PET and SPECT in Psychiatry

Rudi A.J.O. Dierckx
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Editors
Rudi A.J.O. Dierckx
Department of Nuclear Medicine
and Molecular Imaging
University Medical Center Groningen
University of Groningen
Groningen
The Netherlands

University of Ghent
Ghent
Belgium

Andreas Otte
Faculty of Electrical Engineering
and Information Technology
University of Applied Sciences Offenburg
Offenburg
Germany

Erik F.J. de Vries
Department of Nuclear Medicine
and Molecular Imaging
University Medical Center Groningen
University of Groningen
Groningen
The Netherlands

Aren van Waarde
Department of Nuclear Medicine
and Molecular Imaging
University Medical Center Groningen
University of Groningen
Groningen
The Netherlands

Guest Editor
Johan A. den Boer
PRA International, Zuidlaren
The Netherlands

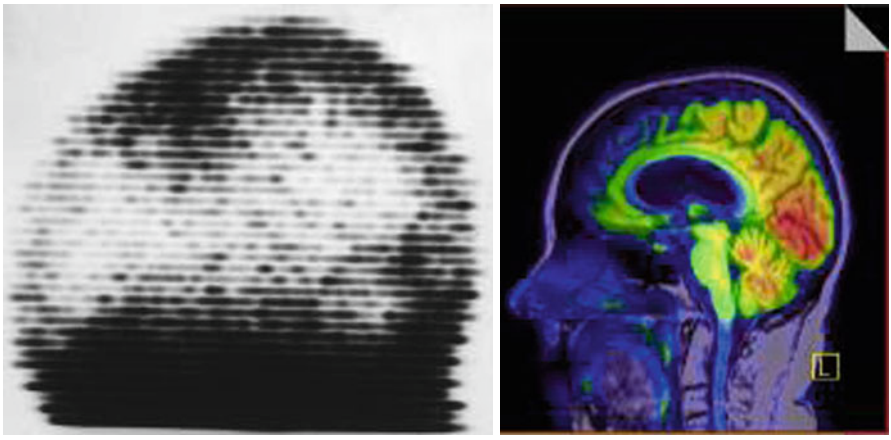
Department of Nuclear Medicine
and Molecular Imaging
University Medical Centre Groningen
(UMCG), Groningen
The Netherlands

ISBN 978-3-642-40383-5 ISBN 978-3-642-40384-2 (eBook)
DOI 10.1007/978-3-642-40384-2
Springer Heidelberg New York Dordrecht London

Library of Congress Control Number: 2014933210

Foreword

In this ambitious undertaking, the editors have assembled the most comprehensive and updated compilation of material, describing the use of single-photon and positron emission tomography in the neurosciences. Three volumes address the use of SPECT and PET in psychiatry, in neurology and in neurobiological systems. A large international team of experts have come together to accomplish this task.



On the *left*, a 1969 blood–brain barrier scan in cerebral lymphoma and on the *right* a PETMR study in frontotemporal dementia. Institute of Nuclear Medicine 2012

The progress achieved in this area has been staggering. The two images below, obtained half a century apart, speak a thousand words.

In this context, this volume triad is needed and timely. Novel instrumentation and probes, and significant advances in the understanding of the pathophysiology of the various pathological entities described in these texts, have led to clear clinical benefit. This is apparent in the movement disorders, in the identification of non-lesional MR focal epilepsies, and now in a rapidly emerging field, in the diagnosis of fibrillar amyloid plaque deposition, in mild cognitive-impaired individuals. The next few years will see a rapid expansion of this already fast progressing field.

The editors are to be congratulated in bringing together and to print this significant volume of expertise and experience.

Peter J. Ell, FMedSci, DR HC
Emeritus University College London,
Institute of Nuclear Medicine

Preface

The neuroscientist of today disposes of a powerful instrumentarium for functional 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 this instrumentarium, positron emission tomography (PET) and single-photon emission computed tomography (SPECT) have become forerunners in the functional imaging arena, much more than functional magnetic resonance imaging, and for this reason, this book is dedicated to PET and SPECT.

Although there have been some textbooks on PET or SPECT in the neurosciences, e.g. De Deyn et al. 1997, or Otte et al. 2004, the number of these books is limited, and – to the best of our knowledge – there is no recent comprehensive publication on PET and SPECT in the neurosciences, especially a compilation by a large number of international experts, as it is undertaken in the project at hand.

When the idea to edit a book on PET and SPECT in neurosciences came up, it was soon realized that all the new data would never fit into one single volume. Hence it was decided to write a trilogy. *PET and SPECT in Psychiatry* is the first volume of this trilogy: volume 2 (*PET and SPECT in Neurology*) and volume 3 (*PET and SPECT in Neurobiological Systems*) will complete the series.

In all volumes, we have tried to assemble the combined expertise of renowned authors whose dedication to the investigation of psychiatric and neurological disorders or of neurobiological systems through nuclear medicine technology has achieved international recognition. Prior to writing the trilogy, Rudi Dierckx organized an International Symposium on PET and SPECT in Neurology and Psychiatry in Groningen, the Netherlands (April 23–25, 2012). At this symposium, many of the authors included in this trilogy were invited to present a state-of-the-art review of their specific field of research. The editors, who are nuclear medicine specialists, radiochemists and biologists with a strong exposure to neurosciences, have also invited experts from the psychiatry, neurology and molecular neurobiology fields to enhance the editorial board as guest editors for each volume of the trilogy. For volumes 1, 2 and 3, these were respectively Johan A. (Hans) den Boer, Professor in Biological Psychiatry; Klaus L. (Nico) Leenders, Professor in Neurology; and Paul Luiten, Professor in Neurobiology. Furthermore, we tried to increase the quality of our books by introducing an external peer-review system with experts in the field in

addition to review by the editors. The external peer reviewers are listed in the corresponding *Appendix*.

We are very happy that our book is produced by one of the premier publishers in the field. This guarantees a high quality of reproduction and allows for the inclusion of many colour figures, which is essential in the field of functional neuroimaging.

We are intrigued by the enthusiastic response from contributors from all over the world who made this endeavour successful. We also would like to thank all external peer reviewers who have done an excellent work for ensuring the quality of this compilation. Finally, we would like to thank Dr. Ute Heilmann and Dr. Sylvana Freyberg from Springer-Verlag for their continuous help and support during the development of this book.

We sincerely hope that this book will become 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. In addition, the trilogy may be interesting and important for industry, as PET and SPECT imaging of the brain is becoming more and more important in today's ageing population.

May this book serve as a guide towards the present use of PET and SPECT in brain disorders and as a catalyst for future research. There is much to be explored, and the engine has been started already.

Groningen, The Netherlands — Rudi A.J.O. Dierckx
Offenburg, Germany — Andreas Otte
Groningen, The Netherlands — Erik F.J. de Vries
Groningen, The Netherlands — Aren van Waarde
Groningen, The Netherlands — Johan A. den Boer

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Contents

Contributors

Paul Allen Department of Psychosis Studies, Institute of Psychiatry, King's College London, London, UK

Audrée Arcelin Department of Exercise Science, Concordia University, Montreal, QC, Canada

Kurt Audenaert Department of Psychiatry and Medical Psychology, University Hospital, Ghent University, Ghent, Belgium

Chawki Benkelfat Department of Psychiatry, McGill University, Montreal, QC, Canada

Department of Neurology and Neurosurgery, McConnell Brain Imaging Center, Montreal Neurological Institute, McGill University, Montreal, QC, Canada

Bart N. van Berckel Department of Radiology and Nuclear Medicine, VU University Medical Center, Amsterdam, The Netherlands

Stijn Bijttebier Department of Psychiatry, Unit for Suicide Research, Ghent University, University Hospital, Ghent, Belgium

Johan A. den Boer PRA International, Zuidlaren, The Netherlands

Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen (UMCG), Groningen, The Netherlands

Jan Booij Department of Nuclear Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Fokko J. Bosker University Center for Psychiatry, University Medical Center Groningen, Groningen, The Netherlands

Matthijs G. Bossong Department of Psychosis Studies, Institute of Psychiatry, King's College London, London, UK

Wim van den Brink Department of Psychiatry, Addiction Research, Amsterdam Institute for Addiction Research, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Carlos Buchpiguel Department of Radiology, Nuclear Medicine Service, Clinical Hospital, School of Medicine, University of São Paulo, São Paulo, Brazil

Geraldo F. Busatto Department of Psychiatry, Faculty of Medicine, Universidade de São Paulo, São Paulo, Brazil

Cindy Casteels Division of Nuclear Medicine, Department of Imaging and Pathology, University Hospitals Leuven, KU Leuven, Leuven, Belgium

Nucleaire Geneeskunde en Moleculaire Beeldvorming, Katholieke Universiteit Leuven, Universitair Ziekenhuis, Leuven, Belgium

Marco Cavallo Department of Mental Health, "San Luigi Gonzaga" Hospital Medical School, University of Turin, Turin, Italy

Department of Translational Medicine, "Amedeo Avogadro" University of Eastern Piedmont, Novara, Italy

Diane C. Chugani Division of Clinical Pharmacology and Toxicology, Carman and Ann Adams Department of Pediatrics and the Department of Radiology, Children's Hospital of Michigan, Detroit Medical Center, Wayne State University School of Medicine, Detroit, MI, USA

Ralf Clauss Nuclear Medicine, Royal Surrey County Hospital, Guildford, Surrey, UK

Thomas I.F.H. Cremers Department of Biomonitoring and Sensoring, University of Groningen, University Center for Pharmacy, Groningen, The Netherlands

Jeffrey W. Dalley Department of Psychology, University of Cambridge, Cambridge, UK

Department of Psychiatry, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK

Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK

Debby Van Dam Laboratory of Neurochemistry and Behavior, Institute Born-Bunge, University of Antwerp, Wilrijk, Belgium

Thien Thanh Dang-Vu Department of Exercise Science, Concordia University, Montreal, QC, Canada

Center for Studies in Behavioral Neurobiology, Concordia University, Montreal, QC, Canada

Jacques Darcourt Nuclear Medicine Department, Centre Antoine Lacassagne. UMR CEA TIRO, Université de Nice Sophia Antipolis, Nice, France

Renaud David Memory Center CMRR – CHU Nice, Université de Nice Sophia Antipolis, Nice, France

Stefanie Desmyter Department of Psychiatry, Unit for Suicide Research, Ghent University, University Hospital, Ghent, Belgium

Martin Desseilles Department of Psychology, University of Namur Medical School, Namur, Belgium

Clinique Psychiatrique des Frères Alexiens, Henri-Chapelle, Belgium

Peter Paul De Deyn Department of Biomedical Sciences, Laboratory of Neurochemistry and Behavior, Institute Born-Bunge, University of Antwerp, Wilrijk, Belgium

Department of Neurology Alzheimer Research Center, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Department of Neurology and Memory ClinicHospital Network Antwerp (ZNA) Middelheim and Hoge Beuken, Antwerp, Belgium

Rudi A.J.O. Dierckx Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

University of Ghent, Ghent, Belgium

André Dobbeleir Faculty of Veterinary Medicine, Department of Veterinary Medical Imaging and Small Animal Orthopaedics, Ghent University, Merelbeke, Belgium

Andrej Doma Department of Nuclear Medicine, University Medical Center Ljubljana, Ljubljana, Slovenia

Janine Doorduin Department of Nuclear Medicine and Molecular Imaging, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Alex G.G. Doruyter Medical Imaging and Clinical Oncology, Nuclear Medicine Division, Tygerberg Hospital, Stellenbosch University, Cape Town, South Africa

Lars Farde Department of Clinical Neuroscience, Center for Psychiatric Research, Karolinska Institutet, Stockholm, Sweden

Vanda Faria Department of Psychology, Uppsala University, Uppsala, Sweden

Mats Fredrikson Department of Psychology, Uppsala University, Uppsala, Sweden

Vibe G. Frokjaer Center for Integrated Molecular Brain Imaging and Neurobiology Research Unit, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Thomas Furmark Department of Psychology, Uppsala University, Uppsala, Sweden

Elsmarieke van de Giessen Department of Nuclear Medicine (F2N), Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Andor W.J.M. Glaudemans Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Rita Z. Goldstein Department of Psychiatry and Department of Neuroscience, Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, The Leon and Norma Hess Center for Science and Medicine, New York, NY, USA

Paul Gravel Department of Psychiatry, McGill University, Montreal, QC, Canada

Department of Neurology and Neurosurgery, McConnell Brain Imaging Center, Montreal Neurological Institute, McGill University, Montreal, QC, Canada

Jan Cees de Groot Department of Radiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Renaud Guignard Nuclear Medicine Department, Centre Antoine Lacassagne. UMR CEA TIRO, Université de Nice Sophia Antipolis, Nice, France

Bartholomeus (B.)C.M. Haarman University of Groningen, University Medical Center Groningen, Academic Centre of Psychiatry, Groningen, The Netherlands

Department of Psychiatry, Mood and Anxiety Disorders, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Joanna Udo de Haes Clinical Pharmacology, Merck Sharp and Dohme, Oss, The Netherlands

Christer Halldin Department of Clinical Neuroscience, Center for Psychiatric Research, Karolinska Institutet, Stockholm, Sweden

Cornelis van Heeringen Department of Psychiatry, Unit for Suicide Research, Ghent University, University Hospital, Ghent, Belgium

Minke E. Jongsma Department of Biomonitoring and Sensoring, University of Groningen, University Center for Pharmacy, Groningen, The Netherlands

Valtteri Kaasinen Department of Neurology and Turku PET Centre, University of Turku and Turku University Hospital, Turku, Finland

Siegfried Kasper Division of Biological Psychiatry, Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria

Hans C. Klein Program for Geriatric Psychiatry, University Center Psychiatry, Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, Groningen, The Netherlands

Onno L. De Klerk Topreferent Trauma Center, Geestelijke Gezondheids Zorg Drenthe, Assen, The Netherlands

Michael Koenigs Department of Psychiatry, University of Wisconsin-Madison, Madison, WI, USA

Michel Koole Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Koen Van Laere Division of Nuclear Medicine, Department of Imaging and Pathology, University Hospitals Leuven, KU Leuven, Leuven, Belgium

Nucleaire Geneeskunde en Moleculaire Beeldvorming, Katholieke Universiteit Leuven, Universitair Ziekenhuis, Leuven, Belgium

Rupert Lanzenberger Division of Biological Psychiatry, Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria

Marco Leyton Department of Psychiatry, McGill University, Montreal, QC, Canada

Department of Neurology and Neurosurgery, McConnell Brain Imaging Center, Montreal Neurological Institute, McGill University, Montreal, QC, Canada

Jennifer I. Lissemore Department of Psychiatry, McGill University, Montreal, QC, Canada

Oupam Malhi Department of Exercise Science, Concordia University, Montreal, QC, Canada

Silja Mcilwrick Cognitive Science Center, University of Amsterdam, Amsterdam, The Netherlands

Gladys Mikolajczak Department of Psychiatry, University of Liege, Liege, Belgium

Pieter J. Naudé Department of Molecular Neurobiology, University of Groningen, Groningen, The Netherlands

Antonia S. New The Mental Health Patient Care Center and the Mental Illness Research Education and Clinical Center, James J. Peters Veterans Affairs Medical Center, Bronx, NY, USA

Department of Psychiatry, Mount Sinai School of Medicine, New York, NY, USA

Willem A. Nolen University of Groningen, University Medical Center Groningen, Academic Centre of Psychiatry, Groningen, The Netherlands

Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Thomas E. Nordahl Department of Psychiatry and Behavioral Sciences, University of California at Davis School of Medicine, UC Davis Medical Center, Sacramento, CA, USA

David J. Nutt Neuropsychopharmacology Unit, Imperial College London, London, UK

Nozipho Nyakale Nuclear Medicine Department, Steve Biko Academic Hospital, University of Pretoria, Pretoria, South Africa

Jordan O'Byrne Department of Exercise Science, Concordia University, Montreal, QC, Canada

Center for Studies in Behavioral Neurobiology, Concordia University, Montreal, QC, Canada

Richard Oude Voshaar University of Groningen, University Medical Center Groningen, University Center of Psychiatry, Groningen, The Netherlands

Marco Pagani Institute of Cognitive Sciences and Technologies, CNR, Rome, Italy

Department of Nuclear Medicine, Karolinska Hospital, Stockholm, Sweden

Kathelijne Peremans Department of Veterinary Medical Imaging and Small Animal Orthopaedics, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium

M. Mercedes Perez-Rodriguez The Mental Health Patient Care Center and the Mental Illness Research Education and Clinical Center, James J. Peters Veterans Affairs Medical Center, Bronx, NY, USA

Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Nicole Praschak-Rieder Division of Biological Psychiatry, Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria

Maia Pujara Department of Psychiatry, University of Wisconsin-Madison, Madison, WI, USA

Kieran Rea Pharmacology Department, National University of Ireland, Galway, Ireland

Lindsay Reed Department of Exercise Science, Concordia University, Montreal, QC, Canada

A.A.T. Simone Reinders Department of Psychosis Studies, King's College London, Institute of Psychiatry, London, UK

Rixt F. Riemersma-Van der Lek University of Groningen, University Medical Center Groningen, Academic Centre of Psychiatry, Groningen, The Netherlands

Department of Psychiatry, Mood and Anxiety Disorders, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Luis H. Ripoll Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Philippe Robert Memory Center CMRR – CHU Nice, Université de Nice Sophia Antipolis, Nice, France

Henricus G. Ruhé Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Program for Mood and Anxiety Disorders, Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Program for Mood Disorders, Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Program for Mood and Anxiety Disorders, University Center for Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Bruce Russell School of Pharmacy, University of Auckland, Grafton, Auckland, New Zealand

Mike Sathekge Nuclear Medicine Department, Steve Biko Academic Hospital, University of Pretoria, Pretoria, South Africa

Larry J. Siever The Mental Health Patient Care Center and the Mental Illness Research Education and Clinical Center, James J. Peters Veterans Affairs Medical Center, Bronx, NY, USA

Mount Sinai School of Medicine, New York, NY, USA

Arjen J.C. Slooter Department of Intensive Care Medicine, University Medical Center Utrecht, University of Utrecht, Utrecht, The Netherlands

Debby Sookman Department of Psychiatry, McGill University, Montreal, QC, Canada

Department of Psychology, Obsessive-Compulsive Disorder Clinic, McGill University Health Center, Montreal, QC, Canada

Michael Soyka Department of Psychiatry, Ludwig Maximilian University, Psychiatric Hospital, Munich, Germany

Privatklinik Meiringen, Meiringen, Switzerland

Bart De Spiegeleer Drug Quality and Registration, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium

Christoph Spindelegger Division of Biological Psychiatry, Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria

Dan J. Stein Department of Psychiatry and Mental Health, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

Gilles N. Stormezand Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Akihiro Takano Department of Clinical Neuroscience, Center for Psychiatric Research, Karolinska Institutet, Stockholm, Sweden

Robin Tyacke Neuropsychopharmacology Unit, Imperial College London, London, UK

Eva Vandermeulen Faculty of Veterinary Medicine, Department of Veterinary Medical Imaging and Small Animal Orthopaedics, Ghent University, Merelbeke, Belgium

Dick Veltman Department of Psychiatry, Addiction Research, Amsterdam Institute for Addiction Research, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Simon Vermeire Faculty of Veterinary Medicine, Department of Veterinary Medical Imaging and Small Animal Orthopaedics, Ghent University, Merelbeke, Belgium

Yannick Vermeiren Laboratory of Neurochemistry and Behavior, Institute Born-Bunge, University of Antwerp, Wilrijk, Belgium

Tiago S. Vieira Nuclear Medicine Department, Centro Hospitalar de São João, Porto, Portugal

Nidhusha Vijayakumar Department of Exercise Science, Concordia University, Montreal, QC, Canada

Anniek K.D. Visser Department of Nuclear Medicine and Molecular Imaging, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Mariza Vorster Nuclear Medicine Department, Steve Biko Academic Hospital, University of Pretoria, Pretoria, South Africa

Aren van Waarde Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Tim Waelbers Faculty of Veterinary Medicine Imaging and Small Animal Orthopaedics, Department of Veterinary Medical, Ghent University, Merelbeke, Belgium

James M. Warwick Department of Nuclear Medicine, Faculty of Health Sciences, Tygerberg Hospital, Stellenbosch University, Cape Town, South Africa

Medical Imaging and Clinical Oncology, Nuclear Medicine Division
Tygerberg Hospital, Stellenbosch University, Cape Town, South Africa

Ben H.C. Westerink Department of Biomonitoring and Sensoring, University of Groningen, University Center for Pharmacy, Groningen,
The Netherlands

Matthäus Willeit Division of Biological Psychiatry, Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria

Antoon T.M. Willemsen Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Max Zöttl Department of Psychiatry, Canterbury Health Ltd., Priory Clinic, Canterbury, Kent, UK

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 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 radiolabeld 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 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 the 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 brain.

A. Takano (✉) • C. Halldin • L. Farde
Department of Clinical Neuroscience, Center for Psychiatric Research, Karolinska University Hospital, R5:02, Stockholm SE-171 76, Sweden
e-mail: akihiro.takano@ki.se

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_1,

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 C-11 (half-life, 20.4 min) or F-18 (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 C-11 or F-18, 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 C-14 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 C-11-labeled drugs and 12 h for F-18-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.

At least 1 % of injected radioactivity in the brain has been the finding for most of the drugs viewed as having acceptable brain exposure. However, no strict guidelines have yet been established for decision making. 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 good predictor of brain exposure of the candidate drugs (Schou et al. 2013).

Although the drugs used in the field of psychiatry are mainly targeted to the CNS, whole body PET measurements can provide useful information in relation to potential side effects. 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). This requirement has increased the costs of PET-microdosing studies in the human subjects.

1.2.2 PET Receptor Occupancy to Demonstrate Target Engagement and 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 tools, 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 (Chapter 2).

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

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).

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 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 recent 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,

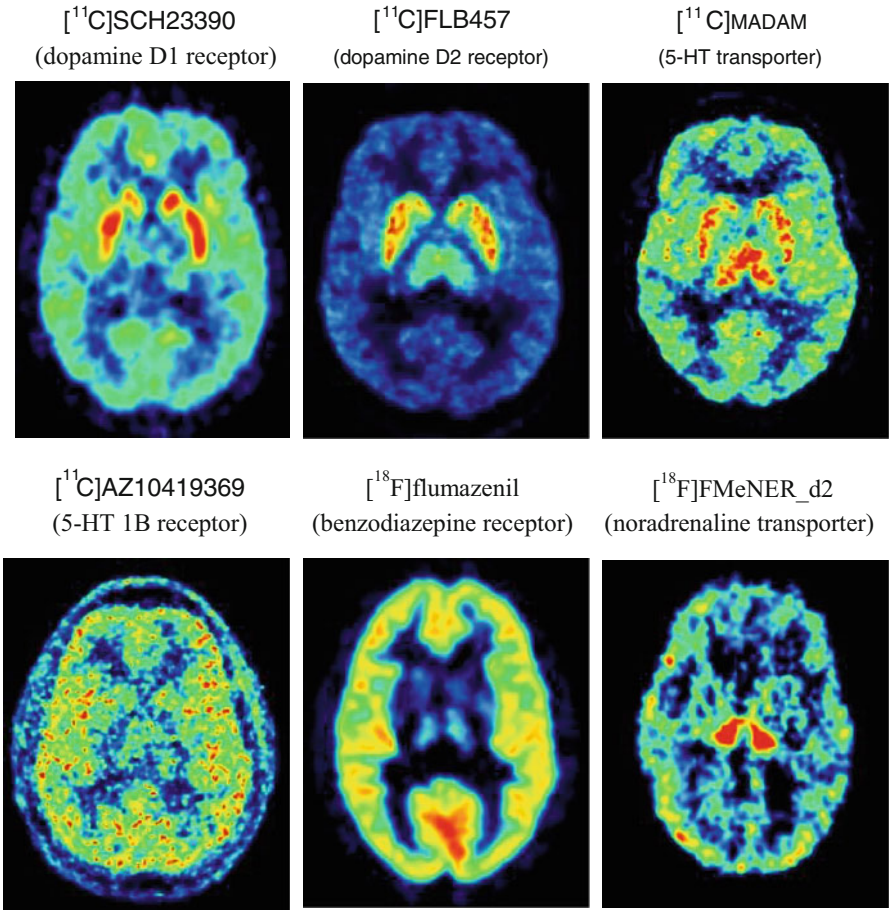

Fig. 1.1 Horizontal brain sections through the striatal level showing the regional distribution of the binding of commonly used PET radioligands. Images represent radioactivity summed after radioligand injection (9–51 min for [11C]SCH23390, 0–87 min for [11C]FLB457, 7–93 min for [11C]MADAM, 3–63 min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

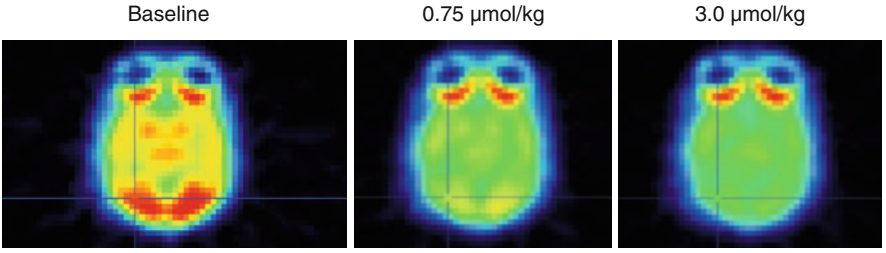

Fig. 1.2 Horizontal PET images showing [11C]AZ10419369 binding to the 5HT1b-receptor at baseline and after AZD3483 i.v. administration in a cynomolgus monkey

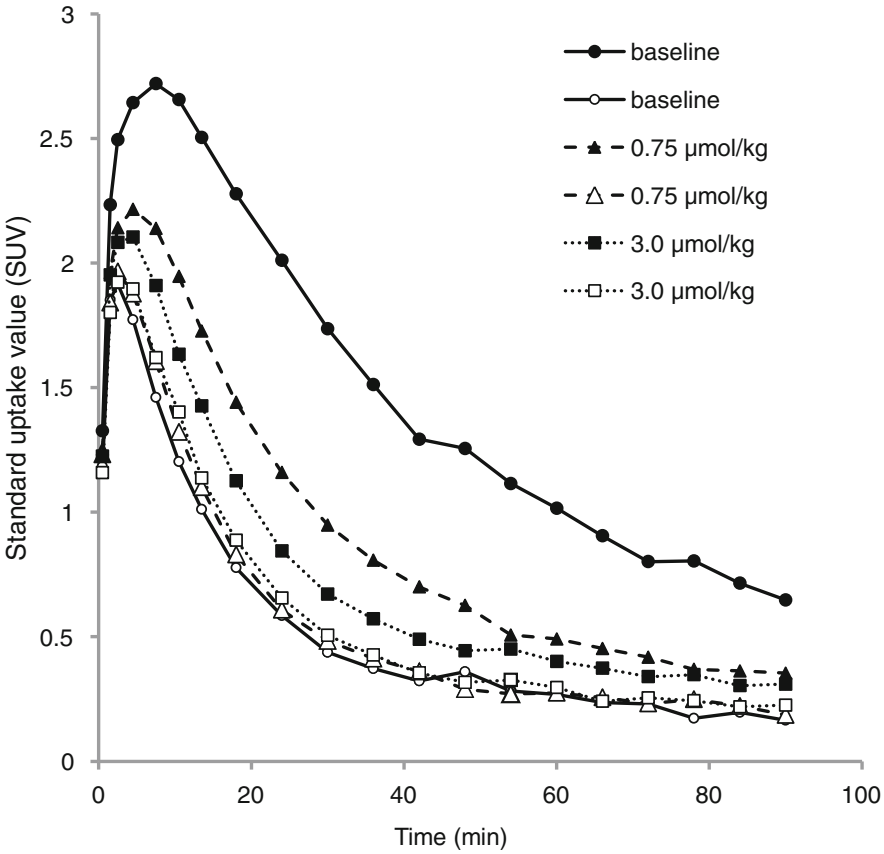

Fig. 1.3 Time activity curves for the regional [^{11}C]AZ10419369 binding in a cynomolgus monkey illustrated in Fig. 1.2. *Filled marks* represent occipital cortex. *Open marks* represent the cerebellum

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 5HT1B 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 (Kiplasma values (Karlsson et al. 1995)) are reliable.

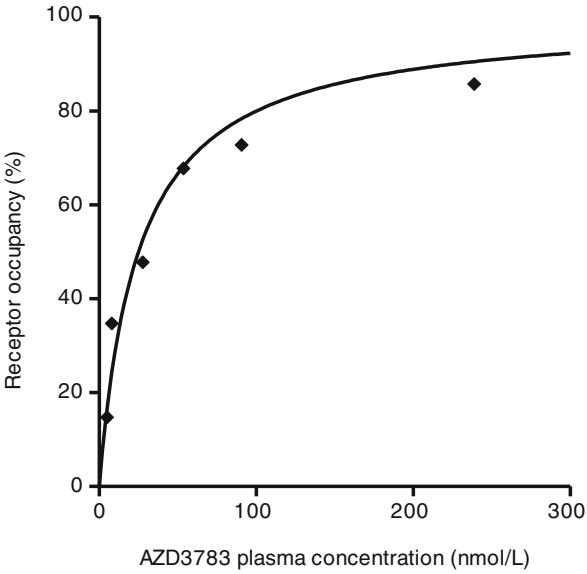

Fig. 1.4 The curvilinear relationship between plasma concentration of the 5HT1b receptor antagonist AZD3783 and target receptor occupancy in cynomolgus monkeys (Modification of figure in Varnäs et al. 2011)

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.

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, amyloid imaging in Alzheimer disease (AD) has been successful (Klunk et al. 2004; Rinne et al. 2010; Jack et al. 2011; Cselényi et al. 2012; Gelosa and Brooks 2012; Mathis et al. 2012). Building on the historical observation of amyloid deposits in AD brains postmortem, the reference radioligand [^{11}C]PIB was developed to allow for in vivo imaging (Klunk et al. 2004). Recently, numerous new and improved PET radioligands for amyloid imaging have been reported such as [^{18}F]AZD4694 (Cselényi et al. 2012; Gelosa and Brooks 2012; Mathis et al. 2012). The PET radioligands have initiated a series of studies on the pathophysiology and clinical diagnosis of AD (Jack et al. 2011). In addition, PET imaging of amyloid deposits in AD has shown potential to detect effects of drug treatments aimed at reducing the amyloid plaque burden (Rinne et al. 2010).

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. Recently imaging of the translocator protein (TSPO), which indicates activated microglia activity, has shown higher binding in schizophrenia (van Berckel et al. 2008; Doorduin et al. 2009) as well as correlation between TSPO binding and clinical symptoms of schizophrenia (Takano et al. 2010). Such development of new imaging markers could also be useful as efficacy biomarker in psychiatric drug development.

As discussed above, the discussed PET approaches can provide unique information to facilitate drug development. However, the success of the 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 time scale 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 dopamine 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 are 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 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. 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 preferable 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, but 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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PET Quantification in Neuropsychiatry

2

Michel Koole, Cindy Casteels, and Koen Van Laere

Contents

Abstract

PET quantification in neuropsychiatry focuses on the quantification of dynamic brain PET data. Starting from the basics of dynamic PET imaging, different methodologies are presented to extract time-dependent activity concentration for specific brain regions, both manually and automatically. The latter methodology uses predefined VOI templates and has the advantage of being operator independent. Once time-activity curves are available for the brain regions of interest,

M. Koole (✉)
Department of Nuclear Medicine and Molecular Imaging,
University Medical Center Groningen, University of Groningen,
Hanzeplein 1, Groningen 9700 RB, The Netherlands
e-mail: m.koole@umcg.nl

C. Casteels • K. Van Laere
Division of Nuclear Medicine, Department of Imaging and Pathology,
University Hospitals Leuven, KU Leuven, Leuven, Belgium

Nucleaire Geneeskunde en Moleculaire Beeldvorming,
Katholieke Universiteit Leuven, Universitair Ziekenhuis,
Herestraat 49, Leuven 3000, Belgium

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_2, © Springer-Verlag Berlin Heidelberg 2014

kinetic modeling is described using different compartmental models. These compartments represent the different states of the radiotracer such as the bound state. This way, the PET signal of specifically tracer can be separated from tracer that is free or nonspecifically bound. In this context, quantitative endpoints such as distribution volume and binding potential are discussed. Next to compartment modeling, graphical analysis techniques for reversible and irreversible tracer kinetics are discussed. These techniques are computational efficient and therefore suitable for creating parametric image data. These parametric image data allow voxel-wise statistical comparison of dynamic PET data. In terms of different options for the input function which is needed for tracer kinetic modeling, we discuss different possibilities including a reference tissue model. Finally, we elaborate on the advantages and limitations of a bolus/constant infusion approach to quantify tracer uptake under steady-state conditions.

2.1 Introduction

Functional neuroimaging has been an established research tool in neuropsychiatry demonstrating relationships between behavioral and neurobiological factors. Among functional imaging modalities, magnetic resonance spectroscopy (MRS) allows mapping of the distribution and concentration of metabolites involved in neuro-energetics and amino acid neurotransmission (Puts and Edden 2012). Especially glutamate/glutamine and γ-aminobutyric acid (GABA)/glutamine cycles appear to be sensitive to psychiatric disorders such as depression (Duman and Aghajanian 2012; Kendell et al. 2005; Sanacora et al. 2012; Walter et al. 2009). On the other hand, functional magnetic resonance imaging (fMRI) measures the neural activity indirectly and is able to study alternations in the steady-state functional connectivity related to major depressive disorder (Enzi et al. 2012; Greicius 2008; Kühn and Gallinat 2013).

Positron Emission Tomography (PET) and in particular brain PET enables the in vivo mapping of neurobiological functions such as blood flow (Kim et al. 2009), metabolism (Luyten et al. 2012), enzyme activity, neuro-receptor binding site density (Gérard et al. 2011), or occupancy (Van Laere et al. 2012). A typical PET study involves the injection of a radiotracer (a compound labeled with a radionuclide) into the venous blood stream of a subject. This radiotracer is delivered to the brain by the arterial flow, and after crossing the blood–brain barrier, it might bind reversibly or irreversibly to neuro-receptors and transporter vesicles or be metabolized by endogenous enzymes. On the other hand, if the tracer is inert, it would diffuse across the blood–brain barrier 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 and to study aspects of the complex interaction of several neurotransmitter systems in the brain (Kenneth et al. 2002; Savitz and Drevets 2013; Smith and Jakobsen 2009). Compared to MR-based techniques, PET has the particular advantage that it is highly sensitive and quantitative. Moreover, PET can quantify nano-molar molecular concentrations without any pharmacological effects. 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, 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. The most challenging to the development of in vivo PET tracers is actually the relatively small window of an appropriate combination of lipophilicity, molecular weight, and affinity.

Several radiolabeled molecules have been developed targeting specific receptor systems of interest in psychiatric disorders. Next to the serotonin and dopaminergic brain function, PET imaging of neuroinflammation and the endocannabinoid system has been proven very interesting especially in relation to schizophrenia (Doorduin et al. 2009; Wong et al. 2010) and alcohol dependence (Hirvonen et al. 2012). 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) (see Fig. 2.1) 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 (Seeger et al. 2003; Tu et al. 2011). This enzyme mainly hydrolyzes the important second messengers cyclic adenosine monophosphate (cAMP) (Bender and Beavo 2006; Fujishige et al. 1999), downregulating protein kinase A (PKA) activity (Nishi et al. 2008), and therefore the phosphorylation of various intracellular targets downstream of PKA such as DARPP-32 as an integrator of dopamine and glutamate signals (Surmeier et al. 2007). This role in striatal signaling has made PDE10A an enzyme of particular interest as it is likely involved in several neuropsychiatric and neurodegenerative disorders (Hebb and Robertson 2007; Siuciak and Strick 2006). For instance, PDE10A protein levels of Huntington's disease (HD) patients are reduced in the caudate nucleus and putamen compared with samples from age-matched controls (Hebb et al. 2004), while the progressive loss of PDE10A in two different HD transgenic mice strains correlates with progression and severity of motor symptoms. PDE10A inhibition may constitute a new approach for the treatment of HD and of other disorders with

altered MSN activity, such as schizophrenia (Grauer et al. 2009) and addiction (Menniti et al. 2006). In this context, a suitable PDE10A tracer that allows in vivo quantification of PDE10A would lead to a better understanding of the role of PDE10A activity in specific disease states. Moreover, this tracer could be used as a tool for early clinical evaluation of emerging PDE10A medication and may also present new diagnostic opportunities.

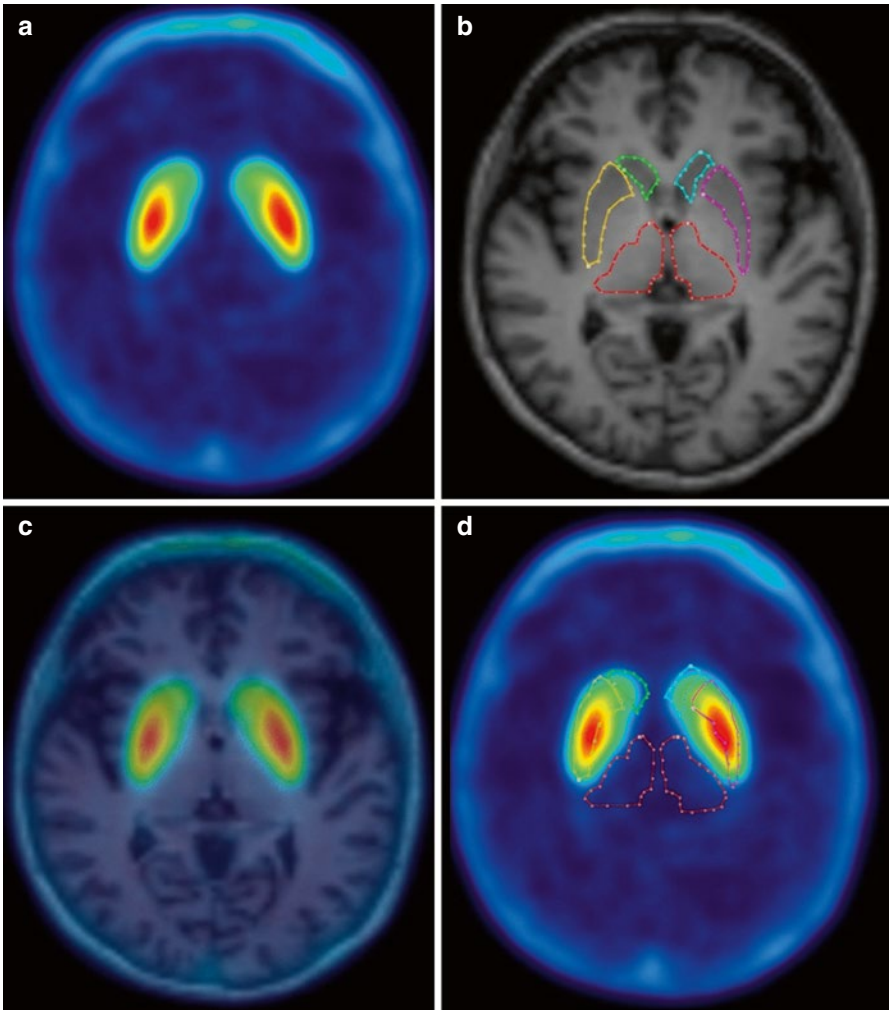

Fig. 2.1 Time-activity curves of a PET tracer targeting PDE10A (Van Laere et al. 2013) for the putamen, caudate nucleus, and thalamus. (**a**) represents an average SUV image (averaged over 60–90 min interval), (**b**) the corresponding T1-weighted MRI dataset with delineated brain structures, (**c**) the co-registered MR and PET dataset, and (**d**) the PET dataset with the brain structures transferred from the registered MR dataset

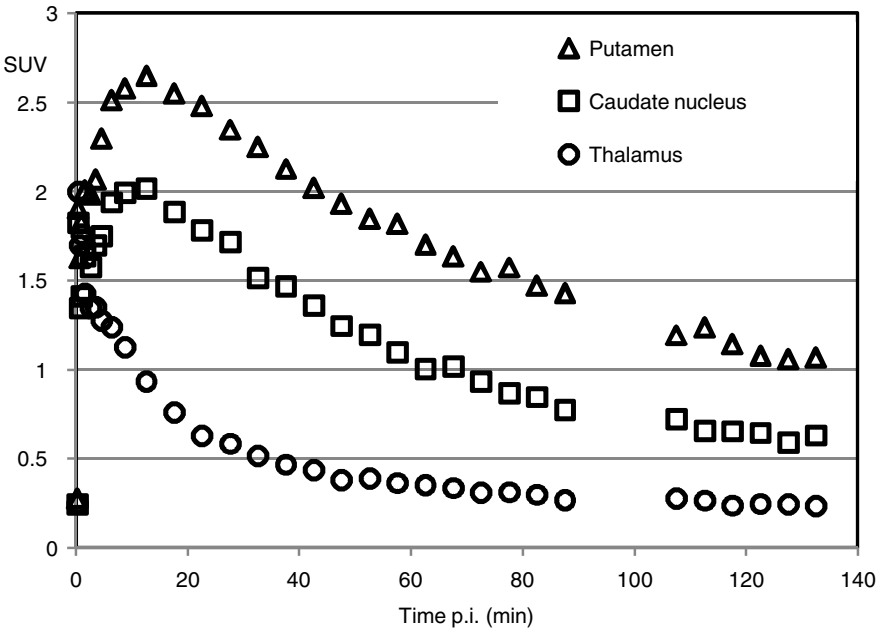

Fig. 2.1 (continued)

Since each PET probe is characterized by its particular kinetic behavior in the brain, understanding its dynamics and quantification is a critical component for designing imaging protocols, setting up clinical studies and interpreting results.

2.2 Dynamic PET Quantification

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 specifically bound, nonspecifically bound, and free 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 are to be considered. On the one hand, dynamic PET data characterize the kinetic behavior of the PET tracer in brain tissue, while, on the

other hand, an input function is needed to describe the time-dependent amount of tracer that is delivered to the brain tissue. Third, relatively complicated mathematical analysis will model the tracer kinetics on basis of the dynamic PET data and an input function.

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). These TACs form the basis in 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. This way high-resolution anatomical MR information can be used to facilitate manual delineation of the appropriate volume-of-interest (VOI) especially when the PET data itself provide limited anatomical landmarks (see Fig. 2.1).

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 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 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, white matter, and cerebrospinal fluid. Because of differences in activity concentration between these tissue compartments, the PET signal of the target tissue is confounded. One can correct for this partial volume effect by using spatial distribution maps for the white matter, grey matter, and cerebrospinal fluid 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. 2007). This way, the actual tracer uptake per unit grey matter 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.

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 department 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 of each compartment 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 analog 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.

The first compartmental model that was described is the diffusion model for regional cerebral perfusion PET imaging (Frackowiak et al. 1980).

2.3 Compartmental Modeling of Brain Perfusion

PET can be used to study neuronal activation by measuring the changes in regional cerebral perfusion and local large vessel blood flow since changes in neuronal activity are very closely related to perfusion. These PET studies use blood flow tracers like water or butanol which enter brain tissue via diffusion Perhaps it is worthwhile noticing that the term perfusion is used to distinguish the blood flow per unit tissue from the physical flow (ml/min), although the term flow and perfusion has been used interchangeably in the literature.

Kety and Schmidt first described this basic exchange model for nonradioactive substances using the Fick principle (Kety and Schmidt 1948). The Fick principle states that when a fluid with known flow F runs through a compartment which is in steady state, the rate at which substance is extracted from the fluid by the compartment is equal to the difference in concentration when entering and leaving the compartment. Applying this principle to the passage of tracer within capillaries and considering the smallest scale such that the blood compartment represents a single capillary and the compartment is the tissue in the immediate vicinity (see Fig. 2.2), the change in tracer concentration in tissue C_T can be described as difference in tracer concentration between arterial blood C_A and venous blood C_V:

$$\frac{dC_T(t)}{dt} = F\left(C_A(t) - C_V(t)\right). \tag{2.1}$$

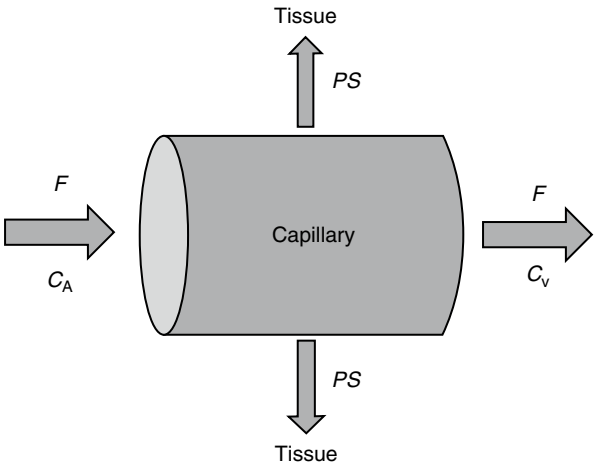

Fig. 2.2 Schematic overview of the exchange of a substance between capillary and tissue where C_A denotes the concentration of a substance in arterial blood, C_V the concentration in the venous blood, F the flow (units per min), and PS the product of the permeability P (cm/min) and the surface S (cm^2/g) of the capillary

In this context, the partition coefficient ρ was defined as the ratio of the tissue to venous blood concentration. For tracers with high extraction, one can assume that tracer concentration in the venous blood will be in equilibrium with the tissue concentration. Therefore, the tracer concentration in tissue C_T is described by

$$\frac{dC_T(t)}{dt} = FC_A(t) - \frac{F}{\rho}C_T(t). \tag{2.2}$$

Since tracer concentration can be measured in arterial blood and in tissue and one typically assumes that the same input function is valid for all brain tissue, Eqn. (2.2) can be solved for blood flow and partition coefficient as a function of tissue and arterial blood concentration. Note that this model is only valid when blood flow remains constant during PET imaging and the PET tracer is inert and rapidly and freely diffusible in brain tissue.

2.4 One-Tissue Compartmental Model

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. The distribution volume 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 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

$$C_{PET}(t) = (1 - V_B) C_T(t) + V_B C_B(t). \tag{2.3}$$

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. For the human brain, the assumption that blood occupies about 5 % of the brain volume is valid (Phelps et al. 1979), corresponding to a V_B value of about 0.05.

Considering a one-tissue compartment model for describing the bidirectional flux of tracer between 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 blood to tissue is $K_1 C_A$, while the tracer flux from tissue to blood is $k_2 C_T$. Therefore, the net tracer flux into tissue is describes as

$$\frac{dC_T(t)}{dt} = K_1 C_A(t) - k_2 C_T(t). \tag{2.4}$$

$C_T(t)$ 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 $C_A(t)$.

If we consider tracer exchange on its smallest scale between a blood capillary and the surrounding tissue (see Fig. 2.2), the fraction that is extracted during one capillary pass is equal to

$$E = \frac{C_A - C_V}{C_A}. \tag{2.5}$$

If we take into account the boundary condition that during the first pass of tracer through tissue the tracer flux from tissue to blood is effectively zero because $C_T(0) = 0$ and apply this boundary condition to (2.1) and (2.4), the following equation is valid:

$$\frac{dC_T(t)}{dt} = K_1 C_A(t) = (FE) C_A(t). \tag{2.6}$$

This indicates that the delivery rate constant K_1 equals the product of blood flow and first pass extraction fraction. Considering the capillary as a cylindrical tube, the extraction fraction can be interpreted using the Renkin-Crone capillary model (Crone 1963; Renkin 1959) which states that

$$E = \frac{C_A - C_V}{C_A} = 1 - \exp\left(-\frac{PS}{F}\right). \tag{2.7}$$

In this equation, P is the permeability of the capillary membrane and S is the capillary surface area per unit tissue mass. Using this approximation the following equation for K_1 is valid:

$$K_1 = F\left(1 - \exp\left(-\frac{PS}{F}\right)\right). \tag{2.8}$$

This means that K_1 is closely related to blood flow when the extraction fraction is large ($PS >> F$) 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 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:

$$V_T = \frac{C_T(t)}{C_A(t)} = \frac{K_1}{k_2}. \tag{2.9}$$

2.5 Two- and Three-Tissue Compartment Model

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:

$$\frac{B}{F} = \frac{B_{max}}{K_d + F}. \tag{2.10}$$

In this equation, B represents the tracer concentration bound to the receptor, and 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 $F << K_d$, resulting in the following equation:

$$\frac{B}{F} = \frac{B_{max}}{K_d}. \tag{2.11}$$

This equation actually corresponds to the binding potential (BP) defined as the product of receptor density and affinity. 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 blood–brain barrier by passive diffusion, one can reasonably assume that under equilibrium conditions, the concentration free tracer in arterial plasma equals the concentration free tracer in brain tissue. However, to estimate the concentration of specifically bound tracer, a one-tissue compartment model needs to be extended to a kinetic model containing multiple compartments. The most generalized kinetic model describing ligand-receptor kinetics consists of 3-tissue compartments (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 arterial plasma and tissue through the blood–brain barrier, and 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 three-tissue compartment model, the activity concentration in brain tissue $C_T(t)$ is given by

$$C_T(t) = C_F(t) + C_{NS}(t) + C_S(t). \tag{2.12}$$

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:

$$\frac{dC_F(t)}{dt} = K_1 C_P(t) - k_2 C_F(t) - k_3 C_F(t) + k_4 C_S(t) - k_5 C_F(t) + k_6 C_{NS}(t), \tag{2.13}$$

$$\frac{dC_S(t)}{dt} = k_3 C_F(t) - k_4 C_S(t), \tag{2.14}$$

$$\frac{dC_{NS}(t)}{dt} = k_5 C_F(t) - k_6 C_{NS}(t). \tag{2.15}$$

Considering the equilibrium condition where no net exchange between compartments is observed, gradients in (2.13), (2.14) and (2.15) can be set to zero. Substitution

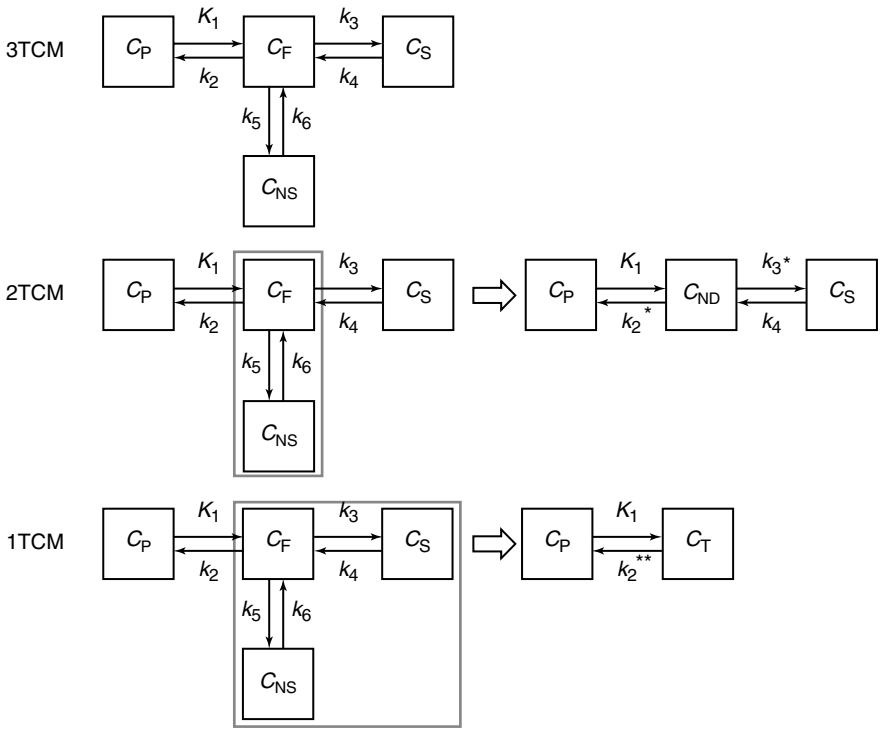

Fig. 2.3 Overview of the different compartment models: a three-tissue compartment model (3TCM) with C_P the activity concentration in arterial plasma, C_F the concentration of free radioligand in tissue, C_S the concentration of tracer that is bound specifically and C_{NS} the concentration of tracer 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 represents the exchange rate constants between the free tracer and nonspecific binding. 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 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

of (2.14) and (2.15) in (2.13) yields the following equations for the distribution volume of free tracer, specific bound tracer, and nonspecific bound tracer:

$$V_F = \frac{C_F(t)}{C_P(t)} = \frac{K_1}{k_2}, \tag{2.16}$$

$$V_S = \frac{C_S(t)}{C_P(t)} = \frac{k_3}{k_4} V_F, \tag{2.17}$$

$$V_{NS} = \frac{C_{NS}(t)}{C_P(t)} = \frac{k_5}{k_6} V_F. \tag{2.18}$$

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

$$V_T = V_F + V_{NS} + V_S = \frac{K_1}{k_2}\left(1 + \frac{k_3}{k_4} + \frac{k_5}{k_6}\right). \tag{2.19}$$

If we consider equilibrium conditions for (2.14) and compare with (2.11), the following equation is valid:

$$\frac{k_3}{k_4} = \frac{V_S}{V_F} = \frac{C_S}{C_F} = \frac{B}{F} = \frac{k_{on} B_{max}}{k_{off}} = \text{BP}. \tag{2.20}$$

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 with the following differential equations describing this model:

$$C_T(t) = C_{ND}(t) + C_S(t), \tag{2.21}$$

$$\frac{dC_{ND}(t)}{dt} = K_1 C_P(t) - k_2^* C_{ND}(t) - k_3^* C_{ND}(t) + k_4 C_S(t), \tag{2.22}$$

$$\frac{dC_S(t)}{dt} = k_3^* C_{ND}(t) - k_4 C_S(t). \tag{2.23}$$

The corresponding tissue distribution volume is given by

$$V_T = V_{ND} + V_S = \frac{K_1}{k_2^*}\left(1 + \frac{k_3^*}{k_4}\right). \tag{2.24}$$

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

$$\text{BP}_{ND} = \frac{C_S}{C_{ND}} = \frac{V_S}{V_{ND}} = \frac{k_3^*}{k_4}. \tag{2.25}$$

It is worthwhile noticing that the non-displaceable binding potential BP_{ND} is defined relative to the concentration non-displaceable radiotracer, whereas the binding potential BP is defined relative to the concentration 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 two-tissue compartment model 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 two-tissue compartment 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 single-tissue compartment is possible where kinetics described by (2.4) and (2.9) are valid.

