPAO	15 MDD (5)	11	4 days	6–12, bilateral	5 excellent responders: global normalization of baseline hyperperfused regions towards normal Nonresponders: none	5 excellent responders: normalization in frontal regions Nonresponders: none	–

Navarro et al. (2004a)	^{99m}Tc-HMPAO	14 MDD (14)	28	12 months	8–14	None	Normalization of bilateral frontal hypoperfusion, no significant difference between ECT remitters and healthy controls at long-term scan	–
Takano et al. (2006)	^{99m}Tc-HMPAO	8 MDD (8)	12	5 days (post 1) and 1 month (post 2)	5–10, bifrontotemporal	Decrease in the right cuneus at post 1	Post 1: right hippocampal gyrus	–
							Post 2: right medial frontal	
Vangu et al. (2003)	^{99m}Tc-HMPAO	13 MDD (7)		3–11 (mean 5.3 ± 2.3) days	4–14, bilateral frontotemporal	None	Responders: left frontal, anterior cingulate gyrus	–
							Nonresponders: none	
Bajc et al. (1989)	^{99m}Tc-HMPAO	8 MDD, 3 schizoaffective disorder		Imaging during acute ECT		Parietal, occipital cortex	Frontal, temporal cortex, basal ganglia	–

DDST delusional disorder somatic type

34.3.4.3 Serotonin and Dopamine Changes in ECT

The mechanisms underlying the therapeutic effect of ECT are not completely known, and potential targets considered are brain 5-HT_2 and 5-HT_{1A} receptors, as well as dopamine D2 receptors. While various antidepressant medications cause the downregulation of brain 5-HT_2 (Eison et al. 1991; Meyer et al. 2001; Yatham et al. 1999), it has been shown that ECT upregulates 5-HT_2 receptors in rodents (Kellar et al. 1981).

The effect of ECT on human brain 5-HT_2 was assessed by Yatham et al. (2010) using ^{18}F-setoperone, an agonist with a high affinity and specificity for serotonin 5-HT_2 receptors. A widespread reduction in brain 5-HT_2 receptors was observed in patients with depression after ECT, with peak changes in the parahippocampal gyrus and the medial prefrontal cortex. The ability of ECT to further downregulate brain 5-HT_2 receptors in antidepressant non-responsive individuals may explain its efficacy in patients with antidepressant-refractory depression. Downregulation of brain 5-HT_2 receptors after ECT was also observed by a team of Strome et al. (2005), who studied the effect of ECT to binding of ^{18}F-setoperone on brain 5-HT_2 receptors in nonhuman primates. The discrepancy between the effects of ECT on the brain 5-HT_2 receptors in studies on humans, primates, and rodents might be due to species differences in brain 5-HT_2 receptor regulation. Likewise, a widespread reduction of binding of a radioligand ^{11}C-WAY100635, a highly selective and potent antagonist to postsynaptic brain 5-HT_{1A} receptors, was also demonstrated in cortical and subcortical regions, except the occipital cortex and the cerebellum (Lanzenberger et al. 2012).

In contrast, no effect of ECT on 5-HT_{1A} receptor binding was found by Saijo et al. (2010b) using the same radioligand in nine depressed patients. The difference in the results could be due to the significantly higher number of ECT sessions, used by Lanzenberger in comparison with Saijo, or the interaction between ECT and various concomitant pharmacological treatments that might affect 5-HT_{1A} receptor binding.

The effect of ECT on dopamine D2 receptors in the human brain was studied by Saijo et al. (2010a), using the dopamine D2/D3 agonist radioligand ^{11}C FLB457. A comparison was made between D2 receptor binding in pre- and post-ECT scans in 7 MDD patients and 11 healthy controls. No significant differences were seen in D2 receptor binding between patients with MDD and healthy controls. Posttreatment scans revealed significant reduction in D2 receptor binding in the right rostral anterior cingulate, suggesting that one of the mechanisms of ECT could be related to dopaminergic alteration in that area. The results were consistent with findings of Kuroda et al. (2006) in their rTMS study using ^{11}C-raclopride PET.

Hellwig et al. (2018) investigated the effect of sleep deprivation and ECT on striatal DAT (dopamine transporter) availability in 16 medication-free MDD patients and 12 matched controls. No significant differences were found when comparing striatal DAT availability between patients and healthy volunteers, consistent with results of Fall et al. (2000), who assessed DAT availability after ECT in six Parkinson's disease patients with mild depression.