If a specific brain region is devoid of receptors, the brain tissue of that region can be considered reference tissue. Consequently, BP_{ND} can be estimated for any target region using the tissue distribution volumes of reference and target tissue as follows:

$$BP_{ND} = \frac{C_S}{C_{ND}} = \frac{C_T - C_R}{C_R} = \frac{V_T - V_R}{V_R}. \tag{2.26}$$

C_T and V_T, respectively, represent the tracer concentration and distribution volume of the target region, while C_R and V_R, respectively, represent those of the reference region. It is worthwhile noticing that in this context $\frac{V_T(t)}{V_R(t)}$ is often termed the distribution volume ratio (DVR) such that $BP_{ND} = DVR - 1$.

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 (2.26) 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:

$$BP_{ND} = \frac{V_T - V_R}{V_R} = \frac{V_S}{V_F + V_{NS}} = \frac{BP}{\left(1 + \frac{V_{NS}}{V_F}\right)}. \tag{2.27}$$

Assuming that the level of nonspecific binding is relatively constant, the bias should be limited to only a scaling factor.

2.6 Model Selection

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. For tracers that cross the blood–brain barrier via passive diffusion, a low molecular weight is mandatory. Lipophilicity of the tracer should be within the small range of allowing adequate permeability of the blood–brain barrier while avoiding unacceptable binding to plasma proteins or high levels of nonspecific binding in the brain. Finally, a high affinity ligand is needed to provide high levels of specific binding to the receptor. However, affinity of the tracer should be such that the opposing goals of high specific binding and washout of the brain are balanced.

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 one-tissue compartment model would be an appropriate model.

If a one-tissue model 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 time-activity curve. 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 distribution volume V_T, BP, or BP_{ND}. In terms of transport rate constants, 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 of (2.23) 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 glucose analog 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 post injection, dephosphorylation (k_4) of the FDG-6-PO4 is not observed (Lucignani et al. 1993) and the assumption that $k_4 = 0$ is valid.

For radioligands with irreversible kinetic behavior, 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, taking into account (2.28), 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 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 radio-metabolites 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 radio-metabolites 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 (Casteels et al. 2012) 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.

To illustrate reversible tracer kinetics, we present sample kinetic data of [^{11}C] verapamil (Fig. 2.4a), a PET tracer that allows the in vivo assessment of P-glycoprotein (P-gp) functionality in the blood–brain barrier (BBB). P-gp acts as an efflux pump playing a neuroprotective role by preventing many structurally divergent lipophilic molecules from entering the brain. However, it can also be a determinant factor in the treatment response to potential antipsychotic drugs. Suspected to be involved in several neurodegenerative and psychiatric brain disorders, P-gp function is reported to be regionally increased for patients with chronic schizophrenia (De Klerk et al. 2010) and major depressive disorder (De Klerk et al. 2009). Figure 2.4a compares a 1TCM and 2TCM describing the tracer kinetics of

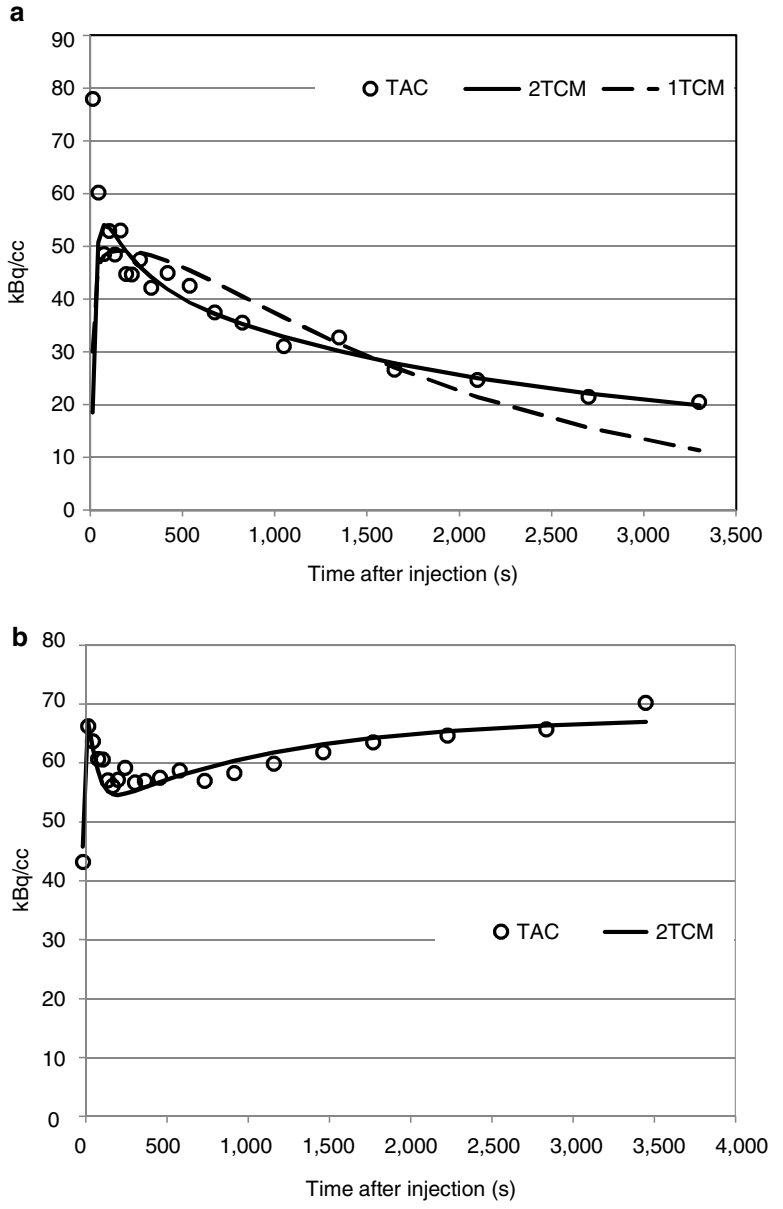

Fig. 2.4 (**a**) Comparison of fitting results of 1TCM and 2TCM fitted to the whole brain TAC of [^{11}C]verapamil using an arterial input function corrected for metabolites. (**b**) Representative TAC of [^{11}C]5-HTP uptake in a rodent brain, demonstrating irreversible tracer kinetics together with the fitting results of 2TCM with k_4 set to zero using an arterial input function corrected for metabolites

the whole brain uptake. The graph shows that 2TCM is clearly the more appropriate kinetic model for this particular PET tracer compared to 1TCM.

As an example of irreversible tracer kinetics, we evaluated the uptake of 5-hydroxy-L-[β-^{11}C]tryptophan ([^{11}C]5-HTP) in the rodent brain (Visser et al. 2013). [^{11}C]5-HTP will undergo the same conversions as 5-HTP which is the substrate for the enzymatic action of aromatic amino acid decarboxylase (AADC) for the production of 5-HT (Visser et al. 2011). Trapping rate of [^{11}C]5-HTP provides a quantitative measure for serotonin synthesis. Figure 2.4b presents the tracer kinetics of [^{11}C]5-HTP in the rodent brain, clearly demonstrating irreversible kinetics together with the fitting results of 2TCM with k_4 set to zero.

2.7 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. 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.

Demonstrating this approach for 1TCM, both sides of (2.4) can be integrated and written as

$$C_T(T) = K_1 \int_0^T C_P(t)\,dt - k_2 \int_0^T C_T(t)\,dt. \tag{2.29}$$

If we divide both sides by $C_T(T)$ and k_2 while taking into account that $V_T = \frac{K_1}{k_2}$, we get the following equation:

$$\frac{\int_0^T C_T(t)\,dt}{C_T(T)} = V_T \frac{\int_0^T C_T(t)\,dt}{C_T(T)} - \frac{1}{k_2}. \tag{2.30}$$

This form has originally been proposed by (Logan et al. 1990) where V_T can be identified with the slope of the resulting straight line. Actually, for this approach no explicit assumption is needed in terms of compartmental model. The only prerequisite is that the tracer demonstrates reversible binding such that V_T is a valid endpoint. For a true 1TCM, the Logan plot is linear at all times. In case of a 2TCM, the Logan plot becomes linear at later time points such that the slope of this linear part also provides an estimate for the tissue distribution volume V_T. A representative Logan plot is presented in Fig. 2.5a for the same kinetic data of [^{11}C]verapamil as shown in Fig. 2.4a. V_T estimates using the Logan plot are susceptible to

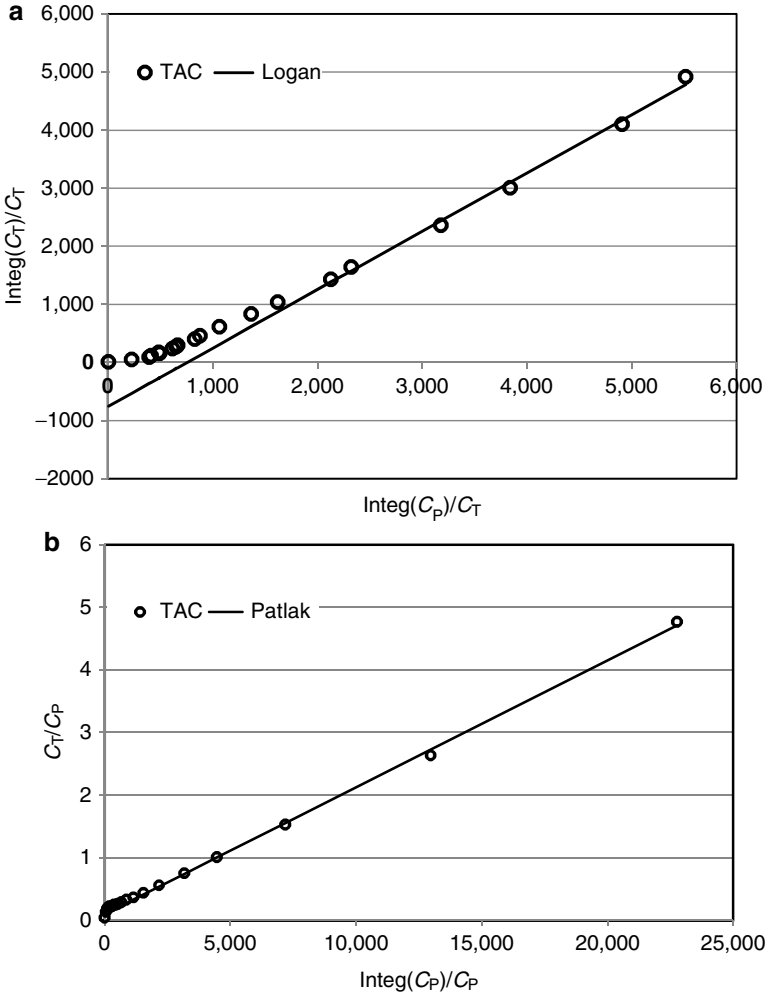

Fig. 2.5 (**a**) Logan plot for whole brain TAC of [^{11}C]verapamil using an arterial input function corrected for metabolites. (**b**) Patlak plot for whole brain TAC of [^{11}C]5-HTP in a rodent brain using an arterial input function corrected for metabolites

noise-induced bias. Several strategies have been proposed to decrease this bias at the expense of increased variability (Ichise et al. 2002; Logan et al. 2011).

While the Logan plot allows a linear regression analysis for a tracer demonstrating reversible binding, a graphical analysis approach can also be derived for a tracer with irreversible binding kinetics. Setting $k_4 = 0$ in (2.22) and (2.23), one gets the following equations:

$$\frac{\mathrm{d}C_{\mathrm{ND}}(t)}{\mathrm{d}t} = K_1 C_{\mathrm{P}}(t) - k_2 C_{\mathrm{ND}}(t) - k_3 C_{\mathrm{ND}}(t), \tag{2.31}$$

$$\frac{\mathrm{d}C_{\mathrm{S}}(t)}{\mathrm{d}t} = k_3 C_{\mathrm{ND}}(t). \tag{2.32}$$

If we assume that $C_{\mathrm{ND}}(t)$ and are in equilibrium, meaning that there is no net tracer transfer between the two compartments, the derivative in (2.31) can be set to zero and both sides of (2.32) can be integrated, yielding the following equation for the tracer concentration in tissue:

$$C_{\mathrm{T}}(T) = C_{\mathrm{ND}}(T) + C_{\mathrm{S}}(T) = V_{\mathrm{ND}}(T) C_{\mathrm{P}}(T) + \frac{K_1 k_3}{k_2 + k_3} \int_0^T C_{\mathrm{P}}(t)\,\mathrm{d}t. \tag{2.33}$$

If both sides of (2.33) are divided by the tracer concentration in plasma $C_{\mathrm{P}}(t)$, the following representation of the measured data is obtained:

$$\frac{C_{\mathrm{T}}(T)}{C_{\mathrm{P}}(T)} = V_{\mathrm{ND}}(T) + K_{\mathrm{i}} \frac{\int_0^T C_{\mathrm{P}}(t)\,\mathrm{d}t}{C_{\mathrm{P}}(T)}. \tag{2.34}$$

This linearization is called the Patlak plot. When tracer concentration of non-displaceable compartment and plasma are in equilibrium, the Patlak plot becomes linear and the metabolic rate K_{i} can be estimated as the slope of the linear part of the Patlak plot while the intercept provides an estimate for the distribution volume of the non-displaceable compartment. As an example, a Patlak analysis of the same dynamic PET data of [^{11}C]5-HTP, as presented in Fig. 2.4b, is shown in Fig. 2.5b.

Patlak analysis can be further simplified if the intersect is neglected and both sides of (2.34) are multiplied by $\frac{C_{\mathrm{P}}(T)}{\int_0^T C_{\mathrm{P}}(t')\,\mathrm{d}t}$ (Thie 1994). Thus, the metabolic rate can be approximated by

$$K_{\mathrm{i}} \approx \frac{C_{\mathrm{T}}(T)}{\int_0^T C_{\mathrm{P}}(t)\,\mathrm{d}t}. \tag{2.35}$$

If we assume that the PET signal is mainly determined by the tissue signal $C_{PET}(T) \cong C_T(T)$, K_i can be approximated by the fractional uptake ratio FUR defined as

$$\mathrm{FUR}(T) = \frac{C_{\mathrm{PET}}(T)}{\int_0^T C_P(t)\,\mathrm{d}t}. \tag{2.36}$$

FUR is also closely related to the standardized uptake value (SUV) defined as

$$\mathrm{SUV}(T) = \frac{C_{\mathrm{PET}}(T)}{\frac{\text{Injected Dose}}{\text{Weight}}}. \tag{2.37}$$

If we define $\frac{\text{Injected Dose}}{\text{Weight}}$ as a concentration C_{WB}, we can introduce a distribution volume V_{WB} defined as $V_{WB} = \frac{C_{WB}}{C_P(0)}$ and a plasma clearance rate k_p for time T defined as $k_P = \frac{C_P(0)}{\int_0^T C_P(t)\,\mathrm{d}t}$; the FUR is related to SUV by the relation

$$\mathrm{FUR}(T) = V_{WB} k_P(T) \mathrm{SUV}(T). \tag{2.38}$$

Therefore, FUR can be considered an approximation to the Patlak slope while FUR and SUV are proportional. Major disadvantage of SUV is that varying plasma dynamics are not taken into account. FUR and SUV have been successfully validated for the quantification of the specific binding of the CB1R tracer [^{18}F]MK-9470 in the human brain (Sanabria-Bohórquez et al. 2010).

2.8 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 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 carotids. 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 (Zanotti-Fregonara et al. 2011a). 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 is 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. 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; Lammertsma et al. 1996). 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 (Mourik et al. 2009; Zanotti-Fregonara et al. 2009, 2011b, c) 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 2003; 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. 2012). 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 (Visvikis et al. 2004).

We have already described that BP_{ND} can be obtained from the DVR of the target region with specific tracer binding relative to the reference region devoid of specific binding if similar non-displaceable tracer concentration is assumed for both target and reference region. However, BP_{ND} can also be estimated from a reference tissue model where the TAC of the reference region is used as indirect input function to the kinetic model of the target region (Hume et al. 1992). This way neither blood samples nor labor-intensive radio-metabolite analysis is needed such that dependency on reference devices such as well counter or dose calibrator is completely avoided.

Instead of elaborating on a full reference tissue model which is based on 2TCM to describe tracer kinetics of a target region (Lammertsma et al. 1996), we will discuss 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. If we consider a 1TCM for target and reference region, we get the following equations (see (2.4)):

$$\frac{\mathrm{d}C_{\mathrm{T}}(t)}{\mathrm{d}t} = K_1 C_{\mathrm{P}}(t) - k_{2\mathrm{a}} C_{\mathrm{T}}(t), \tag{2.39}$$

$$\frac{\mathrm{d}C_{\mathrm{R}}(t)}{\mathrm{d}t} = K_{1\mathrm{R}} C_{\mathrm{P}}(t) - k_{2\mathrm{R}} C_{\mathrm{R}}(t). \tag{2.40}$$

$C_P(t)$ 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 kinetics 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 by taking into account (2.9), (2.24), and (2.25):

$$V_{\mathrm{ND}} = \frac{K_1}{k_2} = \frac{K_{1\mathrm{R}}}{k_{2\mathrm{R}}}, \tag{2.41}$$

$$V_{\mathrm{T}} = \frac{K_1}{k_2}\left(1 + \mathrm{BP}_{\mathrm{ND}}\right) = \frac{K_1}{k_{2\mathrm{a}}}, \tag{2.42}$$

$$k_{2\mathrm{a}} = \frac{k_2}{1 + \mathrm{BP}_{\mathrm{ND}}}. \tag{2.43}$$

Solving (2.40) for $C_{\mathrm{P}}(t)$ gives the following expression for the tracer concentration in plasma:

$$C_{\mathrm{P}}\left(t\right) = \frac{1}{K_{1\mathrm{R}}}\left(\frac{\mathrm{d}C_{\mathrm{R}}\left(t\right)}{\mathrm{d}t} + k_{2\mathrm{R}}C_{\mathrm{R}}\left(t\right)\right). \tag{2.44}$$

Substitution of (2.44) in (2.39) and integrating both sides yields the following equation:

$$C_{\mathrm{T}}\left(T\right) = \frac{K_1}{K_{1\mathrm{R}}}C_{\mathrm{R}}\left(T\right) + \frac{K_1}{K_{1\mathrm{R}}}k_{2\mathrm{R}}\int_0^T C_{\mathrm{R}}\left(t\right)\mathrm{d}t - k_{2\mathrm{a}}\int_0^T C_{\mathrm{T}}\left(t\right)\mathrm{d}t. \tag{2.45}$$

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

$$C_{\mathrm{T}}\left(T\right) = RC_{\mathrm{R}}\left(T\right) + k_2\int_0^T C_{\mathrm{R}}\left(t\right)\mathrm{d}t - k_{2\mathrm{a}}\int_0^T C_{\mathrm{T}}\left(t\right)\mathrm{d}t. \tag{2.46}$$

Expression (2.46) is similar as the multilinear reference tissue model (MRTM) (Ichise et al. 2003) and computationally efficient for voxel-wise estimation of $\mathrm{BP}_{\mathrm{ND}}$ image data. On the other hand, $\mathrm{BP}_{\mathrm{ND}}$ 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 radio-metabolites 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 pre-clinical 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.

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 reference tissue model can be further simplified and the DVR of target tissue relative to reference tissue as index for specific binding can be approximated by the SUV ratio of the target region relative to the reference region:

$$\mathrm{DVR} = \frac{V_T}{V_R} \cong \frac{C_T(T)}{C_R(T)} \cong \frac{C_{T,PET}(T)}{C_{R,PET}(T)} = \frac{\mathrm{SUV}_T(T)}{\mathrm{SUV}_R(T)} = \mathrm{SUVR}(T). \tag{2.47}$$

As an example, SUV ratios relative to the cerebellum have been used to quantify the brain retention of the Pittsburgh compound B (PIB), a PET tracer binding to amyloid deposits (Lopresti et al. 2005). However, this approximation needs validation with full kinetic modeling for each tracer separately.

2.9 Steady-State PET Measurements Using a Bolus/Constant Infusion

The tissue distribution volume V_T is defined as the ratio at equilibrium between tissue and plasma tracer concentration. Although equilibrium is not reached after fast bolus injection of a tracer, V_T can be estimated using dynamic PET scanning, plasma input function, and compartmental modeling (see (2.9), (2.19), and (2.24)). If a region without specific binding is available, the binding potential BP_{ND} can be estimated from the V_T values of the target and reference region (see (2.26)). Following a tracer bolus injection, tissue to plasma ratios and tissue ratios between different regions eventually become constant over time in case of reversible tracer binding. The tissue to plasma ratio of this transient equilibrium is called the apparent distribution volume V_{APP}. V_{APP} is biased compared to the true tissue distribution volume V_T because at transient equilibrium, tracer concentrations in blood and tissue are changing due to plasma clearance of tracer activity although ratios remain constant. In order to achieve constant tracer concentrations in tissue and blood, a constant infusion of the radiotracer can be given. Once steady-state conditions are reached, V_T can easily be determined as the ratio between the tissue concentration measured with a single PET scan $C_{T,PET}$ and the plasma activity of the intact tracer estimated using a single blood sample C_P:

$$V_T = \frac{C_{T,PET}}{C_P}. \tag{2.48}$$

In practice, multiple short PET scans and blood samples are acquired to demonstrate constant radioactivity levels in specific brain regions and in blood. If a brain region with no specific binding is available, no blood measurements are necessary and binding potential BP_{ND} can be calculated relative to the reference region as follows:

$$BP_{ND} = \frac{C_{T,PET} - C_{R,PET}}{C_{R,PET}}, \tag{2.49}$$

with $C_{R,PET}$ representing the PET tracer concentration measured in the reference region.

Major advantage of a bolus/infusion approach is the simple and straightforward quantification represented by (2.48) and (2.49) for which no model assumption is

required in terms of compartmental modeling. Using a single tracer synthesis, a bolus/infusion design provides powerful within-scan methodology for detecting changes in binding levels between control and stimulus conditions and measuring both exogenously and endogenously induced displacement of tracer binding (Carson et al. 1997). Additional advantage of a bolus/infusion approach is the reduced study time compared to two sequential bolus injection protocols. Furthermore, concentration differences between the arterial and venous blood compartment are likely to be small at equilibrium. This means that if blood activity measurements are needed for quantification, venous sampling might be adequate instead of the more invasive arterial sampling. Possible drawback is that only V_T can be estimated when measuring at equilibrium. Compartmental modeling of dynamic bolus studies on the other hand allows the estimation of individual rate parameters, such as K_1, as a measure of blood flow. One has to keep in mind however that the estimates for these individual rate constants can be biased by errors in the input function or by wrong assumptions about the selected model for the compartmental analysis. V_T on the other hand is generally accepted as a robust quantitative endpoint for PET neuro-receptor studies.

A priming bolus injection can precede the constant tracer infusion to accelerate the process of establishing true equilibrium. This acceleration of reaching steady state is important because of the short half-life of PET tracers. In practice, a bolus/infusion approach is better suited for PET studies with [^{18}F]-labeled tracers or tracers with even a longer half-life, while the statistical quality of bolus injection studies is expected to be better for short-lived PET tracers. However, optimization of the bolus/infusion protocol in terms of timing and noise reduction should increase the sensitivity for the detection of biological signals (Watabe et al. 2000).

Of particular interest is the optimal ratio between priming bolus and infusion dose which is region dependent since regions with high specific binding and therefore slower kinetics require longer time to reach equilibrium (Pinborg et al. 2000). Based on data from previous bolus injection experiments, the optimal dose balance between priming bolus and infusion can be estimated. However, this optimal balance can be subject to individual and group differences due to changes in peripheral tracer metabolism.

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3 Pharmacological Interventions That Have the Potential to Alter Neurotransmitter Levels in the Human Brain

Fokko J. Bosker, Janine Doorduin, Minke E. Jongsma, Anniek K.D. Visser, Joanna Udo de Haes, Thomas I.F.H. Cremers, Kieran Rea, Robin Tyacke, David J. Nutt, Johan A. den Boer, and Ben H.C. Westerink

Contents

F.J. Bosker, PhD (✉)
University Center for Psychiatry, University Medical Center Groningen (UMCG), Hanzeplein 1, Groningen 9713 GZ, The Netherlands
e-mail: f.j.bosker@umcg.nl

J. Doorduin, PhD • A.K.D. Visser, MSc
Department of Nuclear Medicine and Molecular Imaging, University of Groningen, University Medical Center Groningen, Hanzeplein 1, Groningen 9713 GZ, The Netherlands

M.E. Jongsma, PhD • T.I.F.H. Cremers, PhD • B.H.C. Westerink, PhD
Department of Biomonitoring and Sensoring, University of Groningen, University Center for Pharmacy, Antonius Deusinglaan 1, Groningen 9713 AV, The Netherlands

J.U. de Haes, PhD
Clinical Pharmacology, Merck Sharp and Dohme, Molenstraat 110, Oss 5342 CC, The Netherlands

K. Rea, PhD
Pharmacology Department, National University of Ireland, University Road, Galway, Ireland

R. Tyacke, PhD • D.J. Nutt, MD, PhD
Neuropsychopharmacology Unit, Imperial College London, South Kensington Campus, London W12 0NN, UK

J.A. den Boer, MD, PhD
PRA International, Zuidlaren, The Netherlands

Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen (UMCG), Hanzeplein 1, Groningen 9713 GZ, The Netherlands

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_3, © Springer-Verlag Berlin Heidelberg 2014

Abstract

Monitoring of neuronal activity in vivo is one of the greatest challenges in neuropsychiatry. Theoretically, levels of intra and extra synaptic neurotransmitters can be estimated through competition with suitable PET ligands at their receptors. When validating candidate receptor PET ligands for competition studies it is essential to manipulate neurotransmitter levels in vivo using interventions with drugs that have negligible affinity for the receptors aimed at and are allowed to be used in humans. Neurochemical evidence for pharmacological interventions mostly originates from microdialysis studies in animals. First we will give a brief historical and methodological overview of the microdialysis technique. We will focus on serotonin and present microdialysis data of various pharmacological interventions in rats that have the potential to alter serotonin levels in humans. Our primary aim is to broaden the arsenal of pharmacological tools for PET competition studies, in particular because the type of neuronal manipulation might be a critical factor. Microdialysis of glutamate is briefly discussed, merely to illustrate some of the shortcomings of the technique.

3.1 Introduction

Monitoring of neuronal activity in vivo is one of the greatest challenges in neuropsychiatry. The brain is a very complex organ protected by a blood–brain barrier, and direct neurobiological assessment is difficult because invasive techniques are normally not allowed in humans. Measurement of neurotransmitters and their metabolites in cerebrospinal fluid, receptor binding of blood platelets or white blood cells, and so-called neuroendocrine strategies have been adopted as substitutes for assessing neurobiological function (Syvälahti 1994), but these are relatively crude and indirect approaches to extract information from the normal or pathological brain. Postmortem studies may have some merit (Stockmeier 1997), but the progressive character of many neuropsychiatric diseases and the fact that many patients

have been treated with drugs for a substantial part of their lives limit the worth of most postmortem data (not to mention the effects of dying tissue on brain physiology, such as inactivation of enzymes and an instantaneous and massive release of neurotransmitters). On the other hand, neuroimaging has matured with a still growing number of receptor-specific PET ligands becoming available. This will likely render the indirect assessment of cerebral receptor function via blood cells or neuroendocrine strategies largely obsolete in the near future. However, neuronal function is characterized not only by the number and affinity of receptors but also by the concentrations of neurotransmitters in and outside the synaptic cleft. Theoretically, levels of intra- and extrasynaptic neurotransmitters can be estimated through competition with suitable PET ligands at their receptors. For dopamine this approach seems successful, as witnessed by a significantly reduced ^{11}C-raclopride binding potential for dopamine D_2 receptors in the basal ganglia when increasing the levels of the monoamine via pharmacological (e.g., methylphenidate; Volkow et al. 1994; Udo de Haes et al. 2005a) or psychological (e.g., monetary reward task; Zald et al. 2004) challenges. Yet, in combined PET and microdialysis studies in monkeys, it was demonstrated that modification of ^{11}C-raclopride binding is not directly related to synaptic dopamine concentrations but also depends on the mechanism of the neuronal manipulation (Tsukada et al. 1999, 2000). Imaging of synaptic neurotransmission using in vivo binding competition techniques has been critically reviewed by Laruelle (2000). He concluded that the relationship between the magnitude of changes in binding potential measured with PET or SPECT and the magnitude of changes in dopamine concentration measured by microdialysis supports the use of these noninvasive techniques to measure changes in neurotransmission, but also noted that several observations remain unexplained.

For serotonin the competition approach appeared less successful (for review, see Paterson et al. 2010). For instance, competition studies in humans, monkeys, and rodents using the 5-HT_{1A} receptor ligand ^{18}F-MPPF were not conclusive, showing significant effects only when serotonin levels were massively increased (>30×) using the 5-HT releaser (and reuptake inhibitor) fenfluramine in rats (Udo de Haes et al. 2002, 2005b, 2006). It came rather unexpected that a similar fenfluramine challenge in conscious monkeys had no effect on the ^{18}F-MPPF binding potential (Udo de Haes et al. 2006). However, a combined β-probe and microdialysis study could demonstrate significantly decreased ^{18}F-MPPF binding in rat hippocampus following a fenfluramine challenge (Zimmer et al. 2002). Interestingly, the positive results with ^{18}F-MPPF were both obtained from rats, using alternative imaging techniques such as the β-probe (Zimmer et al. 2002) and ex vivo autoradiography (Udo de Haes et al. 2005b).

Lately more promising results were reported when targeting at 5-HT_{1B} receptors using ^{11}C-AZ10419369 (Finnema et al. 2010, 2012), but 5-HT_{1A} receptor agonists such as ^{11}C-CUMI-101 might also be of interest (Milak et al. 2011). One can only speculate why the PET competition approach has been more successful for dopamine than for serotonin. Maybe the answer can be found in the much higher extracellular levels of dopamine in the basal ganglia, different cellular locations of the receptors, or physicochemical properties of the PET ligands.

When validating candidate receptor PET ligands for competition studies, it is essential to manipulate neurotransmitter levels in vivo using interventions with drugs that have negligible affinity for the receptors aimed at and are allowed to be used in humans. It must also be taken into consideration that the mechanism of the neuronal manipulation can be a critical factor (Tsukada et al. 1999, 2000; Laruelle 2000).

Neurochemical evidence for pharmacological interventions mostly originates from microdialysis studies in animals. We will focus on serotonin and present microdialysis data of various pharmacological interventions in rats that have the potential to alter serotonin levels in humans. Our primary aim is to broaden the arsenal of pharmacological tools for PET competition studies, in particular because the type of neuronal manipulation might be a critical factor. We will also briefly discuss microdialysis of glutamate merely to illustrate some of the shortcomings of the technique. First we will give a brief historical and methodological overview of the microdialysis technique.

3.2 History of Microdialysis

The first reports on intracerebral microdialysis in animals stem from the early 1980s (e.g., Zetterström et al. 1982). Microdialysis was developed to circumvent the tissue damage associated with its membrane-less push-pull forebear, which could pressurize brain tissue when the push and pull pumps were not perfectly aligned. Microdialysis does not involve exchange of fluid with brain tissue, and owing to the membrane, it also provides cleaner samples, which can often be injected without purification into a high-performance liquid chromatograph (HPLC). A disadvantage of microdialysis is its modest recovery of the analyzed compounds at practicable flow rates, which in the early years challenged the analytical capabilities of many laboratories. For a long time, it was even necessary to boost serotonin and acetylcholine levels by including a serotonin reuptake inhibitor and a cholinesterase inhibitor in the perfusion fluid, respectively. It is obvious that such measures have an impact on (local) neurochemistry in the brain, for instance, by influencing local and global feedback mechanisms. It must also be noted that insertion of a microdialysis probe into the brain is an invasive procedure that will provoke cellular reactions in its direct environment (Benveniste and Diemer 1987). These effects were somewhat lessened when the relatively crude U-shaped probes from the first studies were replaced by the more sophisticated transversal and Y-shaped probes, but the transversal probes in particular could be very stressful for the animals thus trading one problem for another.

It was soon realized that solid criteria were needed to establish the neuronal origin of neurotransmitters sampled by microdialysis. These classic criteria for exocytotic release were mostly based on in vitro studies, showing that neurotransmitter release depends on K^+/Na^+ exchange (K^+ stimulation, tetrodotoxin infusion) and mobilization of Ca^{2+} ions (Ca^{2+} depletion). In addition the release of many neurotransmitters is controlled by presynaptic autoreceptors (local or systemic administration of agonists/antagonists). This approach worked satisfactorily for the monoamines including serotonin (see Fig. 3.1), but unfortunately not that well for glutamate and only

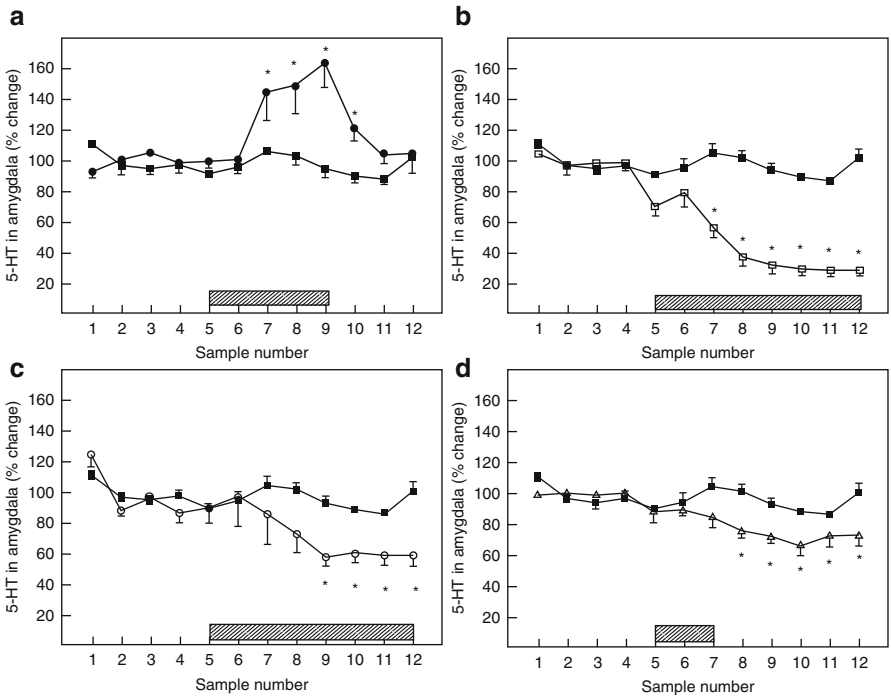

Fig. 3.1 Validation of the neuronal origin of serotonin (5-HT) sampled by a microdialysis probe (exposed tip length, 1 mM) in the central nucleus of the amygdala (CeA) of freely moving rats. (**a**) Local administration of high concentrations of potassium through the probe (60 mM for 60 min). (**b**) Administration of tetrodotoxin (1 μM for 105 min) through the probe. (**c**) Perfusion with calcium-free Ringer supplemented with EGTA (1 mM for 105 min). (**d**) Local application of the 5-HT_{1B} agonist RU 24969 (300 nM for 30 min). Measurements in the CeA were performed in the presence of 10 μM fluvoxamine (flow rate = 1.5 μl/min; sample time =15 min). *Horizontal bars* indicate perfusion with the test substance. The bars are corrected for the lag time in the microdialysis system. *significantly different from Ringer, Bonferroni contrast test following ANOVA; $p < 0.05$. Key: ■ Ringer ($n = 7$); ● potassium ($n = 7$); □ TTX ($n = 7$); ○ calcium-free Ringer ($n = 7$); Δ RU 24969 ($n = 4$) (From Bosker et al. 1997)

partly for GABA. For glutamate this could largely be attributed to an insufficient spatial and temporal resolution of the microdialysis technique making it almost impossible to discriminate the neuronal from the astroglial pool under baseline conditions (van der Zeyden et al. 2008), but for GABA, it also appeared to be a general analytical problem (Rea et al. 2005; van der Zeyden et al. 2008).

3.3 Methodology of Microdialysis

Basically a microdialysis probe consists of an inlet and an outlet tube connected by a membrane. Performance of the membrane in terms of recovery and responsiveness greatly depends on its physical (molecular weight cutoff) and chemical (hydrophobicity) properties. The most popular Y-shaped microdialysis probe is a concentric

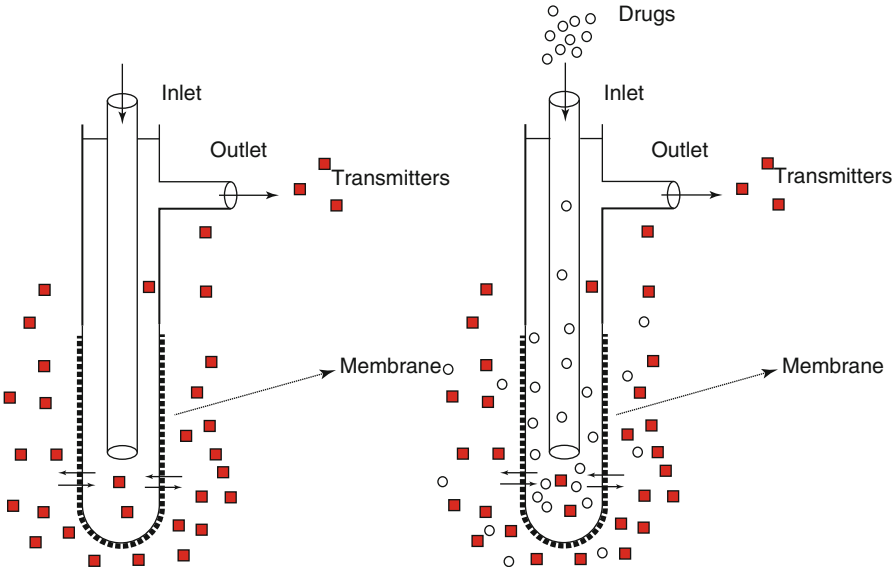

Fig. 3.2 Schematic representation of a Y-shaped microdialysis probe with both anterograde and retrograde perfusion

design with an outer diameter of approximately 300 μm (see Fig. 3.2). Probes are inserted into the brains of laboratory animals at coordinates derived from a dedicated atlas (for instance, Paxinos and Watson 1986) using a stereotaxic instrument. In rodents, surgery takes place under anesthesia, and the animals are allowed to recover from surgery for at least 24 h before the microdialysis experiments commence.

A microdialysis experiment begins by connecting the inlet of the probe via tubing to a high-performance perfusion pump carrying a syringe filled with Ringer solution (artificial CSF) to be perfused through the probe at a constant flow rate mostly in the range of 1–2 μl/min. It is important that membrane and tubing are essentially inert to minimize sticking of endogenous or exogenous compounds. It is common practice to perfuse the probe for 2 h prior to the actual microdialysis experiment to obtain a stable baseline. Samples can be collected in vials using a fraction collector for later analysis (off-line) or in an HPLC injection loop for immediate analysis (semi-online).

Theoretically, microdialysis does not involve exchange of fluid with brain tissue, but endogenous compounds (anterograde microdialysis) and exogenous compounds (retrograde microdialysis) are able to diffuse through the membrane driven by the concentration gradients between the extracellular fluid in the brain and the perfusion fluid pumped through the microdialysis probe (see Fig. 3.2). Except for glutamate, it is thus possible to directly measure the effects of most pharmacological interventions on the release of neurotransmitters. At the end of the experiments, the animals are sacrificed and the location of the probe is verified histologically. Monoamines can be analyzed with either HPLC and electrochemical detection or

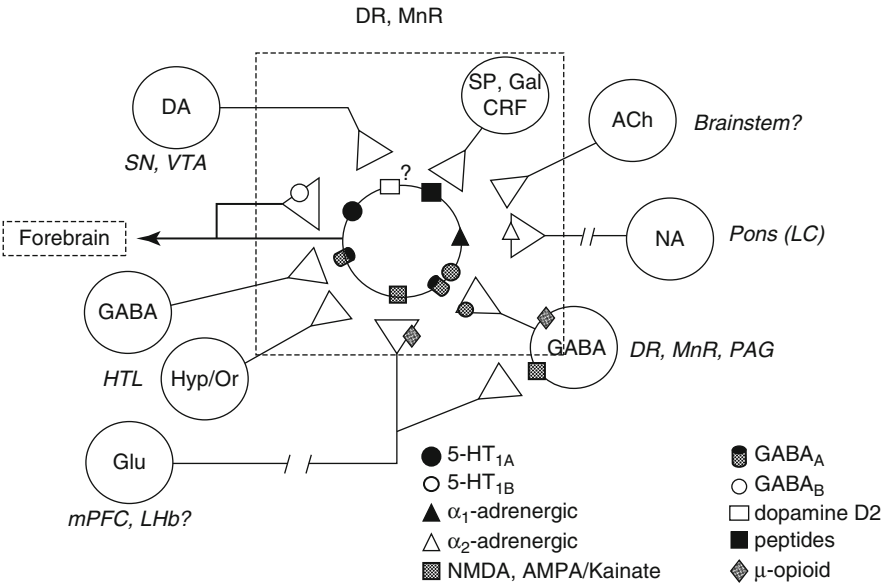

Fig. 3.3 Schematic depictions of serotonergic interactions with other neurotransmitter systems

liquid chromatography with mass spectrometry (LC-MS). The latter method is more expensive but also more accurate and sensitive, and it allows the measurement of many neurotransmitters in one run, including glutamate and GABA.

It is important to note that the here-described methodology refers to rodents. For nonhuman primates (NHP), the methodology is different in several important areas. For instance, NHP are allowed to recover for at least 2 weeks before the microdialysis studies commence, and the artificial CSF for NHP is also different from that used in rodents and not always based on a Ringer solution. In addition, the pre-experimental perfusion is usually shorter (1 h), due to restrictions on how long the NHP can be restrained during the study. Finally, NHP are usually not sacrificed following these studies, and the location of the guide cannula is often verified via MRI. For more details, we refer to the microdialysis studies in rhesus monkeys by Bradberry (2002), Wilcox et al. (2005), Howell et al. (2006), Banks et al. (2009), (Andersen et al. 2010), Murnane et al. (2010); in squirrel monkeys by Czoty et al. (2002), Bauzo et al. (2009, 2012), Manvich et al. (2012); the review of the microdialysis methodology in NHP by Bradberry (2000); and the protocols by Saunders et al. (2001).

3.4 Pharmacological Interventions for Serotonin

It is common practice to manipulate serotonin levels in PET competition studies using serotonin reuptake inhibitors or releasers, but there are other options available as outlined below. Figure 3.3 schematically depicts various interactions of the

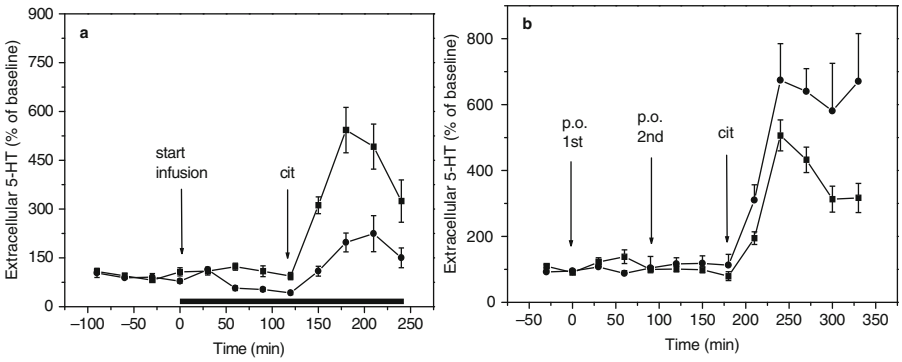

Fig. 3.4 (**a**) Microdialysis of 5-HT in hippocampus of freely moving rats (flow rate = 1.5 µl/min; sample time = 15 min). Effect of local 5-HT synthesis inhibition on the response to citalopram following retrograde infusion of the aromatic amino acid decarboxylase inhibitor NSD 1015 (3-[hydrazinomethyl] phenol dihydrochloride). ■: no synthesis inhibition, $t = 120$ citalopram 10 µmol/kg s.c.; ●: synthesis inhibition following local infusion of 10 µM of NSD 1015 at $t = 0$, $t = 120$ citalopram 10 µmol/kg s.c. (From Bosker et al. 2010). (**b**) Microdialysis of 5-HT in hippocampus of freely moving rats (flow rate = 1.5 µl/min; sample time = 15 min). Effect of oral tryptophan depletion on the response to citalopram. ■ low tryptophan, ● normal tryptophan. *First arrow* at $t = 0$: first oral administration of low tryptophan amino acid mixture; *second arrow* at $t = 90$: second oral administration; *third arrow* at $t = 180$: subcutaneous administration of citalopram 10 µmol/kg s.c. (From Bosker et al. 2010)

serotonergic system with other neurotransmitters in the cell body area. However, such interactions may vary between brain areas and also the effect of pharmacological interventions on serotonin release, in particular between cell body and axon terminal areas.

3.4.1 Manipulation of Extracellular Serotonin Levels Through Synthesis and Reuptake Inhibition

A well-known strategy to manipulate serotonin levels in the brain is through the synthesis of the monoamine. Release and synthesis of serotonin depends on the availability of its precursor molecule, the essential amino acid tryptophan. This notion has been used to demonstrate the role of serotonin in antidepressant efficacy, as witnessed by the relapse of depressive symptoms following depletion of serotonin by tryptophan depletion in patients successfully treated with antidepressants (Delgado et al. 1990).

We have investigated the effects of 5-HT synthesis inhibition on the response to citalopram following retrograde infusion of the aromatic amino acid decarboxylase inhibitor NSD 1015 (3-[hydrazinomethyl] phenol dihydrochloride) and by oral tryptophan depletion. The microdialysis experiments in rats clearly show that inhibition of serotonin synthesis by local NSD 1015 infusion as well as tryptophan depletion significantly decreases the effect of an SSRI on extracellular serotonin levels (see Fig. 3.4a, b).

However, the effect of tryptophan depletion on basal serotonin levels was not significant. This indicates that synthesis might not be a limiting factor under normal conditions, but only when serotonin reuptake is inhibited (see also Bosker et al. 2010). The latter would be in agreement with a competition PET study using ^{18}F-MPPF, which could not demonstrate increased 5-HT$_{1A}$ receptor binding following tryptophan depletion in healthy volunteers (Udo de Haes et al. 2002).

Inversely, serotonin levels are only moderately increased following intraperitoneal administration of tryptophan in rats (Fig. 3.5a). However, when given prior to an SSRI, a strong dose-dependent augmentation of its effect on serotonin levels was observed (Fig. 3.5a). This also indicates that under normal conditions, synthesis is capable of maintaining serotonin levels but that reuptake inhibition puts an extra demand on synthesis.

3.4.2 Manipulation of Extracellular Serotonin Levels Through Synthesis, Reuptake Inhibition, and Receptors Involved in the Regulation of Release and/or Synthesis

Synthesis and release of serotonin are controlled by somatodendritic 5-HT$_{1A}$ and presynaptic 5-HT$_{1B}$ autoreceptors. Blocking the 5-HT$_{1A}$ and 5-HT$_{1B}$ autoreceptors by, respectively, WAY 100.635 and GR 129735 augments the effect of the selective serotonin reuptake inhibitor citalopram on extracellular serotonin levels (Cremers et al. 2000a). Another form of negative feedback control of serotonin release is mediated by 5-HT$_{2C}$ receptors on GABA-B-ergic neurons (Cremers et al. 2007). Blocking the 5-HT$_{2C}$ receptors by SB 242084 augments the effect of the selective serotonin reuptake inhibitor citalopram on extracellular serotonin levels (Cremers et al. 2004). We have combined these SSRI augmentation strategies with tryptophan supplementation and monitored the effects on extracellular serotonin using microdialysis in hippocampus of freely moving rats (Fig. 3.5b, c, d).

SSRI augmentation with tryptophan in combination with inhibition of receptor-mediated feedback mechanisms seems a promising pharmacological intervention to increase extracellular serotonin levels in humans. The critical role of serotonin synthesis following reuptake inhibition and tryptophan supplementation is emphasized when serotonin levels are further increased using an augmentation strategy based on antagonism of 5-HT$_{1B}$ receptors involved in feedback control of serotonin synthesis and release (Fig. 3.5d).

It is clear that the very potent combination of citalopram, tryptophan, and 5-HT$_{1B}$ antagonist GR 129735 cannot be used in competition studies with 5-HT$_{1B}$ receptor PET tracers. It is also important to note that the augmentation strategies in these microdialysis studies were performed with experimental drugs, which are not currently available for use in humans. The antihypertensive drug pindolol has been used to antagonize 5-HT$_{1A}$ receptors in clinical SSRI augmentation studies. Eventually pindolol appeared to have partial agonist properties, and its dose was probably too low to bind sufficient 5-HT$_{1A}$ receptors (Artigas et al. 2001; Cremers et al. 2001).

For the 5-HT$_{2C}$ receptor augmentation strategy, a feasible alternative exists in the form of the antihypertensive drug ketanserin (Cremers et al. 2004; Udo de Haes

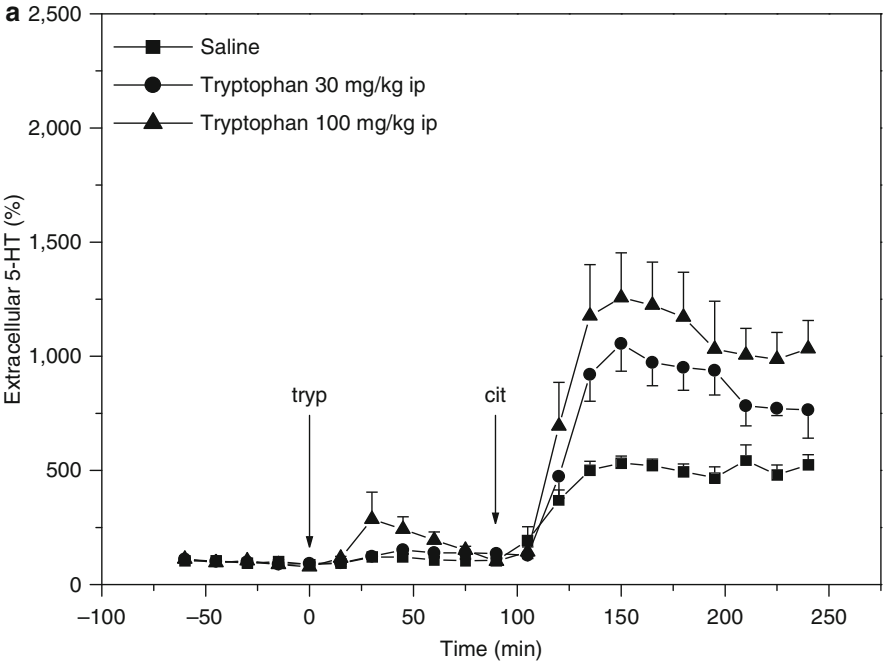

Fig. 3.5 (**a**) Microdialysis of serotonin (5-HT) in hippocampus of freely moving rats (flow rate = 1.5 µl/min; sample time = 15 min). Effect of tryptophan administration on the response to citalopram. ■ $t = 0$ saline i.p., $t = 90$ citalopram 10 µmol/kg s.c., ● $t = 0$ tryptophan 30 mg/kg i.p., $t = 90$ citalopram 10 µmol/kg s.c., ▲ $t = 0$ tryptophan 100 mg/kg i.p., $t = 90$ citalopram 10 µmol/kg s.c. (From Bosker et al. 2010). (**b**) Microdialysis of serotonin (5-HT) in hippocampus of freely moving rats (flow rate = 1.5 µl/min; sample time = 15 min). Citalopram and tryptophan administration synergistically increase 5-HT levels. Theoretically the effect is counteracted by an increased activation of somatodendritic 5-HT_{1A} autoreceptors involved in feedback control of 5-HT synthesis and release (Cremers et al. 2000a, b and references therein), yet the effect of 5-HT_{1A} antagonist WAY 100635 is only marginal. $t = 90$ citalopram (10 µmol/kg s.c.) and WAY 100.635 (1 µmol/kg s.c.). ■ $t = 0$ saline i.p., ● $t = 0$ tryptophan 30 mg/kg i.p., ▲ $t = 0$ tryptophan 100 mg/kg i.p. (From Bosker et al. 2010). (**c**) Microdialysis of serotonin (5-HT) in hippocampus of freely moving rats (flow rate = 1.5 µl/min; sample time = 15 min). Citalopram and tryptophan administration synergistically increase 5-HT levels. Theoretically the effect is counteracted by an increased activation of 5-HT_{2C} receptors on GABA-B-ergic neurons involved in feedback control of 5-HT release (Cremers et al. 2007), yet the effect of 5-HT_{2C} antagonist SB 242084 appears only marginal. $t = 90$ citalopram 10 µmol/kg s.c. and SB 242084 1 µmol/kg s.c. ■ $t = 0$ saline i.p., ● $t = 0$ tryptophan 30 mg/kg i.p., ▲ $t = 0$ tryptophan 100 mg/kg i.p. (From Bosker et al. 2010). (**d**) Microdialysis of serotonin (5-HT) in hippocampus of freely moving rats (flow rate = 1.5 µl/min; sample time = 15 min). Citalopram and tryptophan administration synergistically increase 5-HT levels. Theoretically the effect is counteracted by an increased activation of presynaptic 5-HT_{1B} autoreceptors involved in feedback control of 5-HT synthesis and release (Cremers et al. 2000a, b and references therein), which is indeed supported by the marked effect of 5-HT_{1B} antagonist GR 129735. $t = 90$ citalopram 10 µmol/kg s.c. and GR 129735 1 µmol/kg s.c. ■ $t = 0$ saline i.p., ● $t = 0$ tryptophan 30 mg/kg i.p., ▲ $t = 0$ tryptophan 100 mg/kg i.p. (From Bosker et al. 2010)

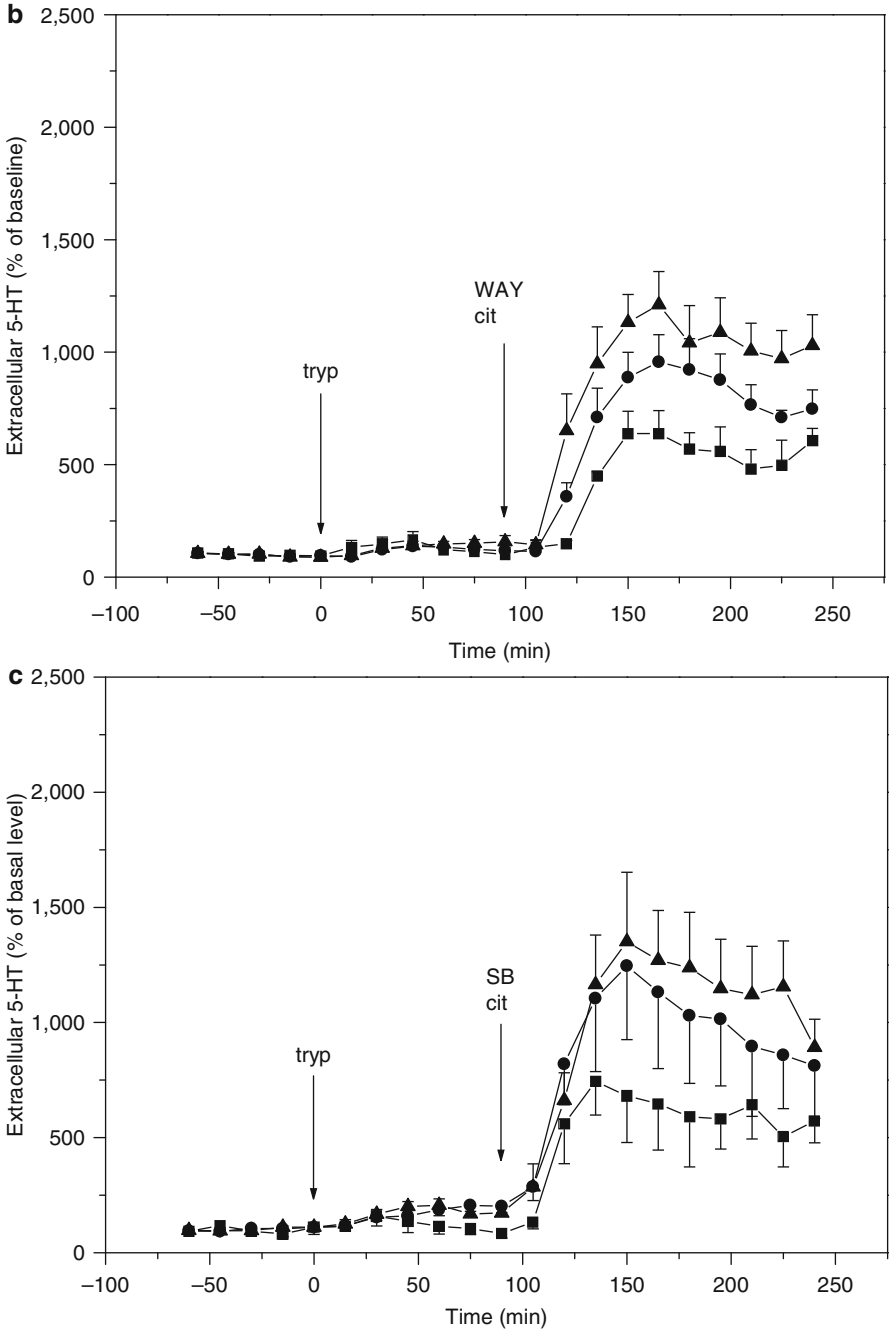

Fig. 3.5 (continued)

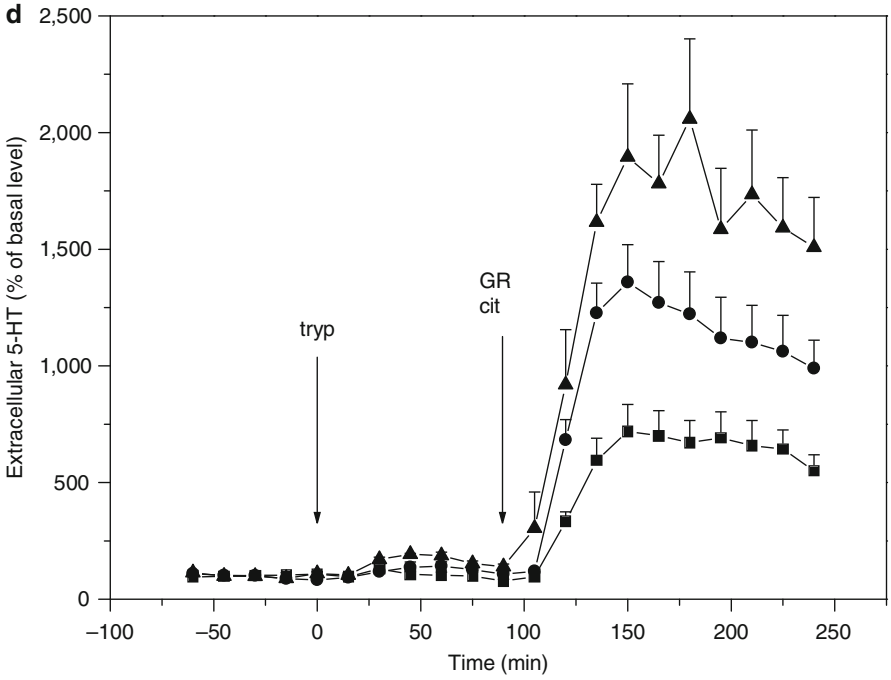

Fig. 3.5 (continued)

et al. 2005b). Compared to 5-HT_{1B} receptor antagonism both 5-HT_{1A} and 5-HT_{2C} antagonism seem to have little added value to the coadministration of citalopram and tryptophan, but an advantage of ketanserin could be its potential in minimizing the risk of serotonin syndrome through its blockade of $5HT_2$ receptors (Bosker et al. 2004).

3.4.3 Manipulation of Extracellular Serotonin Levels with Releasing Agents

Several serotonin-releasing agents are known, including parachloroamphetamine, fenfluramine, and dexfenfluramine. At higher doses, serotonin releasers might also display reuptake-inhibiting properties. Fenfluramine and dexfenfluramine have been registered as anorectics, but were withdrawn from the European market because long-term administration was associated with heart problems. It is not inconceivable, however, that for study purposes a single dose of fenfluramine in humans will be permitted by medical ethical committees in European countries (see, e.g., Finnema et al. 2010, 2012). The effect of fenfluramine on extracellular serotonin levels is very profound (see Fig. 3.6), and significant reductions of

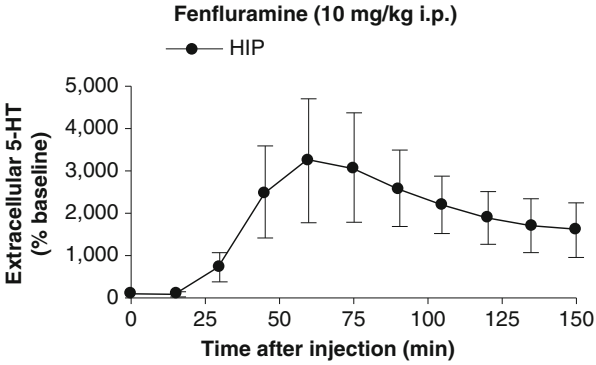

Fig. 3.6 Effect of fenfluramine (10 mg/kg i.p.) on serotonin (5-HT) levels in ventral hippocampus of freely moving rats (flow rate = 1.5 µl/min; sample time = 15 min) (From Udo de Haes et al. 2005b)

^{18}F-MPPF binding at 5-HT$_{1A}$ receptors in various brain areas could be demonstrated following administration in rats (Udo de Haes et al. 2005b).

3.4.4 Manipulation of Extracellular Serotonin Levels Through Interaction with the Noradrenergic System

The noradrenergic system interacts with the serotonergic system via α_1 and α_2 adrenoceptors (Rea et al. 2010). The specific noradrenaline reuptake inhibitor reboxetine had no effect on basal serotonin levels but significantly augmented the effect of citalopram on serotonin levels (see Fig. 3.7), preferentially through α_1 adrenoceptors in axon terminal areas (Rea et al. 2010). SSRI augmentation with reboxetine or administration of the combined serotonin and noradrenaline reuptake inhibitor venlafaxine seems a potent and safe pharmacological intervention to increase serotonin levels in PET competition studies.

3.4.5 Manipulation of Extracellular Serotonin Levels Through Interaction with the GABA-A System

Benzodiazepines are often used in combination with an antidepressant to diminish symptoms of anxiety, which can manifest in the early phase of treatment. Benzodiazepines are functional agonists of GABA-A receptors in potentiating the effects of GABA through binding at an allosteric site of the GABA-A receptor/chlorine channel complex. Figure 3.8a, b show that the benzodiazepines oxazepam and temazepam significantly reduce the effect of an SSRI on serotonin levels. Clearly, benzodiazepines have the potential to modulate the effects of SSRI-based interventions in PET competition studies. It is to note that these microdialysis data are consistent with a study in humans, showing that acute diazepam administration decreases 5-HT function (Nutt and Cowen 1987).

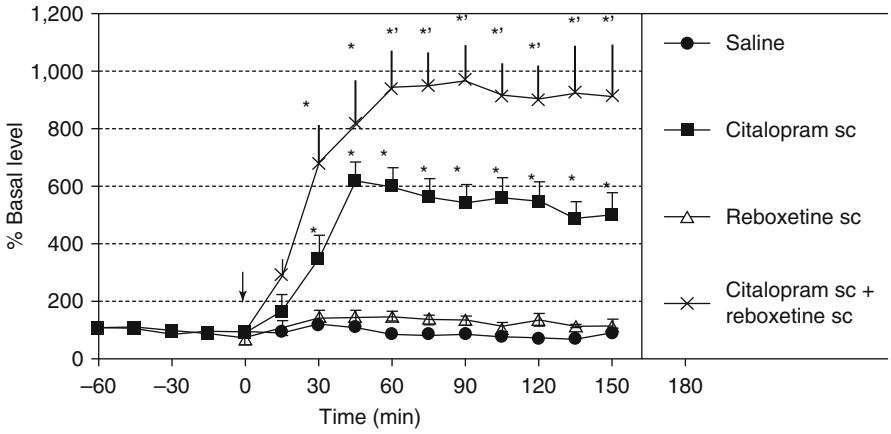

Fig. 3.7 Time course of the effect of citalopram (3 mg/kg s.c.), reboxetine (5.0 mg/kg s.c.), and the combination of the two on serotonin levels in ventral hippocampus (flow rate = 1.5 μl/min; sample time = 15 min). Results are expressed as mean ± s.e. mean % change from predrug baseline levels. Systemic administration of compounds occurred at $t = 0$ as indicated by the arrow. The observed serotonin levels with the combination ($p < 0.01$*') were significantly different from results observed with citalopram administration alone ($p < 0.01$*) (From Rea et al. 2010)

3.5 Discussion

We have shown several pharmacological interventions that have the potential to alter serotonin levels in the human brain. It is important to note that all the microdialysis experiments were performed in hippocampus and that the effects might be different in other brain regions, especially in cell body areas such as the dorsal and median raphe nuclei. Moreover, microdialysis estimates extracellular neurotransmitter levels, and we can only speculate what the effects of these pharmacological interventions will be on the synaptic serotonin concentrations. Another point of concern is the translation of animal data to the human condition as outlined below.

3.5.1 General Translational Aspects

When translating animal data to the human condition, it is important to realize that pharmacodynamics as well as pharmacokinetics might exhibit differences between species. A well-known example with respect to pharmacodynamics is the presynaptic 5-HT_{1B} autoreceptor, which displays different properties in humans compared with rodents (Hoyer et al. 1988; Adham et al. 1992). When developing antiaggression medication (*serenics*) for humans, Solvay Pharmaceuticals made a crucial and expensive misjudgment by initially performing the preclinical studies in rats instead of (guinea) pigs, which do possess the human receptor homologue.

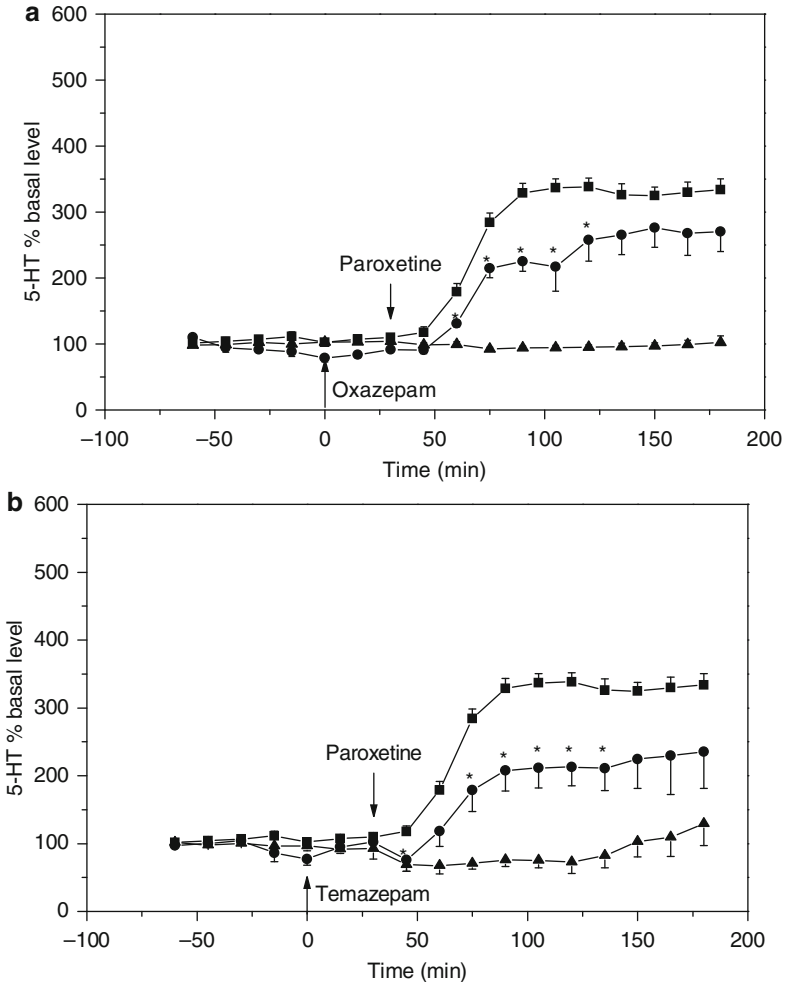

Fig. 3.8 (**a**) Effects of administration of paroxetine (5 mg/kg s.c.) (■, $n=10$, vehicle $t=0$, paroxetine $t=30$), oxazepam (1 μmol/kg s.c.) (▲, $n=5$, oxazepam $t=0$, vehicle $t=30$), and paroxetine (5 mg/kg s.c.) together with oxazepam (1 μmol/kg s.c.) (●, $n=4$, oxazepam $t=0$, paroxetine $t=30$) on serotonin (5-HT) levels in hippocampus (flow rate = 1.5 μl/min; sample time = 15 min). * denotes significant vs. paroxetine alone (From Cremers et al. 2010). (**b**) Effect of administration of paroxetine (5 mg/kg s.c.) (■, $n=10$, vehicle $t=0$, paroxetine $t=30$), temazepam (1 μmol/kg s.c.) (▲, $n=4$, temazepam $t=0$, vehicle $t=30$), and paroxetine 5 mg/kg together with temazepam (1 μmol/kg s.c.) (●, $n=4$, temazepam $t=0$, paroxetine $t=30$) on serotonin (5-HT) levels in hippocampus (flow rate = 1.5 μl/min; sample time = 15 min). * denotes significant vs. paroxetine alone (From Cremers et al. 2010)

Pharmacokinetic differences are also evident, as witnessed by the generally far more rapid elimination of drugs in rodents. For instance, SSRIs can have a ten times shorter half-life time in rodents compared with humans. This necessitates multiple injections (stressful) or the use of osmotic mini-pumps (expensive) in rodents to

mimic steady-state conditions with long-term SSRI treatment in humans (Cremers et al. 2000b).

Other confounding factors may be the disease process in humans and the invasive microdialysis procedure in animals which both may influence pharmacodynamics as well as pharmacokinetics.

3.5.2 Specific Translational Aspects Related to Microdialysis

Microdialysis enables measuring extracellular neurotransmitter levels in vivo, at least when the criteria of neuronal origin are fulfilled. For many classical neurotransmitters such as the monoamines and possibly also GABA, this might work, but not for extracellular glutamate under basal conditions (Timmerman and Westerink 1997). Attempts have been made to assess neuronal glutamate via an indirect approach based on glutamatergic interaction with other neurotransmitter systems that do fulfill the criteria of exocytotic release. For instance, using dual-probe microdialysis, the well-defined interaction between glutamate and dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) has been studied. Infusion of the glutamate reuptake inhibitor TBOA into the VTA (via retrograde microdialysis) significantly increased local glutamate levels and also dopamine levels in the NAc (Evering – van der Zeyden 2011). It is important to note that the corresponding dopamine response in the NAc was somewhat blurred in comparison with the TBOA-induced glutamate increase in the VTA. Moreover, the TBOA-induced glutamate increase in the VTA appeared to be largely tetrodotoxin independent, which could indicate that the effect on dopamine in the NAc was the result of either a non-synaptic event or diffusion of TBOA into the NAc.

Conclusion

The authors believe that the here-presented microdialysis data can be used as basis for pharmacological interventions in PET competition studies but also want to emphasize that microdialysis has its limitations and that one must be cautious when interpreting the data, in particular with glutamate.

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The Role of P-Glycoprotein in Psychiatric Disorders and in Psychiatric Treatment

4

Onno L. de Klerk

Contents

Abstract

With regard to protection of the brain, the endothelial capillary cell harbours an important efflux pump on its surface, called P-glycoprotein (P-gp). This multi-specific pump has a large capacity and is capable of extruding an unusual broad range of potentially toxic substances from the brain. Some research findings

O.L. de Klerk
Topreferent Trauma Center, Geestelijke Gezondheids Zorg Drenthe, Dennenweg 9, Assen 9404 RA, The Netherlands
e-mail: onno.klerkde@ggzdrenthe.nl

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_4, © Springer-Verlag Berlin Heidelberg 2014

suggest that this pump plays a role in neuropsychiatric disorders, since these disorders have inflammatory features that are associated with decreased function of P-gp. Other studies have indicated that many of the current antidepressant and antipsychotic agents may modulate the function of P-gp.

In this review, we discuss the current state of knowledge concerning the role of P-glycoprotein on pharmacokinetics of psychiatric drugs and the impact of modulation of P-glycoprotein on major psychiatric disorders.

4.1 Introduction

The microenvironment within the brain is precisely controlled by the blood–brain barrier (BBB), and neuronal transmission is secured in this way (Hawkins and Davis 2005). The BBB protects against the direct influence of potentially harmful endogenous or exogenous substances. The BBB has to be a stable structure to exert its protective function, but on the other hand, the BBB requires the ability to adapt to fast-changing conditions (Chaudhuri 2000). The protective function of the BBB is exerted in two ways. In addition to being a physical barrier, the BBB is a complex transport and metabolic barrier due to its highly reactive and dynamic endothelium. The major components of the anatomical barrier are the specialised non-fenestrated tightly joined endothelial cells with tight junctions (see Fig. 4.1) (Bernacki et al. 2008; Grant et al. 1998; Hawkins and Davis 2005).

An important component in the protection of the brain against toxic influences is the multispecific efflux pump P-glycoprotein. This pump, a 170 kD protein, located at the luminal side of the capillary endothelial cells, has a large capacity and is capable of extruding a wide array of structurally divergent substrates. The brain uptake of the majority of antidepressants and antipsychotics, as well as many other psychotropic drugs and endogenous compounds, is hampered by the activity of P-glycoprotein.

In the following paragraphs, the main components of the BBB will be discussed. Subsequently, relevant issues in reference to the function of P-glycoprotein and other efflux pumps in the blood–brain barrier related to several major psychiatric disorders (mood disorders, stress-related disorders and neurodegenerative disorders, such as dementia) are addressed, such as a possible role of P-glycoprotein as a susceptibility factor in depressive disorders. Furthermore, the current state of knowledge concerning the role of P-glycoprotein on pharmacokinetics of psychiatric drugs and the impact of modulation of P-glycoprotein on major psychiatric disorders will be discussed.

4.2 Components of the BBB

4.2.1 Endothelial Cells

Brain endothelial cells (EC) are unlike other endothelial cells in the body. Compared to the leaky capillaries formed by mesenteric endothelium, the brain endothelium is 50–100 times tighter, as indicated by the transendothelial electric resistance

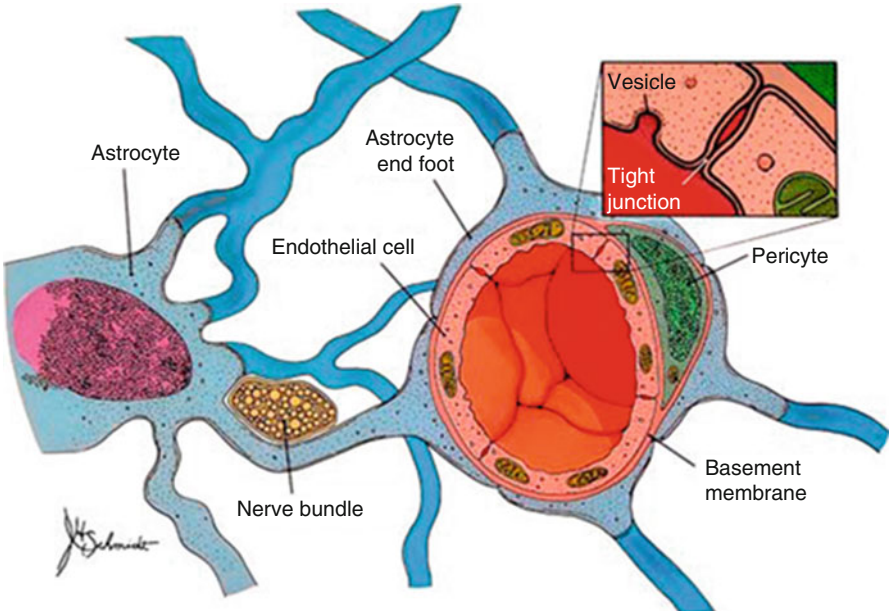

Fig. 4.1 Cross section of a brain capillary, depicting the main components

(TEER) (Pardridge 2005). They differ phenotypically by a lack of fenestrations and the presence of tight junctions. The rate of pinocytosis is minimal and free membrane diffusion applies mainly to small lipophilic molecules like ethanol or nicotine (Pardridge 2002b). The ECs are surrounded by a basal lamina, which further restricts the microvascular integrity (Hamann and Schimrigk 1995; Pardridge 2002b). ECs are rich in mitochondria, necessary for their high metabolic demands. Specific enzymes expressed by ECs (monoamine oxidases, epoxy hydrolase, endopeptidases, etc.) are important elements, constituting the so-called metabolic barrier, and participate in the regulation of brain penetration of drugs and their metabolism (Henry and Duling 1999; Leung et al. 2009; Pardridge 2002a). ECs have an extensive transport system on their surface, which is carrier mediated or receptor mediated.

4.2.2 Tight Junctions

Tight junctions are the closely associated areas of two cells whose membranes join together forming a virtually impermeable barrier to fluid. This is accomplished by their structure, as it is composed of a branching network of sealing strands, a complex of transmembrane (junctional adhesion molecule-1, occludin and claudins) and cytoplasmic proteins (Hawkins and Davis 2005; Jiang et al. 2008). Each strand acts independently from the others. The tight junctions prevent the passage of molecules and ions through the space between cells, the so-called paracellular flux. In order to

pass the blood–brain barrier, molecules must enter the endothelial cells. Together with the endothelial cells, the tight junctions play the most substantial role in maintaining the BBB.

4.2.3 Astrocytes, Microglia and Pericytes

Astrocytes, microglia and pericytes surround the endothelial cells and form the 'second line of defence' in the BBB. Astrocytes are star-shaped glia cells that perform many functions, including the biochemical support of endothelial cells. Their end-feet, encircling the endothelial cells, aid in the maintenance of the blood–brain barrier, as they regulate the homeostasis of brain water and electrolytes (Bernacki et al. 2008; Choudhuri and Klaassen 2006; Hawkins and Davis 2005). In addition, they interconnect endothelial cells with surrounding neurons. Astrocytes secrete proteins that can have an opposite effect on neurons and endothelial cells. For example, thrombospondin, an astrocyte-derived protein, stimulates neurogenesis on the one hand while it counteracts the effects of angiogenesis (Choi and Kim 2008). Current in vitro cellular models for the study of BBB function often incorporate astrocytes with endothelial cells. Studies have shown that when astrocytes are removed from an in vitro BBB model, an increased permeability is observed (Hamm et al. 2004). Many transporters (see below) are under the control of astrocytes (Omidi et al. 2008). In pathological conditions, astrocytes mediate the immune response; they synthesise proinflammatory cytokines and chemotactic factors, which eventually trigger the breakdown of the BBB (Jiang et al. 2008). The pericyte, another foremost cell type in the CNS, intimately embraces the brain endothelial capillary. Less is known about their role at the BBB, although they seem to stabilise the formation of capillary-like structures when they are added to a coculture of astrocytes and endothelial cells (Ramsauer et al. 2002).

Microglia are omnipresent throughout the brain parenchyma. They are the immune effectors in the CNS, as they can release a large number of immunoregulatory, inflammatory and cytotoxic mediators (Dheen et al. 2007). They surround the brain capillaries and stay in a resting state until they are activated, which can be induced by a variety of stimuli (Dijkstra et al. 2004; Guillemin and Brew 2004). Figure 4.1 shows the main components of the BBB.

4.2.4 Neurons

Neurons lie in close proximity of the brain capillaries and their needs, including protection and the unrestricted provision of nutrients, are optimally met. Neuronal tissue needs an abundant supply of oxygen. At rest, 80–92 % of its ATP comes from oxidative metabolism of glucose (Mintun et al. 2001). Given the dynamic nature of neural activity and the considerable metabolic needs of nervous tissue, the microcirculation of the brain must be highly responsive to the tissue it supplies. Iadecola found that blood flow was increased in response to local neuronal activation and

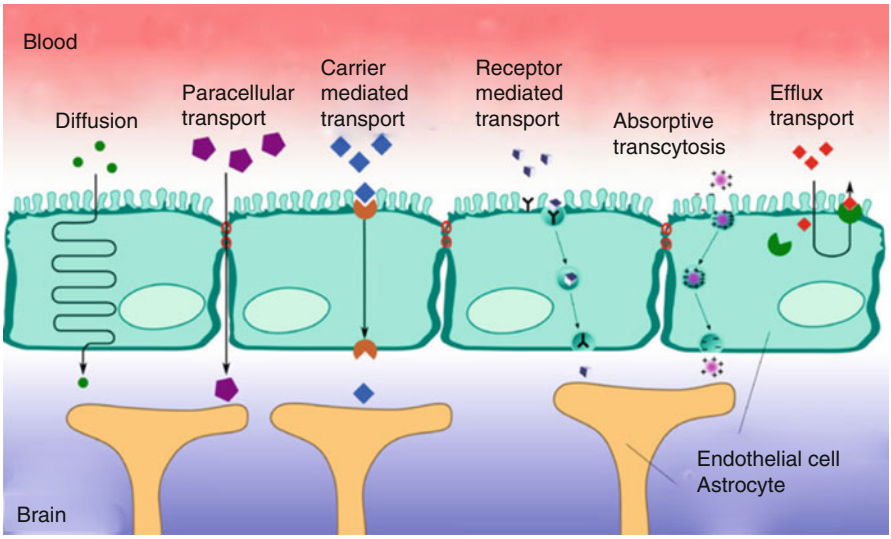

Fig. 4.2 Transport mechanisms at the blood–brain barrier (Adapted from http://upload.wikimedia.org/wikipedia/commons/2/24/Blood-brain_barrier_transport.png (no copyright))

proposed a role for nitric oxide as a messenger between blood and neuronal tissue (Iadecola 1993). This 'metabolic coupling' of regional brain activity to blood flow is the basis of functional neuroimaging. However, data from positron emission tomography (PET) and functional MRI studies indicate that during short-term functional activation, cerebral blood flow and cerebral metabolism (oxygen consumption) are not directly linked (Fox et al. 1988; Mintun et al. 2001).

4.3 Transport Across the BBB

There are two tightly controlled ways of transport for molecules and cells across the BBB (see Fig. 4.2). The paracellular route, or junctional route, is restricted by the interendothelial tight junctions. Tight junctions not only restrict paracellular flux but also maintain the polarity of enzymes and receptors on luminal (blood) and abluminal (brain) membrane domains (Matter and Balda 2003; Wolburg and Lippoldt 2002). Due to the presence of tight junctions, only lipid-soluble substances or those transported through an active mechanism can cross the BBB (Bernacki et al. 2008).

The transendothelial route further restricts the passage of molecules by three distinct transport systems. Small lipid-soluble molecules can penetrate the brain EC through diffusion, unless their molecular weight exceeds 400–600 Da (Pardridge 2006). All other transport to the brain is via endogenous catalysed transport systems on the capillary membrane. As we will describe below, three main transport systems function at the BBB: (1) carrier-mediated transport, which relies on a molecular

carrier present on both the luminal side and the abluminal side of the BBB; (2) receptor-mediated transport for endogenous large-molecule peptides such as insulin (Duffy and Pardridge 1987) or transferrin (Jefferies et al. 1984); and (3) active efflux transporters such as P-glycoprotein and many other active efflux transport systems within the BBB (see Fig. 4.2).

4.3.1 Carrier-Mediated Transport

Carrier-mediated transport is a highly selective form of transport for small molecules such as ions, glucose and amino acids. Examples of carrier-mediated transport systems include the GLUT1 glucose transporter, the OAT (organic anion transporter) and organic anion-transporting polypeptide family (OATP), the monocarboxylate transport family and the LAT1 (large neutral amino-acid transporter) (Tsuji 2005). This form of BBB transport is a saturable process which can be unidirectional or bidirectional. Carrier-mediated channels can be gated and can function ion and energy independent, like the LAT1 (Smith and Stoll 1998). The membrane spanning pores are highly stereospecific. The substrate forms a complex with the carrier in order to be translocated to the opposite side of the membrane. L-DOPA is such a drug that utilises the LAT1 to enter the brain. Once transported through the BBB, L-DOPA is reformulated to dopamine (Kanai and Endou 2003). Another example is valproic acid, which is delivered to the brain via a medium-chain fatty transporter (Adkison and Shen 1996). Uptake of valproic acid was reduced in the presence of medium-chain fatty acids, but not short-chain fatty acids, indicating that valproic acid is taken up by a transport system for medium-chain fatty acids. The monocarboxylate transport family also appears to be involved in the transport of valproic acid, possibly as efflux transporter (Adkison and Shen 1996; Tsuji 2005).

4.3.2 Receptor-Mediated Transport

Another main transport mechanism at the BBB is receptor-mediated transport, which involves a vesicular trafficking system of the endothelial cells (Fig. 4.2). The influx of several brain nutrients like leptin (Ziylan et al. 2009) and insulin (Matter and Balda 2003) occurs by this form of transport. Circulating molecules are bound to a specific receptor at the plasma membrane, to form a receptor-ligand complex. When the ligand is bound to the receptor, the process of invagination is initiated. Dependent on subsequent intracellular processes, the vesicles are either sent to the basolateral side of the cell, where they are released, or the complex is dissociated from the ligand in the cell. A similar transport system is called ‘absorptive-mediated transcytosis’ which does not require specific binding to a receptor. Instead, binding is nonspecific, for example, to negative charges on the plasma membrane. The receptor-mediated transcytosis offers a promise as drug vector for drug delivery into the brain (Jones and Shusta 2007).

4.3.3 Efflux Transport

Uncharged, small lipophilic compounds enter the brain much better than other molecules, because they can diffuse passively across the endothelial cells. However, an ATP-driven efflux system exists at the luminal wall of the capillary wall, which can extrude a variety of structurally diverse drugs, drug conjugates and metabolites and other compounds from the cell. These efflux proteins involved belong to the superfamily of ABC (ATP-binding cassette) transporters, an extensive and functionally highly diverse family of membrane transporters. Export of these compounds occurs in an active, ATP-dependent manner and can take place against a considerable concentration gradient. The human ABC transporter is classified into eight subfamilies (ABCA–ABCH) (Dean 2009). P-glycoprotein (P-gp, ABCB1), multidrug resistance protein ABCC subfamily (formerly denoted as MRP), ABCC4 and ABCC5 (and possibly ABCC1 and ABCC2; see below) (Dean 2009; Yu et al. 2007; Zhang et al. 2004; Zhou et al. 2008) and the breast cancer-related protein (BCRP, ABCG2) have been localised in the apical membrane of the brain endothelial cell and have a role in efflux at the BBB. Of these, P-gp is the best-studied transport protein. Its most striking property is transport of a wide range of structurally different substrates, including many CNS drugs. As a consequence, the net penetration of substrate drugs and other substrate compounds from the blood into the brain tissue can be dramatically decreased. Various members of the ABCC family show considerable differences in their tissue distribution, substrate specificity and proposed physiological function. These proteins play a role in drug disposition and excretion and thus are implicated in drug toxicity and drug interactions. ABCC primarily transports anionic compounds, such as glutathione S-conjugates and oxidised glutathione (Jedlitschky et al. 1994). Furthermore, ABCC transport appears to be dependent upon intracellular glutathione (Renes et al. 1999).

4.4 Localisation and Function of P-gp

Of all efflux pumps discovered at the BBB so far, P-gp is the best described. It has been shown that P-gp exerts an important influence on the penetration of psychoactive drugs at the BBB (Linnet and Ejsing 2008; Liu et al. 2008). P-gp is found at the luminal side of the endothelial cells, where it extrudes hydrophobic compounds from the cell. It was discovered in 1976 in drug-resistant ovary cells from Chinese hamsters (Juliano and Ling 1976). Human P-gp is encoded by the multidrug resistance gene (MDR1), which is now denoted as ABCB1 (ATP-binding cassette gene B1). P-gp contains 1,280 amino acids and has a molecular weight of 174 kD (Sharom 2006).

Cerebral P-gp is present not only at the BBB but also at the blood-CSF barrier (Rao et al. 1999). Apart from the CNS, P-gp is present in kidneys, gut and other organs that have an epithelial lining. Interestingly, while in normal conditions P-gp is not found in neurons, neuronal P-gp expression was reported in pathological conditions, such as

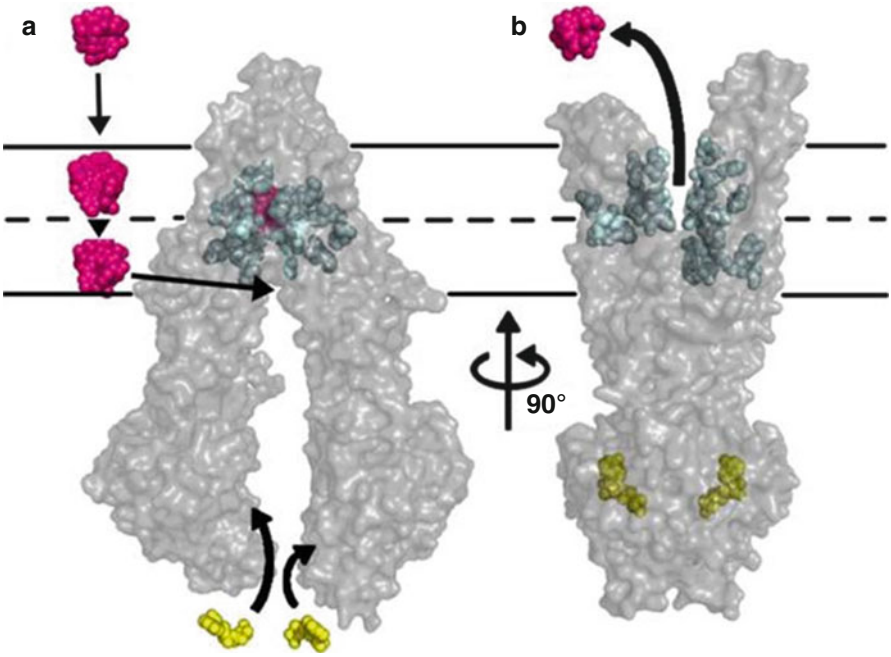

Fig. 4.3 Model of substrate transport by P-gp. (**a**) Substrate (*magenta*) partitions into the bilayer from outside of the cell to the inner leaflet and enters the internal drug-binding pocket through an open portal. The residues in the drug-binding pocket (cyan spheres) interact with a substrate in the inward-facing conformation. (**b**) ATP (*yellow*) binds to the nucleotide-binding domains, causing a large conformational change presenting the substrate and drug-binding site(s) to the extracellular space. In this model of P-gp, exit of the substrate to the inner leaflet is sterically occluded, providing unidirectional transport to the outside (Reprinted with permission from Aller et al. (2009))

refractory epilepsy, cortical dysplasia and glioneuronal tumours (Lazarowski et al. 2004; Volk et al. 2004; Aronica et al. 2003). The physiological function of ABCB1 has not been unambiguously identified yet (Banerjee and Bhat 2007; Sharom 2006), but it involves the protection of the brain from compounds that have gained access to the circulation. The fact that it is being expressed in damaged neuronal tissue, as well as in malignancies, affirm such a function (Lazarowski et al. 2004; Volk et al. 2004). It needs to be considered that xenobiotic or drug concentrations in the brain might also be affected by intestinal P-gp limiting oral bioavailability.

Its imposing ability to transport hundreds of structurally divergent drugs, natural products and peptides renders this protein a fascinating molecule. P-gp is composed of two transmembrane-bound domains, each consisting of six transmembrane helices and two nucleotide-binding sites, which hydrolyse ATP, enabling substrate transport (see Fig. 4.3) (Aller et al. 2009). P-gp substrates are known to partition into the lipid bilayers and accumulate to high concentrations. In the inner leaflet of the lipid bilayer, the compounds can then get in contact with the drug-binding pocket of the transporter (Aller et al. 2009; Banerjee and Bhat 2007). Initiated by

ATP binding, a conformational change of the transporter molecule then brings the drug-binding site to the outer leaflet or extracellular surface, thereby promoting unidirectional transport to the extracellular space.

4.5 In Vivo Imaging of P-gp at the BBB

In the last decade considerable effort has been put into gaining further insight into the role of P-gp under pathophysiological conditions. Different substrates of P-gp have been radiolabeled and imaged using single-photon emission computed tomography (SPECT) and positron emission tomography (PET) (Kannan et al. 2009).

A P-gp tracer that meets the criteria of a useful ligand is a selective substrate for P-gp, produces a good signal after P-gp blockade and generates few radiolabeled metabolites that contribute to the PET signal. The principle of PET imaging of P-gp activity amounts to measure the difference in cerebral uptake of a radiolabeled P-gp substrate (i.e. radioligand) under two different conditions, for example, major depressive disorder versus healthy control, or before and after drug inhibition. The function of P-gp can be quantified by calculating the distribution volume (V_T) of the ligand, which inversely reflects P-gp function (Lubberink et al. 2007). V_T is an estimate of the brain tissue-blood partition coefficient of activity of the radiotracer at equilibrium and is defined as the influx rate constant k_1 over the efflux rate constant k_2.

Several radiolabeled P-gp substrates are available for PET, such as [^{11}C]-verapamil and [^{11}C]-carvedilol, [^{11}C]-loperamide and [^{11}C]-desmethyl-loperamide (Elsinga et al. 2005; Hendrikse et al. 1998; Seneca et al. 2009). Of these, the in vivo studies with [^{11}C]-verapamil outnumber all other ligands and it is the only tracer used in clinical studies (Elsinga et al. 2005; Lubberink et al. 2007; Sasongko et al. 2005). The (R)-enantiomer of [^{11}C]-verapamil can be considered superior to the racemic mixture. Although the feasibility of in vivo measurement of P-gp function by [^{11}C]-verapamil PET (VPM-PET) has been confirmed by several research groups (Lee et al. 2006; Lubberink et al. 2007; Sasongko et al. 2005), it is not an ideal tracer, because its brain uptake is low. The production of several metabolites of the parent compound [^{11}C]-verapamil does not appear to be a problem, since the main metabolite is also a P-gp substrate (Lubberink et al. 2007). Several strategies have been launched in search of an optimal tracer that is capable of detecting subtle changes in function (in particular increased P-gp activity). The development of a radiotracer that is not a substrate but works as a pure inhibitor could bypass this problem, but so far the results of this strategy are ambiguous, possibly due to the fact that these inhibitors have affinity as a substrate too (Syvanen and Hammarlund-Udenaes 2010). Several new imaging strategies may still hold the unfulfilled promise of a method to study drug interactions with P-gp, for example, radiolabeling of a new drug candidate after administration of an inhibitor or a double PET scan to evaluate the effect of a P-gp modulator. Another strategy that could work is the co-administration of a P-gp inhibitor that can increase the baseline signal (Wagner et al. 2009). This new strategy may enable accurate estimation of dose–response relation of a given drug or facilitate prediction of drug interactions at the BBB (Bauer et al. 2012; Kreisl et al. 2010).

4.6 Relevance of P-gp in Relation to Antidepressants, Mood Stabilisers and Antipsychotics

Different in vitro approaches and in vivo models (ABCB1ab (–/–) knockout mice) have been used to assess the impact of P-gp on pharmacokinetics of psychiatric drugs (O'Brien et al. 2004). In vitro data have indicated that most antidepressants and antipsychotics have affinity for P-g (Maines et al. 2005; Störmer et al. 2001; Szabo et al. 1999; Weber et al. 2005; Weiss et al. 2003). Many of the in vitro data are contrary, which is inherent to the different methods and materials used.

Most research focusing on the inhibitory effects of antidepressants and antipsychotics has been done with various cell lines expressing (recombinant) human P-gp. As a measure of the P-gp-inhibitory potency of the drug, a prototypic P-gp substrate, such as calcein-AM or rhodamine 123, was often used. The concentration needed to displace 50 % of the prototypic compound (called IC_{50} or EC_{50}) was used as measure of the inhibitory effect on P-gp activity.

For most compounds, the ability to inhibit P-gp has been compared to a typical comparator, such as verapamil or cyclosporine A. It must be considered that these inhibitors significantly differ in their potency to affect P-gp transport function (Achira et al. 1999). For example, haloperidol appeared to be a weak inhibitor compared to PSC833 (Wang et al. 2006), whereas it proved to be a much stronger inhibitor in comparison to verapamil and ivermectin (El Ela et al. 2004).

Some antidepressants have only shown inhibition without demonstrated substrate affinity (i.e. desipramine, imipramine, reboxetine) (Szabo et al. 1999; Weber et al. 2005). Besides, the translation of in vitro results to the human case could be complicated by differences in substrate specificity for P-gp across species (Baltes et al. 2007). A more reliable method of studying affinity for P-gp is based on studies in knockout mice, which lack the ABCB1ab genes encoding P-gp. Affinity for P-gp has been demonstrated in knockout mice for most of the common antidepressants (Doran et al. 2005; Ejsing et al. 2006; Störmer et al. 2001; Uhr et al. 2000, 2003; Uhr and Grauer 2003) and antipsychotics (Doran et al. 2005; Ejsing et al. 2005; Kirschbaum et al. 2008; Schinkel et al. 1996; Wang et al. 2003, 2004, 2009).

Despite the differences in the experimental set-up that partly explain the controversies regarding the interaction between P-gp and antidepressants and antipsychotics, it is feasible to say that the majority of the antidepressants and antipsychotics have shown (mostly weak) affinity as a P-gp substrate and that most have a weak inhibitory effect on P-gp in vitro. Contradictory to the results of most serotonergic antidepressants, St. John's wort, a phytopharmaceutical with antidepressant effect, has shown in vitro inductory effect (Ott et al. 2010). Some authors have argued that the inhibitory effect of antidepressants on P-gp is clinically irrelevant (Uhr and Grauer 2003; Weber et al. 2005; Weiss et al. 2003), since the drug concentrations used in most studies necessary for P-gp inhibition were far above the therapeutic dose range. On the other hand, others have suggested that some antidepressants may be strong inhibitors in vivo (Peer et al. 2004; Störmer et al. 2001; Wang et al. 2008). For antipsychotics comparable differences between the individual drugs have been described.

The impact of cerebral P-gp in man for the bioavailability of psychoactive drugs cannot be satisfactorily deducted from the in vitro data. It needs to be considered that antidepressants and antipsychotics can generally access the brain and therefore cannot be high-affinity substrates of P-gp-like compounds that do not exhibit any relevant brain penetration based on its interaction with P-gp. Moreover, CNS-active drugs are in general characterised by a fairly high lipophilicity. Recent data demonstrated that it can be more difficult to detect an interaction with P-gp when drugs pass membranes efficaciously by rapid diffusion due to their lipophilic characteristics (Luna-Tortos et al. 2008).

Most of the antidepressants and antipsychotics, as well as several mood stabilisers, demonstrated a significantly greater, albeit small, brain/plasma ratio in ABCB1a knockout mice compared to wild-type mice (mean = 1.8 for antidepressants, 4.9 for antipsychotics). The value of the studies using the knockout mouse model is limited by the fact that a one-dose model is mostly used, representing only the acute modulatory effect on P-gp. There are only two reports on long-term treatment on P-gp activity in vivo (Grauer and Uhr 2004; Kirschbaum et al. 2010). For amitriptyline, it was demonstrated that the brain uptake in WT and KO mice was equal for the parent compound (amitriptyline), whereas a much higher cerebral concentration was measured for its metabolites in the knockout mice. It was suggested that chronic administration of amitriptyline induces upregulation of the P-gp pump, thus inhibiting its own access to the brain. In an elaborative study, they refined their results and demonstrated that 4 h after a single dose of amitriptyline, the initial differences (present at 1 h post injection) in cerebral uptake had disappeared, in contrast to the metabolites, pleading against an upregulatory mechanism (Uhr et al. 2007). Differences in cerebral uptake between the parent compound (amitriptyline) and its metabolites can also be explained by a differential affinity of P-gp for the respective molecules. Miura et al. demonstrated that small molecular changes can turn a strong P-gp substrate into a weak one (Miura et al. 2007). Another notion is that the effect of a non-substrate on P-gp activity can apparently vary over time (Störmer et al. 2001).

In spite of the findings of the preclinical work on the role of P-gp in the uptake of drugs used for the major psychiatric disorders, there are arguments pleading against a significant role for P-gp. For example, antipsychotic drugs like risperidone and haloperidol may significantly differ in their interaction with P-gp but have a comparable clinical efficacy.

Because direct evidence for a major role of P-gp in pharmacokinetics has been lacking, CNS side effects of drugs with potential P-gp inhibiting effects may erroneously have been attributed to other causes. Cytochrome P450 3A4, a major drug metabolising enzyme, shows a striking overlap in substrate specificity with P-gp (Fromm 2004; Zhou et al. 2008). Several CNS effects have been ascribed to interactions between drugs concurrently inhibiting Cyp3A4, without notice of a potential concomitant P-gp inhibiting effect of these drugs in vitro (Gelisse et al. 2007; Jover et al. 2002; Sheehan et al. 2006).

Cortisol is a substrate of P-gp as well. Its uptake into the brain is thwarted by P-gp (Karssen et al. 2001; Ueda et al. 1992). It has been well established that depression coincides with dysregulation of the HPA axis, characterised by negative

feedback inhibition and elevated cortisol levels (Holsboer 2000). As some of the in vitro data have suggested that P-gp is inhibited by the action of antidepressants (Pariante et al. 2001), it has been hypothesised that antidepressants exert their antidepressant effect partly by the inhibition of P-gp, leading to an intracerebral cortisol increase and normalisation of the HPA axis. However, antidepressants appear to have an insignificant effect on plasma cortisol levels (Weber et al. 2006). Besides, cortisol entry to the brain is not regulated by P-gp only, as Mason et al. found in mice (Mason et al. 2010). In conclusion, data supporting the hypothesis that P-gp inhibition plays a role in normalisation of a hyperactive HPA axis are lacking.

Mood stabilisers belong to different drug classes. Lithium is the drug of first choice in the treatment of bipolar disorders. Although lithium itself is not a substrate of P-gp, lithium shares many properties with magnesium (Mg^{2+}), such as a synergistic effect on the Na/K ATP-ase (Murck 2002). Mg^{2+} appears to play a key role in P-gp-mediated efflux through ATP hydrolysis (Singh et al. 2009). It may thus be conceived that lithium has a similar impact on the function of P-gp. Other drugs registered as mood stabilisers include the antiepileptic drugs carbamazepine, valproic acid and lamotrigine. These agents appear to have no, or at most a weak, affinity for P-gp. Reports on the effect of different antiepileptic drugs on P-gp expression in brain capillary cell lines have been equivocal (Ambroziak et al. 2010; Lombardo et al. 2008; Yang et al. 2008).

4.7 Modulation of P-gp at the BBB by Stress (In Vitro Studies)

An understanding of the physiological regulation of P-gp is key to therapeutic strategies in the treatment of psychiatric disorders, since most of the drugs used for depression and psychosis seem to be P-gp substrates. Stress is the hallmark of many psychiatric diseases, including depression and psychosis, and it appears that all sorts of stress responses evoked by a variety of environmental stimuli, such as cytotoxic agents, heat shock, irradiation, genotoxic stress and inflammation are able to influence either the expression or the activity of P-gp (Sukhai and Piquette-Miller 2000). P-gp is regulated at various levels of expression including DNA, mRNA and protein.

There is increasing evidence for the role of cytokines in the pathogenesis of depression (Schiepers et al. 2005). Proinflammatory cytokines are produced by different immune cells upon presentation of an antigen, and their secretion is believed to be the prime event in the subsequent neurophysiological responses taking place during immune stimulation. Several animal models are applied (Sukhai and Piquette-Miller 2000; McRae et al. 2003), and although results of the in vivo studies are somewhat conflicting, most demonstrated that P-gp expression and activity can be involved in different ways during an inflammatory episode, the degree and direction of the change in P-gp activity depending on the model and the inflammatory mediator used (McRae et al. 2003; Roberts and Goralski 2008).

Several in vitro studies have tried to extricate the signalling pathways of the involved cytokines and other chemotactic compounds leading to a functional change

of P-gp at the BBB. Hartz and colleagues define a pathway through which P-gp is acutely modulated. They describe a sequence of events, starting with TNFα (tumour necrosis factor), releasing endothelin-1, which in turn activates nitric oxide synthase and then protein C kinase, ultimately reducing P-gp transport (Hartz et al. 2004; Hartz et al. 2006). The same group showed that this regulation is biphasic: after an initial rapid decrease of P-gp activity following exposure to TNF and endotheline-1, an increase in transport activity was found at 6 h post exposure. Similar data are presented by others. For example, the results by Tan and colleagues showing an increase in P-gp expression following BBB breakdown by activated T-cells suggest both a role in immune cell-mediated cytotoxicity and a counterregulatory role in promoting cell survival and maintaining BBB integrity. They hypothesise that the latter role may be relevant in later stages of the inflammation (Tan et al. 2002). In vivo studies focusing on such a biphasic response in cytokine regulation and in P-gp activity in depressive or psychotic disorders are warranted and can be best worked out in animal models.

4.8 Depressive Disorder, Stress-Related Disorders and P-gp

A few studies have focused on BBB characteristics in relation to psychological stress. Rats subjected to perinatal stress had an increased permeability as measured by the uptake of Evans blue (Gomez-Gonzalez and Escobar 2009). Acute stress (e.g. immobilisation stress or forced swim) increases BBB permeability likewise (Sinton et al. 2000; Chandler et al. 2002; Esposito et al. 2001). In respect to the effect of chronic stress on BBB function, studies are lacking, but in major depressive disorder (MDD), BBB dysfunction has been suggested as a potential mechanism (Gudmundsson et al. 2007).

If P-gp is a susceptibility factor in stress-related disorders, animal models could be used to demonstrate their modulatory role in stress. To date, evidence is sparse. In one study, describing the anxiolytic-like effect of tariquidar (a P-gp inhibitor) in mice sensitised by a mild stressor, it was suggested that P-gp inhibition led to an increase of corticosteroids, which, in turn, would enhance the negative feedback control of the HPA axis (Thoeringer et al. 2009).

In two PET studies with [^{11}C]-verapamil, an increased function of P-gp at the BBB in temporal and frontal areas was found both in a group of medicated patients with MDD and schizophrenia (de Klerk et al. 2010b; de Klerk et al. 2009). Caution in the interpretation of the results of both studies is justified, since the findings were complicated by the use of either antidepressants or antipsychotics. The increase in P-gp function might be a result of the disorder itself or a result of antidepressant treatment. A sequel to these studies was set up to disentangle the possible contribution of antidepressant therapy and MDD. Rats were subjected either to chronic stress or to a continuously administered antidepressant. Using [^{11}C]-verapamil PET as a measure of P-gp activity, an indication was found for decreased P-gp activity in the stressed rats, whereas venlafaxine appeared to have an opposite effect on P-gp activity (de Klerk et al. 2010a). A confirmation study correlating the in vivo results

from both studies to P-gp expression at protein and mRNA level is under way. Although the in vivo imaging study may provide an indication for a susceptibility role of P-glycoprotein in depressive disorders, in the light of the limited evidence so far, it is impossible to interpret the findings without great restrictions.