A group by Baldinger-Melich et al. (2019) investigated the impact of ECT on monoamine oxidase A (MAO-A) levels in treatment-resistant depressive patients. MAO-A, being the key enzyme responsible for the degradation of serotonin, dopamine, and norepinephrine, maintains the homeostasis of cerebral serotonin concentration in humans (Shih et al. 1999). The levels of MAO-A in MDD, suicide victims, postpartum period, and severe atypical depression are up to 40% higher compared to healthy controls (Meyer et al. 2006). MAO-A levels were found to be similar in TRD patients and healthy controls, and ECT did not significantly reduce MAO-A availability. The authors concluded that the reason for non-reduction of MAO-A availability after ETC in depressed patients was probably related to the continuous antidepressant pharmacotherapy in these patients.

34.4 Psychotherapy

Psychotherapy has been established as an effective treatment in psychiatric disorders, including depression and OCD. In the last decades, several different psychological treatments have been developed and proved effective through many hundreds of randomized trials. Various psychotherapy techniques are about equally effective as pharmacotherapy, with combined treatments being more effective than one of these alone (Abramowitz 2006; Cuijpers 2017). The most common psychotherapy techniques include CBT, BT, interpersonal therapy, and psychodynamic therapy. The investigation of the mechanisms of action of psychotherapy has up to the last decade been only possible at the cognitive and behavioral level. A recent advance in functional neuroimaging has enabled investigation of the neurophysiological mechanisms of these treatments. These new findings will allow the development of new diagnostic biomarkers and a better personalized treatment (Linden and Fallgatter 2009).

34.4.1 Imaging of Psychotherapy in Obsessive–Compulsive Disorder

Several studies have investigated the effect of psychological treatment on neural activity in OCD patients with either PET or SPECT. Baxter et al. (1992) analyzed changes in cerebral metabolic activity using FDG-PET in nine OCD patients receiving BT, nine receiving fluoxetine, and four healthy controls. A significant decrease of activity in the head of the right caudate nucleus was reported in responders, and a further decrease in the left thalamus and the right ACC was observed in the drug-treated patient group. Values in nonresponders and normal controls did not change from baseline. Schwartz et al. (1996) combined data of nine new OCD patients treated with BT and nine BT-treated patients from a previous study by Baxter et al. (1992). Greater glucose metabolic rates of the bilateral caudate were found in responders to BT compared to poor responders.

Nakatani et al. (2003) measured baseline and posttreatment regional cerebral blood flow using Xenon-enhanced SPECT in 22 OCD patients who responded to BT. A significant reduction of cerebral blood flow was seen in the right head of caudate that correlated with clinical improvement.

Yamanishi et al. (2009) used ^{99m}Tc-ethyl cysteine dimer (^{99m}Tc ECD) SPECT to evaluate changes in regional cerebral blood flow after treatment with BT in 45 SSRI-resistant OCD patients. Treatment responders had significantly decreased rCBF in the right medial PFC, right OFC, and left middle frontal gyrus. Increased rCBF was observed in the right fusiform gyrus, cuneus, and angular gyrus. No changes in rCBF were reported in nonresponders. Clinical improvement correlated with a decrease in OFC activity.

Apostolova et al. (2010) investigated changes in cerebral glucose metabolism using FDG-PET in 16 OCD patients treated with either paroxetine ($n = 7$) or CBT ($n = 9$). Successful treatment was associated with an increase of glucose metabolism in the right caudate in both groups. This was attributed to the effect of therapy on concomitant affective and anxiety disorders and the large proportion of early-onset OCD in the sample.

Saxena et al. (2009) used FDG-PET to measure changes in glucose metabolism in 10 OCD patients receiving intense short-term CBT and in 12 healthy controls. In an OCD patient group, a significant decrease of metabolism was reported in bilateral thalami and an increase in right dorsal ACC, compared to a decrease in left dorsal ACC in controls.

van der Straten et al. (2017) performed a meta-analysis of 8 PET and 6 SPECT studies, which included 188 OCD patients before and after pharmacological and psychological treatment. A decrease in metabolism in the caudate, OFC, and thalamus on PET and a decrease in blood flow in the caudate on SPECT were associated with clinical improvement. No differences between the CBT- and medication-treated groups were seen concerning the effects on the caudate nucleus.