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

Although the status of both MDD and schizophrenia as neurodegenerative disorders is tenuous, both disorders have neurodegenerative features. In depression, it has been hypothesised that neuroinflammation ultimately leads to neurodegeneration (Maes et al. 2009). The coincidence of structural brain changes and decreased regional blood flow has been well established in MDD as well as in schizophrenia. Loss of the integrity of the blood–brain barrier is a cardinal phenomenon in many neurodegenerative disorders including Alzheimer dementia. In the PET studies on Parkinson's disease a role for P-gp in neurodegeneration has been suggested, but this is based on small differences in tracer uptake between patients and control group (Bartels et al. 2008b).

The decreased P-gp function in old age, which has been indicated by [^{11}C]-verapamil PET studies, will certainly accentuate the problems encountered in pharmacotherapy in the elderly (Bartels et al. 2008a; Bauer et al. 2009). The decline in activity might be linked to the pathology in late-life depression such as the cognitive changes. A major role of P-gp is however refuted by the fact that the incidence of MDD decreases with age (Kessler et al. 2003).

4.10 Polymorphisms of P-gp and Their Effect on Function

Since the first report on a polymorphism in the ABCB1 gene, the quest for more variations in the DNA sequence explaining phenotypical differences has not stopped. Substantial progress has been made in identifying single nucleotide polymorphisms (SNPs) in the entire ABCB1 gene. Reports in the literature have particularly focused on C3435T (noncoding exon 26), after an initial report on altered duodenal P-gp expression and functionality associated with the TT variant (Hoffmeyer et al. 2000), but later on the SNPs G2677T/A and C1236T have generated interest as well.

Studies within the field of psychiatry have particularly focused on treatment response to antidepressants or antipsychotics. Other studies refer to side effects, and two studies pertain to the occurrence of ABCB1 polymorphisms in mood disorders and schizophrenia. In two studies, the diagnosis of depression was found to be associated with a haplotype of 13 ABCB1 polymorphisms (Dong et al. 2009). In the other study, mood disorders were associated with the haplotype of 129-2677-3435 (T-A-C) and with a lower frequency of ABCB1 alleles at −1517, −41 and −129 and a higher frequency of 2677A (Qian et al. 2006). In this study no association was found between ABCB1 and schizophrenia.

Most studies on the genetic effects of the SNPs C3435T, G2677T/A and C1236T or ABCB1 haplotypes showed little or no effect on treatment response (Table 4.1). A strong effect of a single transporter gene on a phenotypic response in complex disorders like MDD and schizophrenia is not amenable. A few reports on antipsychotic- or antidepressant-related side effects associated with polymorphisms have been published, and a few groups have communicated on the effect of ABCB1 polymorphisms and plasma concentrations of antipsychotics or antidepressants (Table 4.2). For risperidone, displaying high substrate affinity for P-gp, only modest genetic effects were reported in side effects (weight gain) and in treatment response (Kuzman et al. 2008; Xing et al. 2006).

The contradictions in observations for the major polymorphisms of ABCB1 are partly accountable to differences in methodology and to ethnic differences between study groups. In most studies, the sample size is too small to draw firm conclusions.

Thus, none of the SNPs of ABCB1, nor any of the haplotypes, can definitely be connected to phenotypical variation, but instead some may serve as biological marker for pinpointing a disease or susceptibility to drug-related side effects. In the near future, it is to be expected that analysis of SNP patterns in large patient cohorts with identical phenotypic features will identify SNP profiles that characterise susceptibility factors. Genome-wide association studies (GWAS) are the type of study designed to identify such a genetic variation. This strategy may be best worked out in a subset of patients with severe, recurrent and early onset form of depression, since this group of patients has shown an elevated genetic contribution (Zhao et al. 2009).

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

Other members of the ABC family that are expressed in the BBB include multidrug resistance proteins (MRP1, -2, -4 and -5) (ABCC genes) and breast cancer-related protein (BCRP/ABCG2 gene) (Cooray et al. 2002; Zhang et al. 2004). The exact location of some of the MRPs within the BBB is still debated (Zhang et al. 2004). The reasons for this uncertainty are the differences in transporter profiles between species as well as inferior antibody specificity. The predominant location of MRP1 is probably the basolateral membrane (Warren et al. 2009). Among the non-P-gp efflux transporters, MRP1 and BCRP have the highest expression in the human BBB, which however is much lower (around 20-fold) than that of P-gp (Slot et al. 2008).

The MRPs transport anionic compounds, including sulphate, glucuronide and glutathione (GSH) conjugates (Pedersen et al. 2008). Three typical antipsychotics (thioridazine, chlorprothixene and flupentixol), all carrying a sulphur atom, were found to inhibit MRP2 in vitro (Pedersen et al. 2008). Of the few reports on involvement of MRP1 or MRP2 in the transport of an antidepressant, no significant inhibition was found (Okamura et al. 2009). BCRP appears to be involved in the efflux of antipsychotics. For the major antipsychotics, Wang et al. demonstrated a similar profile of inhibition to that of P-gp (Wang et al. 2006), albeit that for most antipsychotics at least a 5-fold higher concentration was needed to

Table 4.1a Treatment response to antidepressants and antipsychotics related to ABCB1 polymorphisms

Drug	DSM[a] diagnosis	*ABCB1* variant	rs-id[b]	*n* cases [c]	Outcome measure[d,e,f,g,h,i]	References	*p*-value[j]
Amitriptyline		G2677T/A	rs2032583	50	% change in HAMD response after 3 weeks	Laika et al. (2006)	n.s.
Amitriptyline, venlafaxine or citalopram	MDD	Intron 4	rs2235015	133	% change in HAMD-21 score after 4 weeks	Uhr et al. (2008)	0.0024
		(C/T) intron 22	rs2032583	132			0.00007
Desipramine	MDD	UTR	rs17064	272	% change in HAMD-21 score after 8 weeks	Dong et al. (2009)	n.s.
		Haplotype block 1			Remission versus non-remission after 8 weeks		0.02
Paroxetine	MDD	(C/T) intron 22	rs2032583	124	% change in HAMD-21 score after 8 weeks	Sarginson et al. (2010)	0.024
		Intron 4	rs2235015				n.s.
		(A/G) intron 21	rs2235040				0.028
	MDD	G2677T/A	rs2032583	68	% change in HAMD response after 6 weeks	Kato et al. (2008)	0.01
		C3435T	rs1045642				n.s.
		C1236T	rs1128503				n.s.
		Haplotype 3435C-2677G-1236T					0.014
	MDD	G2677T/A	rs2032582	127	% change in HAMD response after 6 weeks	Mihaljevic et al. (2008)	n.s.
		C3435T	rs1045642				n.s.
Duloxetine	MDD	(A/C) (intron 22)	rs10280101	238	Response after 5 weeks	Perlis et al. (2010)	n.s.
		(A/G) (intron 22)	rs7787082	237			n.s.
		(C/T) intron 22	rs2032583	238			n.s.
		(A/G) intron 21	rs2235040	239			n.s.
Citalopram	MDD	C1236T	rs1128503	652	Response (395) versus nonresponse (257) on (different doses) after 12 weeks	Peters et al. (2008)	n.s.
		G2677T	rs2032582				n.s.
		C3435T	rs1045642				n.s.
Escitalopram	MDD	C1236T	rs1128503	100	Remission versus non-remission after 8 weeks	Lin et al. (2011)	n.s.
		C3435T	rs1045642				0.045
		Haplotype block 1 (intron26–27)					0.003
		Haplotype block 2 (incl. exon13)					n.s.

Fluoxetine	MDD	G1236A	rs1128503	142	% change in HAMD-21 score after 8 weeks	Dong et al. (2009)	n.s.
		(T/C)	rs10276036				n.s
		(T/A)	rs2235020				n.s
		(C/G)	rs2214103				n.s.
		Haplotype block 1		272	Remission versus non-remission after 8 weeks		0.03
		Haplotype block 2		272	Remission versus non-remission after 8 weeks		0.04
Fluoxetine or desipramine	MDD	Haplotype block 3		272	% change in HAMD-21 score after 8 weeks		0.01
Nortriptyline	MDD	C3435T	rs1045642	160	MADRAS score after 6 weeks	Roberts et al. (2002)	n.s.
Olanzapine	S	C3435T	rs1045642	41	BPRS change after 6 weeks, related to olanzapine concentration	Lin et al. (2006)	n.s.
		G2677T/A	rs2032582				0.03
		C1236T	rs1128503				0.04
Risperidone	S	G2677T	rs2032582	54	>50 % improvement on PANSS score	Jovanovic et al. (2010)	n.s.
		C3435T	rs1045642	58			n.s.
	S	C1236T	rs1128503	115	% change on BPRS after 8 weeks	Xing et al. (2006)	0.021
		G2677T	rs2032582				n.s.
		C3435T	rs1045642				n.s.

[a]*DSM diagnosis* diagnostic statistical manual, *MDD* major depressive disorder, *S* schizophrenia, *CIT* citalopram, *UTR* untranslated region
[b]*rs-id* reference sequence identity
[c]*n* number
[d]*HAMD-21* Hamilton Depression Rating Scale (21-item version)
[e]*MADRAS* Montgomery-Asberg Rating Scale
[f]*BPRS* Brief Psychiatric Rating Scale
[g]*CIT* citalopram
[h]*C/D* concentration to dose
[i]*PANSS* positive and negative symptom scale
[j]*n.s.* nonsignificant

Table 4.1b Side effects of antidepressants and antipsychotics related to ABCB1 polymorphisms

Drug	DSM[a] diagnosis	*ABCB1* variant	rs-id[b]	*n*[c] cases	Outcome measure[d]	References	*p*-value[e]
Amitriptyline	MDD	G2677T/A	rs2032582	50	C/D ratio	Laika et al. (2006)	n.s.
Clozapine	S	C3435T	rs1045642	75	C/D ratio	Sirot Jacqenoud et al. (2009)	0.046
		G2677T/A	rs2032582				n.s.
Fluvoxamine	MDD	C3435T	rs1045642	62	Higher C/D ratio in T-genotypes	Fukui et al. (2007)	0.026
Fluvoxamine, Paroxetine, sertraline, venlafaxine or citalopram	MDD		rs2235040A rs2032583C	424	(rs2235040)A and (rs2032583)C allele associated with more side effects	de Klerk et al. (2012)	0.001 0.002
Olanzapine	S	C3435T	rs1045642	41	Weight gain related to olanzapine concentration	Lin et al. (2006)	n.s.
	S	C3435T	rs1045642	56	Weight gain (>7 % vs. <7 %)	Kuzman et al. (2008)	n.s.
		G2677T/A	rs2032582				n.s.
	S	C3435T	rs1045642	122	C/D ratio (variable doses)	Ghotbi et al. (2010)	n.s.
		G2677T	rs2032582				n.s.
Risperidone	S	C3435T	rs1045642	47	Weight gain (>7 % vs. <7 %)	Kuzman et al. (2008)	0.015
		G2677T	rs2032582				0.031
		Haplotype 3435T-2677T					0.033
	S	G2677T	rs2032582	83	Higher C/D ratio (active moiety) in TT-genotypes	Jovanovic et al. (2010)	0.001
		C3435T	rs1045642		Higher C/D ratio (active moiety) in TT-genotypes		0.004
	S	C3435T	rs1045642	85	C/D ratio (risperidone and/or 9-OH-risperidone)	Yasui-Furukori et al. (2004)	n.s.
		G2677T/A	rs2032582				n.s.

[a]*DSM diagnosis* diagnostic statistical manual, *MDD* major depressive disorder, *S* schizophrenia
[b]*rs-id* reference sequence identity
[c]*n* number
[d]*C/D* concentration to dose
[e]*n.s.* nonsignificant

inhibit BCRP (compared to P-gp) (Matsson et al. 2007). For the antidepressants maprotiline and desipramine, no significant inhibition of BCRP was reported (Matsson et al. 2009).

In conclusion, the clinical relevance of the MRPs in conferring resistance to the major psychiatric drugs at the BBB is probably negligible in comparison to P-gp, given the lower substrate affinity and the much lower expression in the BBB. BCRP might exert a more significant role at the BBB (Matsson et al. 2009) and is probably more subsidiary to P-gp function than the MRPs. Nevertheless, the impact of BCRP in drug disposition at the BBB in vivo is still uncertain (Urquhart and Kim 2009).

4.12 Concluding Remarks and Future Directions

In conclusion, the role that P-gp plays in depressive and psychotic disorders is far from clear. Most antidepressant and antipsychotic drugs have a weak to moderate affinity as a substrate for P-gp, and some may have inhibitory properties as well, which may be relevant in drug-drug interactions. P-gp may be involved in a depressive or psychotic episode as well, since evidence exists for a (temporarily) decrease in activity and expression during a neuroinflammatory event, which characterises the pathophysiology of these disorders.

Given the importance of P-glycoprotein in drug transport at the BBB and its involvement in neuroinflammation, it is comprehensible that the protein is of great interest in the field of neuroscience. At this time, the understanding of the precise role in neuropsychiatric disorders and drug disposition is incomplete, but new developments in neuroimaging, pharmacogenetics and molecular biology are in full progress and it will be only a matter of time to accomplish this. As outlined above, an important step forward in the identification of genetic variants has been made, albeit the complex regulatory pathways involved in P-gp modulation require further considerations in pharmacogenetic studies. Studies with larger sample size will be needed to detect modest effects. Progress in PET imaging largely depends on development of new tracers that approach the unmet needs of an ideal tracer.

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Part II

Depression and Related Disorders

Molecular Imaging of Depressive Disorders

5

Henricus G. Ruhé, Anniek K.D. Visser, Vibe G. Frokjaer, Bartholomeus (Benno) C.M. Haarman, Hans C. Klein, and Jan Booij

Contents

H.G. Ruhé, MD, PhD (✉)
Department of Psychiatry, Mood and Anxiety Disorders, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Department of Psychiatry, Program for Mood Disorders, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

University of Groningen, University Medical Center Groningen, University Center for Psychiatry, Hanzeplein 1, Groningen 9713 GZ, The Netherlands

Mood and Anxiety Disorders, University Center for Psychiatry, University Medical Center Groningen, University of Groningen, Room 5.16., Hanzeplein 1, Groningen 9700 RB, The Netherlands
e-mail: h.g.ruhe@umcg.nl

A.K.D. Visser
Department of Nuclear Medicine and Molecular Imaging, University of Groningen, University Medical Center Groningen, Hanzeplein 1, Groningen 9713 GZ, The Netherlands

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_5, © Springer-Verlag Berlin Heidelberg 2014

V.G. Frokjaer
Center for Integrated Molecular Brain Imaging and Neurobiology Research Unit, Copenhagen University Hospital, Rigshospitalet, Juliane Maries Vej 24, DK-2100, Copenhagen, Denmark

B.(B.)C.M. Haarman, MD
Department of Psychiatry, Mood and Anxiety Disorders, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

University of Groningen, University Medical Center Groningen, Academic Centre of Psychiatry, Hanzeplein 1, Groningen 9713 GZ, The Netherlands

H.C. Klein, MD, PhD
Program for Geriatric Psychiatry, University Center Psychiatry, Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, CC44, Hanzeplein 1, Groningen 9713 GZ, The Netherlands

J. Booij, MD, PhD
Department of Nuclear Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, Amsterdam 1105 AZ, The Netherlands

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, 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. Furthermore, future longitudinal molecular imaging studies in the same subjects at different clinical mood states 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.

5.1 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). 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). 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), 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 (Goodwin 2003; Nivoli et al. 2011; Yatham et al. 2009).

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 have not yet been developed enough for reliable measurements in MDD.

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. 9.

Despite large advances by this research, to date the pathophysiology behind MDD and BD cannot be fully explained. This could be due to insufficient acknowledgement of the heterogeneity of the clinical phenotypes of depression, 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.

5.2 Metabolism and Cerebral Blood Flow

From the 1990s of the last century onwards, 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. 2012). 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 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; Milak et al. 2009). Regarding increased sgACC activity, results are more consistent, especially after corrections for partial volumes (Drevets 1999). Persistent increased sgACC metabolism has been reported especially in nonresponsive patients (Mayberg 2003), which was the basis for targeting this region by 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 is 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).

In BD in the depressed state, comparable dysfunction was found, although not consistently (Gonul et al. 2009). Global 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 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 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).

5.3 Imaging of Monoamine Systems

5.3.1 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 base 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.

5.3.1.1 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 into 5-hydroxy-tryptamine (5-HT), or serotonin, by aromatic amino acid decarboxylase (AADC). Produced 5-HT is taken up by 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 into 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. 5.3.3, 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 labelling 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 5.1). 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

Table 5.1 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^* Cingulate left: 12 % ↓ K^* Mesial temporal lobe right: 9 % ↓ K^* (ns) Mesial temporal lobe left: 11 % ↓ K^* Male: Cingulate cortex right: 3 % ↓ K^* (ns) Cingulate cortex left: 9 % ↓ K^*	 −1.09 −0.91 −0.64 −0.78 −0.21 −0.58
Agren and Reibring (1994)[a,b]	6 MDD 8 HC	[^{11}C]5-HTP	Drug free (>10 days)	Whole brain: 30 % ↓ uptake Medial prefrontal cortex lower level: 766 % ↑ k_3-l_3[c] Medial prefrontal cortex upper level: 114 % ↑ k_3-l_3[c]	[d] 4.84 2.59
Agren et al. (1991)[b]	6 MDD 8 HC	[^{11}C]5-HTP	Drug free (>10 days)	Overall: 29 % ↓ SUV Dorsolateral prefrontal cortex: 27 % ↓ SUV Medial area: 26 % ↓ SUV Basal ganglia: 21 % ↓ SUV (ns) Caudate nucleus: 22 % ↓ SUV (ns) Lentiform nucleus: 15 % ↓ (ns)	−0.93 −0.83 −0.82 −0.54 −0.57 −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 then *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

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 rely. Pindolol prevented this decrease and increased the rates in terminal areas even more (Nguyen et al. 2009).

In summary, these studies indicate that 5-HT synthesis, mainly in 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, causing symptoms of MDD. 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, described in Sect. 5.3.1.3.

5.3.1.2 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 onwards (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 binding competes with endogenous serotonin (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 golden 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 March 2012, 22 separate studies investigated the SERT in unipolar MDD (Table 5.2A) and four in BP (Table 5.2B). Most studies were small (16 studies with less than 20 MDD patients), which generally limits the statistical power to detect differences with less than large effect sizes (<0.8). Thirteen studies used PET tracers ([^{11}C]DASB or [^{11}C](+)McN5652), and 13 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 studied, 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, 170 MDD patients have been investigated in total versus 233 controls. All studies investigated drug-free patients (of whom 27/146 were reported drug naive) in a depressed state; one study investigated remitted patients (of whom 9/24 were drug naive) (Bhagwagar et al. 2007).

The PET ligand [^{11}C]DASB was used in seven studies (Bhagwagar et al. 2007; Cannon et al. 2007; Meyer et al. 2001c, 2004a, b; Reimold et al. 2008; Selvaraj et al. 2011). 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 two studies ($n=37$) reported a decrease in SERT availability (Parsey et al. 2006b; Selvaraj et al. 2011), and five studies ($n=59$) reported no difference (Cannon et al. 2007; Ichimiya et al. 2002; Meyer et al. 2004a; Reimold et al. 2008; Reivich et al. 2004). 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).

In the thalamus, two studies ($n=22$) reported a decrease in SERT availability (Reimold et al. 2008; Selvaraj et al. 2011), while two studies ($n=24$) reported no difference (Meyer et al. 2004a; Reivich et al. 2004) and 2 studies ($n=25$) an increase (Cannon et al. 2007; Ichimiya et al. 2002).

Table 5.2 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*					
Selvaraj et al. (2011)	12 MDD 24 HC (males only)	[^{11}C]DASB	Drug-free ≥4 months (4 drug naive)	Amygd: 0 %↓ (p=.99) in MDD	0.0
				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 49 HC	[^{123}I]β-CIT	Drug-free ≥4 weeks (34 drug naive)	Midbr: 2 %↓ (p=.73) in MDD	−0.1
				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 6 NES (BDI <19)	[^{123}I]-ADAM	Drug-free >3 weeks	Midbr 18 %↓ (p=.001) in MDD L/R temp lobe 15 %↓ (p<.01) in MDD L/R bas. ganglia 3 %↓ (n.s.) in MDD	−3.0 −2.0 −0.2
Reimold et al. (2008)	10 MDD 19 HC	[^{11}C]DASB	Drug-free >5 half-lives of previous drugs	Thal 16 %↓ (p=.005) in MDD Midbr 6 %↓ (p=.26) in MDD Amygd 1 %↓ (p=.45) in MDD Thal SERT inversely correlated with anxiety (p=.02) and age, but not with depression severity (n.s.)	−1.1 −0.3 −0.0
Bhagwagar et al. (2007)	24 MDD (recovered) 20 HC (males only)	[^{11}C]DASB	Drug-free >3 months (9 drug naive)	No overall differences (p=0.28) Amygd 0 %↑ (n.s.) in MDD ACC 0 %↑ (n.s.) in MDD Caudate 9 %↑ (n.s.) in MDD PFC 5 %↑ (n.s.) in MDD Hippoc 7 %↑ (n.s.) in MDD Insula 0 %↑ (n.s.) in MDD Thalamus 4 %↑ (n.s.) in MDD Dorsal raphe 15 %↑ (n.s.) in MDD No association with DAS scores	 0.0 0.0 0.3 0.2 0.3 0.0 0.1 0.4
Cannon et al. (2006b, 2007), Laje et al. (2010), Liu et al. (2011)	18 MDD 18 BD 34 HC	[^{11}C]DASB	Drug-free >3 weeks	Midbr 8 %↑ (n.s.) in MDD Thal 27 %↑ (p=.0001) in MDD Striat 12 %↑ (p=.04) in MDD Insula 15 %↑ (p=.02) in MDD PAG 22 %↑ (p=.009) in MDD pgACC 16 %↑ (p=.06) in MDD 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)	0.4 1.4 0.8 1.1 1.0 0.7

(continued)

Table 5.2 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size[a]
Lehto et al. (2006, 2008b), Joensuu et al. (2007, 2010)	29 MDD 19 HC	[^{123}I]nor β-CIT	Drug naïve	Midbr 10 %↓ (p=.0002) in MDD No correlation with MDD severity Linear inverse correlation with atypical score (Lehto et al. 2006)	−1.1
				In MDD in MPFC 26 %↓ (p=.024) in SS vs. other genotypes; in Midbr 1 %↓ (n.s.)	−1.2
	Subgroup: 8 MDD+dysthymia vs. 11 MDD			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 43 HC	[^{11}C] McN5652	Drug-free ≥2 weeks (12 drug naïve)	BP ↓ (p<.02) over all regions in MDD	
				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)	
				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 32 HC	[^{123}I]β-CIT	Drug-free	Females: Thal 22 %↓ (p=.005) in MDD[b]	−1.0
				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 12 HC	[^{123}I]-ADAM	Drug-free	Midbr 21 %↑ (p=0.07) in MDD In MDD males<females (n.s.) No correlation with MDD severity	0.4

Catafau et al. (2006)	10 MDD 10 HC	[^{123}I]-ADAM	Drug-free >6 months	Midbr 4 %↓ (p=.52) in MDD Thal 11 %↓ (p=.09) in MDD Striat 5 %↑ (p=.62) in MDD	−0.3 −0.8 0.3
Newberg et al. (2005)	7 MDD 6 HC	[^{123}I]-ADAM	Drug-free > 3 weeks	Midbr 7 %↓ (p=.01) in MDD Sign. correlation with MDD severity	−1.4
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 4 HC	[^{11}C](+)McN 5652	Drug-free for ≥5 half-lives	L PFC17%↑ (p=.013) in MDD R ACC 24 %↑ (p=.043) in MDD Thal 17 %↑ (n.s.) in MDD Midbr 25 %↑ (n.s.) in MDD	2.9 1.9 0.4 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 21 HC (males only)	[^{11}C](+) McN5652	Drug-free	Thal 23 %↑ (p=.002) in MDD/BD Midbr −2 % ≈ (n.s.)	1.0 0.1
Meyer et al. (2001c)	13 MDD 13 HC	[^{11}C]DASB	Drug-free (11 drug naive)	Striat no differences (p=.82)[d] 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) PFC n.s. Thal n.s.	0.9 (1 h) 0.8 (4 h) – –

(continued)

Table 5.2 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]	Effect size[a]
Willeit et al. (2000)	11 SAD 11 HC	[^{123}I]β-CIT	Drug-free ≥6 months	Midbr 2 %↑ (p=.95) in MDD (4 h) Thal 7 %↓ (p=.31) in MDD (4 h) Midbr 7 %↓ (p=.39) in MDD (24 h) Thal 15 %↓ (p=.026) in MDD (24 h)	0.2 −0.6 −0.5 −1.2
Kugaya et al. (2004), Malison et al. (1998b)	15 MDD 15 HC	[^{123}I]β-CIT	Drug-free	Midbr 18 %↓ (p=.02) in MDD No correlation with MDD severity Higher SERT predicted treatment response (Kugaya et al. 2004)	−0.8
B. *Bipolar depression*					
Chou et al. (2010)	24 BD (10 BP-I) (euthymic) 28 HC	[^{123}I]-ADAM	Mood stabilizers and antipsychotics allowed; no SSRI/SNRI >1 year	Midbr 8 %↓ (p=.27) in BD-I+BD-II Midbr 25 %↓ (p=.042) in BD-I Midbr 3 %↑ (n.s.) in BD-II In BD-I SERT correlated inversely with duration of illness	−0.3 1.2 0.1
Oquendo et al. (2007)	18 BD (10 BP-I) 41 HC	[^{11}C](+)McN 5652	Drug-free ≥2 weeks (2 drug naive)	Midbr 27 %↓ (p=.02) in BD[e] Amygd 26 %↓ (p=.02) in BD Hippoc 23 %↓ (p=.02) in BD Thal 23 %↓ (p=.02) in BD Putamen 16 %↓ (p=.02) in BD ACC 23 %↓ (p=.02) in BD No correlation with severity. No effect of 5-HTTLPR genotype	−0.8[e] −0.6 −0.7 −0.8 −0.3 −0.6

Cannon et al. (2006b), Laje et al. (2010)	18 BD (5 BP-I) 37 HC	[^{11}C]DASB	Drug-free ≥1 month(1 drug naive)	Thal 14 % ↑ (p = .003) in BD Insula 13 % ↑ (p = .015) in BD pgACC 16 % ↑ (p = .017) in BD sgACC 9 % ↑ (n.s.) in BD Striat 8 % ↑ (p = .06) in BD Midbr 5 % ↓ (n.s.) in BD DCC 19 % ↑ (p = .004) in BD PCC 14 % ↑ (p = .05) in BD 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)	0.9 0.7 0.8 0.4 0.5 −0.4 0.8 0.6
Ichimiya et al. (2002)	7 MDD and 6 BD 21 HC (males only)	[^{11}C](+)McN 5652	Drug-free	Thal 23 %↑ (p = .002) in MDD/BD Midbr −2 %≈ (n.s.)	1.0 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}

In the striatum, four studies ($n = 82$) reported no difference in SERT availability (Meyer et al. 2001c, 2004a, b; Selvaraj et al. 2011). Age was negatively correlated with SERT availability (Meyer et al. 2001c). In other regions only significant increases were reported in the right ACC (Reivich et al. 2004) and PAG (Cannon et al. 2007).

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, and dorsal ACC (Cannon et al. 2007) (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. However, 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). Recently, 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, most studies used the less expensive, easier to handle, alternative SPECT imaging, with a total of 228 MDD patients versus 194 healthy controls being scanned. All studies investigated drug-free patients (of whom

94/228 were reported drug naive) in a depressed state. 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 for the midbrain, sometimes for the thalamus/diencephalon and occasionally for the MPFC (Joensuu et al. 2010), were reported. 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, three studies ($n=51$) reported a decrease in SERT (Lehto et al. 2006; Malison et al. 1998b; Newberg et al. 2005), and eight studies ($n=177$) found no difference (Ahonen et al. 2004; Catafau et al. 2006; Dahlstrom et al. 2000; Herold et al. 2006; Hsieh et al. 2010; Ruhe et al. 2009a; Staley et al. 2006; Willeit et al. 2000) in direct comparisons of patients and controls. Of note is that three of the studies, which were poorly powered and reported no difference, in fact reported nonsignificant increases in SERT availability in MDD patients ($n=62$) (Ahonen et al. 2004; Dahlstrom et al. 2000; Herold et al. 2006). One study reported a significant negative correlation between midbrain SERT and depression severity (Newberg et al. 2005).

In the thalamus, one study ($n=32$) reported a decrease in SERT (Staley et al. 2006) and three studies ($n=101$) 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 ($n=81$) 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 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. 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 three PET studies and only one SPECT study (Table 5.2B). 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 with anxiety and OCD comorbidity (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), 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 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 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 recent review Willeit et al. concluded that by genotyping the triallelic 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 in the midbrain and thalamus (Ruhe et al. 2009c), but 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-HT2A 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. 2010a)) 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. 2010b; 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.

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, in general, the majority of studies in unipolar depressed patients reported no differences in SERT availability in the midbrain, more equivocal changes (decrease, no difference, increase) in the thalamus, and no differences in the striatum. 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 these 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 leads 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 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 (Miller et al. 2009b). First the observed differences in SERT availability in the midbrain and thalamus (and possibly also in the caudate nucleus/striatum) between depressed and euthymic patients suggest compensatory flexibility of the SERT expression (Bhagwagar et al. 2007; Selvaraj et al. 2011). However, it cannot be ruled out that these results are incomparable by 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 indeed 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, 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), 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, 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).

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 11 studies investigated the dynamics of short- and long-term (>2 weeks) treatment with antidepressants, respectively (Table 5.3). 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. 5.1). The rapid increase in occupancy occurs at clinically (very) low doses of the antidepressants, while at therapeutic doses a maximum occupancy is reached around 80–90 %. Initial studies with SSRIs reported 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 future studies did not unequivocally replicate this finding (Catafau et al. 2006; Kugaya et al. 2004; Ruhe et al. 2009b, c; Smith et al. 2011), 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). However, in a voxel-wise analysis in elderly patients, Smith et al. found

Table 5.3 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]
Lundberg et al. (2012)	20 MDD 26 HC	[^{11}C] MADAM	≥2 months AMI 30 and 67.5 mg ($n=2$) 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)	Occ[b] putamen: AMI + CLOM: 61 % SSRI: 70 %
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)	42 MDD (32 randomized after 6 weeks)	[^{123}I]β-CIT	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)	Occ (6 weeks PAR 20 mg): Midbr: 71.1 % Thal: 61.3 % 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 mg, 10 mg, 20 mg) or CIT (10 mg 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)
Takano et al. (2006b)	15 HC (males only)	[^{11}C]DASB	Single-dose DLX (5, 20, 40, or 60 mg) ($n=12$) DLX 60 mg for 7 days then stopped ($n=3$)	Occ Thal: 43.6 % (5 mg), 71.3 % (20 mg), 80.6 % (40 mg), 81.8 % (60 mg) 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	4–6days SER 25 mg, 50 mg 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

(continued)

Table 5.3 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome[a]
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
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 9 HC	[^{123}I]β-CIT	6 weeks PAR 20 mg CIT 40 mg (8 days), CIT 40 mg + Bupropion 100 mg (8–16 days)	Occ at 1–3 weeks Midbr: 36.5 %, Thal: 29.1 % Occ at 6 weeks Midbr: 32.6 %, Thal: 23.4 % 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 27 HC	[^{11}C] McN5652	CLOM 20–250 mg, FLV 25–200 mg (long term) CLOM 5–50 mg, FLV 12.5–50 mg (single dose)	Occ[b] Thal: CLOM ≥61.3–100 %; FLV ≥76.6–93.6 % Occ Thal: CLOM ≥83.9–100 %; FLV ≥7.7–87.7 %
Meyer et al. (2001c)	12 MDD 17 HC	[^{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: 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
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: *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 23 h after injection of radioligand

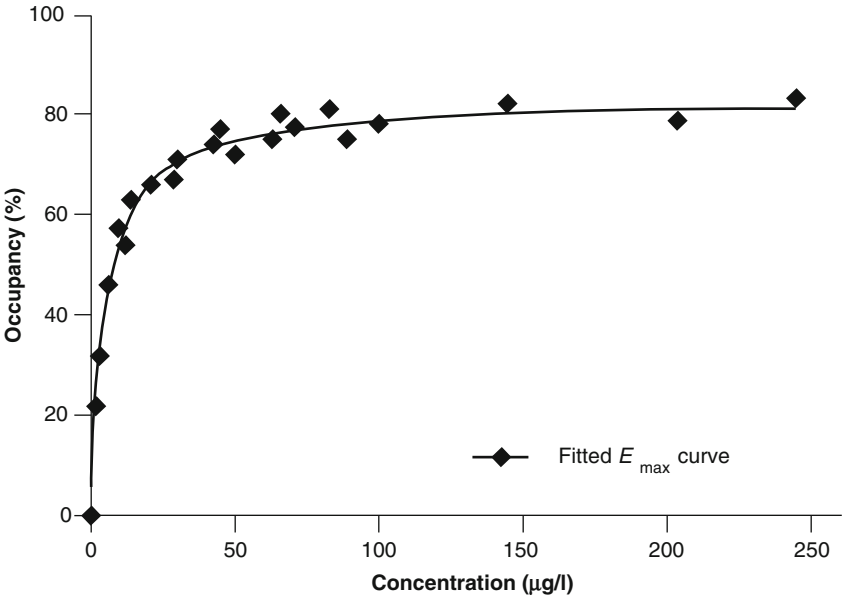

Fig. 5.1 Concentration-occupancy curve. This figure shows a hypothetical E_{max}-curve. The curve is defined with the formula y = (a*x)/(b+x) , in which *a* represents the maximum binding (B_{max}) and *b* the concentration with 50 % occupancy (EC_{50}). Here $B_{max} = 82.8\ \% \pm 0.85$ (SE) and $EC_{50} = 5.09\ \mu g/l \pm 0.32$ (SE)

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 – were 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 promotor 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 flexible 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).

Finally, occupancy studies are increasingly used in the development and evaluation of the effects of antidepressants. First, several SERT occupancy studies indicated that the relation 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. 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 and the (pharmacologically inactive) R-enantiomer) during acute and prolonged treatment (Kasper et al. 2009). They showed that although doses were equivalent, prolonged treatment for 10 days with escitalopram resulted in significantly higher occupancy rates (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 serum level by SERT occupancy 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 in 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 relation between clinical and neurobiological effects of antidepressants.

5.3.1.3 Serotonin Receptor Imaging

5-HT$_{1A}$

The 5-HT$_{1A}$ receptors are presynaptically localized on serotonergic cell bodies relying 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 5-HT in the synaptic cleft often 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 could therefore contribute to the understanding of the mechanisms of antidepressant drugs and elucidate on the underlying mechanisms of nonresponders to SSRIs and the involvement of desensitization of autoreceptors. Over the years, mainly 5-HT$_{1A}$ receptor PET tracers have been developed (Passchier and van Waarde 2001). However, only [*carbonyl*-^{11}C] WAY-100635 (or [^{11}C]WAY-100635) was used for studies that compared healthy controls to patients with MDD. WAY-100635 is a 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; however, 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 the activity measure taken 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), and BP_P (specific binding in respect to total parent radioligand in plasma) (Innis et al. 2007).

Seven 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 5.4A, B). Two studies did not find an effect and five studies even found an increase when BP_F was used as an outcome measure.

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 great 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 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 different 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.

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 lower BP_{ND} to control levels in the medial orbital cortex (Lothe et al. 2012).

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

Table 5.4 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}*					
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
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]

(continued)

Table 5.4 (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 naïve)/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 % ↓ $BP_?$	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
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
Drevets et al. (1999)	12 (4 BD)/8	[^{11}C]WAY-100635	Drug-free (>2 weeks)	Mesiotemporal cortex: 27 % ↓ BP_{ND}	1.16
				Raphe: 42 % ↓ BP_{ND}	1.27
				Hippocampus: 25 % ↓ BP_{ND}	1.12
B. *Bipolar depression 5-HT$_{1A}$*					
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	
				Forebrain: 29–50 % ↑ BP_F	
C. *Unipolar depression 5-HT$_{1B}$*					
Murrough et al. (2011)	10/10	[11C]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 then *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

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). Contradictory, Parsey et al. found a significant increase in BP_F in MDD patients that were drug naïve, 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 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 relation 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).

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-naïve, 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 is also dependent on the kinetic model used.

Several of the studies mentioned above show a trend towards a difference in distribution volume in 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 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 show 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 cerebellum as a reference tissue is due to changes in specific binding in 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). Therefore, most probably, MDD is associated with an increase in binding to 5-HT_{1A} receptors. It is difficult to judge whether this reflects a 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 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).

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 5.4C). 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 operable 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 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 necessitates 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 serve as 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 pathophysiological understanding of MDD (also see Sect. 5.4.1).

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 5.5 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.

Table 5.5 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 20 HC	[11C]MDL	Medication-free >6 months	Frontal 19 %↑ Parietal 25 %↑ Occipital 19 %↑ Temporal no difference → Positive correlation with dysfunctional attitudes in recovered patients	NA
Mintun et al. (2004)	46 MDD 29 HC	[^{18}F]altanserin	Medication-free (4 weeks)	Hippocampus 29 % ↓ Pregenual AC 17 %↓ Subgenual AC 21 % ↓ Gyrus rectus 14 % ↓ Dorsolateral prefrontal 16 % ↓ Lateral temporal 12 % ↓ Superior parietal 17 % ↓ Occipital 9 % ↓	–0.71 –0.36 –0.41 –0.30 –0.36 –0.31 –0.38 –0.21
Meyer et al. (2003)	22 MDD 22 HC	[^{18}F]setoperone	Medication-free (6 months)	No differences between the total groups Cortex↑ by 21–29 % (particularly middle frontal gyrus bilaterally) in severe depression, $N = 11$ Positive association with dysfunctional attitudes	NA NA NA

(continued)

Table 5.5 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Outcome	Effect size
Messa et al. (2003)[b]	19 MDD	[^{18}F]	Antidepressant naive	Frontal 26 %↓	−1.03
	20 HC	fluoroethyl-spiperone	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 10 HC	[^{18}F]altanserin	Untreated	No difference in all regions assessed →	NA
Meyer et al. (1999)	14 MDD 19 HC	[^{18}F]setoperone	Medication-free (>6 months)	Prefrontal cortex 11 %↓ Right/left ratio prefrontal cortex 1 %↑	−0.31 0.025
Biver et al. (1997)	8 MDD 22 HC	[^{18}F]altanserin	Medication-free (10 days)	Right orbitofrontal-insular cortex 17 %↓	−1.08
D'haenen et al. (1992)	19 MDD 10 HC	[^{123}I]ketanserin	Medication-free >7 days (10 pt > 3 weeks)	Sup. frontal 14 %↑ Central sulcus 1 %↑ Parietal 21 % ↑ Prefrontal 7 %↓ Infero-frontal 7 %↑ Anterior temporal 1 %↓ Posterior temporal1% ↑ Occipital 4 % ↓ Right/left ratio infero-frontal cortex↑	0.49 0.03 1.48 −0.32 0.36 −0.03 0.08 −0.16 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 naïve and 15 patients treated for 4 weeks with paroxetine

[c]Late-life depression

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 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 to avoid type II errors, robust detection of differences in 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 towards an association between high frontal 5-HT_{2A} receptor binding and increased risk load (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.

5.3.2 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.

5.3.2.1 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 and co-workers (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 Ågren and co-workers reported on a decreased DOPA uptake in the medical 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).

5.3.2.2 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) 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 form 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 5.6A. Approximately half of these studies did not find statistically significant differences in striatal DAT binding versus age-matched controls. Also, while four studies showed a significant increase of DAT binding in MDD (Amsterdam et al. 2012; Amsterdam and Newberg 2007; Laasonen-Balk et al. 2004; Yang et al. 2008), three studies found the opposite (Meyer et al. 2001b; Sarchiapone et al. 2006;

Table 5.6 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*					
Amsterdam et al. (2012)	24 MDD 84 HC	[^{99m}Tc] TRODAT	Drug-free (>6 m)	7 % increase (put right) 12 % increase (put left) 1 % decrease (caudate right) (ns) 2 % increase (caudate left) (ns)	0.47 1.11 −0.16 0.20
Wu et al. (2011)	13 MDD 10 HC	[^{99m}Tc] TRODAT	Drug-free (>2 years)	35 % decrease (striatum right) 35 % decrease (striatum left)	−4.89 −4.65
Lehto et al. (2008b)[a]	11 MDD 19 HC	[^{123}I] nor-β-CIT	Drug naive	0.1 % decrease striatum (ns)	−0.06
Yang et al. (2008)	10 MDD 10 HC	[^{99m}Tc] TRODAT	Drug-free (>3 m)	12 % increase	1.06
Amsterdam and Newberg (2007)	10 MDD 46 HC	[^{99m}Tc] TRODAT	Drug-free (>1 week)	30 % increase (put right ant) 47 % increase (put right post) 10 % increase (put left ant) 27 % increase (put left post) 12 % increase (caudate right) 18 % increase (caudate left)	1.59 1.39 0.46 0.89 0.72 1.12
Argyelan et al. (2005)	16 MDD 12 HC	[^{99m}Tc] TRODAT	9 drug-free (>2 wks) 7 drug naive	7 % decrease (ns)	−0.23
Staley et al. (2006)	32 MDD 32 HC	[^{123}I]β-CIT	14 drug naive 15 drug free 3 history unknown	1 % decrease in women (ns) 3 % increase in men (ns)	−0.29 0.59
Sarchiapone et al. (2006)[b]	11 MDD 9HC	[^{123}I] FP-CIT	Drug-free (period not described)	20 % decrease (put right) 23 % decrease (left and right) 17 % decrease (caudate right) 18 % decrease (caudate right)	−1.04 −1.19 −0.85 −1.09
Meyer et al. (2001b)	9 MDD 23 HC	[^{11}C] RTI-32	5 drug naive 4 drug-free (>3 m)	16 % decrease (put right) 14 % decrease (put left) 14 % decrease (caudate right) 12 % decrease (caudate left)	−0.92 −0.86 −0.90 −0.75
Dahlstrom et al. (2000)[c]	31 MDD 10 non-MDD	[^{123}I]β-CIT	Drug naive	0.4 % increase (ns)	0.03

(continued)

Table 5.6 (continued)

Authors (year)	Nr pts/ controls	Radiotracer	MDD treatment	Change DAT binding	Effect size
Laasonen-Balk et al. (1999), Laasonen-Balk et al. (2004)	15 MDD 18 HC	[^{123}I]β-CIT	Drug naive	24 % increase (striatum right) 22 % increase (striatum left)	1.12 1.15
Malison et al. (1998b)	15 MDD 15 HC	[^{123}I]β-CIT	6 drug naive	11 % decrease (ns)	−0.43
B. *Bipolar depression*					
Amsterdam et al. (2012)[d]	15 BD 84 HC	[^{99m}Tc] TRODAT	Drug-free (>6 m)	3 % increase (caudate left)[e] 2 % decrease (caudate right) 13 % increase (put left) 5 % increase (put right)	0.28 −0.21 1.15 0.32
Anand et al. (2011)	5 BD euthymic 6 BD depressed (8 BP-I) 13 HC	[^{11}C]CFT	Drug-free (>2 wks)	20 % decrease (caudate left)[f] 21 % decrease (caudate right) 14 % decrease (put left) 17 % decrease (put right) (ns) 7 % decrease (ventr str left) (ns) 1 % decrease (ventr str right) (ns)	−1.38 −0.78 −0.88 −0.57 −0.28 −0.01
Chang et al. (2010)	7 BP-I 10 BP-II 17 HC	[^{99m}Tc] TRODAT	Drug-free (>2 m)	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) 5 % decrease (caudate right) (ns) 4 % increase (ant put left) (ns) 16 % increase (ant put right) (ns) 13 % increase (post put left) (ns) 34 % increase (post put right)	0.91 −0.28 0.25 0.68 0.45 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, *m* months, *wks* weeks

[a]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)

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

[c]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)

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

[e]No significance levels provided

[f]Means and SD estimated from figure

[g]No significant difference in DAT binding ratios was found between the two subgroups of patients

Wu et al. 2011). 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. However, one study did include only anhedonic depressed patients (Sarchiapone et al. 2006).

Most studies did not find a significant correlation between striatal DAT binding and symptomatology (Laasonen-Balk 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; Dahlstrom et al. 2000; Meyer et al. 2001b; Wu et al. 2011). On the other hand, Argyelán and co-workers (Argyelan 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). Finally, Wu et al., who showed decreased DAT binding, used a HDRS score of at least 24 plus psychomotor retardation (Wu et al. 2011). 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, or in severely ill patients, and/or treatment-resistant depression (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 5.6B. While at least 2 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 on 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, or 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 brainstem (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).

DAT Imaging in Other Neuropsychiatric Disorders and Its Association with Depression

As mentioned earlier, depression may occur in about 1 out of 3 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 a SPECT study using [^{99m}Tc] TRODAT-1 (Felicio et al. 2010). Three 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), although this could not be replicated in another neurodegenerative disorder characterized by severe loss of dopaminergic neurons (i.e., Lewy body dementia (Roselli et al. 2009)).

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 (MADRS) scale scores was found, both during withdrawal and after sobriety (Laine et al. 1999). 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. and Árgyelán et al. 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 8 MDD patients in comparison to test-retest data in 8 healthy controls. The occupancy after bupropion treatment was 14 % (6–22 %) (Meyer et al. 2002). Árgyelán 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 (Argyelan et al. 2005).

Interestingly, a recent PET study in monkeys showed that electroconvulsive therapy may induce an increase in striatal DAT and vesicular transporters after finalizing a 6-week electroconvulsive therapy course (Landau et al. 2011).

In ten depressed patients who were treated with the SSRI paroxetine (20 mg/day), a significant increase in striatal DAT binding was observed (Kugaya et al. 2003). On the other hand 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).

5.3.2.3 Postsynaptic Imaging

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 D_1-like receptor binding in vivo, binding to this receptor was 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 D_1-like receptor binding in the striatum in patients with major depression with anger attacks (Dougherty et al. 2006).

Many molecular imaging studies in major depression focused on postsynaptic dopamine $D_{2/3}$ receptors (Table 5.7A). 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). Also one PET study reported on 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 the four studies that showed significant differences between groups, striatal $D_{2/3}$ receptor binding did not correlate

Table 5.7 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*					
Moses-Kolko et al. (2012)	10 MDD 13 HC[a]	[^{11}C]raclopride	8 drug naïve 5 drug-free (>3 wks)	Anteroventral striatum: 9 % decrease (ns) Ventral putamen: 7 % decrease (ns) Dorsal caudate: 10 % decrease (ns) Dorsal putamen: 6 % decrease (ns)	0.46 0.55 0.90 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 m)	Striatum: 2 % decrease (ns)	0.23
Lehto et al. (2008a), Lehto et al. (2009)[b]	10 MDD 10 HC	[^{123}I] epidepride	Drug-free (>6 m)	Right temp cortex: 13 % decrease (ns) Left temp cortex: 6 % decrease (ns) Temporal asymmetry: 7 %	0.65 0.33 1.56
Hirvonen et al. (2008b)	25 MDD 19 HC	[^{11}C]raclopride	Drug-free (>4 m)	Caudate: 2 % increase (ns) Putamen: 1 % decrease (ns) Thalamus: 3 % decrease (ns) Ventral striatum: 4 % decrease (ns)	0.17 0.11 0.24 0.46
Montgomery et al. (2007)	7 MDD 7 HC	[^{11}C]FLB457	Drug-free (>3 m)	Amygdala: 1 % increase (ns) Hippocampus: 0 % change (ns) Frontal cortex: 0 % change (ns) Anterior cing cort: 1 % increase (ns) Thalamus: 10 % increase (ns) Brain stem: 6 % increase (ns) Cerebellum: 5 %increase (ns)	0.05 0.00 0.00 0.06 0.45 0.21 0.22

Meyer et al. (2006b), Kuroda et al. (2006)	21 MDD 21 HC	[^{11}C]raclopride	12 drug naïve 9 drug-free (>6 m)	Striatum: 6–8 % increase	[c]
	9 MDD 16 HC	[^{11}C]raclopride	On medication	Right caudate: 1 % increase (ns) Left caudate: 0 % decrease (ns) Right putamen: 3 % increase (ns) Left putamen: 5 % increase (ns)	0.11 0.03 0.22 0.41
Parsey et al. (2001)	9 MDD 10 HC	[^{123}I]IBZM	Drug-free (>2 wks)	Striatum: 6 % decrease (ns)	0.55
Klimke et al. (1999)	15 MDD 17 HC	[^{123}I]IBZM	Drug-free (>6 m)	Striatum: 1 % decrease (ns)	0.06
Shah et al. (1997)	14 MDD 15 HC[e]	[^{123}I]IBZM	7 drug-free (>3 m) 8 on medication	Striatum right: 6 % increase[d] Striatum left: 4 % increase	0.95 0.52
Ebert et al. (1996)	20 MDD 10 HC	[^{123}I]IBZM	10 drug-free (>6 m) 10 on medication	Striatum right: 8 % increase (ns)[f] Striatum left: 10 % increase (ns)	0.55 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 13 HC (females)[g]	[^{11}C]raclopride	Drug-free (>3 wks) or drug naive	Anteroventral striatum: 5 % decrease (ns) Ventral putamen: 1 % decrease (ns) Dorsal caudate: 3 % increase (ns) Dorsal putamen: 5 % increase (ns)	0.34 0.06 0.28 0.45
Yatham et al. (2002a)	13 BD (nonpsychot) 14 HC	[^{11}C]raclopride	AP naïve	Striatum left: 9 % decrease (ns) Striatum right: 8 % decrease (ns) Caudate: 7 % decrease (ns) Putamen: 9 % decrease (ns)	0.51 0.43 0.37 0.50

(continued)

Table 5.7 (continued)

Authors (year)	Nr pts/controls	Radiotracer	MDD treatment	Change $D_{2/3}$ binding	Effect size
Anand et al. (2000)	13 BD 13 HC	[^{123}I]IBZM	AP-free (>6 m)	Striatum: 4 % decrease (ns)	0.26
Wong et al. (1997)	7 BD (psychot) 24 HC	[^{11}C]NMSP	AP naïve or AP-free (>6 m)	Striatum: 9 % increase (ns)	0.60
	7 BD (non-psychot) 24 HC[h]		AP naïve or AP-free (>6 m)	Striatum: 13 % decrease (ns)	0.81
Pearlson et al. (1995)	7 BD (psychot) 12 HC	[^{11}C]NMSP	AP naïve or AP-free (>6 m)	Striatum: 87 % increase[g]	1.27
	7 BD (non-psychot) 12 HC		AP naïve or AP-free (>6 m)	Striatum: 11 % decrease (ns)[i]	0.22

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, *m* months, *wks* weeks

[a]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

[b]Same sample of patients

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

[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 than nonpsychotic patients suffering from bipolar disorder

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

with neuropsychological scores or clinical variables (D'haenen and Bossuyt 1994; Meyer et al. 2006b; Shah et al. 1997) or it was not reported (Lehto et al. 2008a, 2009). However, 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).

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 paradigm, the amphetamine-induced release can be measured by assessing the decrease in dopamine $D_{2/3}$ receptor availability (see Chap. X, the dopaminergic system, for more details). Using an amphetamine challenge, Parsey and co-workers (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.

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 5.7B). Four of these studies did not find a statistically significant difference as 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-naïve 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.

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 three weeks treatment with amitriptyline (150 mg/daily) led to a decrease in $D_{2/3}$ receptor binding in the 5 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 months 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).

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 [^{11}C]NNC-112. Nevertheless, the reported decreased D_1-like receptor binding in MDD may less likely reflect changes in receptor binding associated with changes in dopamine concentrations, but might reflect 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).

5.3.3 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 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). 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. (2009) 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 a later study, they replicated this finding and showed that increased 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 oncoming 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 (Meyer et al. 2009). Finally, treatment of MDD patients with the reversible inhibitor of MAO-A (RIMA) moclobemide (600 mg) decreased MAO-A density with averagely 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. 2011a). [^{11}C]clorgyline was used in a dose-finding study with a new RIMA: CX157 (Fowler et al. 2010). These studies are summarized in Table 5.8.

Table 5.8 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
MAO-A availability					
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)		>1 year (rMDD)	ACC: 20/13 %↑ ($p<.001$) in MDD/rMDD	1.3/0.8
	28 HC			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 ($p=.02$)	
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 ($p>.1$)	

MAO-A occupancy				
Sacher et al. (2011a)	13 MDD 10 HC	[^{11}C]harmine	>5 weeks (5 drug naive) 6 MDD treated with moclobemide (600 mg) 7 MDD treated with St John's wort (1,200 mg)	Moclobemide Occ ($n=6$)[b,d]: 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, *Ventr. Striat* ventral striatum
[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 %

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 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 levels are only compensated but not changed by treatment, the persistent increased levels of MAO enzyme require prolongation of treatment after response/remission and may also explain recurrence. This is corroborated by MAO enzyme levels in patients with recurrence of their MDD in the forthcoming 6 months. This unifying hypothesis is very interesting, also in the perspective of decreased dopaminergic neurotransmission in a subgroup of depressed patients with treatment-resistant depression (Dunlop and Nemeroff 2007), but due to the limited evidence in small patient groups, it requires more exploration before clinically applicable.

5.3.4 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 the 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 (recovered) MDD patient samples combined one of these approaches with molecular imaging, which will be shortly reviewed hereafter (Table 5.9).

5.3.4.1 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 by relapse (recurrence of depressive symptoms) were reported, indicating that these changes are only occurring in remitted patients who experienced a relapse. Of note, these cortical and limbic regions were also identified in resting state PET

Table 5.9 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*					
Neumeister et al. (2006), Nugent et al. (2008)	27 rMDD (recov) 26 controls	^{18}FDG	None	ATD (rMDD > HC): ↑ rCMRGlu in OFC ($p = .01$), sgACC ($p = .03$), pgACC ($p = .05$). Amygd, Hippoc, Striatum (n.s.) 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 %	
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) 13 controls	^{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	
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: *rMDD* recurrent MDD

and SPECT studies in MDD patients and after sad mood induction, as described in Sect. 5.2. Neumeister et al. also investigated the interaction of genetic polymorphisms of the 5-HTTLPR SERT promotor 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 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 were recovered but still used the antidepressant drugs (mainly SSRIs) that improved their symptoms (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 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, which was not significantly different from test-retest differences (Praschak-Rieder et al. 2005).

5.3.4.2 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. 5.2).

5.3.4.3 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 fact 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 timepoints during prolonged depletion. These studies are probably hard to do because of ethical reasons.

5.4 New Perspectives

5.4.1 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 in use in clinical 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 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). To the best of our knowledge, 5-HT_4 receptor imaging has not yet been applied in clinical populations of MDD or BD.

At the current state of radioligand evolution, most 5-HT receptor imaging is obtained 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 its high- 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 its high- than in its low-affinity state. Therefore, one may expect that an agonist radiotracer will show an increased sensitivity to detect serotonin release when 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 as evaluated in pigs (Ettrup et al. 2011). If available, such tools may allow us to explore the interplay between the serotonergic neurotransmission and experimental challenges either physiological or psychological stimuli or pharmacological interventions. Within the dopamine system, methods have been 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 to valuable insight 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 antagonist radiotracers for this receptor (for details see Chap. X on imaging of the dopamine system).

Other tracers that are promising candidates to be sensitive to 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 relative to placebo, SSRI infusion (citalopram 10 mg) increased [^{11}C]CUMI-101 binding with approximately 7 % in cortical projection areas, but not in the raphe nuclei where the serotonergic neuronal cell bodies are located (Selvaraj et al. 2012). As an explanation, initially, SSRI exposure may 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).

Whether [^{11}C]CUMI-101 will prove to be sensitive to changes in endogenous 5-HT release awaits replication and more thorough validation including 5-HT depletion designs. 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, the 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 expand the pathophysiological insight in, e.g., MDD and BD in order to support development of better 5-HT-related treatments.

5.4.2 Imaging of Other Neurotransmitter Systems

Although the magnitude of research in MDD addresses the serotonergic and dopaminergic systems, other neurotransmitter systems have started to be investigated. For example, 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).

Because the mu-opioid system is thought to regulate the limbic and paralimbic circuits implicated in MDD, Zubieta et al. studied 14 healthy women with a mood induction and [^{11}C]carfentanyl 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). Given this potential regulation, this system would be interesting to study further in MDD, possibly in conjunction with other neuroimaging modalities (see below).

5.4.3 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).

Inflammatory microglia activation is a well-described feature of severe diseases that are accompanied by depressive symptoms. With the microglia tracer [^{11}C] PK11195 and PET, 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, with large emotional and cognitive changes, microglia activation is a core feature (Versijpt et al. 2003). Only recently, an increase in microglia activation was found in psychiatry after a first psychotic episode (van Berckel et al. 2008). During a psychotic episode, this inflammation was found to "condense" 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 aberrant prefrontal functioning in emotion regulation (Muller and Schwarz 2007; Walter et al. 2009).

Whether MDD patients in general suffer from inflammatory upregulation is still a matter of debate, as anti-inflammatory treatments are still unsatisfactory in their depression-reducing effects, while placebo-controlled trials, e.g., with COX inhibitors yield limited positive results (Musil et al. 2011). Nevertheless, we consider inflammatory molecular imaging, for example, with PK11195 as promising to broaden the view from neurotransmitter changes in MDD to potential inflammatory activity, which might lead to new possibilities for interventions.

5.4.4 Imaging the Blood–Brain Barrier

It has been proposed that dysfunction of the blood–brain barrier (BBB) contributes to the pathophysiology of MDD. More specific, influx of proteins or other molecules 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 itself. Since all patients used antidepressants, it cannot be ruled out that these drugs influenced the outcomes by P-gp induction or pharmacokinetic variation 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.

5.4.5 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 another neurotransmitter system (e.g., 5-HT$_{1A}$ receptor in relation with SERT). Indeed these systems have been started to be investigated in conjunction (Frey et al. 2008; Takano et al. 2011). 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. 2011; 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).

5.5 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. Based on fMRI studies, this has been summarized likewise (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 increased the attention of 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.

Recently the reduction of 5-HT (and dopamine) was summarized 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, which remains 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 evacuate 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. For the dopaminergic system, although only in retarded patients, less research has been done, but comparable effects could occur after increased breakdown of dopamine (with unaltered DAT, but increased D_2 receptors). This might suggest that in these retarded patients the MAO-B enzyme might be involved.

Future studies 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 when this endeavor is proceeding, 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 MAO inhibitors, for example.

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.

Finally, with a lack of longitudinal molecular imaging studies in the same subjects at different clinical mood states, it remains unclear whether the changes of SERT and DAT, or the increases in 5-HT_{2A} or D_2 receptors, are compensatory

reactions to reduced serotonin or dopamine or reflect different, potentially causal mechanisms. Also, as outlined in this chapter, the measures in this field are still hindered by suboptimal methodology, tracers, and reference standards, which need further standardization (Innis et al. 2007). We expect that these challenges will be solved in the future.

Conflicts of Interest and Funding HGR declares no conflicts of interest. HGR is supported by a NWO/ZonMW VENI-Grant #016.126.059.

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Functional Brain Imaging of Suicidal Behavior

6

Stefanie Desmyter, Stijn Bijttebier, and Cornelis van Heeringen

Contents

Abstract

This chapter provides a review of the literature on positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging studies of suicidal thoughts and behavior. Main findings from the review include a reduced prefrontal perfusion or metabolism in association with a history of suicide attempts or with suicidal ideation. Studies in resting conditions but especially studies using activation paradigms point at a basal hypofunction with a blunted increase in activation when challenged. Moreover, impairment of the prefrontal serotonergic system in association with suicidal behavior is demonstrated in a number of studies. A substantial number of methodological issues however hamper the interpretation of findings. Future neuroimaging studies need to take these issues into account in order to contribute to our understanding of the neurobiological mechanisms underlying suicidal behavior and thus to the prediction, treatment, and prevention of this important public health problem.

S. Desmyter (✉) • S. Bijttebier • C. van Heeringen
Department of Psychiatry, Unit for Suicide Research,
Ghent University, University Hospital, De Pintelaan 185, Ghent 9000, Belgium
e-mail: stefanie.desmyter@ugent.be; stijn.bijttebier@ugent.be;
cornelis.vanheeringen@ugent.be

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_6, © Springer-Verlag Berlin Heidelberg 2014

Abbreviations

BP	Binding potential
DAT	Dopamine transporter
MDD	Major Depressive Disorder
PET	Positron Emission Tomography
rCMRglu	Regional cerebral metabolic rate of glucose uptake
SERT	Serotonin transporter
SPECT	Single Photon Emission Computed Tomography

6.1 Introduction

The World Health Organization estimates that one million people die from suicide each year, which reflects a global annual suicide rate of 16 per 100,000 or one death every 40 s. Suicide is among the three leading causes of death in people aged 15–44 years. These figures do not include suicide attempts, which are estimated to occur up to 20 times more frequently than completed suicide. The individual and socioeconomic costs are enormous, so prevention programs have been developed in many countries worldwide.

Difficulties in predicting suicidal behavior, even among individuals at high risk, pose however a major challenge to adequate prevention. Limited knowledge of predisposing characteristics contributes to these difficulties. It has become clear that depressed suicidal patients can be distinguished from depressed non-suicidal individuals based on trait-dependent characteristics, which constitute their predisposition for suicidal behavior. Based on current knowledge, a stress-diathesis model has therefore been proposed to explain the interactions between proximal risk factors (such as depression) and these predisposing characteristics (Hawton and van Heeringen 2009).

Neuroimaging studies of depression are discussed in detail elsewhere in this book. This chapter will focus on the use of neuroimaging techniques to study the vulnerability to suicidal behavior. Neuroimaging studies have many advantages over the postmortem studies, which were, until recently, the only approach to the study of changes in brain functions in association with suicidal behavior. In vivo functional neuroimaging of the suicidal brain not only avoids the many methodological drawbacks of postmortem research but also provides the possibility of assessing personality-related, cognitive, and emotional characteristics of suicidal individuals in order to study correlations between cerebral dysfunctions and their cognitive and emotional manifestations, which may contribute to the vulnerability to suicidal behavior (Desmyter et al. 2011).

6.2 Methods

The literature on PET and SPECT imaging studies of the brain in individuals with a history of nonfatal suicidal behavior was reviewed. Literature searches were performed with the search engines “Pubmed” and “Web of Science” using the following

keywords: single photon emission tomography, single photon emission computed tomography, SPET, SPECT, positron emission tomography, PET, and suicide. The first selection was made through an inspection of the abstracts. Although most studies were published in the last decade, the search was performed without a time limit. The reference lists of the selected articles were also checked for additional publications.

6.3 Results/Review of the Literature

The studies in which PET or SPECT brain imaging techniques were used to examine differences between suicidal and non-suicidal subjects will be described in chronological order, starting with PET studies. Table 6.1 summarizes the sample characteristics and limitations of the reported studies.

6.3.1 PET Studies

Oquendo and colleagues published an interesting study in 2003, in which they investigated the brains of 16 high-lethality and 9 low-lethality suicide attempters having a depressive episode. The patients were scanned in resting condition with ^{18}F-FDG PET imaging in order to estimate regional brain activity in conditions where external activation is minimized or standardized. Subjects were scanned after a single-blind placebo and after fenfluramine hydrochloride administration on a second day. Fenfluramine is a serotonin agonist that provokes an increase in the presynaptic release of serotonin. Secondary and proportional to this postsynaptic receptor stimulation, the anterior pituitary gland releases prolactin in the circulation. If the serotonergic system is impaired, a blunted increase in prolactin is found (Malone et al. 1996; Correa et al. 2000). Besides an increase in prolactin, fenfluramine also increases frontal cortex metabolism (Soloff et al. 2003). The authors found that depressed high-lethality suicide attempters showed relative hypometabolism compared to low-lethality attempters in the ventral, medial, and lateral prefrontal cortex. This difference was more pronounced after fenfluramine administration. Lethality of the attempt appeared to be inversely correlated with metabolism in the ventromedial prefrontal cortex after challenge with fenfluramine. A lower mean regional cerebral metabolic rate of glucose uptake (rCMRglu) correlated with higher lethality of suicidal behavior. The authors also demonstrated that higher verbal fluency correlated positively with rCMRglu in the same regions of the prefrontal cortex and that lethality of the suicide attempt inversely correlated with prolactin after challenge. They found a lower CMRglu in high- versus low-lethality suicide attempters. This hypometabolism in frontal cortex structures was related to the degree of suicide intent and impulsivity and not to depression (Oquendo et al. 2003).

Leyton and coworkers (2006) measured regional serotonin synthesis in the brain with PET and α-(^{11}C)-methyl-L-tryptophan trapping in ten patients who had made a high-lethality suicide attempt and in 16 healthy controls. Suicide attempters showed reduced serotonin synthesis in the orbital and ventromedial prefrontal cortices. α-(^{11}C)-methyl-L-tryptophan trapping in these regions correlated negatively with

Table 6.1 Functional neuroimaging of suicidal behaviour – key features of PET and SPECT studies of suicide attempters

Study[a]	Design[b]	Targeted brain region[c]	Subjects[d]	Limitations
PET				
Oquendo et al. (2003)	PET: Regional brain serotonergic function	Whole brain	25 patients (M+F) meeting DSM-III-R criteria of a major depressive episode and who have attempted suicide: 16 patients had a history of high-lethality suicide attempts (mean 42.9 years), 9 patients had a history of lo-lethality suicide attempts (mean 30.4 years)	Small sample size; direct brain injuries not ruled out
Leyton et al. (2006)	PET: α[^{11}C]MTrp trapping	PFC	26 subjects (M+F): 10 patients have attempted suicide (mean 37.7 years) and 16 healthy subject (mean 35.5 years)	Effects of drugs on 5-HT transmission; small sample size; imaging technique possibly not the best to assess 5-HT neurotransmission
SPECT				
Audenaert et al. (2001)	SPET: Serotonin-$_{2A}$ receptor functioning	Frontal cortex	21 subjects, mean 30.4 years (M+F): 9 patients who have attempted suicide and 12 healthy subjects	Impact of alcohol and medication on clearance of the ligand; possible effect of physical trauma on binding index
Audenaert et al. (2002)*	SPECT: Binding potential	Whole brain PFC	40 subjects (M+F): 20 depressed patients who recently (< 7 days) attempted suicide (19–49 years) and 20 healthy subjects (18–50)	Influence of medication; selection bias; at random division of subgroups
van Heeringen et al. (2003)	SPECT: Serotonin-$_{2A}$ receptor functioning	PFC	21 subjects (M+F): 9 patients who have attempted suicide (mean 32.4 years) and 12 healthy subjects (mean 28.9 years)	Small sample size; composition of patient sample; effects of alcohol and medication; possible effect of physical trauma on binding index
Lindström et al. (2004)	SPECT: Brain serotonin and dopamine transporters	Whole brain	24 subjects, mean 38.8 years (M+F): 12 patients who attempted suicide (5 violent and 7 non violent) and 12 healthy matched subjects	Possible type 2 error

Ryding et al. (2006)	SPECT: Serotonin transporter and dopamine transporter	Whole brain	24 subjects (M + F): 12 patients who attempted suicide (mean 38.8 years) and 12 matched healthy subjects	
Amen et al. (2009)	SPECT: In vivo brain differences	Whole brain PFC Subgenual cingulate	36 subjects (M + F): 12 patients meeting DSM-IV criteria for depression who committed suicide since the brain imaging (mean 33.8 years), 12 patients meeting DSM-IV criteria for depression who did not commit suicide and 12 healthy subjects	Heterogeneous sample; medication; lack of data for all subjects
Willeumier et al. (2011)	SPECT: Technetium-99 m hexamethylpropylene amine oxime brain uptake	Whole brain	84 subjects (M + F): 21 patients meeting DSM-IV criteria for depression who committed suicide since the brain imaging (mean 36 years), 36 matched non-suicidal depressed subjects (mean 36 years) and 27 matched healthy subjects (mean 35 years)	Follow-up study of Amen et al. (2009), with only 9 additional patients who committed suicide
van Heeringen et al. (2010)	SPECT: Regional cerebral blood flow under resting conditions	Whole brain	39 subjects (M + F): 39 admitted patients, treated for a depressive episode according to DSM-IV-TR criteria, subdivided in 3 groups according to level of mental pain	Impact of medication

[a] *Study*: *Study of good methodological quality
[b] *Design*: *PET* Positron Emission Tomography, *SPECT* Single Photon Emission Computed Tomography, *SPET* Single Photon Emission Tomography, *α[11C]MTrp* α-[11C]methyl-l-tryptophan
[c] *Targeted brain region*: *PFC* prefrontal cortex
[d] *Subjects*: *BD* bipolar disorder, *BD-I* bipolar depression type I, *BD-II* bipolar depression type II, *BPD* borderline personality disorder, *F* Female, *M* Male, *MDD* major depressive disorder

suicide intent. Elevated α-(^{11}C)-methyl-L-tryptophan trapping was seen in the left thalamus, right paracentral lobule, and the left middle occipital cortex. The investigators concluded that low serotonin synthesis in the prefrontal cortex might lower the threshold for suicidal behavior.

6.3.2 SPECT Studies

A few studies used SPECT imaging to study functional changes in brain functions. Audenaert and coworkers (2001) studied nine patients who had recently (1–7 days) attempted suicide and compared these to 12 age-matched healthy controls using ^{123}I-5-I-R91150 SPECT. They found a significantly reduced binding index in the frontal cortex in the patient group. The binding index was significantly lower in the deliberate self-injury patients compared to the deliberate self-poisoning subjects. The results indicate a decrease in the number and/or in the binding affinity of 5-HT_{2A} receptors. Further analysis revealed a significant negative correlation between 5-HT_{2A}-receptor binding and levels of hopelessness, a very important clinical predictor of suicidal behavior (van Heeringen et al. 2003).

In a split-dose ^{99m}Tc-ECD SPECT activation paradigm, Audenaert and colleagues (2001) included 20 depressed patients who had recently attempted suicide and compared them to 20 healthy volunteers. The neuropsychological activation consisted of a verbal fluency test. When compared to healthy volunteers, patients showed a blunted increase in perfusion in the prefrontal cortex during specific verbal fluency tasks. When comparing the activated brain regions between healthy volunteers and patients in the category fluency paradigm, a statistically significant blunting of the perfusion was observed in the patient group in the left gyrus frontalis inferior, right gyrus parietalis inferior, and bilateral gyrus cinguli anterior. There were no regions with significantly increased perfusion in the patient group compared to the controls. When comparing the activated brain regions between healthy and depressed subjects in the letter fluency paradigm, the authors found a statistically significant blunting of the perfusion in the depressed group in the left and right gyrus temporalis medius, right gyrus cinguli anterior, and hypothalamic region. There were no regions with significantly increased perfusion in the patient group compared to control subjects. The authors suggest that the blunted increase in prefrontal blood perfusion might be a biological reason for reduced drive and loss of initiative in attempted suicide patients.

Serotonin and dopamine transporter binding in association with suicidal behavior was assessed in two SPECT studies using the mixed monoamine transporter tracer ^{123}I-β-CIT. Lindström and colleagues (2004) measured the whole brain binding potential (BP) of the serotonin transporter (SERT) and dopamine transporter (DAT) in 12 patients after a serious suicide attempt and in 12 matched healthy controls. No significant differences in BP between study groups were found. In patients, but not in controls, there was a significant correlation between whole brain 5HTT and DAT BP. In suicide attempters, high impulsiveness was significantly correlated with low SERT BP, which was not found in controls. Ryding and coworkers

(2006) further analyzed the measurements of the previous study, examining regional serotonin reuptake (5HTT) and dopamine reuptake (DAT) capacity (binding potential, BP). They observed no significant difference concerning the regional levels of SERT or DAT binding potential. However, they found regional significant negative correlations between SERT BP and impulsiveness among suicide attempters but not in controls. Significant correlations between solidity (the level of initiative or impulsivity) and local 5-HTT BP in suicide attempters were found in the right inferior frontal (orbital) and bilateral temporal cortical regions, subcortically in the midbrain, thalamic and bilateral basal ganglia regions, and in the left cerebellar hemisphere. Moreover, the patients showed a significant negative correlation between whole brain DAT BP and mental energy. Regional significant correlations were found solely in bilateral basal ganglia regions. These correlations were not found in controls.

Amen and colleagues (2009) carried out a study using brain ^{99m}Tc HMPAO SPECT imaging at rest and during a cognitive activation task. They compared the brain scans of 12 psychiatric inpatients, who committed suicide between 10 days and 36 months after the scan, with 12 non-suicidal depressed subjects and 12 healthy controls. Comparing the suicide versus the control group in resting condition, they noted generally lower regional cerebral blood flow in the suicide patients throughout the cortex, with no clusters of high activity. Reduced perfusion was found in the premotor and primary motor cortex, corpus callosum, cingulate, and anterodorsal cortex. A significant area of low activity was the nucleus accumbens, extending into the ventromedial prefrontal cortex, into the left and right putamen. When comparing the suicide group with the non-suicidal depressed group, hemispheric asymmetries were found with the suicide patients showing significantly higher perfusion in the right hemisphere with no relative regional cerebral blood flow deficits. The largest cluster of increased perfusion centered in the right insular cortex. Subjects were additionally challenged with Conner's Continuous Performance Test, a 15-min computerized go/no go task measuring omissions, commissions, and reaction time. The perfusion deficits present at baseline were attenuated in the depressed group but exacerbated in the suicide group during concentration. The authors noted that deficits in the middle and frontal gyri were better perfused in non-suicide depressed patients, but degraded in suicide subjects during concentration. The authors generally concluded that the results were consistent with prior imaging studies on depression and were indicative of impaired impulse control and limbic dysregulation, including significant perfusion deficits in the medial, prefrontal, and subgenual areas and ventral tegmentum.

In an extension of the previous study, the study group included nine additional patients who committed suicide after the SPECT scan. When the scanning data of these 21 patients were compared with those from a group of 27 healthy subjects and another control group of 36 non-suicidal depressed persons, global decreases in blood flow and activity patterns in the suicide group versus the healthy control group were found. This decrease was most pronounced in the precuneus and the prefrontal cortex. Other deficits were found in the rolandic operculum, postcentral

gyrus, the caudate, thalamus, and insular cortex. When comparing the suicide group and the matched non-suicide depressed patients, more subtle, global decreases in blood flow and activity patterns were observed. In the cohort of completed suicides, the subgenual cortex appeared to be hypoperfused in 18 patients as compared with the healthy control group (Willeumier et al. 2011).

The functional neuroanatomy of mental pain in depression was investigated by Van Heeringen and colleagues (2010) in a group of depressed individuals using ^{99m}Tc-ECD SPECT. They found that, when compared with patients with low levels of mental pain, those with high levels of mental pain showed relatively increased perfusion in the right dorsolateral prefrontal cortex, occipital cortex and inferior frontal gyrus, and in the left inferior temporal gyrus and relatively decreased perfusion in the medulla. The findings point at an association between mental pain in depressed patients and an increased risk of suicide and between high levels of mental pain and changes in perfusion in brain areas that are involved in the regulation of emotions.

6.4 Discussion

The findings from this review of the literature on PET and SPECT imaging studies of suicidal behavior can be summarized as follows. Overall, a reduced prefrontal perfusion or metabolism in association with a history of suicide attempts or with suicidal ideation is the most robust finding from these perfusion and metabolism studies of the brain of patients vulnerable to suicidal behavior. Studies in resting conditions but especially studies in activation conditions support a basal hypofunction with a blunted increase in activation when challenged. Moreover, impairment of the prefrontal serotonergic system of these patients was demonstrated in a number of studies.

Before drawing any conclusions concerning the impact of this research on our knowledge of the suicidal brain and thus on the prediction and prevention of suicidal behavior, several methodological issues need to be addressed. The comparison of findings from different studies is hampered by differences in techniques of imaging and analysis. Moreover, the description of anatomical localizations of findings is not identical between the study groups. The definitions of suicidal behavior also differ ranging from a history of suicide attempts or thoughts to current suicidal ideations or intentions. Clear descriptions of the study populations were rather scarce and imprecise. Moreover, the studies that have been carried out with PET and SPECT were done in small sample size groups, which limit the power to detect small group differences or which can amplify individual differences due to biological heterogeneity. In some studies, patients and controls were not matched for potential biasing characteristics such as demographic variables, psychiatric comorbidity, and treatment. Finally, the study population used in more recent studies all consist of patients with a history of suicide attempts, while the studies dated from before 2006 generally studied recent severe suicide attempts, limiting the comparability between these studies.

Taken together, these methodological issues raise the question to what extent the current findings from PET and SPECT studies of suicidal behavior may help to understand the neurobiological basis of this behavior.

At this point, the application of PET and SPECT imaging to the problem of suicidal behavior is research oriented, and there is currently no indication for routine functional neuroimaging in the diagnosis of suicide risk. The significant correlation between decreased binding potential of prefrontal 5-HT_{2A} receptors and increased levels of hopelessness in patients vulnerable to suicidal behavior is one of the most clinically relevant findings. There was consistence in reports of a reduced prefrontal blood perfusion during verbal fluency tasks in suicidal patients. High levels of mental pain are associated with changes in perfusion in brain areas that are involved in the regulation of emotion.

Our review of neuroimaging studies of suicidal behavior published between 1990 and 2010 (van Heeringen et al. 2011) led to the conclusion that many brain areas appear to be involved, including the prefrontal cortex, the limbic system, the basal ganglia, and extensive connections between these areas. A more recent review (Desmyter et al. 2013), which includes a substantial number of more recent studies, narrows the focus of attention by suggesting that suicidal behavior is associated particularly with changes in a fronto-cingulo-striatal network. Recent neurobiological research outside the suicidological domain has clearly demonstrated the major role of this network in decision-making.

Most probably not coincidentally, recent neuropsychological studies in suicide attempters have also identified changes in decision-making processes as crucial characteristics of the predisposition to suicidal behavior. Violent suicide attempters differ from affective controls in their performance on a decision-making task in that suicide attempters make more disadvantageous choices, i.e., choose options with high immediate reward (Jollant et al. 2008). A subsequent functional neuroimaging study indeed showed that suicide attempters (1) performed worse on a decision-making task than affective controls and (2) showed reduced activation in the orbitofrontal (and occipital) cortex for the contrast between risky (disadvantageous) and safe (advantageous) choices (Jollant et al. 2010). The insufficient contrast between risky and safe choices prevents advantageous guiding of long-term behavior.

Taken together with the results from recent functional MRI studies, these findings suggest, first, that suicidal behavior is associated with disturbances in the attribution of importance to stimuli, i.e., undue importance to signals of others disapproval and insufficient importance to risky choices. Secondly, changes in the prefrontalstriatal network are associated with changes in the representation of value to different outcome options, which may lead to the choice of immediate reward over abstract and delayed reward in the process of decision-making. The development of unbearable emotional pain following perception of signals of others' disapproval may be associated with a choice for immediate alleviation of pain, not taking into account the possibility of a better future. Disturbed intertemporal reward discounting may thus play an important role in the vulnerability to suicidal behavior. As the serotonergic neurotransmission system is involved in the modulation of this process of delay discounting (Schweighofer et al. 2007), this may explain

the demonstrated association between prefrontal serotonergic dysfunctioning and levels of hopelessness in suicide attempters.

Further research is necessary, and functional neuroimaging will help us to better understand the underlying neurobiological mechanisms of suicidal behavior.

Future research with PET and SPECT should clearly describe study populations and study targets, i.e., suicidal behavior, history, and/or thoughts. These targets may indeed be characterized by different underlying neurobiological mechanisms. Moreover, it is of great importance to have an affective control group (e.g., depressed patients without a history of suicide) next to healthy controls to rule out the effects of this psychiatric disorder on the imaging results of suicidal behavior. In addition, the increasing use of functional magnetic resonance imaging, which already has provided promising results (Jollant et al. 2008, 2010; Reisch et al. 2010; Dombrovski et al. 2012), will further broaden our knowledge particularly in the context of multimodal imaging, i.e., the combination of different imaging techniques in one study.

Future neuroimaging studies can be expected to contribute to a greater understanding of the mechanisms underlying suicidal behavior by studying associations between relevant characteristics (e.g., hopelessness, impulsivity, interpersonal sensitivity) and brain functions, thereby targeting particular brain areas such as the prefrontal-striatal network. Such studies may well facilitate the development of neurocognitive biomarkers for suicidal behavior, which will be of great clinical importance by increasing the possibilities to predict the occurrence of suicidal behavior. The growing knowledge of the neurobiological mechanism underlying suicidal behavior can be expected to help the clinician in detecting and preventing suicidal behavior. Moreover, brain imaging has promising prospects concerning the evaluation of the effect of treatments such as medication, psychotherapy, and neuromodulation techniques.

Conclusion

In spite of the substantial impact of suicidal behavior at individual, social, and public health levels, relatively few neuroimaging studies have been carried out using PET or SPECT in suicidal populations. Overall, the most robust findings in suicidal patients are a relative hypometabolism and impairment of the serotonergic system in the prefrontal cortex. Several methodological issues make it difficult to come to conclusions at this point. Further neuroimaging research is necessary to elucidate the neurobiological mechanisms underlying suicidal behavior in order to increase possibilities of prediction, treatment, and prevention.

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SPECT and PET in Late-Life Depression

7

Tiago S. Vieira, Richard Oude Voshaar, Peter Paul De Deyn, Rudi A.J.O. Dierckx, and Aren van Waarde

Contents

T.S. Vieira (✉)
Nuclear Medicine Department, Centro Hospitalar de São João, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
e-mail: tiago.sampaio.vieira@gmail.com

R.Oude Voshaar
Department of Geriatric Psychiatry, University Medical Center Groningen, University of Groningen, University Center of Psychiatry, 30.001, Groningen 9700RB, The Netherlands

P.P. De Deyn
Department of Neurology, Alzheimer Research Center, University Medical Center Groningen, University of Groningen, Groningen 9713 GZ, The Netherlands

Department of Biomedical Sciences, Laboratory of Neurochemistry and Behavior, Institute Born-Bunge, University of Antwerp, Universiteitsplein 1, Wilrijk B-2610, Belgium

Department of Neurology and Memory Clinic, Hospital Network Antwerp (ZNA) Middelheim and Hoge Beuken, Lindendreef 1, 2020 Antwerp, Belgium

R.A.J.O. Dierckx
Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, 30.001, 9700RB Groningen, The Netherlands

University of Ghent, Ghent, Belgium

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_7, © Springer-Verlag Berlin Heidelberg 2014

A. van Waarde
Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, 30.001, 9700RB Groningen, The Netherlands

Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands

Abstract

Late-life late onset depression (i.e., depression with an age of onset above 60 yrs) 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.

7.1 The Concept of Late-Life Depression

7.1.1 Prevalence and Burden of Late-Life Depression

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 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 recent meta-analysis challenged these findings identifying a pooled prevalence rate of 7.2 % (95 % CI, 4.4–10.6 %) for major depressive disorder 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 major depressive disorder. The previously reported meta-analyses identified a pooled prevalence of 9.8 % for minor depression (Beekman et al. 1999) and, respectively, 13.5 and 17.1 % 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 major depressive disorder, 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.

Late-life depression is a devastating condition for both individual patients as well as society. Patients suffering from late-life depression experience greater functional disability and cognitive decline than those without (Dombrovski et al. 2007; Lenze et al. 2005). Moreover, late-life depression 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 as well as physiological abnormalities intrinsically related to late-life depression. Moreover, the association between chronic somatic diseases and late-life depression 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 recently culminated in an overarching theory proposing depression as a disease of accelerated aging (Wolkowitz et al. 2011).

Late-life depression 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 late-life depression 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 late-life depression 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.

7.1.2 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 late-life depression 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 recent meta-analyses 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- and late-life depression. 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 in early age, whereas late-life depression has been hypothesized to be more strongly associated with (cerebro)vascular disease, frailty-associated processes, and neurodegenerative biological abnormalities (Baldwin and Tomenson 1995; Brodaty et al. 2001; 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 late-life depression 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 in learning and memory (Herrmann et al. 2007; Kohler et al. 2010b; 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. 2010a). Executive dysfunctioning in late-life depression 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 (Baldwin et al. 2004; Sheline et al. 2010; Sneed et al. 2007), which has led to the introduction of the "depression-executive dysfunction syndrome" aimed to describe a subtype of late-life depression 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).

7.2 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 late-life depression 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. 2014).

7.2.1 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 late-life depression. 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 7.1).

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 7.1. 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) 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 major depressive disorder. 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 late-life depression 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, Huntington, and Alzheimer's disease.

Table 7.1 SPECT and PET studies of regional cerebral blood flow in late-life depression

Study groups and subject numbers	Age (y)	Tracer	Findings (depression-related)	Reference
Major depressive disorder (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)
Major depressive disorder (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)
Major depressive disorder (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)
Major depressive disorder (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)
Major depressive disorder (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 7.1 (continued)

Study groups and subject numbers	Age (y)	Tracer	Findings (depression-related)	Reference
Depressed patients (10) Parkinson patients with (10) and without (10) depression Healthy controls (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)
Geriatric depression (17) Alzheimer's dementia (23) Age-matched controls (12)	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)
Major depressive disorder (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)
Major depressive disorder (18) Age-matched controls (13)	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)
Elderly depressed patients (39) Alzheimer's dementia (15) Healthy volunteers (11)	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)
Elderly depressed patients (175) 39 subjects scanned and followed up after 2 y, 10 scanned twice	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)
Alzheimer's with depression (17) Alzheimer's without depression (11) Age-matched volunteers (57)	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 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) Healthy controls (5)	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)

Major depressive disorder (30) Healthy controls (20)	72 ± 8	^{99m}Tc-HMPAO	Flow reduced in anterior frontal regions, particularly left No correlation with symptom severity	Navarro et al. (2001)
Major depressive disorder (9) Age-matched healthy subjects (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)
Depressed nondemented (7) Depressive pseudodementia (7) Alzheimer's dementia (7) Healthy controls (7)	67 ± 8	^{99m}Tc-HMPAO	Left frontal flow in depressed subjects significantly reduced Depressive pseudodementia group showed right temporal and bilateral parietal flow reductions similar to AD group AD group has additional right frontal perfusion deficit	Cho et al. (2002)
Alzheimer's disease (32) Healthy controls (19)	77 ± 6	^{99m}Tc-ECD	Frontal hypoperfusion appears correlated with negative symptoms but correlation is at limit of significance	Vercelletto et al. (2002)
Major depressive disorder (35), scanned during acute depression and in remission, after 12 months Age-matched healthy controls (20)	73 ± 8	^{99m}Tc-HMPAO	Flow significantly reduced in left anterior frontal region This deficit disappears during successful treatment No correlation between flow reduction and clinical symptoms	Navarro et al. (2002)
Nonvascular depression (11) Vascular depression (9) Scanned before/after remission	67 ± 11	^{123}I-IMP	Patients with vascular depression have lower left anterior frontal flow than patients with nonvascular depression Perfusion improves in both groups during remission, particularly in left anterior temporal region	Kimura et al. (2003)
Alzheimer's with depression (8) Alzheimer's without depression (35)	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)
Major depressive disorder, in remission after ECT (14) and after drug treatment (22) Age-matched healthy controls (25)	74 ± 11	^{99m}Tc-HMPAO	After 12 months in remission, no perfusion deficits were observed anymore in both patient groups	Navarro et al. (2004a)

(continued)

Table 7.1 (continued)

Study groups and subject numbers	Age (y)	Tracer	Findings (depression-related)	Reference
Major depressive disorder, 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)
Major depressive disorder (10) Early Alzheimer's disease (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)
Depression (32) Age-matched healthy controls (17) Scanned performing a simple and a more complex reaction time task	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)
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)
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) Scanned twice with interval of 9 y Screened annually for depression	69 ± 7 (at scan 1)	^{15}O-water	Higher scores for depression associated with longitudinal decreases of flow in frontal (♂, ♀) and temporal (♂) regions Similar flow patterns in subclinical and clinical depression	Dotson et al. (2009)
M. Parkinson with depression (11) Idem without depression (14) Depression only (12) Depressed scanned before/after citalopram treatment (12 weeks)	64 ± 10	^{99m}Tc-HMPAO	Major depression in PD appears associated with "spotted" hypoperfusion in lower part of right frontal lobe Perfusion deficits become smaller after treatment But none of these effects were statistically significant	Palhagen et al. (2009)

Depression + cogn impairment (127) Mild cognitive impairment (149) Alzheimer's dementia (131) Cognitively normal controls (123)	63 ± 11	^{99m}Tc-HMPAO	Depressed, cognitively impaired subjects have reduced flow in medial temporal cortex, thalamus, lentiform nucleus Frontal perfusion deficits seen only in AD, associated with conversion from MCI to AD. Depression early symptom of neurodegeneration?	Staffen et al. (2009)
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)
Major depressive disorder (37) Healthy controls (27)	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)
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)
Major depressive disorder (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)
Major depressive disorder 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)

2. Several investigators have examined whether the magnitude or regional extent of flow changes is correlated with the severity of depressive symptoms. In a few published articles, flow values and scores on depression scales were significantly and inversely correlated (Bonne et al. 1996; Kang et al. 2012; Liao et al. 2003; Sabbagh et al. 1997; Sackeim et al. 1990). However, in other studies no significant correlation between flow and depression severity was observed (Awata et al. 1998; Dolan et al. 1994; Galynker et al. 2000; Navarro et al. 2001, 2002; Philpot et al. 1993; 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 (Awata et al. 2002; Bonne et al. 1996; Halloran et al. 1999; Ishizaki et al. 2008; Kimura et al. 2003; Navarro et al. 2002, 2004a; 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 (Hanada et al. 2013; Navarro et al. 2004b). 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 certain 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 late-life depression. Curran et al. (1993)) detected perfusion deficits in anterior cingulate and frontal cortex only in male patients. Lesser et al. (1994) observed reduced flow in orbitofrontal and temporal areas of depressed individuals which were more striking in men than in women. Dotson et al. (2009) found more widespread decreases of flow in elderly depressed males than in females. 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 dis-

ease, 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 late-life depression (Ebmeier et al. 1997, 1998; Kimura et al. 2003; Lesser et al. 1994; 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. 1997, 1998). 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, but may not be accurate enough to differentiate Alzheimer's dementia from mild cognitive impairment, or mild cognitive impairment from depression with cognitive impairment (Staffen et al. 2009). Early diagnosis of degenerative dementias may require the combination of SPECT with other molecular imaging techniques.

7.2.2 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 7.2). FDG-PET studies also support the concept that late-life depression relies on dysfunctioning of the frontal lobe, whereas the involvement of other brain regions is more variable and controversial.

Table 7.2 PET studies of regional cerebral glucose metabolism in late-life depression

Study groups and subject numbers	Age (y)	Tracer	Findings (depression-related)	Reference
Late-life depression (7) Multiple-infarct dementia (6) Alzheimer's disease (6) Healthy controls (6)		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 (**)		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)
Late-life depression (8) Alzheimer's disease (8) Age-matched controls (8)	71 ± 6	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	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	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	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	FDG	Depression (both in MSA and PSP) associated with dorsolateral prefrontal glucose hypometabolism	Herting et al. (2007)
Major depressive disorder (10), nonresponders to antidepressants	51 ± 4	FDG	rCMRglu decreased not only in prefrontal but also in cingulate and parietal regions (bilaterally) and right temporal area	Fujimoto et al. (2008)
Geriatric depression (16) Age-matched controls (13)	65 ± 9	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	FDG	Depression in MCI is associated with reduced rCMRglu In the right superior frontal gyrus	Lee et al. (2010)
Late-life depression (9) Control subjects (7) Scanned at baseline, after 8 weeks of citalopram (patients only), and after 2 years of follow-up	68 ± 8	FDG	Patients show greater increases of rCMRglu in anterior cingulate and insula than controls Seven out of nine patients remitted	Marano et al. (2013)

7.2.3 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 Chap. 5 of this volume (Ruhé et al. 2014).

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]FLB457, 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 Chap. 5.

Since late-life depression is considered as both a risk factor and a premonitory symptom of dementia (Dal Forno et al. 2005; Gao et al. 2013; Kohler et al. 2010b; Lieberman 2006; Marano et al. 2013; Schweitzer et al. 2002), studies with cholinergic tracers and probes for ß-amyloid or tau deposition are of particular interest (see Table 7.3). 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 can in

Table 7.3 PET studies with cholinergic and ß-amyloid tracers in late-life depression

Study groups and subject numbers	Age (y)	Tracer	Findings (depression-related)	Reference
Parkinson disease with (6) and without (12) dementia Normal controls (10)	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)
Parkinson disease (22) Healthy controls (9)	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)
Remitted major depression with (7) and without (2) cognitive impairment Healthy elderly (7)	72 ± 6	[^{11}C]PiB	Normal tracer retention in LLD without MCI Increased retention in LLD with MCI, ranging to levels observed in AD	Butters et al. (2008)
Mild cognitive impairment (23) Cognitively normal (20)	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)
Major depressive disorder (20) Age-matched healthy controls (19)	67 ± 8	[^{18}F] FDDNP	Depressed subjects have increased tracer retention in lateral temporal regions and cingulate	Kumar et al. (2011)
Remitted from depression (28) Healthy control subjects (18)	50–76	[^{11}C]PiB (+ MRI)	Previous depressive episodes NOT associated with increased tracer retention in the brain But associated with vascular damage as depressed group had more white matter lesions	Madsen et al. (2012)
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) Normal cognition (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. (2013)

some cases be as high as that observed in patients with Alzheimer's disease (Butters et al. 2008). This preliminary result is consistent with the hypothesis that depression is a premonitory symptom of dementia because of a shared underlying neurobiological mechanism. A subsequent 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 major depressive disorder (Kumar et al. 2011).

In contrast to these positive findings, two recent PET studies (Madsen et al. 2012; Kim et al. 2013) did not observe any relationship between retention of [^{11}C]PiB and previous or present depressive symptoms, although in the latter study, tracer uptake was positively correlated with the frequency of delusions and irritability. A final 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. 2013).

In summary, most PET studies support the hypothesis that deposition of amyloid plaques and tau tangles in the aging brain can result in both cognitive and noncognitive behavioral symptoms.

Conclusion

Imaging studies, particularly the more recent 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 supports 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

8

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

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 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.

C. Spindelegger • M. Willeit • N. Praschak-Rieder • R. Lanzenberger • S. Kasper, MD (✉)
Division of Biological Psychiatry, Department of Psychiatry and Psychotherapy, Medical University of Vienna, Waehringer Guertel 18-20, Vienna 1090, Austria
e-mail: biol-psychiatry@meduniwien.ac.at

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_8, © Springer-Verlag Berlin Heidelberg 2014

8.1 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 and colleagues (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 SAD 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). Furthermore, seasonal depressive symptoms are reported with a higher frequency during summer and attributed to intense heat and humidity in some parts of the world (Avasthi et al. 2001; Morrissey et al. 1996). 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 non-seasonal 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 an 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 an effective therapy 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 about neuroimaging in SAD and seasonal effects on brain monoamine pathways.

8.2 Structural and Functional Magnetic Resonance Imaging

8.2.1 Structural MRI Studies

Volumetric studies in non-seasonal depressed patients showed a nonspecific brain atrophy including an increase in ventricular-brain ratio, increased cerebrospinal fluid volume and sulcal atrophy (Steffens and Krishnan 1998). Additionally, a lateralisation of atrophy was found to the left medial temporal lobe in patients with a late-onset depression (Greenwald et al. 1997), whereas other studies were not able to demonstrate grey matter differences in this region (Coffey et al. 1993; Pantel et al. 1997). In addition to the findings of Greenwald, Drevets et al. (1997) were able to show a left-lateralised reduction in grey matter volume in the subgenual prefrontal cortex (Brodmann area 24) in patients with familial forms of major depressive disorder (MDD) and bipolar disorder (BD). The subgenual prefrontal cortex is a region mediating emotional and autonomic responses to socially significant or provocative stimuli. Given the suggested critical role of the hippocampus in the pathophysiology of depression (Campbell and Macqueen 2004), several studies revealed smaller sizes of this region in patients with a depressive episode (Caetano et al. 2004; Frodl et al. 2002b; Shah et al. 1998; Sheline 1996). In addition, contradictory results of structural abnormalities in the amygdala in depression have been shown. An enlargement of the amygdala was found in patients with a first episode of major depression (Frodl et al. 2002a), whereas this enlargement was not found

in recurrent depression (Frodl et al. 2003). A smaller amygdala volume in depressed patients was reported by Sheline et al. (1998). The structural changes in grey matter mentioned above were only found in patients suffering from non-seasonal depression, and there is still a lack of volumetric MRI investigations in the field of SAD.

Only two MRI studies focusing on structural abnormalities in SAD patients were available in the literature. In line with a hyperactivity of the hypothalamic-pituitary adrenal (HPA) axis in depression, larger pituitary volumes have been found in patients with major depression (Krishnan et al. 1991). In contrast to these findings, 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 (Sheline et al. 1998). Recently, 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. Although no significant changes of pituitary volumes have been found in this study, pituitary volumes in winter correlated positively with the severity of depression in patients. While some studies have suggested adrenal gland enlargement in non-seasonal depression (Kessing et al. 2011), to our knowledge, there are no investigations focusing on adrenal gland volumes in SAD.

In sum, recent data on structural changes in SAD provide no clear evidence of structural brain alteration in SAD.

8.2.2 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 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.

8.3 Single Photon Emission Computed Tomography (SPECT)

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, this monoamine neurotransmitter 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). 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 can be assessed in vivo via the non-specific 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). By means of this technique, Neumeister et al. first demonstrated seasonal effects on brain SERT binding by investigating a small sample of healthy females ($n = 11$; Neumeister et al. 2000). Variations in the availability of thalamus/hypothalamus SERT binding sites were found between summer and winter with higher SERT availability in summer. A recent study of SERT availability in a larger sample of non-seasonal depressed patients ($n = 49$) demonstrated opposite findings with significantly higher [^{123}I]ß-CIT binding in winter (Ruhe et al. 2009). However, a significant reduction in SERT availability was only shown in male depressed patients.

Only a limited number of SPECT studies have been conducted in patients with SAD. In a study by Willeit et al. (2000), drug-free SAD patients ($n = 11$) 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. Based on animal (Laruelle et al. 1993) and post-mortem displacement studies (Staley et al. 1994), [^{123}I]ß-CIT is known to bind predominantly to SERT in the midbrain. Therefore, the finding of Willeit et al. may reflect a reduced SERT availability in untreated depressed patients with SAD in winter, a result that is partly in line with findings in non-seasonal depression (Ruhe et al. 2009). A study on SERT binding in platelets of patients with SAD and healthy controls failed to show differences between the two groups (Willeit et al. 2008). However, this study showed increased efficiency in SERT-mediated 5-HT uptake during winter depression. After

successful light therapy and during natural remission in summer, SERT function returned to control levels.

The dopaminergic system was also suggested to be involved in the pathophysiology of SAD by a [^{123}I]ß-CIT study of the Vienna group (Neumeister et al. 2001). In contrast to the midbrain, [^{123}I]ß-CIT binds—after achieving equilibrium binding (later than in the midbrain)—predominantly to dopamine transporters (DAT) in the striatum. According to that, Neumeister et al. were able to show a reduced availability of striatal DAT in untreated SAD patients in winter time.

A recent 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.

Apart from transporter and receptor studies, an investigation on 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 an increased left frontal rCBF in patients with SAD (Praschak-Rieder et al. 1998). Following successful bright light treatment, normalisation in left frontal rCBF was found.

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. 8.4). However, independent replications in larger samples of patients with SAD are still warranted.

8.4 Positron Emission Tomography (PET)

During the last decades, only two PET studies specifically investigating patients with SAD were conducted. Both studies on cerebral metabolism used [^{11}F]deoxyglucose ([^{11}F]FDG) to investigate if patients with SAD showed abnormalities in cerebral metabolic rates. A study by 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 PET-scanned after at least 10 days of light treatment (*on-lights*). To avoid possible order effects, three patients were investigated in the *off-lights* condition first and after 10 days of

Table 8.1 Neuroimaging in patients with SAD

Method	Author	Subjects	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 of blue light in SAD
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)		Increased left frontal rCBF in patients with SAD. Normalisation in 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
	Goyer et al. (1992)	9 summer SAD/45 HC	Altered glucose metabolism in orbital frontal cortex and left inferior parietal lobule in SAD

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

light treatment. The other three patients were studied during the *on-lights* condition first and after 10 days of discontinuation of light treatment. Light treatment consisted of 2.5 h of 2,500-lux full-spectrum light twice a day (morning between 6 and 9 AM, evening between 6 and 9 PM). Patients with SAD showed lower global metabolic rates under *on-* and *off-lights* condition, suggesting that a lowered metabolic state might be a trait marker of SAD. As suggested by the authors, an alternative explanation for the failure to detect differences in patients during *on-* and *off-light* condition may have been the insufficient length of light therapy. However, light therapy was sufficient to reverse depressive symptoms in these patients.

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

In contrast to the small number of studies investigating SAD patients (see Table 8.1), several neuroimaging studies analysing seasonal effects on monoaminergic neurotransmitter systems have been conducted.

As mentioned before, SPECT studies using the non-selective radioligand [^{123}I] ß-CIT revealed contradictory results with respect to seasonal effects on SERT binding (Neumeister et al. 2000; Ruhe et al. 2009). A PET study by Praschak-Rieder et al. conducted in a larger group of healthy drug-naïve subjects ($n = 88$) (Praschak-Rieder

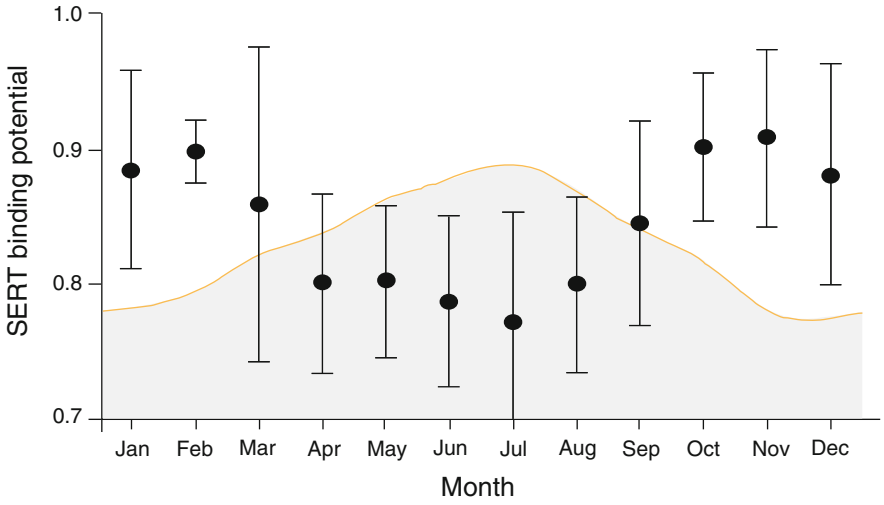

Fig. 8.1 Reciprocal peaks and troughs of serotonin transporter (*SERT*) binding and duration of sunshine in 88 healthy subjects. *Shaded area*: duration of sunshine in Toronto, Ontario (range, between 2.4 and 9.2 h a day. SERT BP_{ND} measured by the selective SERT radioligand [^{11}C]DASB and positron 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 et al. (2012))

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. This study revealed high [^{11}C]DASB binding potential (BP_{ND}) values in autumn and winter in six different predefined regions of interest (ROI). A uniform decrease of regional BP_{ND} values was found in spring and summer (Fig. 8.1). Peak differences in [^{11}C]DASB BP_{ND} values between months with highest and lowest binding potential values as large as 40 %. Furthermore, [^{11}C]DASB BP_{ND} values showed a negative correlation with the duration of daily sunshine and day length. In accordance with this study, Kalbitzer et al. (2010) 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 in [^{11}C]DASB binding. In contrast, 5-HTTLPR l-allele homozygous subjects did not exhibit seasonal variation of SERT availability. The methodology used in both studies does not allow for differentiation between the influence of daily sunshine and the astronomical photoperiod (daylight minutes) on [^{11}C]DASB binding because both parameters are highly intercorrelated. Although the negative correlation between [^{11}C]DASB binding and duration of daylight was found in both studies, a study by Murthy et al. (2010) did not replicate these findings.

Additionally, effects of season on SERT binding were demonstrated by Buchert and colleagues (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.

In summary, variations in SERT, with higher serotonin transporter availability in times of less light, as shown by the aforementioned studies, may facilitate extracellular serotonin loss during winter, potentially leading to hyposerotonergic symptoms and lower mood. To our knowledge, there are no studies on seasonal variations in SERT binding in patients with SAD. However, the data provided by Ruhe et al. (2009) suggest that there is a similar increase in SERT binding in patients with major depressive disorder in winter.

Recently, a study by Spindelegger et al. (2012) revealed light-dependent alterations of brain serotonin 1A (5-HT$_{1A}$) receptor binding. Among the different subtypes of serotonin receptors, the inhibitory 5-HT$_{1A}$ receptor has a particular role. Located on GABAergic and glutamatergic neurons in limbic and cortical brain regions, the receptor mediates the inhibition of postsynaptic firing (Varnas et al. 2004). In contrast, 5-HT$_{1A}$ receptors located on serotonergic neuronal somatodendrites inhibit serotonergic cell firing and modulate 5-HT transmitter release into the synaptic cleft. Consequently, these 5-HT$_{1A}$ autoreceptors constitute the decisive factor in a negative auto-regulatory loop of serotonin release (Bundgaard et al. 2006). 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). One recent animal study provided evidence for seasonal alterations in 5-HT$_{1A}$ receptor expression (Naumenko et al. 2008). The study by 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. 8.2). Up to 30 % differences in regional 5-HT$_{1A}$ BP$_{ND}$ were found between the different exposure groups.

In regard to the effects of season on serotonergic neurotransmission, higher SERT availability in times of less light was revealed in four different studies using SPECT and PET. Furthermore, serotonin receptor binding has been shown to be influenced by external factors such as global radiation. However, these results warrant independent replication. Altogether, these findings underline the importance of research in the field of the effects of season on the serotonergic system, as they provide additional insights into regulatory processes in 5-HT neurotransmission. Consequently, future studies investigating serotonergic target structures such as SERT or serotonin receptors should consider seasonal effects.