Brody et al. (1998) examined pretreatment FDG-PET predictors of response to two different treatments for OCD. 18 OCD patients were treated with interpersonal psychotherapy (ITP) and 9 received fluoxetine. They found that greater pretreatment cerebral metabolic activity in the left orbitofrontal cortex was significantly associated with greater symptomatic improvement after ITP while lower activity within this same ROI was associated with greater improvement after treatment with fluoxetine.

Response to CBT and antidepressant pharmacotherapy in patients with panic disorder resulted in a decrease of glucose metabolism in right frontal and temporal regions in both treatment groups (Prasko et al. 2004).

In summary, the majority of listed studies report a decrease of rCBF after treatment in caudate nucleus, thalamus, and OFC, which is associated with improvement corresponding to normalization of the cortico-striato-thalamo-cortical (CSTC) circuit overactivity. This supports the CSTC model hypothesis in OCD, as proposed by Saxena et al. (1998).

34.4.2 Imaging of Psychotherapy in Depression

Several research groups investigated effects of various psychotherapy procedures on regional neuronal activity, dopaminergic and serotonergic function, and neuroinflammation markers in depressed patients.

Brody et al. (2001) compared CMRGlu in MMD patients treated with either IPT (14 patients) or SSRI (10 patients) and in 16 healthy controls. Regional brain metabolic abnormalities seen at baseline tended to normalize with both treatment procedures. A decrease in prefrontal cortex and left anterior cingulate gyrus and an increase in left temporal lobe were reported.

Goldapple et al. (2004) compared CMRGlu changes in 14 patients receiving CBT and in 13 patients treated with SSRI. A widespread decrease of activity in frontal regions was associated with both types of therapy, and an increase in hippocampus, parahippocampus, and dorsal cingulate was seen in CBT group.

Kennedy et al. (2007) compared changes in pre- and posttreatment CMRGlu between a group of 12 patients treated with CBT and 12 patients receiving venlafaxine. Decreased activity was noted after both treatment regimens bilaterally in the orbitofrontal cortex and left medial prefrontal cortex, and increased metabolism was reported in the right occipital–temporal cortex. Changes specific to CBT responders include an increase of activity in the ventromedial frontal cortex and right occipital–temporal cortex and a decrease in the thalamus.

Martin et al. (2001) used ^{99m}Tc-HMPAO SPECT to compare changes in rCBF after IPT and venlafaxine, a serotonin–norepinephrine reuptake inhibitor antidepressant. Increase in the right basal ganglia was seen in both types of therapy, and an increase in the right posterior cingulate followed IPT.

Roffman et al. (2014) performed an FDG-PET study on 16 MDD patients. They evaluated neural correlates of treatment response immediately before and after a brief psychodynamic psychotherapy. The pretreatment glucose metabolism in the right posterior insula was markedly and positively correlated with depression severity. Posttreatment decrease of CMRGlu in the right insula was associated with reduction in depression scores, which in turn was consistent with a higher patient insight rating. Pretreatment metabolism in the right precuneus was significantly increased among patients who completed treatment and was positively associated with psychological mindedness.

34.4.2.1 Neuroinflammation Biomarker Changes in Depression After CBT

Four neuroimaging studies explored the role of inflammation in generating symptoms of a major depressive episode in humans by investigating translocator protein density. 18 kDa translocator protein (TSPO) is a marker of microglial density and neuroinflammation, and total distribution volume (TSPO V_T) is used as a measure of total ligand binding.

Hannestad et al. (2013) used PET with ^{11}C-PBR28 to compare the baseline level of TSPO in 12 depressed patients and 10 healthy controls but found no statistically significant difference in binding between the two groups.

Setiawan et al. (2015) used ^{18}F-FEPPA PET tracer to determine baseline levels of TSPO in 20 patients with MDD relative to 20 healthy control subjects. They found significantly elevated values across areas of the prefrontal cortex, the ACC, and the insula. Greater TSPO V_T in the ACC correlated with greater depression severity.

The same tracer was used by Li et al. (2018) in a study of baseline distribution of neuroinflammation biomarker in the brain in 40 MDD patients and 20 healthy controls and changes after supportive psychotherapy (SPT) ($n = 20$) and CBT ($n = 20$). Before therapy, TSPO V_T was significantly elevated in neocortical gray matter, frontal cortex, temporal cortex, and hippocampus in MDD relative to the control subjects, consistent with the results of the Setiawan group (Setiawan et al. 2015). TSPO V_T was significantly reduced during the treatment period in the CBT group, but not in the SPT group, and reduction in TSPO V_T correlated with the improvement of depressive symptoms. The correlation in the hippocampus was consistent in both SPT and CBT groups.