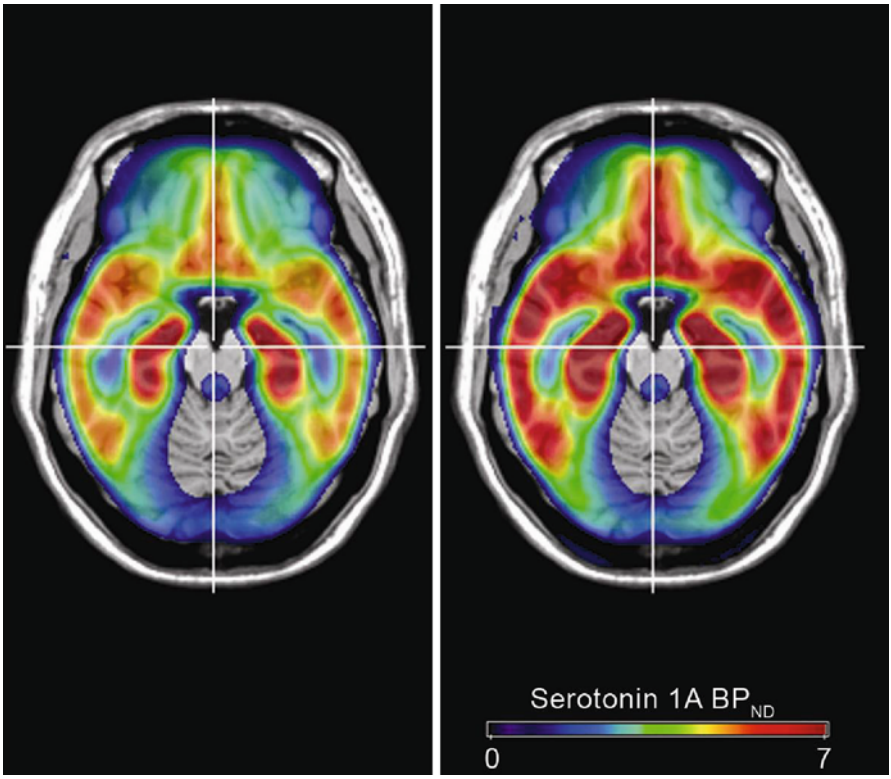

Fig. 8.2 Mean serotonin-1A receptor binding potential (5-HT_{1A} BP_{ND}) in subjects exposed to low amounts of global radiation (*left*) versus subjects exposed to high amounts of global radiation (*right*) showing 5-HT_{1A} BP_{ND} values in the group exposed to a low amount of global radiation, especially in limbic brain regions. Subjects exposed to low amounts of global radiation ($n=22$): 5-day accumulation of global radiation was lower than 8,946 J/cm^2; subjects exposed to high amounts of global radiation ($n=14$): 5-day accumulation of global radiation was higher than 8,946 J/cm^2 (Modified according to Spindelegger et al. (2012))

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 fall and 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 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.

8.5 Summary

Seasonal affective disorder and its subsyndromal form constitute 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 decades, only a limited number of studies specifically investigating SAD have been conducted. Apart from brain metabolic changes, monoamine systems in the human brain have been revealed to have a key role in seasonal modulation of behavioural and psychological domains. One of the most consistent findings is the seasonal variation of serotonin transporters with higher availability in winter as shown by four neuroimaging studies using different imaging technologies (Buchert et al. 2006; Kalbitzer et al. 2010; Praschak-Rieder et al. 2008; Ruhe et al. 2009). Other intriguing findings, such as seasonal changes in dopamine neurotransmission (Eisenberg et al. 2010; Tsai et al. 2011) or light-induced alterations in serotonin receptors (Spindelegger et al. 2012), are still awaiting replication. Given the lack of neuroimaging studies in SAD, further research (e.g. seasonal variations in monoamine oxidase activity) is needed to enhance the progress in understanding the molecular background of SAD and seasonal changes in the human brain. Furthermore, knowledge of seasonal effects on brain monoamine function might lead to additional treatment strategies in SAD.

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Bipolar Disorders

9

Bartholomeus (Benno) C.M. Haarman,
Rixt F. Riemersma-Van der Lek, Henricus G. Ruhé,
Jan Cees de Groot, Willem A. Nolen, and Janine Doorduin

Contents

B.(B.)C.M. Haarman, MD (✉) • R.F. Riemersma-Van der Lek • W.A. Nolen
Program for Mood and Anxiety Disorders, Department of Psychiatry,
University Medical Center Groningen, University of Groningen,
Hanzeplein 1, Postbus 30.001, 9700 RB Groningen, The Netherlands

Department of Psychiatry, University of Groningen, University Medical Center Groningen,
Hanzeplein 1, 9713 GZ Groningen, The Netherlands
e-mail: b.c.m.haarman@umcg.nl

H.G. Ruhé
Program for Mood and Anxiety Disorders, Department of Psychiatry,
University Medical Center Groningen, University of Groningen,
Hanzeplein 1, Postbus 30.001, 9700 RB Groningen, The Netherlands

Department of Psychiatry, University of Groningen, University Medical Center Groningen,
Hanzeplein 1, 9713 GZ, Groningen, The Netherlands

Program for Mood Disorders, Department of Psychiatry, Academic Medical Center,
University of Amsterdam, Amsterdam, The Netherlands

Program for Mood and Anxiety Disorders, University Center for Psychiatry, University
Medical Center Groningen, University of Groningen, Room 5.33., Hanzeplein 1, 9700 RB
Groningen, The Netherlands

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_9, © Springer-Verlag Berlin Heidelberg 2014

J.C. de Groot
Department of Radiology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands

J. Doorduin
Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands

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

9.1 Introduction

Bipolar disorder (BD) (APA 2000) 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, while 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 of 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 (APA 2000). 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, it is labeled as a mixed episode. 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 (Merikangas et al. 2007; Pini et al. 2005). 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, the diagnosis is more complicated in practice. On average, there is a lag time of about 6 years after the first episode before the right diagnosis is made, and another 6 years before adequate treatment is started. This is in part impeded by the precedence of depressive episodes without obvious (hypo)manic symptoms in the beginning of the disease in most cases (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 bringing the genes to expression. 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). In the last two 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.

9.2 PET/SPECT

9.2.1 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 opposite directed 511 kV gamma rays after annihilation of positrons with electrons, the radionuclides in SPECT directly emit gamma rays. Because the gamma rays being specifically in the opposite direction, PET 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 to handle tracers.

9.2.2 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 the subcortical regions. 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. It is generally accepted that CMR and CBF are physiologically coupled and both are indeed closely correlated in healthy controls (Drevets 2000). This appeared also to be the case in BD. 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 the controls (Rush et al. 1982), but others did not find a difference between the different mood states (Silfverskiöld and Risberg 1989; Tutus et al. 1998) (Table 9.1).

9.2.2.1 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,

Table 9.1 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	+	^{11}FDG-PET resting state	Decreased left dorsolateral prefrontal cortex and left amygdala in the manic BD patients compared to HC
Bauer et al. (2005)	9 BD-I (9 E) 1 BD-II (1 E)	+	^{11}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
Baxter et al. (1985)	5 BD (5 M, 2 Mi, 5 D) 11 MDD HC	+	^{11}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	+	^{11}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

Table 9.1 (continued)

Study (author, year)	Subjects	Medication	Method	Main findings
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
Brooks et al. (2006)	8 BD (8 D) 27 HC	–	^{11}FDG-PET CPT	No statistically significant differences in performance in CMR between the two groups were found
Buchsbaum et al. (1986)	16 BD (16 D) 4 MDD 24 HC	–	^{11}FDG-PET electrical stimulation to the forearm	Global cerebral metabolism was found to be significantly higher in subjects with affectiveness (both unipolar and bipolar depressed) compared to normal controls
Culha et al. (2008)	16 BD (16 E) 10 HC	+	99mTc-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	+	^{11}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	–	^{11}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
Dunn et al. (2002)	27 BD (27 D) 31 MDD	–	^{11}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
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

(continued)

Table 9.1 (continued)

Study (author, year)	Subjects	Medication	Method	Main findings
Gyulai (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 pathologic 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 (2001)	14 BD-I (11 D, 4 E) 29 BD-II (22 D, 7 E) 43 HC	–	^{11}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
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
Mah et al. (2007)	13 BD-II (13 D) 18 HC	+	^{11}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
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

Table 9.1 (continued)

Study (author, year)	Subjects	Medication	Method	Main findings
Rubinsztein (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

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

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). CMR activation related to a decision-making task was also decreased in manic patients in this region (Rubinsztein et al. 2001).

Euthymic patients demonstrated an 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).

9.2.2.2 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), 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).

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 a comparable CBF increase in the ACC during induced sadness (Krüger et al. 2006).

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, striatum (including nucleus caudatus), and all parts 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 (Bauer et al. 2005; Brooks et al. 2009; Drevets et al. 2002; Ketter et al. 2001; Mah et al. 2007). Additionally, amygdala and ventral striatal CMR correlated positively with depression severity and with cortisol levels (Drevets et al. 2002; Ketter et al. 2001). 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).

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).

9.2.2.3 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).

9.2.2.4 Corticolimbic Theory of Mood Disorders

Partly based on the abovementioned molecular imaging results, complemented with functional MRI (fMRI) research, a recent 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.

The corticolimbic theory has some overlap with several neurological networks that have been described and are thought to lay on 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, the 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 in 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 (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).

9.2.3 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 9.2).

9.2.3.1 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 by the presynaptic neuron for reuse 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-dimethylamino methylphenylsulfanyl)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

Table 9.2 Overview of PET/SPECT studies on neurotransmitter systems in BD patients

Neuro-transmitter	Study (author, year)	Subjects	Medication	Target	Method	Main findings
Serotonin	Yahtam 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-HT2A receptor binding in manic patients
	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 the midbrain of euthymic BD-I patients when compared to euthymic BD-II patients and healthy controls
	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 brainstem 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
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 9.2 (continued)

Neuro-transmitter	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 D2-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
	Yatham et al. (2002a)	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
	Suhura 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. (2002)	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 et al. (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 brainstem binding was nearly identical between BD and SZ patients and were higher than in the control group
Choline	Cannon et al. (2006a)	16 BD (16 D) 17 MDD 23 HC	–	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	–	M_2	^{18}F-FP-TZTP PET	Decreased receptor binding in BD is associated with genetic variation within CHRM2

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

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 the midbrain of euthymic BD-I patients when compared to euthymic BD-II patients and healthy controls (Chou et al. 2010). 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, which was comparable to MDD (Cannon et al. 2006b, 2007).

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 investigating the treatment effect of valproate on the 5-HT$_2$-receptor binding, using ^{18}F-setoperone, demonstrated no difference before or after treatment in manic patients (Yatham et al. 2005b).

9.2.3.2 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 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 inhibition 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 stimulation 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 in 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 the dimer forms of the receptor (Ginovart 2005).

In untreated nonpsychotic manic patients compared to controls, studies with the butyrophenone methylspiperone (Pearlson et al. 1995; Wong et al. 1985) and the benzamides iodobenzamide and raclopride (Anand et al. 2000; Yatham et al. 2002b) did not find striatal D_2-density difference. 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 the 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 the mood-stabilizing antiepileptic valproate sodium did not alter the D_2-receptor density in nonpsychotic manic patients (Yatham et al. 2002b).

Concerning the D_1-recepter, 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 ^{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). 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.

9.2.3.3 Choline

Acetylcholine is a neurotransmitter in both the peripheral nervous system and the 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 ($^{18F\text{-}FP\text{-}TZTP}$) (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.

9.3 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 mitochondrial dysfunction theory to illustrate the even broader neuroimaging field in this type of BD research and which form starting points for future molecular imaging research.

9.3.1 Neuroinflammation

The "macrophage theory of depression" postulates an aberrant proinflammatory 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 founded by a higher frequency of autoimmune diseases in mood disorders, aberrant proinflammatory cytokines, and elevated proinflammatory 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 (Bunevicius et al. 2007; Carta et al. 2004). 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 neopterine, IL-1β, IL-6, and TNF-α in mood disorders and in particular in MDD. With regard to the serum concentration of these compounds, increased levels were also described in BD when compared to controls, although not in all studies (Hoekstra et al. 2006; O'Brien et al. 2006). To investigate the proinflammatory state of monocytes in a more precise and robust manner, a Q-PCR analyses of CD14+ purified monocytes was 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 a 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 proinflammatory cytokines to the HPA-axis disturbances in major mood disorders (Almawi et al. 1991; Ito et al. 2006; Pariante et al. 1999).

Tryptophan, the precursor amino acid of serotonin, can be metabolized to downstream metabolites, known as kynurenines via an alternative pathway. IDO is an oxygenase that catabolizes the first and rate-limiting step in this oxidative degradation. The IDO activity in monocytes/macrophages is enhanced by proinflammatory cytokines, e.g., during infections and when there is physical or mental stress (Babcock and Carlin 2000). Under such circumstances, tryptophan breakdown is increased, making it less available for serotonin synthesis. When tryptophan is degraded, the next in vivo product is kynurenine, which is the first metabolite of tryptophan (Bender and McCreanor 1985). This kynurenine is again broken down into two pathways: (1) a neuroprotective, kynurenic acid, NMDA receptor antagonist pathway and (2) a neurotoxic 3-hydroxy kynurenine and quinolinic acid, NMDA receptor agonist pathway (Chiarugi et al. 2001). In the brain, this latter part of tryptophan catabolism, the kynurenine pathway, occurs in the astrocytes and microglia where astrocytes produce mainly neuroprotective kynurenic acid, while macrophages produce mainly neurotoxic metabolites like quinolinic acid. Normally, formation of quinolinic acid is faster, while kynurenic acid has a counteractive protective role against quinolinic acid (Perkins and Stone 1982). Based on the above, a hypothesis was proposed that an imbalance between the neurodegenerative and neuroprotective pathways leads to neurodegeneration and brings a person to a chronically depressive episode. This imbalance might be either due to a highly increased neurodegenerative pathway activity or due to a lack of sufficient neuroprotective factor activity (Myint and Kim 2003).

Tryptophan levels and the neuroprotective kynurenic acid were significantly decreased in MDD patients when compared to controls (Myint et al. 2007). Also, in IFN-α treatment of hepatitis C patients, associated with depression and fatigue, IFN-α was found to upregulate the expression of IDO (Curreli et al. 2001). Furthermore, the decrease of plasma tryptophan and the increase of kynurenine and neopterin during IFN-α treatment were found to correlate with the development of depression (Capuron et al. 2002; Wichers et al. 2005).

Molecular imaging can be 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 the PET ligand ^{11}C-PK11195, areas of microglia activation in the brain can be visualized. Besides in various neurological disorders, microglia activation has been found in SZ, where a clear focus of inflammation was found in the hippocampus (van Berckel et al. 2008; Doorduin et al. 2009).

9.3.2 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), an 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 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 in the pathophysiology with regard to other disease mechanisms is still controversial. It has been suggested that FA changes could be related to inflammation-related processes in BD, in analogy to multiple sclerosis (Zanetti et al. 2009). A combined study including a PK11195 PET scan with a DTI-MRI scan could help elucidate this relation.

9.3.3 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).

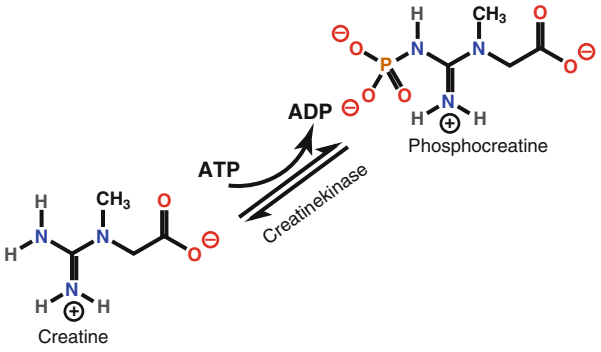

Fig. 9.1 Creatine energy buffer reaction

Magnetic resonance spectroscopy (MRS) is a neuroimaging technique that allows the investigation of the metabolism on a cellular level. It is an 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-acetylaspartate (NAA) relates to cell viability and 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. 9.1) cells with an abundance of ATP can store 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) were described, when compared to controls, supporting the mitochondrial dysfunction theory. Findings in other MRS metabolites such as a reduced pH and an increased lactate, exponents of cell metabolism exhaustion, add indirectly to this theory (Dager et al. 2004; Kato et al. 1993).

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 in 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 effects of 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, to which combined PET-MRI study efforts can be of help, as described above.

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 study 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 draw into detail. The role of molecular imaging as the main imaging technique in metabolism studies has been taken over by fMRI, but they are 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 neuronal, immune 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 medication-naïve 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 the withdrawal interferes with the investigated mechanism.

Another complicating factor is that the molecular imaging studies are limited in patient size because of careful ethic 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 continuous extending range of possible 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, e.g., vulnerability for relapses and 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 an overlap with other psychiatric disorders, which also makes it important to study it not only in BD but also in the other disorders, in order to further understand the similarities as well as the differences between the various disorders.

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PET and SPECT in Psychiatric Complications of Parkinson's Disease

10

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.

V. Kaasinen
Division of Clinical Neurosciences and Turku PET Centre,
University of Turku and Turku University Hospital, POB 52, FIN-20521 Turku, Finland
e-mail: valtteri.kaasinen@tyks.fi

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_10, © Springer-Verlag Berlin Heidelberg 2014

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

10.1 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.

10.2 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 (3–80 %) (Schwarz et al. 2011). Some studies in PD have reported prevalence rates of 5–10 % for major depression and up to 50 % for any depression (e.g., major plus minor or subsyndromal depression) (Tandberg et al. 1996). 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 towards 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).

10.2.1 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. Some studies indicate that the effect may be lateralized to the left hemisphere. However, in the most recent study, 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). The results by Koerts and colleagues therefore seem to confirm the results of most studies using DAT binding as an indicator of presynaptic dopaminergic function. The current evidence concerning the relationship between DAT/FDOPA and depression in PD indicates lower binding in depressed patients (Hesse et al. 2009; 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).

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; Rinne et al. 1990). PET studies with [^{11}C]SCH 23390 and [^{11}C]NNC 112 have, however, indicated that D1-like receptors are unaltered in PD (Cropley et al. 2008; 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 10 PD patients and 9 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).

10.2.2 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 is also recent 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 downwards 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.

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 7 PD patients with depression and 7 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 9 early nondepressed PD patients and 9 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.

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).

10.2.3 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).

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 (Le Jeune et al. 2009). Again, the interpretation of the results is difficult due to the low number of investigated patients in some studies.

10.3 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 six 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 8 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 is only one small FDG study 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).

There is a lack of monoaminergic imaging studies in PD hallucinations. In a small pilot study using [^{18}F]setoperone, serotonin 2A receptor binding has been studied in 7 PD patients with visual hallucinations and 7 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). 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). There are no reported corresponding studies in PD. 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.

10.4 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 will debut 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).

10.4.1 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 7 PD patients with pathological gambling and 7 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).

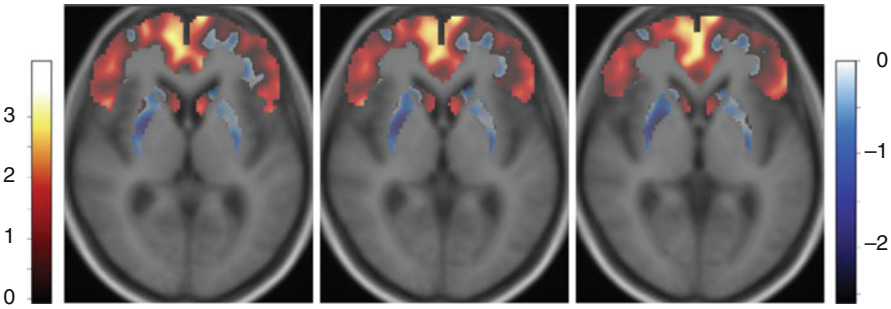

Fig. 10.1 Differences in brain FDOPA uptake between Parkinson's disease patients with impulse control disorders compared to Parkinson's disease patients without behavioral or mood disorders. Statistical pseudo-T map of the voxel-wise group comparison is shown. *Red-yellow* color shows regions with higher binding in patients with impulse control disorders (Courtesy of Dr. J. Joutsa)

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. 10.1) (Joutsa et al. 2012b).

Dopaminergic PET and SPECT studies therefore indicate that striatal dopamine release may be greater in PD patients with repetitive behavioral disorders compared to control PD patients, reflecting supersensitized dopaminergic mesolimbic system to rewards and reward-related cues. The findings concerning baseline dopamine D2 receptor binding are still inconclusive, as are studies focusing on presynaptic function (DAT and FDOPA).

10.4.2 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.

10.5 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). 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).

Conclusions

The great majority of studies concerning neuroimaging and PD psychiatric complications have been published during the last 5 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. For instance, depression has been measured with several different scales. 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 seems to greatly affect 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

11

Yannick Vermeiren, Debby Van Dam,
and Peter Paul De Deyn

Contents

Y. Vermeiren • D. Van Dam
Laboratory of Neurochemistry and Behavior, Institute Born-Bunge, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium
e-mail: yannick.vermeiren@uantwerpen.be; debby.vandam@uantwerpen.be

P.P. De Deyn (✉)
Department of Biomedical Sciences, Laboratory of Neurochemistry and Behavior, Institute Born-Bunge, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium

Department of Neurology and Memory Clinic, Hospital Network Antwerp (ZNA) Middelheim and Hoge Beuken, Lindendreef 1, 2020 Antwerp, Belgium

Department of Neurology, Alzheimer Research Center, University Medical Center Groningen (UMCG), University of Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands
e-mail: dedeyn@skynet.be

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_11, © Springer-Verlag Berlin Heidelberg 2014

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 characteristics, PET and SPECT are also useful tools to investigate the cerebral pathophysiology of BPSD in AD, FTD, and DLB among others.

Below, PET- and SPECT-related neuroimaging in dementia spanning the last two decades has been reviewed. The common use of different PET and SPECT radioligands and other compounds which target different and unique aspects of neurodegeneration in the differential diagnosis of dementia is described. Furthermore, PET and SPECT research in BPSD with a main focus on depression, apathy, and psychosis in AD, DLB, and FTD are illustrated as well. On the whole, both PET and SPECT imaging of neuropsychiatric disturbances in dementia 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]-FP	[^{123}I]-fluoropropyl
[^{123}I]-IBVM	[^{123}I]-iodobenzovesamicol
[^{123}I]-IDEX	[^{123}I]-iododexetimide
[^{123}I]-IMP	N-isopropyl-p-[^{123}I]-iodoamphetamine
[^{123}I]-β-CIT	[^{123}I]-2beta-carbomethoxy-3beta-(4-iodophenyl)tropane
[^{18}F]-FDG	[^{18}F]-fluorodeoxyglucose
3DSRT	3D stereotactic region of interest template
5HT	Serotonin (5-hydroxytryptamine)
^{99m}Tc-ECD	^{99m}technetium-ethyl-cysteinate dimer
^{99m}Tc-HMPAO	^{99m}technetium-hexamethylpropyleneamine oxime
AD	Alzheimer's disease
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
Aβ	Beta-amyloid
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
CMAI	Cohen-Mansfield Agitation Inventory
COX	Cyclooxygenase
CSDD	Cornell Scale for Depression in Dementia
CSF	Cerebrospinal fluid
DA	Dopamine
DLB	Dementia with Lewy bodies
DSM-IV-TR	Diagnostic and Statistical Manual for Mental Disorders IV text revised
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
IAD	Instrumental activities of daily living
IDO	Indoleamine 2,3-dioxygenase
IMPY	6-iodo-2-(4′-dimethylamino-)phenyl-imidazo[1,2]pyridine
MAPT	Microtubule-associated protein tau
MCI	Mild cognitive impairment
MFS	Middelheim Frontality Score
MMSE	Mini-mental State Examination
MXD	Mixed dementia
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
NSAID	Nonsteroidal anti-inflammatory drugs
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PET	Positron emission tomography
PGRN	Progranulin
PiB	Pittsburgh compound-B
PSEN	Presenilin
Py	Person years
rCBF	Regional cerebral blood flow
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

11.1 Dementia: Definition and Epidemiology

11.1.1 Definition

According to the *Diagnostic and Statistical Manual for Mental Disorders IV* (DSM-IV-TR), 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 2000) (Table 11.1).

Table 11.1 Criteria of the dementia syndrome according to DSM-IV-TR

A. Development of multiple cognitive deficits
A1. Memory problems (e.g., amnesia)
A2. At least one or more of the following:
Aphasia (language impairment)
Apraxia (loss of the ability to execute learned purposeful movements despite intact physical abilities)
Agnosia (loss of the ability to recognize objects, persons, sounds, shapes, or smells despite an intact sensory system)
Impairment in executive functioning (e.g., organizing, abstract reasoning)
B. Items described in A1. and A2. cause a significant decline in social and/or occupational functioning compared to a previously higher level of functioning
C. The cognitive deficits in A1. and A2. are not due to:
C1. Other diseases of the central nervous system (e.g., brain tumors, cerebrovascular accidents)
C2. Systemic disorders (e.g., vitamin B12 deficiency, hypothyroidism)
C3. Substance-related diseases
D. Diagnosis of dementia is not applicable if cognitive dysfunctioning occurs exclusively during the course of a delirium
E. Cognitive deficits are not attributed to another Axis I disorder such as depression or schizophrenia

Besides the cognitive aspects, dementia is also characterized by numerous behavioral symptoms entitled *Behavioral and Psychological Signs and Symptoms of Dementia* (BPSD) (Reisberg et al. 1987). BPSD consist of delusional ideation, hallucinations, activity disturbances, agitation/aggression, circadian rhythm disturbances, affective disturbances, and anxiety disorders and are considered a major component of the dementia syndrome. Lastly, basic (BADL) and instrumental activities of daily living (IADL) 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 firstly affected and are later 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 definition above emphasizes that the term "dementia" 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 as well (Fig. 11.1).

11.1.2 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

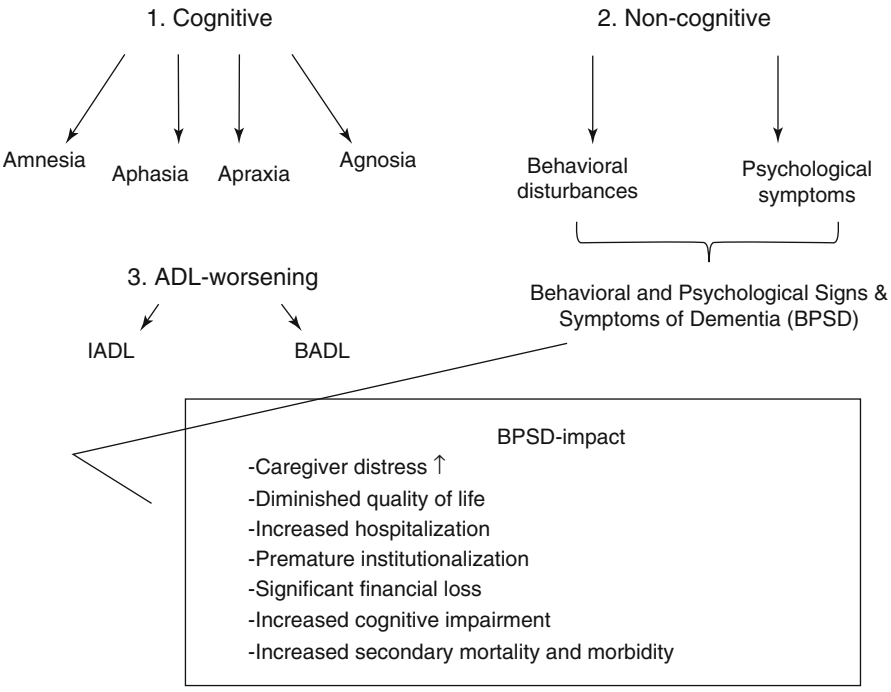

Fig. 11.1 The dementia syndrome consists of cognitive and noncognitive symptomatology. Worsening of BADL and IADL completes the definition. BPSD examples are delusional ideation and hallucinations, activity disturbances, aggression and agitation, sleep disturbances, mood disorders, and anxiety. *Abbreviations*: *BADL* basic activities of daily living, *BPSD* Behavioral and Psychological Signs and Symptoms of Dementia, *IADL* instrumental activities of daily living

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 over- 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 to 10 % in the elderly aged 65 and older. In Europe, the prevalence of dementia varies between 1 % at the age of 60–64 rising up to 34.7 % in elderly aged 95–99 (Hofman et al. 1991). 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 6 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).

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. Moreover, the majority of demented elders live in less developed countries and this proportion will increase considerably in the future.

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 1,000 person years (Py) for men and 33 per 1,000 Py for women (i.e., 41 or 33 persons out of 1,000 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 – independently of gender – at higher risk of developing dementia compared with those receiving higher education (Versporten et al. 2005). Accordingly with the ERDA study, the ANCOG study resulted in a cumulative incidence rate of 36.60 per 1,000 Py with annual incidence rates ranging from 34.39 over 35.16 to 49.09 per 1,000 Py. In America, the average incidence rate varies between 3 per 1,000 Py in people aged 65 up to 69 years old and a maximum of 56 per 1,000 Py in 90-year-olds (Kukull et al. 2002). These figures are consistent with a previously executed large-scale European study (Launer et al. 1999).

11.1.3 Alzheimer's Disease (AD) and Specific Dementia Syndromes

Dementia syndromes are commonly subdivided according to their reversible or irreversible characteristics (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, anxiolytic, or sedatives) (Katzman et al. 1988).

For this chapter, we will be exclusively focusing on primary dementias such as AD, FTD, and DLB. Secondary dementia syndromes and pseudodementias will not be considered in the further discussion of this chapter.

11.1.3.1 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 1907 in a 51-year-old patient who suffered from a progressive cognitive impairment associated with behavioral changes and brain atrophy. AD (code 294.1x) applies with the DSM-IV-TR criteria for the dementia syndrome described above (Table 11.1) (American Psychiatric Association 2000) and is manifested by multiple cognitive deficits such as memory impairment but also aphasia, apraxia, agnosia, and/or executive dysfunctioning. Additionally, AD is encoded based on the presence (294.11) or absence (294.10) of an associated clinically significant behavioral disturbance.

Diagnosis

The *National Institute on Aging and the Alzheimer's Association* workgroups (McKhann et al. 2011) recently 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 subdivided AD into probable, possible, and definite AD. Probable AD is characterized by cognitive deficits in at least 2 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 1 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 (McKhann et al. 1984). 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 new diagnostic entity, biomarker evidence of cerebrospinal fluid (CSF) amyloid beta (Aβ), total and phosphorylated tau levels, positive PET amyloid imaging, or a decreased ^{18}F-fluorodeoxyglucose (FDG) uptake on PET in the temporoparietal cortex may increase the certainty of an active AD pathophysiological process in persons who meet the core clinical criteria for probable AD (McKhann et al. 2011). Patients who met the 1984 NINCDS-ADRDA criteria for probable AD would also correspond with the more recent 2011 criteria described above.

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 an etiologically mixed presentation, such as concomitant cerebrovascular disease. 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.

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 an onset before the age of 65 (Blennow et al. 2006). A mutation in the amyloid precursor protein (APP) gene on chromosome 21 or in the presenilin 1 (PSEN1) or presenilin 2 (PSEN2) genes accounts for most of the familial cases. However, the familial form is rare with 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. So far, only risk genes have been identified such as the apolipoprotein E (APOE) ε4 allele which increases the risk of the disease by three times in heterozygotes and 15 times in homozygotes (Farrer et al. 1997).

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., $A\beta_{1\text{-}40}$ or $A\beta_{1\text{-}42}$ (amyloidogenic pathway). In normal situations, the non-amyloidogenic pathway is mostly active. In familial AD, however, a mutation in PSEN1/PSEN2 (which form

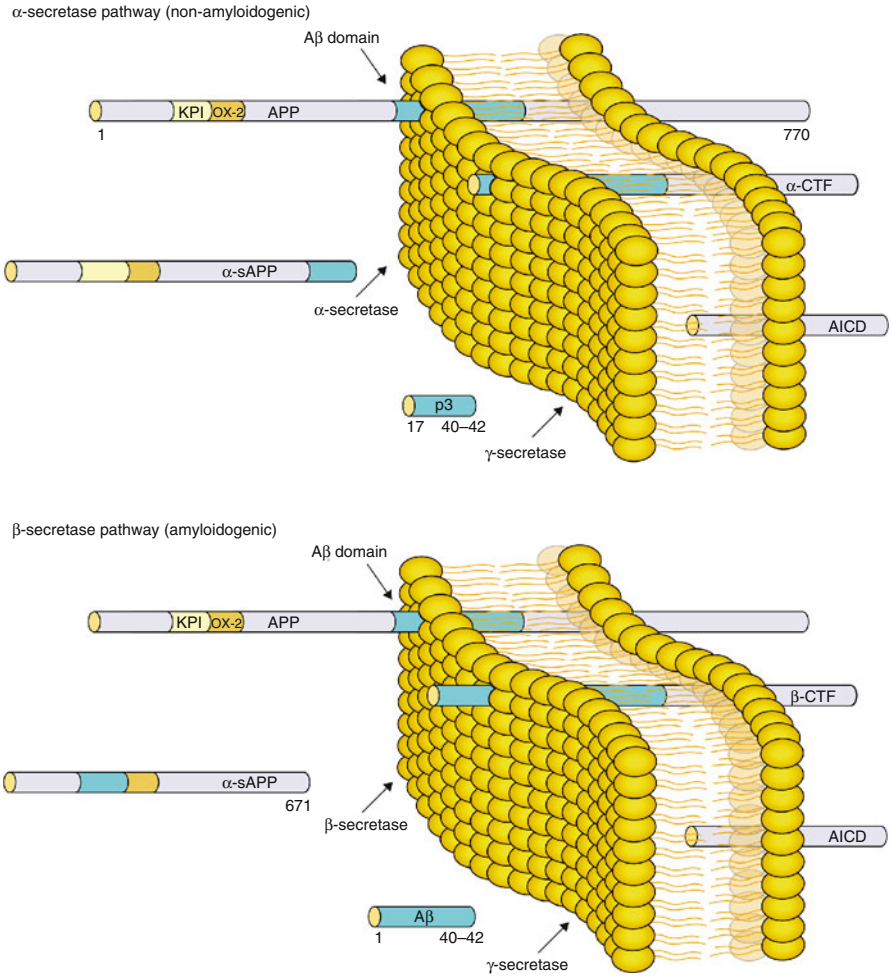

Fig. 11.2 The *amyloid cascade hypothesis* in AD. Amyloid precursor protein (APP) is a large transmembrane protein which is consecutively cleaved by α- and ɣ-secretases (non-amyloidogenic pathway) so that soluble p3 fragments are formed. In familial Alzheimer's disease (AD), however, dysfunctional cleavage of APP by β- and ɣ-secretases (amyloidogenic pathway) releases larger amyloid beta (Aβ) 1–40 and 1–42 fragments which leads to an overproduction of specifically Aβ1-42. $A\beta 1_{-42}$ are hydrophobic, insoluble filaments that will aggregate and form amyloid "senile" plaques, the hallmark of AD pathology. In sporadic AD, Aβ aggregates are formed as well but this time due to a failed Aβ clearance. It has been suggested that an imbalance between Aβ production and clearance lies at the basis of AD pathogenesis as such. *AICD* APP intracellular domain, *CTF* C-terminal fragment, *KPI* Kunitz-type protease inhibitor, *sAPP* soluble APP (Reprinted from Blennow et al. (2006), with permission. Copyright@2006 Elsevier)

the catalytic subunits of the secretases) or around the cleavage site of APP causes an overproduction of the hydrophobic $A\beta_{1\text{-}42}$ and consequently leads to a shifted $A\beta_{1\text{-}40}$/$A\beta_{1\text{-}42}$ balance. As a result, enormous amounts of $A\beta_{1\text{-}42}$ fragments aggregate and form extracellular "senile plaques" (Hardy and Selkoe 2002) (Fig. 11.2). Whereas in familial AD, there is an overproduction of $A\beta_{1\text{-}42}$ due to certain mutations, sporadic

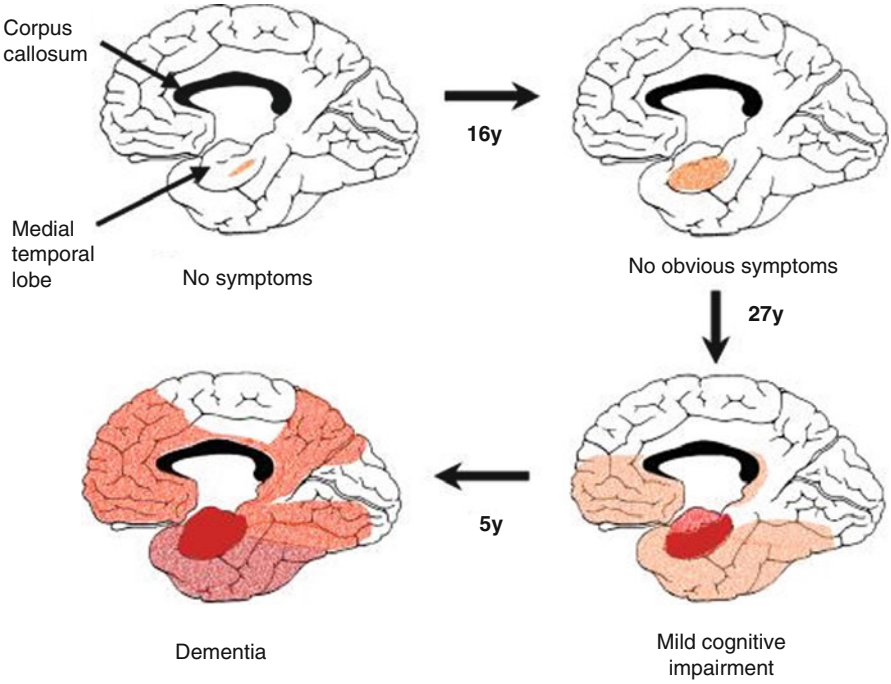

Fig. 11.3 Progressive expansion of neurofibrillary tangles (NFT) in an AD brain, showing the medial aspect of the cerebral cortex. The depth of the *red color* is in proportion to the density of tangles (Reprinted from Smith (2002), with permission. Copyright@2002 National Academy of Sciences, USA)

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) (Fig. 11.3).

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).

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) recently 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 (Van Dam and De Deyn 2006). In 2001, however, it was reported that a subset of NSAIDs reduced $A\beta_{1\text{-}42}$ production in cultured cells and mouse brain through a mode of action different from COX inhibition (Weggen 2001). On the other hand, the initial assumption of possible underlying anti-inflammatory mechanisms of NSAIDs in AD should not be completely abandoned (Van Dam and De Deyn 2006).

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 (5HT), 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 5HT synthesis, which is a neurochemical hallmark in the etiology of depression. Neuroinflammation by upregulating IDO and consequently lowering tryptophan levels has therefore been linked with major depressive disorder in AD patients (Dobos et al. 2010).

11.1.3.2 Other Dementia Subtypes

Except for 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. 11.4) (Small et al. 1997).

Below, DLB and FTD are briefly described as they significantly differ from AD concerning their diagnostic criteria, pathogenesis, disease course, and behavioral profiles.

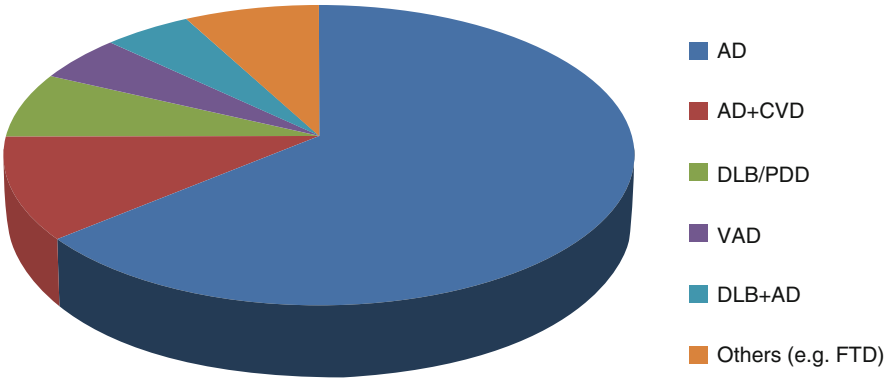

Fig. 11.4 Different etiological diagnoses of dementia. Alzheimer's disease is the most prevalent dementia subtype (64 %), followed by Alzheimer's disease + cerebrovascular disease (AD + CVD) (11 %), dementia with Lewy bodies (DLB)/Parkinson's disease dementia (PDD) (7 %), vascular dementia (VAD) (5 %), dementia with Lewy bodies and Alzheimer's disease (DLB + AD) (5 %), and finally other types of dementia (8 %), such as frontotemporal dementia (FTD) (Based upon Small et al. (1997))

Dementia with Lewy Bodies (DLB)

Dementia with Lewy bodies (DLB) is the third most prevalent dementia subtype and is diagnosed according to McKeith et al. (2005). Comparable with AD, several core and supportive criteria need to be present in order to establish a clinically acceptable DLB diagnosis. The three core criteria are a fluctuating cognition, recurrent and well-described visual hallucinations, and clinical sings of parkinsonism (extrapyramidal symptoms (EPS): tremor, rigidity, and hypokinesia). The presence of only two core criteria is sufficient to diagnose "probable" DLB. Some other supportive criteria are a disturbed REM sleep behavior, a low dopamine transporter reuptake in the basal ganglia proven on SPECT or PET imaging, autonomic dysfunction, depression, and concurrent delusional ideation. Furthermore, DLB patients suffer from neuroleptic sensitivity which severely worsens EPS when classical neuroleptics (antipsychotic medication) are administered (McKeith et al. 2005). 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 (if it is present). The term PDD should be used to describe dementia that occurs in the context of well-established Parkinson's disease (PD) (Geser et al. 2005; McKeith et al. 2005).

The main pathological characteristic of DLB is the presence of cytoplasmatic aggregated inclusions of α-synucleins, 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 vulnerable positions of neurons and glia (Goedert 1999;2001). Specifically in DLB, Lewy body aggregates precipitate in the

substantia nigra (pars compacta) of the basal ganglia and 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).

Frontotemporal Dementia (FTD)

A less frequent neurodegenerative disorder is frontotemporal dementia (FTD). Neary et al. (1998) established the diagnostic criteria of among others FTD, which forms one of the three diagnostic entities of "frontotemporal lobar degeneration (FTLD)" together with primary progressive aphasia and semantic dementia (SD). 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 judgement, 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 (De Deyn et al. 2005; Neary et al. 1998). 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 also likely to be recognized and distinguished from AD solely due to this distinctive behavioral pattern (De Deyn et al. 2005).

Similarly as with AD, FTD can be subdivided into familial (±30 %) and sporadic (±70 %) variants. For familial FTD, 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 (PGRN) (Cruts et al. 2006) and *TAR DNA-binding protein 43* (TDP-43) gene (Arai et al. 2006; Neumann et al. 2006). Mutations in the MAPT gene cause cytoplasmatic tau to aggregate which leads to the formation of tangles and eventually to neuronal death, especially in frontotemporal cortical areas. Neuropathologically, this degenerative phenomenon is known as "Pick's disease," but supranuclear palsy and corticobasal degeneration are also classified as tauopathies (Keith 2008). On the other hand, mutations in both TDP-43 and PGRN genes (non-tauopathies) cause TDP-43 and PGRN aggregates, again leading to a consequent neuronal degradation (Sieben et al. 2012). Histopathologically, these aggregates are visible as tau-negative but ubiquitin (U)-positive inclusions so that non-tauopathies are generally categorized as FTLD-U. Noteworthy, the frontotemporal localization of tau and ubiquitin

lesions in FTLD patients is pathophysiologically crucial to cause the frontal behavioral phenotype clarified above.

Recently, Gijselinck et al. (2012) identified a pathogenic GGGGCC repeat expansion in the C9orf72 promoter region on chromosome 9p21 in FTLD and amyotrophic lateral sclerosis (ALS) patients of a Flanders-Belgian cohort. FTLD and ALS are both clinically, pathologically, and genetically overlapping degenerative diseases. This genetic linkage and association study was performed in 337 FTLD, 23 FTLD-ALS, 141 ALS, and 859 control subjects. The GGGGCC repeat expansion showed to be highly penetrant, explaining all of the contribution of chromosome 9p21 to FTLD and ALS in this cohort. As for now, the function of the C9orf72 gene remains unknown, although it is highly conserved in all vertebrates. Further research of its function might eventually lead to a better insight into the common pathophysiological mechanisms of FTLD and ALS.

11.2 Behavioral and Psychological Signs and Symptoms of Dementia (BPSD)

Besides cognitive disturbances, dementia is characterized by numerous behavioral disturbances as well, categorized as *Behavioral and Psychological Signs and Symptoms of Dementi*a (BPSD) (Finkel et al. 1996; Reisberg et al. 1987). 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). 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. 11.1).

From an etiological point of view, research has repeatedly suggested that there is a neurochemical basis underlying BPSD although its pathophysiological mechanisms are still not well understood (Engelborghs et al. 2008). 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), and dopaminergic (Engelborghs et al. 2008; Lanari et al. 2006) neurotransmitter systems and associated receptors proved to play a critical role in BPSD manifestation, irrespective of the dementia subtype (Vermeiren et al. 2012). 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,

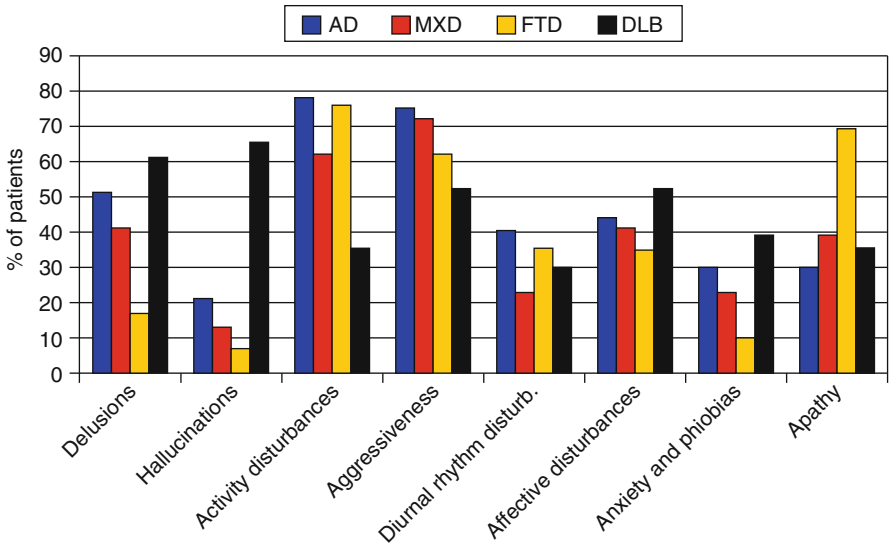

Fig. 11.5 Frequency of dementia-specific BPSD items. This figure shows that, e.g., apathy is much more frequent in FTD as compared to AD/MXD/DLB whereas delusions, hallucinations, and anxieties are less frequently present in FTD compared to DLB. *Abbreviations*: *AD* Alzheimer's disease, *BPSD* Behavioral and Psychological Signs and Symptoms of Dementia, *DLB* dementia with Lewy bodies, *FTD* frontotemporal dementia, *MXD* mixed dementia (Based upon Engelborghs et al. (2005))

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. 2012), 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, e.g., significantly high correlations between CSF taurine levels and depression in AD and CSF glutamate levels and agitation in FTD (Vermeiren et al. 2012).

Engelborghs et al. (2005) showed that different behavioral patterns can be observed depending on the dementia subtype, thereby further stressing that behavioral assessment itself may help in differentiating between different forms of dementia (Fig. 11.5).

In 1996, Jost and Grossberg examined the frequency of BPSD in temporal relationship with the diagnostic progression of AD patients, as is demonstrated in Fig. 11.6. In contrast to the cognitive symptoms in AD which progressively worsen during its course, BPSD are different as some behavioral symptoms are severely present during the early disease stages (e.g., depression) although later on these symptoms might gradually diminish or even completely disappear, to be eventually replaced by other BPSD items (e.g., aggression).

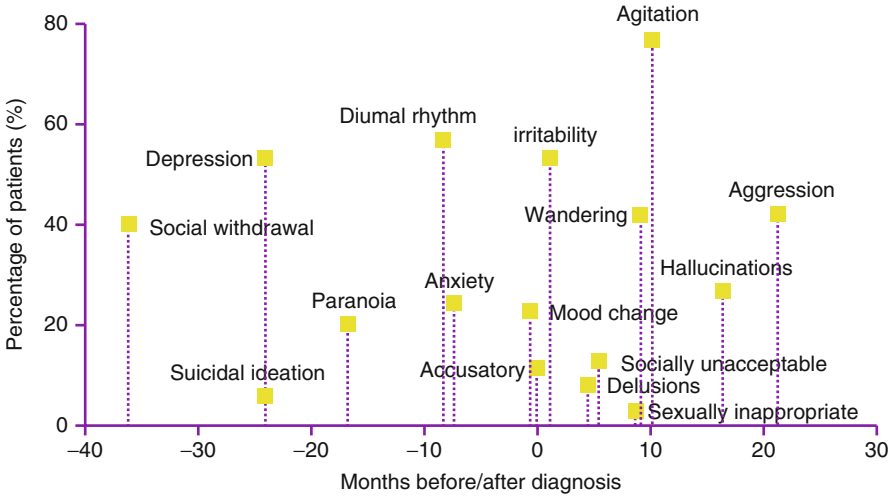

Fig. 11.6 Frequency of BPSD in temporal relationship with the progression of AD diagnosis. The evolution of Behavioral and Psychological Signs and Symptoms of Dementia (BPSD) in 100 autopsy-confirmed Alzheimer's disease (AD) patients before and after their initially established diagnosis is shown above. Especially depression and diurnal rhythm disturbances seem to be significantly present roughly 25 and 9 months before AD diagnosis whereas aggression, agitation, and hallucinations are symptoms that are characteristically manifested approximately 2–3 years later (Based upon Jost and Grossberg (1996))

11.2.1 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 towards 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 as well as delusions are characteristic for specifically DLB patients, as is shown in Fig. 11.5 (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, e.g., 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 of 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. Characteristic symptoms are the presence of one (or more) visual/auditory hallucination(s) and/or delusion(s). Secondly, 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.

11.2.2 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. 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 (Cohen-Mansfield et al. 1989; Lyketsos et al. 2000). Cohen-Mansfield et al. (1989) make a distinction between physically non-agitated 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).

11.2.3 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).

11.2.4 Depression

In AD, depression has a prevalence of 20 (Castilla-Puentes and Habeych 2010) up to 50 % (Starkstein et al. 2005). As shown in Fig. 11.6, depression is mostly present in mild to moderate AD or even 2 years before the established AD diagnosis (Alexopoulos et al. 1988; Jost and Grossberg 1996). 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).

11.2.5 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).

11.2.6 Anxieties and Phobias

Although less frequent, anxiety is a psychological symptom in dementia patients which is present in different variants (De Deyn 2004). The anxiety or fear of being left alone as well as 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 a meeting with the family doctor (Reisberg et al. 1986). This term was firstly described in the late 80s 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).

11.2.7 Apathy

In the context of dementia, apathy has been recently 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 the total 2,354 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 predementia state (Ready et al. 2003; Robert et al. 2009).

11.3 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.

11.3.1 Middelheim Frontality Score (MFS)

The *Middelheim Frontality Score* (MFS) is a clinical and behavioral assessment tool which measures frontal lobe features and secondly, 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 judgement; (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) and complex behavioral routines such 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 cutoff 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).

11.3.2 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 the frequency (De Deyn 2004).

11.3.3 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 3 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).

11.3.4 Geriatric Depression Scale (GDS)

The *Geriatric Depression Scale* (GDS) is the oldest 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 *mild cognitive impairment* (MCI) and non-demented elderly.

11.3.5 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 5 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).

11.3.6 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, and 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).

11.4 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. More recently, positron emission tomography (PET) studies of cerebral metabolism with ^{18}F-fluorodeoxyglucose (FDG) and amyloid tracers such as the *Pittsburgh Compound-B* (PiB) have provided invaluable information regarding specific AD-like brain changes (Johnson et al. 2012). 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 example, 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 but even in asymptomatic states.

Some of the most important PET radioligands and compounds which are widely used in the differential diagnosis of dementia are described below.

11.4.1 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 an indicator of brain metabolism and, when labeled with fluorine-18 (^{18}F) (half-life 110 min), is detected with PET. 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 brains 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, and 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 the early stages of AD whereas in a more advanced stage of the disease, usually the prefrontal association areas become affected (Johnson et al. 2012).

Recently, a meta-analysis showed that hypometabolism of the inferior parietal lobes and precuneus are the most striking neurological findings 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 techniques as FDG-PEt alone does not allow an adequate evaluation of the brain structure (Waldemar et al. 2007).

The pathological hallmark of the AD brain is the extracellular deposition of Aβ-plaques. 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), [^{125}I]-6 (Wang et al. 2002), and [^{3}H]-BTA-1 (Klunk et al. 2003). All compounds have binding properties for Aβ in the nanomolar range and are based on thioflavin, a well-known chemical dye that stains a wide range of amyloid pathologies (Suhara et al. 2008). PET studies using PiB labeled with carbon 11 (^{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). One concern however is the short half-life of PiB labeled with ^{11}C, which renders its use in some diagnostic clinical settings more difficult. Consequently the interest has raised to develop an amyloid-sensitive, radioactive-labeled PiB with longer half-life, such as PiB labeled with ^{18}F (Wong et al. 2010). A very promising ^{18}F-labeled amyloid imaging tracer which has recently been FDA-approved (April 6, 2012) is ^{18}F-florbetapir (^{18}F-AV-45) (Choi et al. 2009). Recent 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. Doraiswamy et al. (2012) even proved that [^{18}F]-florbetapir-PET may help in identifying individuals who are at increased risk for progressive cognitive decline. The same goes for florbetaben (BAY 94–9172), another valuable ^{18}F-PET marker for Aβ imaging which is currently in phase III clinical development with a sensitivity and specificity of 80 and 91 % in an AD versus control comparison (Barthel and Sabri 2011). Last in the series of ^{18}F-labeled amyloid PET imaging tracers is ^{18}F-flutemetamol (phase III trial). Recent 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 7 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.

Amyloid in vivo imaging is a very promising approach but is currently restricted to specialized centers around the world, although in the future it is likely that amyloid imaging techniques will be routinely used in the clinical evaluation of AD patients (Ferreira and Busatto 2011).

Besides amyloid deposits, intracellular NFT consisting of tau protein is a pathological feature of AD as well. The development of PET probes for in vivo imaging of NFT is presently an active research field (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, abbreviated as FDDNP (Agdeppa et al. 2001; Barrio et al. 1999). Unfortunately, FDDNP does not exclusively bind NFT but also Aβ plaques. So, for the moment, no existing PET imaging agents allow an exclusive in vivo evaluation of tau pathology in AD brains (Ono and Saji 2012).

Finally, one last 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 novel radiopharmaceutical is used in PET imaging to determine the activity of the acetylcholinergic 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 dopamine (DA) or serotonin (5HT) 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).