Holmes et al. (2018) compared TSPO V_T in a group of 14 medication-free patients in a major depressive episode of at least moderate severity and 13 in healthy controls using PET tracer ^{11}C-(R)-PK11195. TSPO V_T in the anterior cingulate cortex was significantly higher in depressed patients compared with controls, and this increase was particularly pronounced in patients with suicidal thinking.

34.4.2.2 Dopamine and Serotonin Changes in Depression After Cognitive Behavioral Therapy

Several authors explored dopamine/serotonin system changes after treatment with CBT: psychodynamic psychotherapy in MDD patients had no effect on dopamine D2 receptor binding in the striatum in ^{11}C-raclopride PET study (Hirvonen et al. 2011), but the midbrain 5-HT_{1a} receptor binding of ^{11}C-WAY-100635 significantly increased (Karlsson et al. 2010). Lehto et al. (2008) observed midbrain serotonin transporter (SERT) and striatum dopamine transporter (DAT) densities after 12 months of psychodynamic psychotherapy in depressive patients. Midbrain SERT density increased significantly in atypical but not in nonatypical depression patients, while there were no changes in the levels of DAT.

These findings are consistent with previous studies that provided evidence of a decrease in density of serotonin receptors in depression (Drevets et al. 1999; Hirvonen et al. 2008).

Cervenka et al. (2012) showed a direct relationship between symptom change after 15 weeks of CBT and extrastriatal binding of ^{11}C-FLB457, a high-affinity dopaminergic D2/D3 antagonist in nine patients with social anxiety disorder (SAD) using PET. Negative correlation between the change in D_2 receptor binding potential and the anxiety symptoms change was found for the medial prefrontal cortex and hippocampus.

Tiger et al. (2014) examined ten drug-naïve moderate major depressive patients before and after treatment with Internet-based cognitive behavioral therapy (iCBT) using the 5-HT1B receptor-selective PET radioligand ^{11}C-AZ10419369. A statistically significant reduction of activity after treatment was seen in a part of the dorsal brainstem containing the raphe nuclei, which regulate the serotonin system. No

correlation was observed between baseline PET and treatment response or changes between pre- and posttreatment PET data and clinical improvement.

Amsterdam et al. (2013) investigated the effect of CBT on serotonin transporter (SERT) binding using the selective SERT radioligand [^{123}I]-ADAM SPECT in 20 depressed patients and 10 healthy controls. A low baseline SERT uptake ratio in left and right medial temporal lobes of depressed patients significantly increased after CBT in the responder groups and, to a lesser degree, in the left medial temporal region in the partial and nonresponder groups.

In summary, the specific mechanisms of MDD are not yet fully understood. Abnormalities in serotonergic and dopaminergic systems as well as involvement of neuroinflammatory processes may contribute to the disease. Several PET studies demonstrated changes of different biomarkers, consistent with clinical improvement, after psychotherapy interventions in MDD.

34.5 Lesioning Procedures

The origins of psychosurgery can be traced to antiquity through the practice of trephination, the procedure of craniotomy using the cylindrical saw termed the "trephine." A trephined skull that dates to approximately 5100 BC has been identified in France, and the literature on trephination for the relief of neuropsychiatric symptoms can be dated to 1500 BC.

Swiss psychiatrist Gottlieb Burckhardt performed the first psychosurgical procedure of the modern era in 1888 by excising multiple foci in frontal, parietal, and temporal cortices in six patients. In the early twentieth century, the Estonian neurosurgeon Lodovicus Puusepp performed sections of frontal and parietal lobes, while John Farquhar Fulton and Carlyle Jacobsen presented data on calming behavioral changes associated with the resection of the anterior frontal association cortex. Portuguese neurologist Egas Moniz suggested the ablation of the frontal cortex in humans with psychiatric disease. Together with his colleague Almeida Lima, he performed the first successful psychosurgery by injecting alcohol into the white matter of the frontal lobe of a patient with paranoid delusions and anxiety. After performing over 100 of such operations, Moniz was awarded with the Nobel Prize in Medicine or Physiology in 1949 despite little follow-up or objective results.

The widespread use of lobotomy was seen in the first half of the twentieth century, popularized with the introduction of transorbital frontal lobotomy by Americans Walter Freeman and James Watt. The decline of frontal lobotomy started in the 1950s after the introduction of chlorpromazine, the first effective pharmacological therapy for psychosis, and the spreading awareness about dubious efficacy and severe side effects of the procedure (reviewed in Mashour et al. (2005); Robison et al. (2012)).

Currently there are four commonly employed neurosurgical ablative stereotactic procedures: anterior cingulotomy, subcaudate tractotomy, limbic leucotomy, and anterior capsulotomy. They are typically used for affective and anxiety disorders rather than cognitive disorders in patients who are refractory to pharmacological, psychotherapeutic, or electroconvulsive therapies (reviewed in Mashour et al. (2005)).

34.5.1 Anterior Cingulotomy

In anterior cingulotomy, the anterior portion of the cingulate gyrus is stereotactically lesioned, interrupting tracts between the cingulate gyrus and the frontal lobes. This eliminates the efferent projections of the anterior cingulate cortex to the orbitofrontal cortex and to the limbic system, resulting in a 30–68% response rate in OCD and depression (Ballantine Jr et al. 1987; Dougherty et al. 2002; Jenike et al. 1991; Jung et al. 2006).

Two studies involving FDG-PET identified cerebral metabolic correlates as potential predictors of treatment response to anterior cingulotomy.

Rauch et al. (2001) identified one locus of significant correlation of higher preoperative metabolism and better treatment response for OCD within the right posterior cingulate cortex, approximate Brodmann area 31, while Dougherty et al. (2003) identified two loci, associated with a greater postoperative improvement of major depression—the left subgenual prefrontal cortex and left thalamus.

Greenspan et al. (2008) reported a case report on $H_2{}^{15}O$ PET findings of pain-evoked blood flow response in which perception of pain and temperature was assessed before and after cingulotomy for OCD. The preoperative pain-evoked activation of the bilateral middle cingulate cortex diminished postoperatively, but the activation was seen in the ipsilateral parasylvanian cortex. The study provides evidence for the functional connectivity of the hierarchical pain network.

34.5.2 Subcaudate Tractotomy

Subcaudate tractotomy is primarily used for the treatment of refractory depression. It targets a region of the white matter localized beneath the head of the caudate known as the substantia innominata, interrupting the loop between the cortex and thalamus via the striatum (Shah et al. 2008).

A bifrontal stereotactic tractotomy, a procedure that destroys bifrontal pathways located beneath and in front of the head of the caudate nucleus, was used by Biver et al. (1995) to treat a 37-year-old patient with refractory OCD. Hypometabolism was seen on a posttreatment FDG-PET scan in comparison with the baseline scan in areas known to be associated with depression: the medial part of the orbital cortex, thalamus, caudate nucleus, and subgenual cingulate. Surgical intervention resulted in partial clinical improvement.

34.5.3 Limbic Leucotomy

Limbic leucotomy is the combination of stereotactic lesions created in the anterior cingulotomy and subcaudate tractotomy. A response of 36–50% was reported in 21 patients who underwent limbic leucotomy for OCD or depression (Montoya et al. 2002).

Changes in rCBF following stereotactic limbic leucotomy in patients with medically intractable OCD were assessed using ^{99m}Tc-HMPAO (Kim et al. 2001). The postoperative rCBF was significantly higher in the right medial frontal cortex and left striatum compared to baseline scan, suggesting the blockage of the functional connection of the corticolimbic loop by the procedure.

Sachdev et al. (2001) reported great early- and long-term improvement in a 37-year-old female patient with severe and intractable OCD, treated with bilateral orbitomedial leucotomy. The reduction of metabolism in the caudate head, anterior cingulate, and orbital, medial, and lateral prefrontal cortices and the thalamus was demonstrated at the early postoperative FDG scan compared to preoperative baseline scan, suggesting the functional disconnection between frontal cortical–cortical and cortical–subcortical circuits made by the structural lesion. At 1 year postsurgery, metabolism was still reduced in the anterior cingulate gyrus, caudate, and thalamus compared to baseline.

34.5.4 Anterior Capsulotomy

Anterior capsulotomy targets the fronto-limbic fibers that pass in the anterior limb of the internal capsule.