Please visit http://www.clinicaltrials.gov/ to see ongoing clinical trials concerning the development of novel PET probes related to amyloid and tau imaging or other neurodegenerative-specific disease markers in the differential diagnosis of dementia.

11.5 PET Imaging in Neuropsychiatric Disturbances of Dementia

11.5.1 Alzheimer's Disease

11.5.1.1 Depression and Apathy

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 (5HT) deficiency theory to be strongly related with mood disorders in dementia patients and non-dementing elderly (Sierksma et al. 2010). In vivo imaging studies that used PET have so far focused on 5HT receptors in the limbic brain regions associated with cognitive impairment in AD (Kepe et al. 2006; Meltzer et al. 1998). Ouchi et al. (2009) more recently used a set of 2 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 5HT-transporter marker, and the more common [^{18}F]-FDG-PET. Because the 5HT transporter is located on presynaptic 5HT terminals and regulates 5HT signaling, levels of [^{11}C]-DASB binding in these regions thus reflect the activity of presynaptic 5HT neurons in the dorsal raphe nuclei. Thomas et al. (2006) previously found a marked reduction in the binding of 5HT-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,

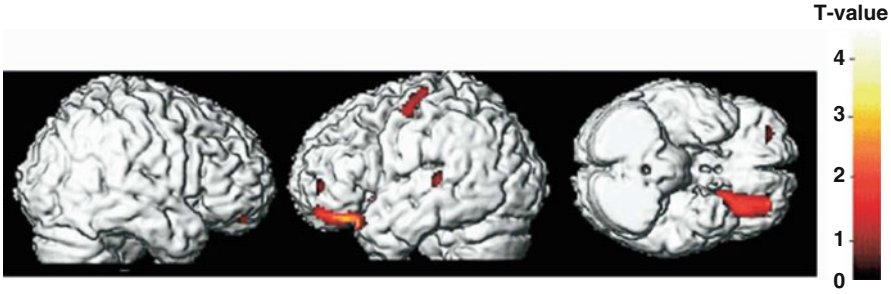

Fig. 11.7 Overlay images of the significant decreases in regional cerebral glucose metabolism in AD patients with clinically significant apathy ($n=17$) compared to AD patients free of apathy ($n=17$). Measured with [^{18}F]-FDG-PET in left orbitofrontal regions (BA 10 and 11) on an MRI template (SPM 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 et al. (2005), with permission. Copyright@2005 Elsevier)

$P<0.01$) as well as significantly lower [^{11}C]-DASB binding potential levels in AD patients, irrespective of depression, compared to healthy controls ($n=10$) in putamen, thalamus, and midbrain ($P<0.05$). Consequently, Ouchi et al. (2009) suggested that a certain degree of presynaptic 5HT function in the subcortical 5HT-projection region is compromised in AD patients even before the development of depression. Secondly, 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 5HT 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 patient group with apathy ($n=17$) revealed significant decreases in glucose metabolism in left orbitofrontal regions (*Brodmann area* (BA) 10 and BA 11) compared to non-apathic AD patients ($n=17$) ($P<0.008$) (Fig. 11.7). In addition, depression in AD patients ($n=10$) was significantly associated with hypometabolism in left and right dorsolateral prefrontal regions (BA 6 and 45) in comparison with nondepressed AD patients ($n=10$) ($P<0.02$) (Fig. 11.8) (Holthoff et al. 2005).

11.5.1.2 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) among others (Jeste and

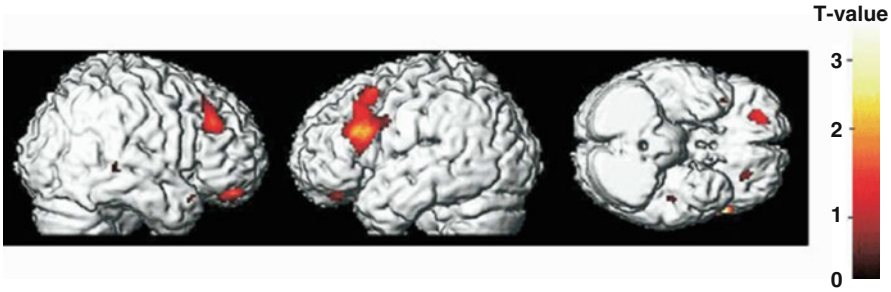

Fig. 11.8 Overlay images of the significant decreases in regional cerebral glucose metabolism in depressed AD patients ($n=10$) compared to nondepressed AD patients ($n=10$). Measured with [^{18}F]-FDG-PET in left and right dorsolateral prefrontal regions (BA 6 and 45) on an MRI template (SPM analysis; $P<0.05$, 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 et al. (2005), with permission. Copyright@2005 Elsevier)

Finkel 2000). Hirono et al. (1998) 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 were 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 (BA 8) (hypometabolism), the right inferior frontal pole (BA 10) (hypometabolism), and the right lateral orbitofrontal region (BA 47) (hypometabolism), confirming a link between delusional ideation and right hemispheric pathology.

More recently, Reeves et al. (2009) tested if delusions were associated with striatal dopamine (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. Reeves et al. (2009) 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 men) than without ($n=16$ of which 6 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 as was mentioned by Reeves et al. (2009).

11.5.1.3 Other Behavioral Syndromes

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) revealed 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 10 AD patients and only reported Behave-AD total scores.

Unfortunately, besides depression, apathy, and psychosis in AD, no in vivo PET imaging studies have been performed yet with regard to aggression, agitation, diurnal rhythm disturbances, or anxiety.

11.5.2 Other Dementia Subtypes

Rackza et al. (2010) examined the 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.

A very recent PET imaging study investigating the neuroanatomy and pathophysiology of BPSD in FTD patients came from Schroeter et al. (2011). In total, 13 FTLD patients underwent [^{18}F]-FDG-PET imaging after being behaviorally rated by the NPI scale. The researchers performed a conjunction analysis across the common neural correlates of the three most relevant behavioral disorders as identified in the single regressor analysis. All three behavioral disorders, i.e., apathy, disinhibition, and eating disorders, were related to mainly frontomedian hypometabolism. Afterwards, 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 in the 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 the 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). Secondly, [^{18}F]-FDG-PET data in 10 DLB patients with delusions revealed a hypometabolism of the right middle frontal gyrus (BA 9) and pars triangularis of the right inferior frontal gyrus (BA 45) 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 (BA 9) thus seems to be associated not only with visual hallucinations but also with delusions in DLB patients.

11.6 SPECT in the Differential Diagnosis of Dementia

The other commonly used nuclear gamma ray-emitting imaging modality besides PET which provides 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, and better quantitative capacity than SPECT; however, SPECT imaging is more practical as a routine clinical diagnostic procedure, and SPECT scanners are widely installed in most hospitals (Kung et al. 2004).

11.6.1 ^{99m}Tc-HMPAO-SPECT

For the differential diagnosis in dementia, the most common tracer applied in SPECT is ^{99m}Tc-HMPAO (hexamethylpropyleneamine oxime). The technetium isotope Tc-99m has a half-life of 6 approximate hours and is bound to HMPAO which allows Tc-99m 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 (Charpentier et al. 2000; Pickut et al. 1997; 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 afterwards 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 five 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 the MMSE scores. More recently, 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 cingulate cortex, and precuneus) combined with 3D fractal analysis may be useful in objectively distinguishing patients with very early AD and MCI from healthy elderly.

11.6.2 [^{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, Goto et al. (2010) found a significantly lower striatal volume on MRI plus a lower occipital SPECT-ratio in the DLB group as opposed to the 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 regional cerebral blood flow (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 among others. Based on these results, Hanyu et al. (2010) consequently suggested that rCBF-deficits in specifically the parietotemporal, posterior cingulate, and frontal brain regions are associated with subsequent rapid cognitive decline and rCBF-deterioration in AD.

11.6.3 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 an 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 8 age-matched control subjects (28.3 ± 1.3), the researchers found a significant decrease in [^{123}I]-IBVM-binding (47–62 %) in the cingulate cortex and parahippocampal-amygdaloid 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 using [^{123}I]-IBVM-SPECT might also be an effective approach to identify potential cholinergic treatment responders.

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 10 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 cingulate cortex 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, a complementary but earlier study of Boundy et al. 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. (2003b) assessed this possibility by studying the binding potential of [^{123}I]-5-I-R91150, a ^{123}I-labeled $5HT_{2A}$-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 $5HT_{2A}$-receptor binding potentials by which they stressed the necessity for matched advanced age study samples.

Finally, several other monoaminergic SPECT-ligands have been developed to distinguish AD- from DLB patients based on the fact that severe nigrostriatal neurodegeneration occurs in DLB but to no extent in AD as well as that due to the overlap in clinical symptoms, particularly in early stages of the disease, the differential diagnosis between both conditions might be 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 (2beta-carbomethoxy-3beta-(4-iodophenyl)tropane) and [^{123}I]-FP(fluoropropyl)-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 dopamine transporter levels which were always found to be significantly lower in DLB patients compared to AD patients (Tatsch 2008). In contrast, corresponding monoaminergic SPECT-ligands which targeted postsynaptic dopamine receptors showed to be much less efficient in differentiating DLB from AD patients.

Regarding the clinical diagnostic issues between AD and DLB patients, another radioligand binding the dopamine transporter located in the presynaptic membrane of dopamine nerve terminals that is frequently used to identify in vivo loss of dopamine transporters in the striatum of DLB patients, is [^{123}I]-ioflupane (Antonini 2007). [^{123}I]-ioflupane combined with SPECT is more familiar under the trade

name of "DaTSCAN." The main advantage of [^{123}I]-ioflupane is that a steady state allowing SPECT imaging is reached at 3 h after a single bolus injection of the radioligand compared with the 18–24 h 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 commonly used in clinical routine for the differential diagnosis between PD and essential tremor although it might also be valuable to differentiate between DLB and AD patients. In general, DaTSCAN favors the diagnostic work-up of DLB (Antonini 2007).

11.6.4 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 an AD brain might also be useful to differentially discriminate between AD patients and control subjects. One example comes from Versijpt et al. (2003a), who studied AD inflammation by using the radioligand [^{123}I]-PK11195 with SPECT imaging. PK11195 is an isoquinoline carboxamide that selectively binds to peripheral benzodiazepine receptors which are expressed on microglia in the brain. Additionally, PK11195 becomes upregulated under inflammatory circumstances. Versijpt et al. (2003a) compared the SPECT images of 10 AD and 9 control subjects and revealed 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 mesiotemporal regions.

As a result, PK11195 may be considered a valuable cellular disease activity marker for the in vivo evaluation of microglial inflammation in AD.

11.6.5 SPECT-Tracers Imaging Aβ-Plaques

The development of PET- as well as SPECT-tracers for amyloid-beta (Aβ) imaging represents an active area of radiopharmaceutical design (Valotassiou et al. 2010). These tracers are either monoclonal antibodies against Aβ, radiolabeled Aβ-peptides or derivatives of histopathological stains such as Congo red, chrysamine-G, and thioflavin-T. 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 specifically targeting amyloid plaques. The researchers evaluated 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 I-125 or H-3, [^{125}I]-IMPY- and [^{3}H]-SB-13-SPECT respectively

showed an abundant 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.

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-specific disease markers in the differential diagnosis of dementia.

11.7 SPECT Imaging in Neuropsychiatric Disturbances of Dementia

During the last two decades, many studies have conducted SPECT-related research regarding neuropsychiatric disturbances in dementia. Generally speaking, literature comprises more SPECT- than PET-related BPSD studies probably because SPECT, as an imaging technique, is more accessible. Of all BPSD items, depression, apathy, and psychosis in AD have been studied the most. Besides these three main behavioral disturbances, also activity disturbances, aggression, and sleep disorders were the subject of SPECT imaging in AD. Last but not least, SPECT imaging of psychosis and apathy in DLB and FTD patients has only been performed very recently over the last 7 years.

The most important SPECT imaging studies related to all these behavioral phenomena are summarized below.

11.7.1 Alzheimer's Disease

11.7.1.1 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 *Hamilton Rating Scale,* 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 cingulate gyrus ($P = 0.022$) of the high-severity AD group compared to the low-severity group. Results pointed to a high 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 *Hamilton Depression Rating Scale* 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. (2000). 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 Tc-99m, to investigate if hypoperfusion in prefrontal cortex or cingulate gyrus is associated with depression in AD. Depression scores were based on NPI depression items, so that 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 cingulate gyrus between the two groups, which is in contrast but also in agreement with previous studies who either found hypoperfusion in cingulate gyrus alone (Liao et al. 2003) or in the prefrontal cortex as well as in the cingulate gyrus (Galynker et al. 2000). Also in 2008, Levy-Cooperman et al. (2008) used the CSDD with a cutoff 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 cingulate gyrus are involved in affect and emotional regulation in AD.

Finally, in 2010, Kataoka et al. again used ^{99m}Tc-ECD-SPECT but afterwards 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.

11.7.1.2 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 an AD patient might be depressed. Therefore, it is very likely that the same affected brain regions of interest in depressed AD patients (prefrontal cortex, cingulate gyrus) might be comparable with those of apathic 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 apathic 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. used ^{99m}Tc-ECD-SPECT imaging again but this time in combination with SPM99 analysis. Brain perfusion patterns were compared between apathic ($n=15$) and non-apathic AD patients ($n=15$) as well as healthy control subjects ($n=11$). SPECT data showed that compared with 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 BA 8, 9, and 10 (bilateral medial frontal gyri) was observed in the apathic AD group but not in the group free of apathy. On the other hand, apathic AD patients tended towards a decreased perfusion in the anterior cingulate gyrus 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 performed with ^{99m}Tc-ECD-SPECT and SPM99 analysis. The lack of initiative score was negatively associated with perfusion in the right anterior cingulate cortex, whereas the lack of interest score 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 again showed a significantly lower perfusion in the right anterior cingulate gyrus 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 cingulate gyrus to be involved in the pathophysiological processes of apathy in the AD brain.

One last and recent study that related to apathy as well as depression in AD comes from Kang et al. (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 as well as depression, unfortunately, only 9 were classified as clinically significant depressed and 9 as clinically significant apathic. In addition, 18 more nondepressed and non-apathic AD patients were classified as an age- and MMSE-score-matched disease control group. Results showed that depressed AD patients had a significantly lower perfusion in the right orbitofrontal and inferior frontal gyri than nondepressed AD patients while apathic AD patients displayed a hypoperfusion in the right amygdala and temporal, posterior cingulate, right superior frontal, postcentral, and left superior temporal gyri compared to non-apathic AD patients. Secondly, 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 cingulate gyrus are involved in the cerebral pathophysiology of depression and apathy in AD.

11.7.1.3 Psychosis

Already in 1994, Starkstein et al. investigated whether delusions in AD were associated with dysfunction in specific brain areas. 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, Broca's area, the prefrontal region, and primary visual cortex. Afterwards, when comparing the SPECT data which were yielded at year 1 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 delusion, i.e., delusion of theft, in only 9 age- and cognitive-matched AD patients by means of ^{99m}Tc-HMPAO-SPECTimaging 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. (2006b) 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 so that AD patients were also 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 normal 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 prefrontal cortex, anterior cingulate gyri, inferior to middle temporal cortices, and parietal cortex of the right hemisphere ($P<0.01$).

More recently, in 2010, Matsuoka et al. studied the relationship between brain perfusion and associated delusion severity in individuals with AD, using SPECT and NPI. 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 the exacerbation of these symptoms.

SPECT imaging has also been used to investigate gender differences in regional perfusion in the brains of psychotic AD patients (Moran et al. 2008). 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 results revealed that perfusion was lower in female patients with psychotic symptoms in the right inferolateral prefrontal cortex and in the 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 or dementia severity, which was estimated by the MMSE. These results support the role of the 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. One example from 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 the right hemispheric pathology as was shown not only by SPECT but also PET imaging data. More neuroimaging research however is essential with regard to hallucinations in AD.

11.7.1.4 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 one SPECT study tried to study the brain's possible underlying physiological processes of wandering behavior in AD patients (Rolland et al. 2005). For this purpose, Rolland et al. (2005) used ^{99m}Tc-ECD-SPECT imaging and the NPI to define wandering in AD subjects. 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 (BA 21) and left parahippocampal gyrus (BA 37). 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. On the contrary, wandering in AD, as a physical activity and aberrant motor behavior, might enhance an extensive cortico-subcortical network interaction.

11.7.1.5 Aggression

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 one of Hirono et al. (2000) used a group of 10 mixed dementia (MXD) patients, i.e., AD + CVD, with and without aggression based on the NPI subscale for aggression. As imaging technique, ^{99m}Tc-HMPAO-SPECT was performed and MXD patients with aggression revealed a significant hypoperfusion in the left anterior temporal cortex ($P<0.001$) and additionally in the bilateral dorsofrontal and right parietal cortex.

The second study of Lanctôt et al. (2004) was slightly different as they used 30 aggressive and 19 nonaggressive AD patients whom 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 regions of interest ($P=0.02$ 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 BA 28, 35, and 36. Lanctôt et al. (2004) 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.

11.7.1.6 Sleep Disorders

Sleeplessness in AD is one last behavioral variant besides depression, apathy, psychosis, activity disturbances, and aggression which has been explored in the neuroimaging field of AD. Noteworthy, literature only mentions one related SPECT study so far (Ismail et al. 2009).

In this specific 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 in total were characterized as having or not having nocturnal sleep loss based on standard 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. Afterwards, 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 (BA 9) ($P=0.016$) in AD patients suffering from nocturnal sleep loss as opposed to AD patients who were free of sleep loss. However, hyperperfusion in the right middle frontal gyrus among AD patients with sleep loss was not supreme, given the fact that the level of hyperperfusion of this region which was found in the healthy control group 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.

11.7.2 Other Dementia Subtypes

Personality changes such as antisocial behavior are a prominent part of the behavioral symptomatology in FTD patients. This matter was studied by Nakano et al. (2006a) who assessed 22 FTD patients with the NPI and categorized 5 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 normal, healthy volunteers was included also, and both groups underwent ^{99m}Tc-ECD-SPECT and SPM99 analysis. Compared to normal 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, BA 47, BA 32, the right caudate nucleus, and left insula of FTD patients, suggesting that mainly a functional decline of the orbitofrontal cortex in FTD patients is related to antisocial behavior (Fig. 11.9). This conclusion is not surprising at all, given the fact that orbitofrontal cortex dysfunction is mostly associated with disinhibiton, facetiousness, sexual and personal hedonism, and lack of concern for others (Nakano et al. (2006a)).

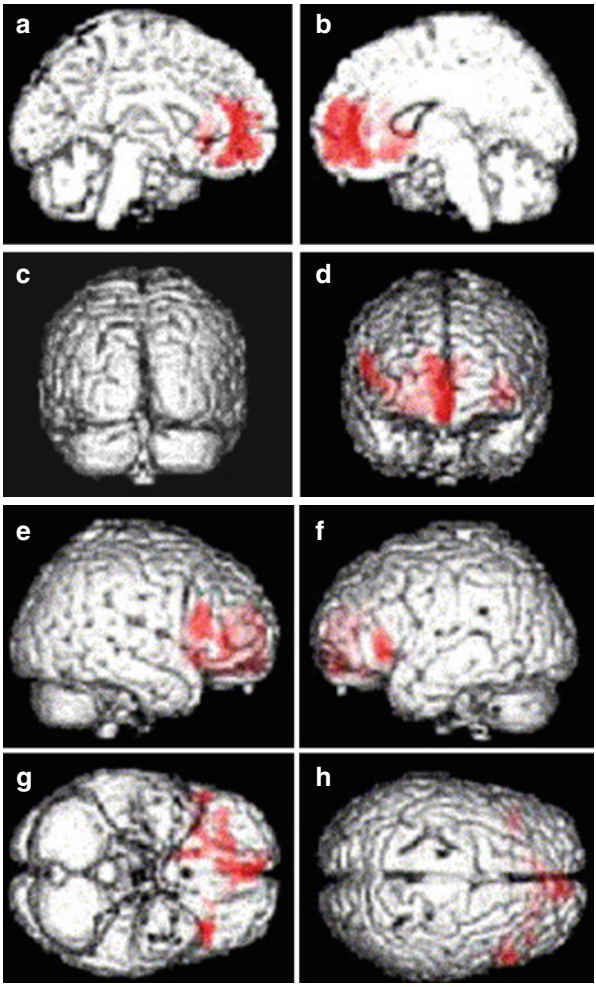

Fig. 11.9 Results of SPM analyses showing rCBF patterns that correlated with antisocial behavioral scores in FTD patients ($n = 22$) displayed on a 3D surface anatomical template ($P < 0.005$, not corrected for multiple comparisons). Views are medial right (**a**), medial left (**b**), posterior (**c**), 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), with permission. Copyright@2006 Elsevier)

The study of Roselli et al. in 2009 targeted BPSD symptoms in 18 well-characterized DLB patients and measured striatal dopamine transporter levels by [^{123}I]-FP-CIT-SPECT imaging after NPI assessment. Imaging data showed a significant correlation between decreased dopamine transporter levels and visual hallucinations. Although no other correlations were observed, delusions, apathy, and depression were also inversely correlated to decreased caudate dopamine transporter 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.

Furthermore, ^{99m}Tc-HMPAO-SPECT imaging in 14 DLB patients with hallucinations showed a significant inverse correlation between brain perfusion in the midline posterior cingulate gyrus and hallucination severity as was illustrated by O'Brien et al. (2005).

Finally, Nagahama et al. (2010) more recently found after using ^{99m}Tc-HMPAO-SPECT imaging 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 may therefore be related to a dysfunction of parietal and occipital association areas, while delusions may rather be associated with dysfunctions of the frontal cortex.

11.8 Concluding Remarks

PET and SPECT neuroimaging techniques have played an important role in the differential diagnosis of dementia over the past two decades. They have both provided invaluable information regarding the characteristic changes that match the pathophysiology of AD among others. 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. PET and SPECT also work very complementary if both imaging techniques are combined. However, the challenge for the future will be to develop novel radioligands which target different and unique aspects of the etiology of dementia so that subjects might be even more adequately recognized even in a presymptomatic or prodromal state.

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. This discriminative capacity even points to the diagnostic utilities of PET and SPECT in BPSD. More PET but also SPECT neuroimaging research however is mandatory with regard to especially activity disturbances, anxieties, hallucinations, diurnal rhythm disturbances, and aggression/agitation to fully

characterize the pathophysiology of each of these neuropsychiatric disturbances not only in AD but also other dementia subtypes.

Acknowledgments This work was supported by the Research Fund Flanders (FWO grant G.0164.09), Interuniversity Poles of Attraction (IAP Network P7/16) of the Belgian Federal Science Policy Office, Methusalem excellence grant of the Flemish Government, agreement between Institute Born-Bunge and University of Antwerp, the Medical Research Foundation Antwerp, the Thomas Riellaerts research fund, and Neurosearch Antwerp. DVD is a postdoctoral fellow of the FWO.

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Imaging of the Antidepressant Drug Response Using SPECT and PET

12

Ralf P. Clauss, Max Zöttl, and Mike Sathekge

Contents

R.P. Clauss, MD, FRCP (✉)
Department of Psychiatry, Nuclear Medicine, Royal Surrey County Hospital,
Egerton Road, Guildford, Surrey GU2 7XX, UK
e-mail: rclauss@nhs.net

M. Zöttl, MD
Department of Psychiatry, Canterbury Health Ltd, Priory Clinic,
92B Broad Street, Canterbury, Kent CT1 2LU, UK

M. Sathekge, MD, PhD
Nuclear Medicine Department, Steve Biko Academic Hospital, University of Pretoria,
Voortrekkers Road and Malan Street, Capital Park, Pretoria, South Africa

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_12, © Springer-Verlag Berlin Heidelberg 2014

Abstract

SPECT and PET imaging has played an important role in the evaluation of pharmaceutical interventions in mood disorders such as depression.

This review highlights the proposed role of monoamines, their precursors and the blood–brain barrier in depression and the antidepressant drug response. Reviewed are trials using SPECT and PET, including levodopa and carbidopa moclobemide and St. John's wort; selegiline; the selective serotonin reuptake inhibitors (SSRIs) citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline; the noradrenaline-dopamine reuptake inhibitor (NDRI) bupropion; the serotonin-noradrenaline reuptake inhibitor (SNRI) venlafaxine; and the tricyclic antidepressants (TCAs) amitriptyline, nortriptyline and desipramine.

So far there is no apparent consensus on SPECT and PET imaging features for depression and its treatment, except that at least 80 % of serotonin transporters have to be occupied by serotonin reuptake inhibitors to achieve a clinically effective antidepressant drug response. The lack of characteristic imaging features may be due to inadequately designed imaging studies with insufficient in- and exclusion criteria, or it may be due to different aetiologies underlying the depressive state. Another possibility is that depression may be a non-regionalised phenomenon with global brain participation, similar to what has been proposed for the generation of the conscious condition.

In the future, it is likely that SPECT and PET imaging will remain an important tool and challenge in individual- and group-based approaches to obtain further information on depression and the antidepressant drug response.

12.1 Introduction

Since the advent of computer-based imaging several decades ago, it has become possible to achieve in vivo quantification of substrates in the brain in conscious and nonconscious patients and in neurological and psychiatric disease. SPECT and PET imaging play an important role in the response evaluation of pharmaceutical interventions in conditions such as mood disorders which are emotional states characterised by feelings and thoughts and mental activities involving consciousness, a continuum of mental states that ranges from full alertness to loss of meaningful communication (Katz et al. 2009). A well-known disorder of mood is depression, a state of low mood that affects a person's feelings, thoughts, behaviour and general health.

In consciousness, oxygen-based amino acids and monoamines are a component of brain function that operates in synapses, sometimes viewed as the main functional unit of the brain in which nerve stimuli are generated with or without external prompting (Liggan and Kay 1999; Südhof 2004; Wasser and Kavalali 2009; Bonansco et al. 2011). It has been proposed that two main networks of oxygen-based neurotransmitter function exist in the brain, namely, the monoamine axes (dopamine, noradrenaline, serotonin) and the amino acid axis (GABA/glutamate) (Clauss 2010, 2011; Nyakale et al. 2010). It has been proposed that mood is driven by monoamines (Schildkraut 1965; Bunney and Davis 1965; Van Praag 1967; Coppen 1969).

Although monoamines act on receptors localised to specific brain regions, they exert their influence globally throughout the brain. This occurs via neuronal circuits and networks which modulate global brain function and metabolism. Hence anomalies and receptor regulation at monoamine input points can have global cerebral effects (Green 2006).

Over the years, three main neurotransmitters are thought to be involved in mood disorders and depression. These are the monoamines dopamine, noradrenaline and serotonin, assumed to regulate emotion, reactions to stress, the drives of sleep, appetite, and sexuality. The monoamine hypothesis of depression is the most prominent chemical imbalance theory of depression today, having led to the development of modern antidepressant drugs, such as the serotonin reuptake inhibitors (SSRIs) (Lieberman 2003).

Monoamines are proposed abnormally high or low in psychiatric disease, for example, high with positive symptoms of schizophrenia and low with its negative ones and with depression. The dopamine theory, for example, attributes the positive symptoms of schizophrenia to an overactive dopaminergic signal transmission, while in depression monoamines are considered low and underactive (Carlsson 1977; Soares and Innis 1999; Abi-Dargham et al. 2000; Schildkraut 1965).

The monoamine hypothesis postulates that deficiencies of certain monoamine neurotransmitters are responsible for features of depression. Dopamine deficiency may be related to lowered attention, motivation, pleasure and reward. Noradrenaline may be related to alertness, energy and anxiety, attention, and interest in life; lack of serotonin may be related to anxiety, obsessions, and compulsions (Nutt 2008).

Some medications that counter depression influence the overall balance of dopamine, noradrenaline and serotonin in the brain. Supporters of the monoamine hypothesis recommend that the choice of antidepressant medication should be based on the possible mechanism of action that impacts most on the symptoms of depression. Anxious and irritable patients should be treated with serotonin or noradrenaline reuptake inhibitors, and those experiencing a loss of energy and enjoyment of life should be treated with noradrenaline and dopamine-enhancing drugs (Nutt 2008).

Cerebral dopamine, noradrenaline and serotonin are brain-produced neurotransmitters that are the end products of a long series of biochemical events that occur within the brain. Dopamine and noradrenaline are sourced from the conditionally essential amino acid tyrosine and the essential amino acid phenylalanine (Fernstrom and Fernstrom 2007). Serotonin is sourced from the essential amino acid tryptophan (Parker and Brotchie 2011). Tyrosine, phenylalanine and tryptophan compete with each other and other amino acids at the large neutral amino acid transporters of the blood–brain barrier to enter the brain (Fernstrom 2013). Once they have entered the brain, they depend on energy, enzymes, oxygen and other raw materials, supplied within the brain to convert them to the desired monoamines. Once the monoamines have been produced, they have to remain at homeostatic levels to be able to generate a normal brain function. It follows that monoamine homeostasis depends on a balance of monoamine production and loss. For adequate monoamine homeostasis, all

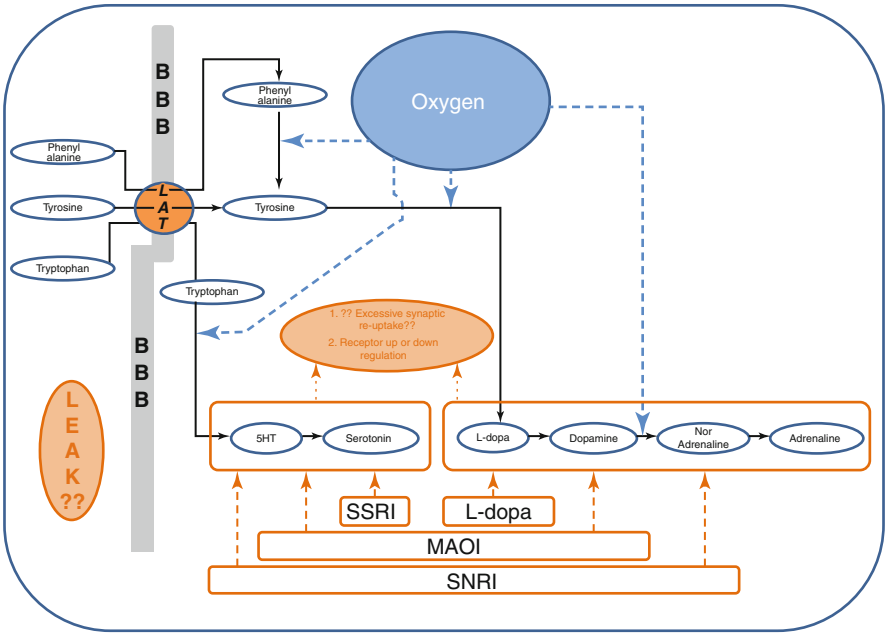

Fig. 12.1 The production pathways of the monoamines dopamine, noradrenaline and serotonin in the brain. The precursors tyrosine, phenylalanine and tryptophan enter the brain through the blood–brain barrier (BBB) after competing for places on the large neutral amino acid transporters (LAT). If sufficient oxygen is available, phenylalanine converts to tyrosine which then converts to L-dopa and dopamine. On oxygenation dopamine converts to noradrenaline and finally adrenaline. With available oxygen, tryptophan converts to 5-hydroxytryptophan (5-HT) which converts to serotonin. Monoamine production has to be maintained to counter metabolic attrition and other causes of depletion, such as leakage through a defective blood–brain barrier. Medications such as serotonin reuptake inhibitors (SSRIs), for example, counter synaptic serotonin reuptake. Other medications are L-dopa and tricyclic antidepressants (TCA) which can be used to supplement deficiencies

elements of production including oxygenation have to function adequately while synaptic removal and losses through metabolic attrition or possible leakage through a defective blood–brain barrier need to be limited.

If depression is caused by monoamine deficiencies, then pharmacological interventions would be a way to redress these, either by replacement or by correcting production anomalies or by stemming loss. For a simplified schematic presentation of the oxygen-reliant intra-cerebral production of the three major mood-associated monoamine neurotransmitters dopamine, noradrenaline and serotonin, please see Fig. 12.1.

In psychiatric disorders such as major depression (MD), potential monoamine deficiencies may benefit from pharmaceutical monoamine supplementation. Supplementation should be considered additional to internally generated monoamines, which depend on adequate precursor supplies, oxygen, cellular and synaptic integrity.

While the monoamine hypothesis explains aspects of biochemical pathology in depression, it does not explain the antidepressant lag time which is the time it takes from first antidepressant application to antidepressant response, often several weeks.

Such lag times may be due to receptor up- or downregulation or binding in adapting neuronal networks and circuits (Malberg and Blendy 2005).

Diurnal neurotransmitter variation may also play a role. For example, noradrenaline and serotonin availability are influenced by sleep when levels transiently decrease in areas such as the pons and amygdala (Shouse et al. 2000).

In a study of mood disorder, six unipolar depressed patients and eight healthy subjects underwent separate (18)F-FDG PET scans during waking and in their first REM sleep period. Compared to healthy controls, the depressed patients showed increased uptake in their tectal regions and in the left sensorimotor cortex, inferior temporal cortex, uncal gyrus-amygdala and subiculum complex during REM sleep (Nofzinger et al. 1999). In a study on sleep deprivation in 14 medicated patients, technetium-99m hexamethylpropyleneamineoxime (99mTc HMPAO) SPECT scans revealed hypoperfusion in the left prefrontal cortex which was reversible upon remission. Before sleep deprivation therapy, the responding patients had a significantly higher anterior cingulate perfusion than nonresponding patients, which normalised after sleep deprivation (Holthoff et al. 1999).

While it is well known that sleep deprivation can temporarily counter depression, it is equally known that repeated REM sleep withdrawal will result in "REM rebound". This "rebound" is associated with symptoms of depression and bipolar disorder. The severity of the rebound is related to the severity of "REM suppression" countered by subsequent increases in REM sleep (Suchecki et al. 2012; Greene and Siegel 2004). In recent drug developments, efforts have been made to explore the effect of sleep influencing medication in depression, for example, by using the melatonergic agonist agomelatine (Kasper et al. 2009).

Hypothyroidism is a well-known cause of depression that can occur due to insufficient thyroid hormone availability in the blood. A prospective cross-sectional study involving 254 patients showed that hypothyroidism increases the risk for critical mood deterioration by sevenfold (Larisch et al. 2004). In a 99mTc HMPAO SPECT study of 24 patients with hypothyroidism, 16 presented with a decreased uptake mostly in the posterior parietal lobes bilaterally and in the occipital lobes, including the cuneus. These areas extended to the bilateral prefrontal cortices when deterioration became more profound. After thyroxine replacement, regional cerebral blood flow improved in 9 of the 16 patients (Nagamachi et al. 2004).

Potential causes of depression are multifaceted with biological, psychological and social factors all playing a role. Its clinical manifestation is often assumed concurrent with anomalies in the monoamine homeostasis of the brain. The term "antidepressant drug" for the purpose of this review encompasses a wide range of substances which relieve aspects of the depressive state.

12.2 SPECT and PET Imaging in Psychiatric Disorders

SPECT and PET imaging of the brain in psychiatric disorders and depression typically comprises two aspects of brain function, namely, brain metabolism and brain neuroreceptor availability.

Brain metabolism can be measured directly by positron emission tomography (PET) using the positron emitting glucose analog [(18)F]-fluorodeoxyglucose ((18) F-FDG) or, indirectly, using the lipophilic cerebral perfusion agent technetium-99m hexamethylpropyleneamineoxime (99mTc HMPAO) that concentrates in neurons and partially in glia (Zerarka et al. 2001). Other tracers include 99mTc ethylcysteinate dimer (99mTc ECD), N-isopropyl-p-[123I]-iodoamphetamine (123I IMP), 133Xe and 195Au (Nikolaus et al. 2000). (18)F-FDG follows the path of glucose into the brain and neuronal tissue where it labels metabolic pathways that reflect the glucose metabolism of the brain (Chételat et al. 2005). The lipophilic amines 99mTc HMPAO, 99mTc ECD and 123I IMP pass through the blood–brain barrier in a blood flow-dependent manner and are trapped within the grey matter of the brain (Colamussi et al. 1999; O'Brien et al. 1999; Weder et al. 1990). (18)F-FDG hence reflects brain metabolism and 99mTc HMPAO, 99mTc ECD and 123I IMP mostly cerebral blood flow.

Neuroreceptor availability can be measured by markers of monoamine receptors. Measurable receptors include D1, D2 and 5-HT receptors and dopamine (DaT) and serotonin transporters (SERT). Multiple tracers can be used for imaging these and other aspects of the antidepressant response. These include amongst others 123 I IBZM, [11C]-raclopride, [123I]beta-CIT, 123 ioflupane (DaT Scan), [(11)C]WAY-100635, alpha-[(11)C]methyl-L-tryptophan, [(123)I]-ADAM, [(11) C]DASB, 123I-FP-CIT, [(18)F]FESP, [11C]verapamil, [(18)F]fluoro-L-dopa, [(11) C]-harmine and [(18)F] MPPF.

12.3 SPECT and PET Imaging in Depression

Early studies investigating depression often made use of brain perfusion tracers to gauge brain metabolism. A finding in these early studies was that of a global cerebral hypoperfusion in depression (Fountoulakis et al. 2004; Kanaya and Yonekawa 1990). This was often more pronounced in temporal, inferior frontal and parietal areas of the brain (Austin et al. 1992; Maes et al. 1993).

In a meta-analysis looking at metabolism and cerebral perfusion in major depression in 337 patients and 321 controls, Nikolaus et al. observed a decreased activity bilaterally in the frontal, parietal and occipital lobes; basal ganglia; and thalamus regions of the brain and right temporally, while the limbic region had a decreased uptake left and an increased uptake right (Nikolaus et al. 2000). In an analysis of major studies looking at the monoamine receptor function in depression until 2012, the same group observed that a complex pattern of dysregulation may exist within and between neurotransmitter systems, possibly linked to the subtype and duration of disease, the predominance of individual symptoms and pharmacological interventions (Nikolaus et al. 2012). Their main observations were that in acute depressive disease:

- Dopamine synthesis increases frontally and pre-frontally, decreasing in remission.
- 5-HT1A binding decreases frontally, pre-frontally and occipitally, expanding to the parietal, temporal and cingulate regions upon remission, while 5-HT2A binding decreases in the cingulate regions, shifting to the parietal regions upon remission.

- SERT binding increases in the insula and decreases in the thalamus and midbrain region, remaining decreased in the midbrain upon remission.

The above studies and others show that anomalies in cerebral blood flow and metabolism occur globally in depressive patients as do anomalies in receptor function. Although regional suppression of fronto-cortical and limbic circuits has been historically considered characteristic of depression, the evidence to date indicates otherwise, namely, that diffuse, rather than regional, abnormalities tend to occur.

12.3.1 SPECT and PET Imaging of Dopamine Receptors

Four major dopaminergic pathways have been identified in the mammalian brain, namely, the nigrostriatal, mesolimbic, mesocortical and tuberoinfundibular pathways. Dopaminergic receptors are metabotropic G protein-coupled receptors classified to two major groups, the D1 (D1, D5) and the D2 group (D2, D3, D4). The D1 type are exclusively postsynaptic, located mostly in the striatum, nucleus accumbens, substantia nigra, olfactory bulb, amygdala, frontal cortex and to a lesser extent in the hippocampus, cerebellum, thalamus and hypothalamus. The D2 type are expressed pre- and postsynaptically mostly in the striatum, nucleus accumbens, olfactory tubercle and to a lesser extent in the substantia nigra, ventral tegmental brain region, hypothalamus, cortical areas, septum, amygdala and hippocampus (for a comprehensive review, see Beaulieu and Gainetdinov 2011). Tracers that can be used to measure D2 density are 123 I IBZM, a SPECT tracer that marks the postsynaptic D2 receptors, and [11C]-raclopride, a PET tracer that measures the D2 receptor binding in the striatum (Laruelle 2000) (Hierholzer et al. 1992). Both IBZM and [11C]-raclopride show increased binding in the striatum when extracellular dopamine is low (Shah et al. 1997) (Laruelle 2000). Results of preclinical and clinical studies implicate that, in addition to serotonin and norepinephrine, dopaminergic mechanisms may play a role in the pathogenesis and treatment of depression (Lemke 2007).

12.3.2 SPECT and PET Imaging of Dopamine Transporters

Dopamine transporters (DaT) are situated in the presynaptic region of the striatal synapses where they pump dopamine from the synaptic cleft into the presynaptic neuronal space. Commonly used tracers to investigate presynaptic dopamine transporter function are the cocaine derivatives [123I]-2-beta-carbomethoxy-3-beta-(4-iodophenyl)-tropane ([123I]beta-CIT) and ^{123}I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ((123) I]FP-CIT, Ioflupane, DaT Scan) (Brücke et al. 1993; Booij et al. 1998). [123I] beta-CIT imaging can also be used for SERT imaging as it partially binds to these receptors as well (Reneman et al. 2002). Responses to neuroactive drugs can be measured by DaT binding in regions of interest in the brain (Warwick et al. 2012). Decreased DaT availability may occur in affective disorders such as those associated with Parkinson's disease (Weintraub et al. 2005).

12.3.3 SPECT and PET Imaging of Serotonin Receptors

Serotonin receptors are also known as 5-HT receptors, mostly G protein-coupled receptors, of which the 5-HT1A receptors appear to play a key role in depressive disorders (Savitz et al. 2009) and to a lesser extent 5-HT2 receptors (van Heeringen et al. 2003). 5-HT1A receptors have been localised by the piperazine PET tracer [(11)C]WAY-100635 mostly to the cerebral cortices, hippocampus and raphe nucleus (Ito et al. 1999).

In an analysis of eight studies investigating the 5-HT1A receptor in the brains of patients with major depressive disorder, four reported a decreased 5-HT1A receptor density, two no change and two an increased density. These discrepant results were thought to be due to possible methodological research factors, but other options have to be considered. The disparate findings do not reliably answer the question of whether 5-HT1A receptors are altered in major depression or in subgroups of these patients (Shrestha et al. 2012).

12.3.4 SPECT and PET Imaging of Serotonin Transporters

The serotonin transporter (SERT) is a monoamine transporter that transports serotonin from the synaptic space to the presynaptic neuron. It is responsible for the removal of extracellular 5-HT. Increased SERT action will result in decreased 5-HT concentrations. Selective serotonin re-uptake inhibitors (SSRIs) and antidepressants which block serotonin transporters lead to increased synaptic and extracellular 5-HT (Bel and Artigas 1992; Blier and De Montigny 1983). In a study to determine whether patients with major depression have diminished serotonin transporter (SERT) availability in the brainstem, [123I] beta-CIT SPECT showed a statistically significant reduction in brainstem uptake in depressed subjects (Malison et al. 1998).

12.4 SPECT and PET Imaging of the Antidepressant Drug Response

Clinical trials using PET and SPECT imaging have been completed for several antidepressant pharmaceuticals including the selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), noradrenaline-dopamine reuptake inhibitors (NDRIs), monoamine oxidase inhibitors (MAOs) and tricyclic antidepressants (TCAs). For the purpose of this review, references have been sourced through PubMed until October 2012, including keywords such as clinical trial, PET, SPECT and antidepressant.

Some of the more common medications that have been investigated by SPECT and PET in depression are described below. They include the dopamine agonists levodopa and carbidopa; moclobemide and St. John's wort; selegiline; the SSRIs citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline; the NDRI bupropion; the SNRI venlafaxine; and the TCAs amitriptyline, nortriptyline and desipramine.

12.4.1 Levodopa and Selegiline

One of the most investigated diseases involving dopaminergic synapses of the striatum is Parkinson's disease (PD). Depression occurs in around 35 % of PD patients, and antidepressants that have dual serotonergic and noradrenergic effects are the drugs of choice for this disease (Aarsland et al. 2011). In an ioflupane study that correlated striatal DaT uptake with anxiety and depression in PD, affected patients had a lower DaT availability than healthy volunteers (Weintraub et al. 2005). A 99TcHMPAO SPECT study that examined regional cerebral blood flow in 52 PD patients showed a significant decrease in regional cerebral blood flow in PD patients with concurrent major depression. The decrease was less severe on treatment, particularly on a levodopa-selegiline combination therapy, less so with levodopa only therapy (Imamura et al. 2011).

12.4.2 Moclobemide and St. John's Wort

Monoamine oxidase A (MAO-A) inhibitor antidepressants raise the levels of multiple monoamines. MAO-A can be measured using the MAO-A marker [(11) C]-harmine. Brain MAO-A occupancy was measured in 13 depressed patients with a clinically effective dose of the selective MAO-A inhibitor moclobemide and after repeated administrations of St. John's wort, a herb purported to have MAO-A inhibitor properties. [(11)C]-harmine binding decreased significantly throughout all measured regions after moclobemide, but St. John's wort did not significantly alter MAO-A density (Sacher et al. 2011).

12.4.3 The SSRIs

It is generally believed that an 80 % serotonin transporter (SERT) occupancy is the therapeutically useful threshold for SSRI antidepressant therapy (Zipursly et al. 2007).

12.4.3.1 Citalopram

99mTc HMPAO SPECT was used to investigate the response of the brain to the SSRI citalopram in 93 patients with MD. The responder group had a regional cerebral blood flow improvement predominantly in the prefrontal and temporal cortices and in the subgenual cingulate cortex after treatment (Brockmann et al. 2009). In another study, 16 depressed older adults and 13 controls underwent 2 resting (18) F-FDG PET studies after placebo and citalopram infusions. Metabolism decreased in the left superior and middle frontal gyri, while an increase was observed in the left inferior parietal lobule, cuneus and thalamus, and in the right putamen (Smith et al. 2009).

The 5-HT1A receptor antagonist pindolol has been used previously to accelerate the clinical effects of antidepressant therapy by preventing negative feedback. Using alpha-[(11)C]methyl-L-tryptophan PET, a double-blind, randomised study compared the changes in its trapping in patients with unipolar depression treated

with citalopram plus placebo versus citalopram plus pindol. The combination citalopram plus pindol achieved a more rapid and greater increase of 5-HT synthesis in prefrontal cortex (Berney et al. 2008).

In a study examining midbrain SERT availability in patients with major depression, the relation of SERT occupancy by citalopram to treatment response was assessed in 21 non-medicated depressed patients by the SERT marker [(123) I]-ADAM SPECT. There was a rapid clinical improvement after citalopram in 54 % of the investigated patients, but only a variable SERT uptake (Herold et al. 2006). In another study, 12 patients with major depression had a SERT marker [(11)C]DASB PET scan after a minimum of 4 weeks high-dose SNRI venlafaxine treatment or sertraline or citalopram. At high therapeutic dose rates, the mean striatal SERT occupancy for each antidepressant was approximately 85 % (Voineskos et al. 2007).

In another study in patients with MD, interregional balance between SERT binding in the raphe nuclei and key regions of depression including bilateral habenula, amygdala-hippocampus complex and subgenual cingulate cortex before treatment was investigated using [(11)C]DASB PET. Measurements were performed before and after a single oral dose, as well as after 3 weeks (mean 24.73 ± 3.3 days) of continuous oral treatment with either escitalopram (10 mg/day) or citalopram (20 mg/day). Treatment response could be predicted by comparing pretreatment SERT binding in the above regions versus median raphe nucleus binding (Lanzenberger et al. 2012).

12.4.3.2 Escitalopram

Escitalopram is a SSRI approved for the treatment of depression and anxiety disorders. It is the S-enantiomer of citalopram, responsible for serotonin reuptake activity. It has been hypothesised that the therapeutically inactive R-enantiomer competes with the serotonin-enhancing S-enantiomer at low-affinity allosteric SERT sites, reducing the effectiveness of the S-enantiomer at the high-affinity sites. SERT occupancy in citalopram- and escitalopram-treated healthy volunteers was measured after single and multiple doses of these drugs. The single-dose study showed no attenuating effect of R-citalopram, but after multiple dosing, SERT occupancy was significantly reduced in the presence of R-citalopram. A pooled analysis suggests that the R-enantiomer build up after repeated citalopram dosing may lead to increased inhibition of the S-enantiomer occupancy of SERT (Kasper et al. 2009). In another study, 25 healthy subjects received a single dose of escitalopram or citalopram. Midbrain binding was measured with the SERT marker [(123)I]-ADAM on 2 study days, once without dosing and once 6 h after a single dose of escitalopram or citalopram. The midbrain-cerebellum/cerebellum ratio was the outcome measure for specific SERT binding in the midbrain. The SERT occupancies of escitalopram and citalopram give indirect evidence of a fractional blockade of SERT by the inactive R-citalopram enantiomer (Klein et al. 2006).

12.4.3.3 Fluoxetine

In a study using 123 I IBZM, the cerebral dopamine-D2 receptors were characterised in 13 patients with major depression. Dopamine receptor binding was

assessed twice, before and during serotonin reuptake inhibition. An increase in dopamine-D2 receptor binding during serotonin reuptake inhibition was found in the striatum and anterior cingulate gyrus in treatment responders, but not in non-responders (Larisch et al. 1997).

In a study that looked at fluoxetine treatment and psychotherapy, it was found that fluoxetine increased [11C]-raclopride binding in the lateral thalamus but that this increase did not correlate with clinical improvement (Hirvonen et al. 2011). In a study to determine the response of SERT to fluoxetine treatment, 23 patients with major depression underwent SPECT scanning using [123I]beta-CIT. Higher pretreatment SERT availability correlated with a positive treatment response (Kugaya et al. 2004).

In a study in unipolar depressed men, common and unique response effects to administration of placebo or fluoxetine were assessed after a 6-week, double-blind trial. Placebo response was associated with regional metabolic increases involving the prefrontal, anterior cingulate, premotor, parietal, posterior insula, and posterior cingulate and metabolic decreases involving the subgenual cingulate, parahippocampus and thalamus. Regions of change overlapped those seen in responders administered active fluoxetine. Fluoxetine response, however, was associated with additional subcortical and limbic changes in the brainstem, striatum, anterior insula, and hippocampus, sources of efferent input to the response-specific regions identified with both agents (Mayberg et al. 2002).

12.4.3.4 Paroxetine

In 12 medication-free depressed patients who completed a 6-week trial of either paroxetine or citalopram, striatal binding was measured with the SERT marker [(11)C]DASB. PET scans were completed before and after 4 weeks of treatment. A significant decrease in striatal SERT binding potential was found after either treatment. An 80 % occupancy of receptors in multiple regions was reported (Meyer et al. 2001a, b). In a study of drug-free depressed outpatients, SERT occupancy was quantified by 123I-FP-CIT SPECT imaging at baseline and after 6 weeks paroxetine. A significant positive relationship between SERT occupancy and clinical improvement existed only in patients who had certain SERT promoter genotypes, namely, the L(A)/L(A) genotype (Ruhé et al. 2009).

In a study of unipolar MD, 24 subjects underwent resting (18)F-FDG scanning before and after 12 weeks either paroxetine or interpersonal psychotherapy. Subjects with MD had regional brain metabolic abnormalities at baseline compared to controls that tended to normalise with treatment. Regional metabolic changes appeared similar with the two forms of treatment (Brody et al. 2001).

In another study of MD, (18)F-FDG PET scans were performed on 13 male patients before and after 6 weeks of paroxetine therapy. After successful paroxetine therapy, increased glucose metabolism occurred in dorsolateral, ventrolateral, and medial aspects of the prefrontal cortex (left greater than right), parietal cortex, and dorsal anterior cingulate. Areas of decreased metabolism were noted in both anterior and posterior insular regions (left) as well as right hippocampal and parahippocampal regions (Kennedy et al. 2001).

12.4.3.5 Fluvoxamine

The effect of chronic treatment with fluvoxamine, a potent SSRI that attaches to 5-HT2 and D2 receptors, was tested in drug-naive unipolar depressed patients using fluoro-ethyl-spiperone ([(18)F]FESP), a high-affinity 5-HT2 and D2 antagonist receptor marker. Fluvoxamine treatment significantly improved clinical symptoms and increased [(18)F]FESP binding in the frontal and occipital cortex of patients who completed the study. No significant changes were found in the basal ganglia where [(18)F]FESP binds mainly to D2 dopamine receptors (Moresco et al. 2000). In studies looking at receptor occupancy, it was found that in effective antidepressant therapy an approximately 80 % of SERT binding occurs (Suhara et al. 2003).

12.4.4 The NDRIs and SNRIs

12.4.4.1 Bupropion

Bupropion is a norepinephrine-dopamine reuptake inhibitor (NDRI) that appears to have a selective affinity for dopamine transporters. In a study to investigate DaT binding after bupropion in depressive patients, bupropion treatment occupied less than 22 % of DaT sites, which raises the question whether there is another mechanism involved during treatment with bupropion (Meyer et al. 2002). In a study that looked at the effect of bupropion and venlafaxine on brain metabolism, 20 patients with unipolar depression received a baseline (18)F-FDG scan, then at least 6 weeks of bupropion or venlafaxine monotherapy. Pretreatment scans showed a frontal and left temporal hypometabolism in depressed outpatients. Alterations in regional metabolism were linked to positive antidepressant responses on bupropion and venlafaxine monotherapy (Little et al. 2005).

12.4.4.2 Venlafaxine

Venlafaxine is a serotonin norepinephrine reuptake inhibitor (SNRI). In a study of patients with MD, seven subjects underwent a 99mTc HMPAO SPECT scan to assess cerebral blood flow changes after venlafaxine. The subjects showed an increased cerebral blood flow bilaterally in the thalamus and a decreased flow in the temporal cortex bilaterally and in the left occipital lobe and right cerebellum (Davies et al. 2003).

Another study was completed in 24 patients with MD. They received a (18)F-FDG PET scan before randomisation and after 16 weeks of antidepressant treatment with either cognitive behavioural therapy (CBT) or venlafaxine. Response to CBT was associated with a reciprocal modulation of cortical-limbic connectivity, while venlafaxine engaged additional cortical and striatal regions (Kennedy et al. 2007).

In another study involving 28 patients with MD, 13 patients had 1-h weekly sessions of IPT from the same supervised therapist (E.M.). Fifteen patients took 37.5 mg twice daily of venlafaxine hydrochloride. 99mHMPAO brain SPECT scans were completed before and after 6 weeks treatment. Both treatment groups improved substantially, more so with venlafaxine (Martin et al. 2001).