The therapeutic effect of anterior capsulotomy for the treatment of OCD is attributed to the interruption of the CSTC circuit. Several case series reported significant improvement in OCD symptoms in 53–77% patients after anterior capsulotomy (Shah et al. 2008; Liu et al. 2008; Rück et al. 2008; Zhan et al. 2014).

In a large study conducted by Zhan and colleagues, bilateral anterior capsulotomy was performed in 53 medically intractable OCD patients (2014). In a follow-up lasting at least 5 years, significant clinical improvement or complete disappearance of OCD symptoms was observed in 62% of patients with another 15% reporting moderate improvement. The baseline level of glucose metabolism on preoperative PET in patients with refractory OCD was higher than that of healthy controls in the anterior cingulate, caudate nucleus, and orbitofrontal cortex. On PET performed 12 months after the capsulotomy, the regional glucose metabolic rate in these areas decreased, and no significant differences remained compared to the healthy controls.

Zuo et al. used a voxel-based analysis of FDG-PET to show metabolic modulation of regionally specific dysfunction in the cortico-striato-thalamo-cortical neurocircuitry by bilateral capsulotomy in 8 refractory OCD patients compared to 80 healthy controls (Zuo et al. 2013). They detected increased baseline uptake in orbitofrontal cortex, cingulate gyrus, and caudate nucleus, as well as in bilateral middle temporal gyrus, the brainstem, and cerebellum. Clinical improvement after capsulotomy correlated with metabolic decrease in the bilateral anterior cingulate cortex and superior frontal gyrus, while negative correlation was observed with metabolic increases in the right middle and inferior occipital gyri.

In a prospective comparison of metabolic and clinical changes after either capsulotomy or DBS in 13 and 16 patients, respectively, Suetens et al. reported preoperative superior frontal and supplementary motor cortex hypometabolism and anterior

cingulate, occipital cortex, and posterior cerebellum hypermetabolism in both groups. Common metabolic decreases to both interventions were observed in anterior cingulate and the prefrontal and orbitofrontal cortices. Compared with DBS, capsulotomy resulted in more intense metabolic changes and additional significant decreases in the mediodorsal thalamus, caudate nucleus, and cerebellum as well as increases in the precuneus and the fusiform and lingual gyrus (Suetens et al. 2014).

In a case report by Riestra et al. (2011), unilateral right anterior capsulotomy was performed in a 45-year-old MDD and comorbid OCD female patient. After the operation, symptoms greatly improved, while higher metabolism in the right caudate nucleus and lower metabolism in the right globus pallidus were present on a pre-operation FDG scan as well as 16 months later.

34.6 Conclusions

In this review, reports of PET and SPECT functional imaging findings in non-pharmacological therapies for the treatment of psychiatric disorders were summarized. The number of published reports in some techniques is low, in the case of psychosurgery due to poor results and high complication rate and in the case of VNS, DBS, and TMS due to novelty of treatment procedure. Because of the advance of fMRi, the number of studies based on nuclear medicine imaging is stagnating.

There are major variations in study results due to different methodologies (precise location of the treatment, duration of treatment prior to scanning, different time points of scanning, small sample size, and different concurrent pharmacotherapies). The divergent findings may also be associated with interindividual variations and complexity of the disease.

Changes induced by different stimulation techniques differ upon hemisphere stimulated and are frequency and amplitude dependent. Several hemisphere-dependent functional circuits may play an important role in the effect of treatment.

The pathophysiological processes underlying different psychiatric diseases, as well as the mechanisms of action of therapeutic techniques, are not yet fully understood. Some of the changes accompanying successful therapeutic procedures resembled those seen with medication, and the suggestion is that, at least in some cases, non-pharmacological and pharmacological therapies may act on a common set of neurological processes. The results of several non-pharmacological therapies are promising. Further imaging studies will result in better understanding of the pathological backgrounds of psychiatric disorders and in improved treatments.

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Correction to: Application of PET and SPECT to the Study of Autism Spectrum Disorders

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Correction to: R. A. J. O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*, https://doi.org/10.1007/978-3-030-57231-0_29

The book was inadvertently published with an incorrect spelling of the author's surname in Chapter 29 as Mukarran whereas it should be Mukarram. This error has now been corrected with this erratum.

The updated online version of this chapter can be found at https://doi.org/10.1007/978-3-030-57231-0_29

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