12.4.5 The TCAs

12.4.5.1 Nortriptyline and Sertraline

Twenty elderly outpatients with major depression were treated with either nortriptyline or sertraline. Resting regional cerebral blood flow was assessed by the planar (133)Xenon inhalation technique after medication washout and following 6–9 weeks of antidepressant treatment. At baseline, the depressed patients had a reduced cerebral blood flow in frontal cortical regions when compared with controls. After treatment, responders showed a reduced perfusion in the frontal regions (Nobler et al. 2000).

12.4.5.2 Amitriptyline

Cerebral blood flow was assessed by HMPAO SPECT in 14 depressed patients with primary fibromyalgia before and after amitriptyline treatment. There was an improvement in the visual analog scale and tender point count after treatment, but the Beck Depression Inventory did not change significantly. After treatment, cerebral blood flow increased bilaterally in the hemithalami and basal ganglia, and decreases were seen in the temporal regions bilaterally and in the left tempero-occipital and right occipital regions. Although perfusion deficits improved parallel to clinical recovery, the Beck depression scores did not change significantly (Adigüzel et al. 2004).

12.4.5.3 Desipramine

To assess brain metabolic correlates of the tyrosine hydroxylase inhibitor alpha-methyl-p-tyrosine (AMPT) after receiving desipramine, a randomised, controlled, double-blind trial in 18 patients who had depression in remission was completed, following AMPT and placebo administration. Regional brain metabolism was measured by (18)F-FDG PET in patients with and without AMPT-induced return of depressive symptoms. Depressive symptoms were experienced by 11 of the 18 patients and led to a decreased brain metabolism, mostly in the orbitofrontal and dorsolateral prefrontal cortex, and thalamus (Bremner et al. 2003).

12.5 SPECT and PET Imaging of the Blood–brain Barrier in Depression and the Antidepressant Response

Blood–brain barrier (BBB) integrity, genetic susceptibility and exposure to neurotoxins are currently discussed as possible contributors in depressive disorders. There have been calls to combine anti-inflammatory treatments with antidepressants to enhance the effectiveness of antidepressant therapy (Davis et al. 2010).

Several observations suggest that inflammatory mechanisms play a role in the cause of a major depressive disorder. For example, there are similarities with “sickness behaviour”, a normal response to inflammatory cytokines. Also, elevations in pro-inflammatory cytokines and other inflammation-related proteins are found in the plasma and cerebrospinal fluid of such patients, as well as in post-mortem studies. Pro-inflammatory cytokines persist in remission and can predict the onset of a

depressive episode, while antidepressant treatment can lead to a normalisation of elevated cytokine levels (Raedler 2011).

When the effect of endotoxins on the brain was measured clinically and by (18) F-FDG PET in nine healthy subjects, there was an increased Montgomery-Åsberg Depression Rating, fatigue, reduced social interest, and increased inflammatory cytokines. There was an increased uptake of (18)F-FDG in the insula and a trend to a decreased uptake in the cingulate regions of the brain (Hannestad et al. 2012).

In another study, the effects of interferon-alpha on cerebral glucose metabolism and its correlation to neuropsychiatric symptoms during low-dose IFN-alpha treatment were evaluated in 11 patients treated with low-dose IFN-alpha for chronic hepatitis. Low-dose IFN-alpha therapy was associated with significant prefrontal hypometabolism on (18)F-FDG that covaried with the depression score. However, this was also seen clinically in nondepressed patients (Juengling et al. 2000).

Whole brain radiation therapy (WBRT) is known to result in psychological side effects including loss of memory, loss of concentration and depression (Kondziolka et al. 2005). A possible consideration in radiation therapy is monoamine leakage through the BBB. Twenty patients with metastatic brain tumours underwent (99) mTc-DTPA brain SPECT before and during WBRT and at 2 weeks after the end of irradiation. It was found that irradiation causes direct damage to BBB function and that BBB permeability increased significantly during and within 2 weeks following 20 and 40 Gy WBRT (Jiang et al. 2010).

In end-stage renal disease, the associated depressive mood and cerebral blood flow was measured in the pre-dialytic period and at least 6 months after dialysis initiation. The pre-dialysis 99mTc ECD brain SPECT scan did not show any cerebral blood flow differences between responders to dialysis and non-responders, but follow-up brain SPECT revealed a significantly higher perfusion in left middle temporal gyrus and right parahippocampal gyrus in responder patients. In non-responders, there was a significantly decreased uptake in the left superior frontal gyrus and right orbitofrontal cortex that did not improve after dialysis (Nam et al. 2011).

P-glycoprotein (P-gp) is an efflux transporter that is expressed in high concentration at the blood–brain barrier and regulates the transport of drugs across the BBB. PET was used to measure brain uptake of [11C]verapamil, which is normally expelled from the brain by P-gp transport. In patients with a major depressive episode, a significant decrease of [11C]verapamil was seen in different areas of the brain, particularly in the frontal and temporal regions (de Klerk et al. 2009). In a study using small-animal PET, [(11)C]verapamil imaging showed that P-glycoprotein function at the blood–brain barrier decreases with chronic stress and increases with chronic administration of venlafaxine (de Klerk et al. 2010).

12.6 SPECT and PET Imaging of Monoamine Precursors, LAT Transport and the Antidepressant Response

Large neutral amino acids are transported across the BBB via large neutral amino acid transporters (LAT) also expressed in cerebral tumours, such as gliomas (Langen and Bröer 2004). LAT 1 competitively transports multiple aromatic amino

acid derivatives, including phenylalanine, L-dopa, alpha-methyldopa, melphalan, triiodothyronine, thyroxine, tyrosine and tryptophan (Uchino et al. 2002). The LAT 2 transporter exhibits a similar transport spectrum to LAT 1 (Segawa et al. 1999). The monoamine precursors phenylalanine, tyrosine and tryptophan are competitively sourced from the cerebral circulation through the BBB by these transporters (Boado et al. 1999). The competitive nature of precursor sourcing permits the possibility of interference in precursor provision through the BBB. This can happen in cases where there is a large blood-borne load of neutral amino acids in certain diets and in peripheral and genetic diseases such as maple syrup urine disease and phenylketonuria (PKU). These diseases are associated with neuropsychiatric and mood disorders such as depression (Strauss et al. 2009).

Previous research has suggested that there is an increased risk for individuals with PKU for developing depression and other mood disorders. Significant associations were observed between biochemical markers indicating poorer dietary control and increasing depressive symptoms in adolescents with early and continuously treated PKU (Sharman et al. 2012). In a study of adult patients suffering from PKU, positron emission tomography was used to measure the utilisation of 6-[(18)F] fluoro-l-dopa in the brain compared to healthy controls. The unidirectional clearance of [(18)F]DOPA to brain was impaired in adult patients suffering from PKU, presumably reflecting the competitive inhibition at the large neutral amino acid carriers by phenylalanine (Wasserstein et al. 2006).

Using [(18)F] MPPF PET, 5-HT1A receptor binding was measured after tryptophan depletion (TD) in various brain regions in patients with citalopram-treated depression. Eight remitted patients with major depressive disorder received [(18)F] MPPF PET scans twice: once after TD and once after sham depletion. No effect on regional 5-HT1A binding was observed after TD, despite an 86 % decrease in total plasma tryptophan and a transient depressive relapse in six of eight patients (Praschak-Rieder et al. 2004).

In some patients, short-term depletion of plasma tryptophan results in a relapse in patients who are recovering from major depression. Patients who clinically improved on SSRIs underwent 2 test days tryptophan depletion or placebo, followed 6 h later by (18)F-FDG PET brain scan. Tryptophan depletion resulted in a decreased brain metabolism in the middle frontal gyrus, thalamus and orbitofrontal cortex (Bremner et al. 1997).

MAO-A binding was measured in regions implicated in affective and neurodegenerative disease using [(11)C]-harmine positron emission tomography in healthy volunteers. Monoamine oxidase A V(T), an index of MAO-A density, was decreased following tryptophan depletion in prefrontal cortex and elevated in the striatum following carbidopa-levodopa administration (Sacher et al. 2012).

12.7 Discussion

Monoamine-based medications can produce remarkable improvements in some patients with mood disorders such as depression. However, the exact mode of antidepressant action and location still remains a mystery, not necessarily predictable.

Based on the above, only a few generalisations can be made:

- Specific diseases such as hypothyroidism and Parkinson's disease may be associated with characteristic SPECT and PET imaging features as may their antidepressant drug response. In depressed hypothyroid patients, thyroxine improves the clinical state and cerebral metabolism in parts of the brain in a proportion of the patients. In Parkinson's disease, application of dopamine agonists improves the symptoms of depression and improves the regional cerebral hypometabolism that is associated with this disease.
- Application of SSRIs results in clinical improvements in depressed patients, particularly when 80 % or more of the serotonin transporter receptor sites are occupied.

SPECT and PET imaging after antidepressant drug intervention has shown varied changes in cerebral blood flow and metabolism throughout the brain bilaterally in the prefrontal, frontal, temporal, cingulate and thalamus regions and in the left occipital region and right cerebellum. Additionally, changes in receptor binding have been observed at D2 and 5-HT receptors and at DaT and SERT transporters.

Similar to the highly complex metabolism and receptor binding that is seen in acute depressive disorders, there is a highly complex response and binding to antidepressant drugs. The question must be asked if there is such a thing as a regional centre for mood disorders and depression and if there is such a thing as a regionalised antidepressant drug response. Although the monoamines can be localised to specific brain regions, it appears that abnormal brain function associated with mood disorders such as depression or activity changes associated with a response to antidepressant medication may not necessarily be predictably localised. Either that or patients investigated for this condition need more restrictive in- and exclusion criteria that control for type of depression, diet and nutrition, REM sleep, thyroid and renal function, infection, inflammation, radiation, and more.

We wish to draw attention to the possibility that mood is associated with the subconscious and conscious condition which possibly involves a non-regionalised global participation of the brain (Edelman et al. 2011). Although monoamine input occurs at certain common points such as the striatum or midbrain regions and although there may be common pathways and common intersections of neurotransmission, the resultant output may differ from situation to situation and from person to person.

Conclusion

SPECT and PET imaging can document changes in brain metabolism and receptor binding after antidepressant action. However, due to the complex and varied presentation of depression and the antidepressant drug response on imaging, so far there is a lack of consensus and guidelines for SPECT and PET scans in this condition. While responses can often be demonstrated in individual patients, there is no overall "group-based" characteristic picture of depression and the antidepressant response. Clinical studies that image individual responses to antidepressant drugs are likely to grow in the future as imaging techniques become more and more refined and further investigation into possible imaging features for this condition are also likely to continue.

Acknowledgement The authors would like to thank Dr S. Nikolaus, Dr H. Hautzel, and Prof KJ Langen for their valuable input in the consideration of this review.

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Part III

Anxiety Disorders

Neurotransmission: A Review of PET and SPECT Studies in Anxiety Disorders

13

Mats Fredrikson, Vanda Faria, and Tomas Furmark

Contents

Abstract

Neuroimaging studies using PET and SPECT to evaluate neurofunctional differences in the brain between patients with anxiety disorders and healthy controls were reviewed. At rest patients with social anxiety disorder display a reduced dopamine-D2 receptor binding potential. Post-traumatic 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 insula 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,

M. Fredrikson, PhD, DMSc (✉) • V. Faria, MSc • T. Furmark, PhD
Department of Psychology, Uppsala University,
Blåsenhus, von Kraemers allé 1A och 1C, 1225, 751 42 Uppsala, Sweden
e-mail: mats.fredrikson@psyk.uu.se

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_13, © Springer-Verlag Berlin Heidelberg 2014

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.

13.1 Anxiety, Genes and Environment

Anxiety involves a subjective experience of fear and apprehension associated with physiological reactions and avoidance or escape behaviour. When the intensity or the frequency of anxiety attacks compromises quality of life, an anxiety disorder is diagnosed. Anxiety may come out of the blue like in panic disorder (PD), result from memory activation as in post-traumatic 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 the case is in generalized anxiety disorder (GAD). These, together with obsessive-compulsive disorder (OCD), are the principal diagnostic categories for the anxiety disorders in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (American Psychiatric Association 1994). In all disorders anticipation of feared events or situations causes negative affect and eventually leads to their avoidance. 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). DSM-5 is under development and will differ from the DSM-IV in many respects. In the DSM-5 OCD is not included as an anxiety diagnosis but will be named "obsessive-compulsive and related disorders" and diagnosed separate from the anxiety syndromes. Also, post-traumatic stress disorder will be a separate entity called "trauma and stressor-related disorders". Anxiety disorders in DSM-5 most likely will include separation anxiety disorder, panic disorder, agoraphobia, specific phobia, social anxiety disorder (social phobia), generalized anxiety disorder, substance-induced anxiety disorder, anxiety disorder associated with a known general medical condition and other specified anxiety disorder and unspecified anxiety disorder. Here we will focus on anxiety disorders as they are diagnosed in the DSM-IV because all published studies reflect that nosology.

13.1.1 Anxiety Aetiology

Recent aetiological 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 likely 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). 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.

13.2 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. The second wave of imaging studies were activation studies, where 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}fluorodeoxyglucose (FDG) and ^{15}oxygen to determine glucose metabolism and regional cerebral blood flow (rCBF). In the anxiety disorders a number of provocation studies have been published, both in specific and social phobias (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 (Bremner et al. 1999a, b; Britton et al. 2005; Fischer et al. 1996; Liberzon et al. 1999; Pissiota et al. 2002; Shin et al. 1997, 1999, 2004; Zubieta et al. 1999). There exist around 20 published studies from the early 1990 to 2011 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, 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 processes (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 behavioural 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, candidate genes for anxiety and learning have been related to brain function using neuroimaging tools, an emerging area termed imaging genetics (cf. Winterer et al. 2005; Bigos and Weinberger 2010).

13.2.1 Meta-analysis and Anxiety Neuroimaging

We 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.

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. All studies had a within-subjects approach and compared activity during symptom provocation to a baseline, while measures of regional cerebral blood flow were taken mostly using PET and more seldom SPECT. To increase specificity and enhance comparisons across studies, we only included studies where brain activations were described in MNI or Talairach space (included were Ahs et al. 2009; Carlsson et al. 2004; Rauch et al. 1995, 1996; Tillfors et al. 2001b, 2002; van Ameringen et al. 2004; Veltman et al. 2004; Lindauer et al. 2004; Bremner et al. 1999a, b; Britton et al. 2005; Liberzon et al. 1999, 2007; Pissiota et al. 2002; Shin et al. 1997, 1999, 2004; Zubieta et al. 1999) and excluded those where only general anatomical references were made (cf. Fredrikson et al. 1993; 1995). A meta-analysis describing group differences in brain activation in response to symptom provocation using visual and auditory stimulation or imaginary procedures to provoke anxiety was performed using the z-scores to estimate the effect size. We extracted the z-scores reported in each publication and calculated means and standard deviations for fear-initiating areas consisting of the amygdala, midbrain and the insula as well as fear-inhibiting areas comprising the anterior cingulate cortex and the orbitofrontal cortex. Also the hippocampus was included. See Fig. 13.1a, b.

13.2.2 Anxiety, Symptom Provocation and the Fear Network

The data from symptom provocation and psychological treatment studies can be interpreted as revealing brain territory involved in the generation and control of anxiety. Generally, these studies show that brain areas forming the fear circuit in humans (Shin and Liberzon 2010) are activated in situations that elicit anxiety symptoms. Examples include panic attacks in PD (Bremner et al. 2000a, b), fear in response to anxiogenic cues in specific phobia (Ahs et al. 2009; Fredrikson et al. 1993, 1995) and anxiety induced by public performance in patients with SAD (Tillfors et al. 2001b; van Ameringen et al. 2004). Figure 13.1 summarizes perfusion results from symptom provocation studies in specific and social phobias (Fig. 13.1a) on the one hand and PTSD on the other (Fig. 13.1b).

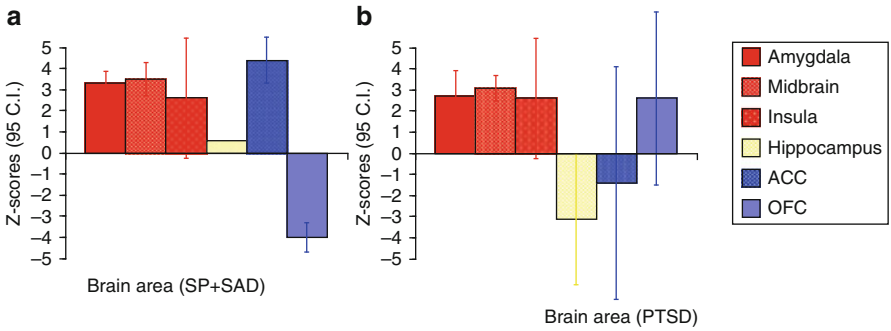

Fig. 13.1 Fear network activity during symptom provocation in (**a**) phobic disorders and (**b**) PTSD. Data are *z*-scores ± 95 % confidence intervals based on regional cerebral blood flow data from symptom provocation studies in SP, SAD and PTSD

Both in phobias and in PTSD, rCBF in the amygdala and the midbrain increases reliably across studies (see Fig. 13.1a, b). Also the insula 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 amygdala-localized memory trace (Agren et al. 2012) while not taxing context-dependent memory representation in the hippocampus. In the phobic disorders, as 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. Thus, like in rodents, the human fear network encompasses the amygdala, the insula, the hippocampus, the anterior cingulate cortex, the orbitofrontal prefrontal cortex and the periaqueductal gray in the midbrain (Shin and Liberzon 2010). A consistent finding is that the amygdala, the insula 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 behavioural 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 related to reduced activity in the orbitofrontal cortex.

The third wave of brain imaging studies using symptom provocation designs are often 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. Del Casale et al. 2012; Miskovic and Schmidt 2012; Hughes and Shin 2011; Freitas-Ferrari et al. 2010; Fredrikson et al. 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 non-traumatic 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. Because there are no longitudinal studies, it is not possible 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 behavioural manifestations of anxiety (Laukka et al. 2011).

13.2.3 Anxiety and Neurotransmission

Brain imaging studies in anxiety disorders have also characterized neurochemistry in the resting state. An advantage with 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 disorders and healthy controls as revealed by PET and SPECT imaging. We searched PubMed and crossed each anxiety 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 post-traumatic stress disorder" to retrieve references. We also extracted studies by using the reference list of resulting publications. There exist around 30 published studies from 1994 to 2011 that have used PET or SPECT tracers to determine dopamine and serotonin neurotransmission with ligands probing 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 have been imaged. With one exception all neurochemical studies have been performed in the resting state. Table 13.1 details and Table 13.2 summarizes the main findings for GAD ($n=2$ studies), SP ($n=1$), SAD ($n=8$), PD ($n=14$) and PTSD ($n=6$).

Most studies have been performed in PD, and data suggest that BZD receptors are downregulated ($n=6/8$) even though conflicting evidence exists ($n=2/8$). Also, $5HT_{1A}$ receptors are downregulated in PD ($n=3/3$). 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 (see Table 13.2).

Social anxiety disorder is the second most investigated condition. A reduced D_2 receptor binding potential ($n=2/3$) is supported, but one study failed to demonstrate differences between patients and controls. With respect to dopamine and serotonin reuptake, mechanisms in SAD data are inconclusive, because only one study

Table 13.1 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 based on PET and SPECT studies				
Maron, 2004b	SERT	GAD (7) HC (7)	SPECT: [^{123}I]nor-β-CIT	= midbrain 5HTT – corr with symptom severity in pts
Tiihonen, 1997b	GABA/BZD	GAD (10♀) HC (10♀)	SPECT: [^{123}I]NNC-13-8241	↓ TP (L)
Neurochemical alterations in SP based on PET and SPECT studies				
Michelgård, 2007	NK1/SP	SP (16) HC (0)	PET: [^{11}C]GR205171	↓ amygdala uptake during anxiety provocation – corr with symptom severity
Neurochemical alterations in SAD based on PET and SPECT studies				
Moriyama, 2011	DAT	PD+SAD (11) PD (21)	SPECT: TRODAT-1	+ corr with symptom severity in putamen and NCaud
Schneier, 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
van der Wee, 2008	SERT/DAT	SAD (12) HC (12)	SPECT: ^{123}I-β-(4-iodophenyl)-tropane	↑ SERT thalamus ↑ DAT striatum 0 – corr
Schneier, 2000	D_2	SAD (10) HC (10)	SPECT:[^{123}I]iodobenzamide	↓ striatum – corr (trend) with LSAS
Tiihonen, 1997a	DAT	SAD (11) HC (28)	SPECT: [^{123}I]β-CIT	↓ striatum 0 – corr
Lanzenberger, 2007	$5HT_{1A}$	SAD (12) HC (18)	PET: [^{11}C]WAY-100635	↓ amygdala, ACC, insula, raphe 0 – corr
Schneier, 2008	D_2	SAD+OCD (7) OCD (8) HC (8)	SPECT: [CI^{123}]-IBZM	↓ striatum (SAD) – corr KSP detachment

(continued)

Table 13.1 (continued)

First author, year	Neurofunction	Patients/controls	Imaging/ligand	Main results
Neurochemical alterations in PD based on PET and SPECT studies				
Maron, 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
Maron, 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
Fujimura, 2009	SERT	PD (14) HC (14)	PET: [^{18}F]SPA-RQ	↓ in widespread areas including amygdala
Hasler, 2008	GABA/BZD	PD (15) HC (18)	PET: [C^{11}]flumazenil	↓ PFC, frontal, temporal, parietal ↑ hipp – corr with symptom severity in hipp + corr with symptom severity in dPFC
Nash, 2008	5HT$_{1A}$	PD (9) PD remission (7) HC (9)	PET: [^{11}C]WAY-100635	↓ raphe, OFC, TP, amygdala 0 – Corr
Maron, 2004a	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 thalamus
Neumeister, 2004	5HT$_{1A}$	PD (16) with comorbid agoraphobia (6) HC (15)	PET: [^{18}F]FC WAY	↓ ACC, PCC, raphe
Bremner, 2000b	GABA/BZD	PD (13) HC (16)	SPECT: [^{123}I]iomazenil	↓ hipp, precuneus ↓ PFC in panic attackers – corr symptom severity in PFC
Kaschka, 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)

Kuikka, 1995	GABA/BZD	PD (17) HC (17)	SPECT: [^{123}I]iomazenil	↑ R > L(ratio in pts) ↑ TP
Schlegel, 1994	GABA/BZD	PD (10) Epileptic pts (10)	SPECT: [^{123}I]iomazenil	↓ FC, occipital, TP
Malizia, 1998	GABA/BZD	PD (7) HC (8)	PET: [C^{11}]flumazenil	↓ globally most pronounced in OFC + insula (R)
Cameron, 2007	GABA/BZD	PD (11) HC (21)	PET: [C^{11}]flumazenil	↓ insula (R + L) 0 – corr
Brandt, 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
Sulivan, 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
Neurochemical alterations in PTSD based on PET and SPECT studies PTSD1				
Czermak, 2008	Nicotinic acetylcholine receptors (β_2 subunit)	PTSD (10) HC (10)	SPECT: [^{123}I]5-1A-85380	↑ MTP + corr with re-experience
Geuze, 2008	GABA/BZD	PTSD (9) Trauma-exposed HC (11)	SPECT: [^{11}C]flumazenil	↓ cortex, hipp, thalamus
Fujita, 2004	GABA/BZD	PTSD (19) HC (19)	SPECT: [^{123}I]iomazenil	= – corr with childhood trauma scores in pts
Bonne, 2005	$5HT_{1A}$	PTSD (12) HC (11)	PET: [^{18}F]FC WAY	=

(continued)

Table 13.1 (continued)

First author, year	Neurofunction	Patients/controls	Imaging/ligand	Main results
Liberzon, 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
Bremner, 2000a	GABA/BZD	PTSD (13) HC (13)	SPECT: [^{123}I]iomazenil	↓ PFC (BA 9) + corr with symptom severity
Murrough 2011	SERT	PTSD (15) HC (15)	PET: [^{11}C]AFM	↓ amygdala – corr symptom severity
Fujimura, 2009	NK1/SP	PTSD (14) HC (14)	PET: [^{18}F]-SPA-RQ	↓ in widespread areas

[a]i.v. D-amphetamine to induce dopamine release

Table 13.2 Alterations in neurotransmission in the anxiety disorders

Neurochemical alterations in the anxiety disorders based on PET and SPECT studies																		
	D_2			$5HT_{1A}$			BZD			DAT			SERT			NK1/SP		
	↓	↑	=	↓	↑	=	↓	↑	=	↓	↑	=	↓	↑	=	↓	↑	=
SAD	2	0	1	1	0	0	0	0	0	1	1	1	0	1	0	0	0	0
PD	0	0	0	3	0	0	6	2	0	0	0	1	1	1	0	0	0	0
PTSD	0	0	0	0	0	1	2	0	1	0	0	0	0	0	0	1	0	0
GAD	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0
SP	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Anxiety	2	0	1	4	0	1	9	2	1	1	1	2	1	2	1	2	0	0

Individual studies of increased (↑), decreased (↓) or similar (↔) transmission as compared to healthy controls for dopamine D2-receptors D_2, dopamine transporter DAT, 5-hydroxytrytamine 1A receptors $5HT_{1A}$, serotonin transporter SERT, benzodiazepine receptors BZD and the neurokinin 1/substance P system NK1/SP

suggests decreased serotonin reuptake. This is consistent with downregulated 5HT receptors. For dopamine reuptake one study reported higher, one lower and one similar uptake activity in SAD patients when compared to controls (see Table 13.2).

In PTSD BZD receptors appear downregulated ($n = 2/3$) even though one study did not reveal differences between patients and controls. For GAD there are 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 two studies investigating NK1/SP system activity, one in PD reporting widespread decreased binding of an NK1 receptor ligand at rest. 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 SP release (Michelgård et al. 2007). 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 social anxiety disorder (Furmark et al. 2005), suggestive of a mechanistic role for the NK1/SP system in anxiety.

To draw general conclusions on neurochemical alterations in anxiety, we applied the following logic. Two independent studies in the same direction are required to permit a general conclusion on alterations in one transmission system within a given disorder. For a conclusion to be valid across the anxiety disorders, the result of at least one study must be consistent with at least another study in another disorder in the same imaging domain. See Fig. 13.2 for a summary of the results when applying these criteria.

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 post-traumatic stress disorder and possibly GAD. Also, monoaminergic neurotransmission seems altered both in SAD and PD consistent with reduced $5HT_{1A}$ receptor availability; see Fig. 13.2. There is insufficient data to evaluate specific phobia with respect to integrating and segregating neurotransmission patterns.

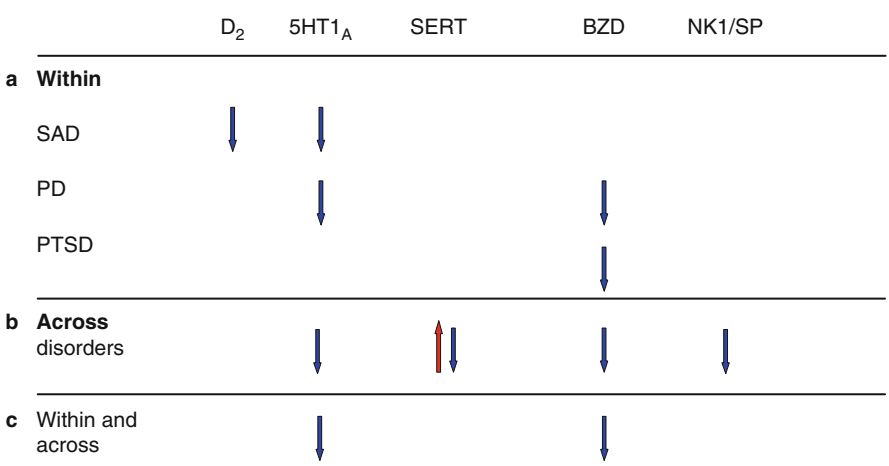

Fig. 13.2 Alterations in neurotransmission (**a**) within and (**b**) across as well as (**c**) within and across the anxiety disorders. *Blue arrows* indicate reduced activity and the *red arrow* increased activity in patients as compared to healthy controls (HC)

Reductions in BZD receptor activity occur most frequently in limbic and frontal areas both for PD and PTSD (See Fig. 13.3a). Monoaminergic alterations, both in serotonergic and dopaminergic neurotransmissions, are localized predominantly in the limbic system (see Fig. 13.3b). Reflecting tracer binding properties monoaminergic reductions are located also in the striatum and the midbrain raphe, areas rich in dopamine and serotonin, respectively (see Fig. 13.3c). 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 13.3 for a summary of studies.

If there is a genetic vulnerability common to the anxiety disorders, a "G-factor" affecting several anxiety disorders alike as demonstrated in twin studies (Hettema et al. 2001), and if this genetically determined factor is reflected in altered neurotransmission, it could be downregulation of $5HT_{1A}$ receptors observed both in SAD and PD as well as reductions in BZD receptor density or affinity reported in PD, GAD and PTSD. From the results, it is not clear if pre- or postsynaptic $5HT_{1A}$ receptors are affected. Because GABA-ergic and serotonin neurotransmission are under tight genetic control (Pinborg et al. 2008), the observed alterations may correspond to or reflect the genetic factor common for GAD, PD and SAD (Hettema et al. 2005).

13.2.4 Anxiety Treatment and Brain Function

For certain disorders and some neural functions, there are also treatment studies. For example, Spindelegger and co-workers (2009) treated patients with PD

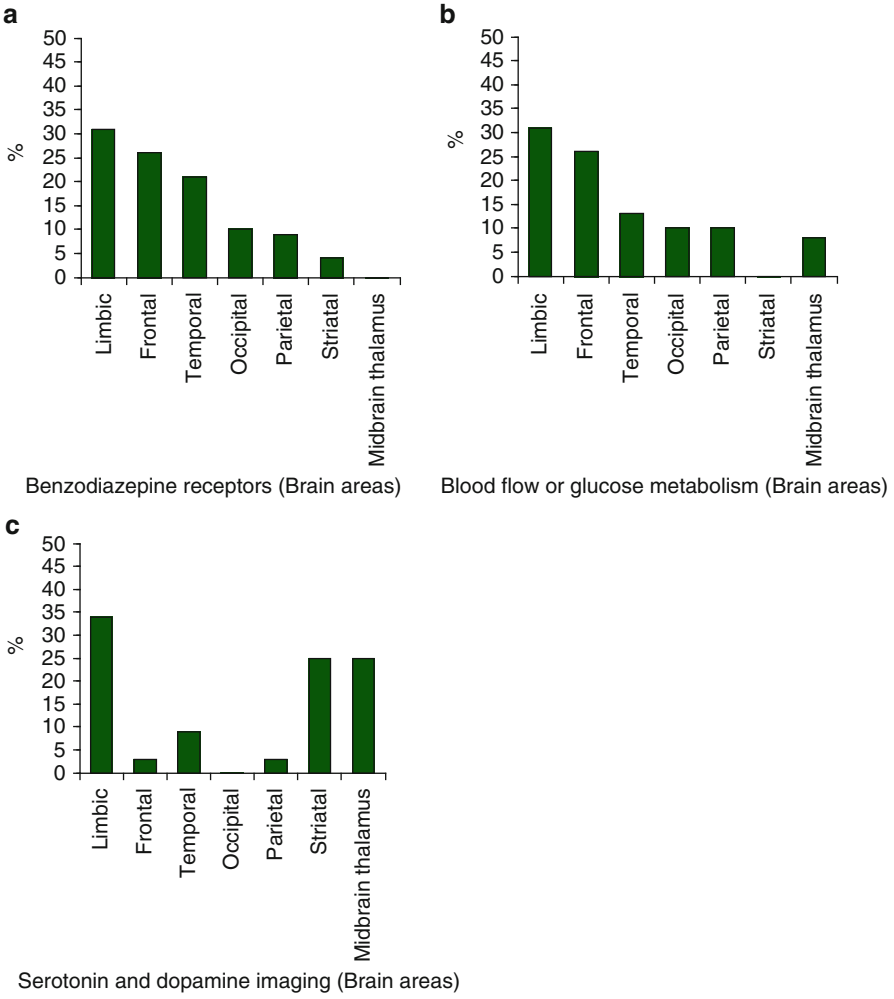

Fig. 13.3 Brain areas most frequently reported as altered for (**a**) benzodiazepine receptors, (**b**) resting perfusion or metabolism and (**c**) monoaminergic functions across all disorders. Data represent the percent alterations observed as related to all affected brain areas (i.e. they add up to 100 % for each graph). Areas are grouped according to the labels on the *y*-axis. Because it is not possible to separate superior areas of the midbrain PAG from inferior areas in the thalamus, in most studies they are evaluated together

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 obscure. It is not clear if there is crosstalk 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

Table 13.3 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, 1993	rCBF	PTSD (6) (comorbid cocaine abuse) HC (7)	PET: H_2O^{15}	↑ trend for OFC
Bisaga, 1998	Glucose	PD♀ (6) HC♀ (6)	PET: ^{18} FDG	↑ hipp, parahipp ↓ inferior parietal, superior temporal
Semple, 2000	rCBF	PTSD (–) (comorbid cocaine abuse) HC (–)	PET: ^{15}O-butanol	↓ FC
Mirzaei, 2001	rCBF	PTSD (8) HC (8)	SPECT: ^{99m}TC-HMPAO	Ratio only – more left lateralized and heterogenous in pts
Bonne, 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. non-exposed HC + corr symptomatology in CBL and visual cortex
Kim, 2007	rCBF	PTSD (19) HC (19)	SPECT: ^{99m}TC-HMPAO	↓ thalamus (R) + corr symptom (re-experience ↑ superior parietal (R) + corr symptom severity
Evans, 2009	Glucose	SAD (15) HC (10)	PET: ^{18} FDG	↓ ACC vmPFC ↑ vmPFC after tiagabine 3–6 mg (GABA reuptake inhibitor)
Molina, 2010	Glucose	PTSD (15) HC (6)	PET: ^{18} FDG	↓ acc, precuneus (BA 7), insula, hipp, FC, PDF, visual cortex, verbal areas ↑ fusiform, temporal, occipital, precuneus (BA 31), CBL

transporter (DAT) binding in the caudate and putamen after 12 weeks of escitalopram treatment in patients with SAD suggesting serotonergic activation of dopamine consistent with the report of decreased DAT binding in SAD but contrary to reports of increased initial binding. Similar paradoxical results were reported by Kent et al. (2002) because serotonin transporter (SERT) binding increased as a function of SSRI even though binding initially is increased rather than decreased in SAD. Thus, the interpretation of alterations in neurotransmission in anxiety

disorders is not unidimensional and restricted to one brain function but multidimensional and related to multiple mechanisms.

13.3 Multiple Mechanisms Mediating Anxiety

Altered neurotransmission could represent a primary vulnerability factor or a secondary scar resulting from repeated anxiety experiences or being correlated with that 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. Fischer et al. (2006) and Kienast et al. (2008) demonstrated positive relations between serotonin and dopamine functions in the amygdala and BOLD reactivity to negative stimuli. 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 amygdala rCBF and anxiety ratings and increased amygdala reactivity, 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 functional serotonergic (Munafò et al. 2008) and dopaminergic polymorphisms to emotionally determined amygdala reactivity (Domschke and Dannlowski 2010) and to modulation of intrinsic couplings within the fear network (Pezawas et al. 2005). One implication of the hypothesis that the monoaminergic as well as other neurotransmission systems modulate fear circuit activity is that all treatments targeting specific neurochemical systems should influence symptomatology through modulating fear network activity. A couple of studies from our and other laboratories are consistent with this notion because reductions in anxiety achieved through administration of SSRI and an NK1 receptor antagonist both attenuated amygdala reactivity in SAD (Furmark et al. 2002, 2005; Faria et al. 2012). In addition, in PTSD prefrontal activity was enhanced by SSRI (Fernandez et al. 2001). Similar findings were recently reported (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). Also, responders but not non-responders, to placebo administration in a recent 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. 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. However, no studies exist on this topic but are presently under way in our research clinic.

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Neurobiology of Posttraumatic Stress Disorder: The Role of Nuclear Neuroimaging

14

Alex G.G. Doruyter, Dan J. Stein, and James M. Warwick

Contents

Abstract

Nuclear neuroimaging plays a valuable role in the noninvasive testing of PTSD models. Correlating abnormalities in function with anatomical imaging, much of this work in patients has focused on isolated structures identified in animal-based research on the neurological basis of fear. Progressing from region-based investigations, recent researchers have incorporated more sophisticated methodological techniques such as

A.G.G. Doruyter • J.M. Warwick
Medical Imaging and Clinical Oncology,
Nuclear Medicine Division, Faculty of Health Sciences,
Tygerberg Hospital, Stellenbosch University,
Francie van Zijlrylaan, Parow, 7500 Cape Town, South Africa

D.J. Stein (✉)
Department of Psychiatry and Mental Health,
Faculty of Health Sciences, University of Cape Town,
J-Block, Groote Schuur Hospital, Observatory, Cape Town, South Africa
e-mail: dan.stein@uct.ac.za

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_14, © Springer-Verlag Berlin Heidelberg 2014

functional connectivity analysis to investigate network dysfunctions in the disorder. On a more fundamental level, nuclear techniques have the advantage of being able to investigate underlying neurochemical systems and recent studies have provided evidence for dysfunction in various neurotransmitter systems in these patients. Some of the limitations of current research and future directions are discussed.

14.1 Introduction

According to the proposed DSM-5 criteria, posttraumatic stress disorder (PTSD) may occur following an event that involves exposure to an actual or threatened serious injury, integrity or death of oneself or others (directly or indirectly). Patients experience intrusive recollections of the event, demonstrate avoidant behaviour, have negative alterations in cognition or mood and suffer alterations in arousal and reactivity. The duration of symptoms must be greater than 1 month and the disturbance must cause significant distress or affect function (Friedman et al. 2011).

The types of trauma that can result in PTSD include interpersonal violence (assault/rape), natural disasters, as well as a range of events which, although not commonly linked to PTSD, are important because they are so prevalent (e.g. motor vehicle accidents). In the USA, lifetime prevalence of PTSD has been reported as between 6.8 and 12.3 % with a 1-year prevalence of 3.5–6 % and represents a significant societal health burden (Norris 1992; Kessler et al. 1995, 2005; Resnick et al. 1993). In the European Union, lifetime prevalence of PTSD has been similarly reported as between 5 and 10 %, with a 1-year prevalence of 2–5 % (Wittchen et al. 2009). Despite clear diagnostic criteria, the diagnosis of PTSD is often challenging due to variability in its presentation, patient resistance to discuss past trauma and frequent psychiatric comorbidity.

Management of PTSD includes both pharmacologic and non-pharmacologic therapies. Despite the availability of clinical treatments, community data indicate that more than one third of patients never fully recover (Kessler et al. 1995). An improved understanding of pathophysiologic dysfunction arguably has the potential to optimise current therapies and to assist the development and individualisation of treatment strategies which may ultimately improve prognosis.

Nuclear neuroimaging research (using single-photon emission computed tomography [SPECT] and positron emission tomography [PET]) has made a significant contribution to elucidating the neurobiology of PTSD. While most neuroimaging research on PTSD is based on magnetic resonance imaging [MRI], PET and SPECT are robust and sensitive techniques which are also ideally suited to examine individual neurochemical systems (Nikolaus et al. 2009; Hughes and Shin 2011). Early nuclear neuroimaging research on PTSD analysed regional metabolism, either directly (measuring regional glucose metabolism) or indirectly (measuring regional cerebral blood flow [rCBF]), and helped shed light on the neurocircuitry of PTSD. Subsequent work has explored the precise neurochemical alterations in neurocircuitry associated with PTSD, as well as the effects of various interventions. Whether such alterations on imaging are as a result of PTSD or represent a functional predisposition to the disorder is as yet uncertain and future studies may determine this.

Reviewing the nuclear neuroimaging literature in PTSD is complicated by differences in methodology (patient preparation, type of radiopharmaceutical, injection conditions, imaging paradigm, variable reporting of anatomical position, imaging modality and reconstruction technique) and analysis techniques (a priori vs. whole brain, ROI-based and univariate vs. multivariate) between studies. Many studies use small sample sizes which are prone to statistical error (Andreasen et al. 1996). Furthermore, there is evidence that differences in PTSD aetiology (Pagani et al. 2005), gender (Shin et al. 2004a) and chronicity (Bonne et al. 2001; Bremner 2003) result in differences in neuroimaging of PTSD. Psychiatric comorbidity is frequent in PTSD which may confound findings (Lanius et al. 2010). Such differences may in part explain why the literature is at times inconsistent in its findings.

This chapter aims to summarise work on the development of a neurobiological model of PTSD as well as to examine the existing imaging research investigating neurochemical changes in PTSD. Future directions for nuclear neuroimaging are also discussed.

14.2 A Neurobiological Model of PTSD

Current models of the neurobiology of PTSD rely on basic neuroscience research on fear. The linking of emotions to a functional neuronal network was first presented by Papez (1937). He proposed that the hypothalamus, cingulate gyrus and hippocampus and their interconnections were the anatomical seat of emotional processing (the limbic system). Subsequent work on the structures of this system as well as its projections and interconnections confirmed its importance (LeDoux et al. 1990; Amaral et al. 1992). The particular significance of limbic structures in fear has been clarified by animal work on fear conditioning, extinction and sensitisation (Charney et al. 1993; Davis et al. 1993; Morgan et al. 1993; Morgan and LeDoux 1995; Cullinan et al. 1995; LeDoux 1995).

Building on these fear-based models, early models of PTSD emphasised alterations in the role of limbic structures such as the amygdala in threat assessment, as well as the role of cortical structures which modulate limbic structures (Rauch et al. 1998). PTSD was associated with exaggerated activation of the amygdala and anterior paralimbic regions, as well as with an exaggerated deactivation of Broca's area and reduced activation in ventral/medial prefrontal cortex (vmPFC), which includes rostral anterior cingulate cortex (rACC), medial prefrontal cortex (mPFC), subcallosal cortex, and orbitofrontal cortex. These data support a model in which the vmPFC ordinarily attenuates the fear response once danger has passed or the meaning of a threatening stimulus has been altered (extinction). In PTSD, amygdala reactivity and impairment in its modulation by the vmPFC was posited to explain deficient fear extinction as well as an incapacity to suppress attention and response to trauma-related stimuli (Figs. 14.1 and 14.2).

A range of work supports an amygdalocentric model. Several studies demonstrate increased amygdalar activity in response to emotional stimuli in PTSD (Rauch et al. 1996, 1997; Shin et al. 1997a; Liberzon et al. 1999; Pissiota et al. 2002; Vermetten et al. 2007). A symptom provocation study using

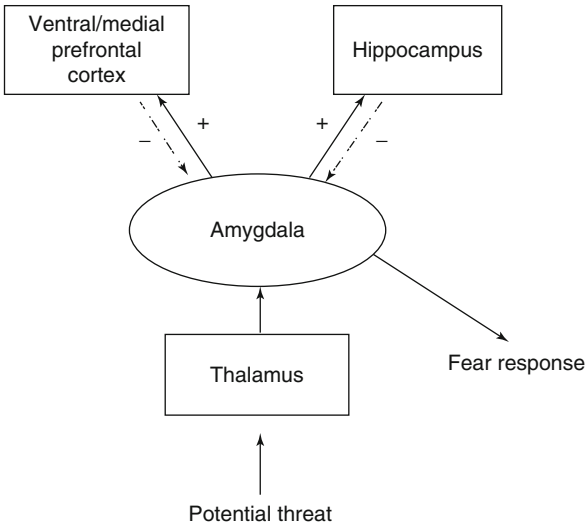

Fig. 14.1 The amygdalocentric neurocircuitry model of posttraumatic stress disorder. Excitatory connections are labelled "+"; inhibitory connections are labelled "–" (From Deckersbach et al. (2006); adapted from Rauch et al. (1998))

[oxygen-15]-carbon dioxide (^{15}O-CO_2) PET found that symptom severity was positively related to rCBF changes in the right amygdala (Shin et al. 2004a). Similarly, in an [oxygen-15]-water (^{15}O-water) PET study, during habituation, acquisition and extinction conditions, PTSD patients were found to have increased activation in the left amygdala with fear acquisition relative to the control group (Bremner et al. 2005). However, findings of amygdala hyperactivity in PTSD are not found in all studies (Britton et al. 2005; Phan et al. 2006; Molina et al. 2010).

Recent nuclear neuroimaging studies have also identified the insula, a region closely related to the amygdala, as hyperactive in PTSD. The insula is heavily interconnected with the amygdala, hypothalamus and periaqueductal gray matter (Paxinos 2003) and regulates the autonomic nervous system (Oppenheimer et al. 1992) as well as being involved in the processing of negative emotions (Phan et al. 2002). Hyperactivity of this region during emotional processing (Osuch et al. 2001; Lindauer et al. 2004; Nardo et al. 2011) most likely represents activation of a network (incorporating amygdala) responsible for generating fear responses to symptom-provoking stimuli (Etkin and Wager 2007). A rest study found a positive correlation between insular activity (as measured by ^{15}O-water) and the intensity of flashbacks with symptom provocation (Osuch et al. 2001). Increased insular activity in PTSD was noted in meta-analyses of PET and fMRI data (Etkin and Wager 2007; Hayes et al. 2012). A positive correlation has also been reported between insular activity and ACTH response in a symptom provocation study in PTSD (Liberzon et al. 2007a) [see later section]. Not all studies support insular hyperactivity in PTSD however (Shin et al. 1997a, b, 1999; Lindauer et al. 2004; Fernandez et al. 2001; Molina et al. 2010).

There is growing work on the precise role of the vmPFC in PTSD. In addition to the evidence that insufficient influence by vmPFC underlies deficits in extinction as well as the capacity to suppress attention and response to trauma-related stimuli in PTSD (Rauch et al. 2006; Bremner et al. 1999a, b, 2005; Shin et al. 1999; Lindauer

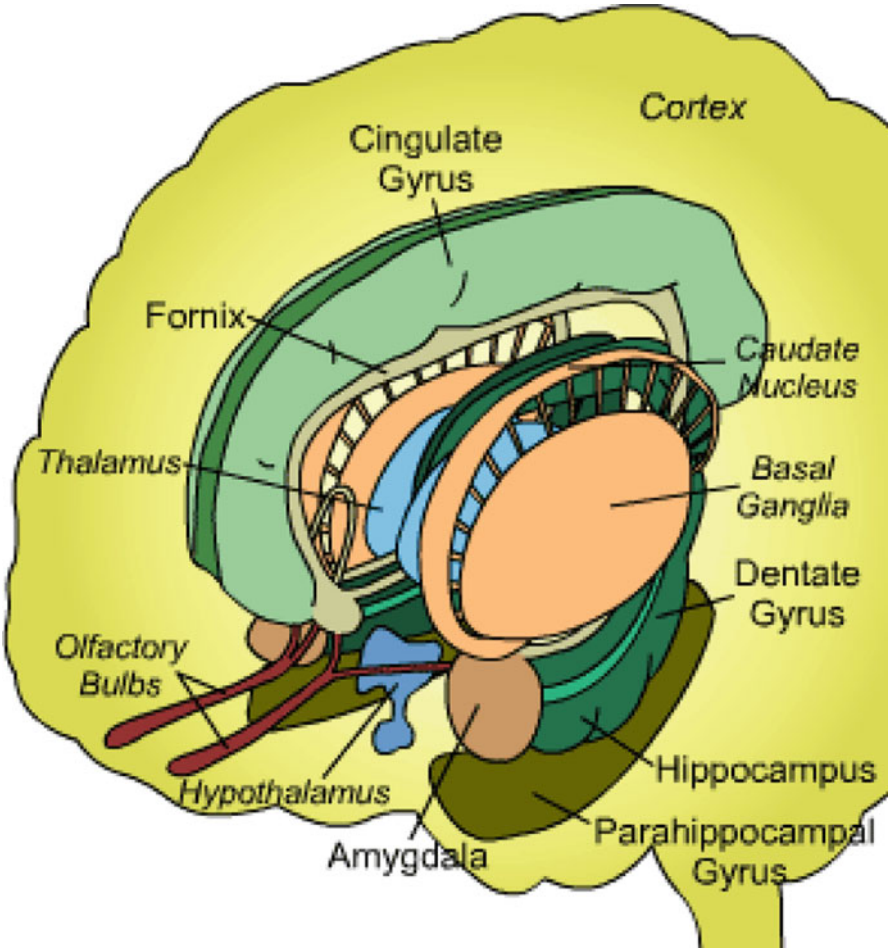

Fig. 14.2 Anatomy of the limbic system: from the Huntington's Outreach Program for Education at Stanford, www.stanford.edu

et al. 2004), a number of studies reveal the inverse relationship between vmPFC and amygdala activity in these patients. In a symptom provocation study using ^{15}O-CO_2 PET, rCBF changes in the medial frontal gyrus were inversely correlated with rCBF changes in the left amygdala and the right amygdala/periamygdaloid cortex. Symptom severity was also negatively related to reductions in rCBF in the medial frontal gyrus (Shin et al. 2004a). The negative correlation between amygdalar activity and vmPFC activity in PTSD was also reported in a recent meta-analysis of PET and fMRI studies (Hayes et al. 2012). Such an inverse relationship between vmPFC and amygdala has not been replicated by all studies (Gilboa et al. 2004; Gold et al. 2011).

The role of the anterior cortex, including the vmPFC, in PTSD is probably complex and may be better understood by understanding it as a number of substructures

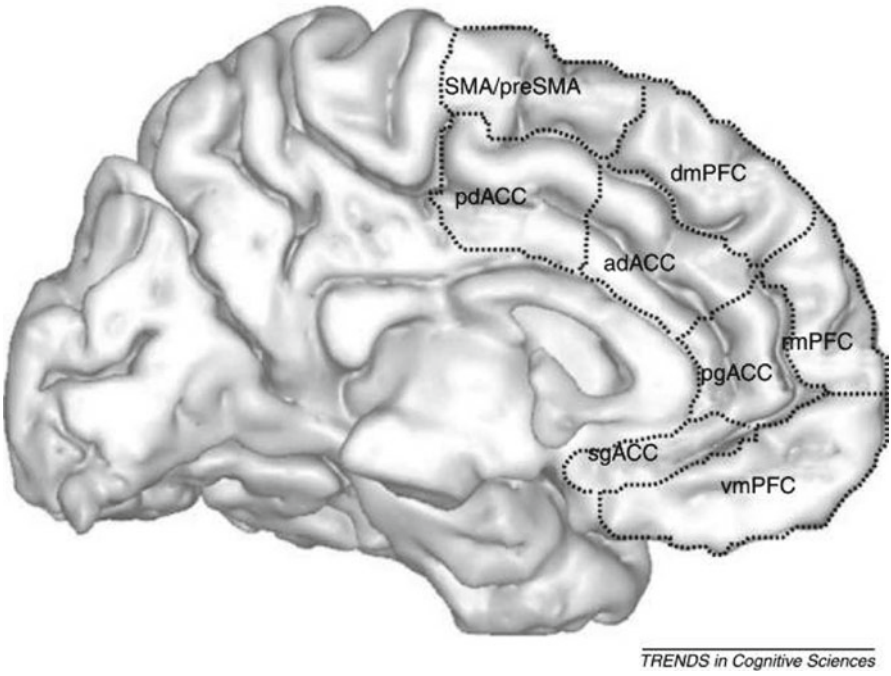

Fig. 14.3 Subdivisions of the mPFC and ACC. *Abbreviations*: *sg* subgenual, *pg* pregenual (rostral), *vm* ventromedial, *rm* rostromedial, *dm* dorsomedial, *ad* anterior dorsal, *pd* posterior dorsal (From Etkin et al. (2011))

with interrelated roles. The vmPFC includes rostral anterior cingulate cortex (rACC), medial prefrontal cortex (mPFC), subcallosal cortex and orbitofrontal cortex. The anterior cingulate cortex (ACC) and vmPFC are overlapping regions, sharing the rACC. The gating function ascribed to the vmPFC in modulating conditioned fear responses (Rauch et al. 1998) has been ascribed to the ACC (Hamner et al. 1999). This latter model, largely based on animal research (e.g. Sparenborg and Gabriel 1992), proposed an amygdala-locus coeruleus-anterior cingulate circuit whereby efferent noradrenergic projections from the locus coeruleus may dampen the anterior cingulate function, thereby allowing external and internal stimuli to produce the exaggerated emotional and behavioural responses characteristic of PTSD (Fig. 14.3).

Examining the activation of the ACC as a whole is probably too simplistic, since there is evidence for functional specialisation of subregions of the ACC. The rostral anterior cingulate cortex (rACC) is involved in the assessment of emotional information as well as the regulation of emotional responses (Mohanty et al. 2007). There is evidence that the rACC has a gating function as proposed by Hamner et al. (1999) and this is consistent with the amygdalocentric model (Rauch et al. 1998). The majority of nuclear neuroimaging studies have reported reduced rCBF (on ^{15}O-water PET) to rACC in PTSD patients during symptom provocation (Bremner et al. 1999a, b; Britton et al. 2005). A study that used ^{15}O-water PET with a cognitive activation

paradigm also reported diminished rCBF in rACC in PTSD compared to trauma-exposed controls (Bremner et al. 2004). Some symptom provocation studies have however reported either decreased (Shin et al. 1997a; Liberzon et al. 2007a) or equal activation (Liberzon et al. 1999) in rACC in PTSD patients compared to control groups.

The dorsal anterior cingulate cortex (dACC) appears to be involved in cognitive processing including conflict monitoring, response selection, error detection (Bush et al. 2000; Carter et al. 1999), aversive conditioning (Milad et al. 2007; Büchel et al. 1998) and the anticipation and perception of pain (Chua et al. 1999; Derbyshire 2000). Subregional analysis has yielded the dACC as an additional node of potential importance in PTSD. Most nuclear neuroimaging research supports the hyperactivation of dACC in PTSD. In a study using [technetium-99m] ethyl cysteinate dimer (^{99m}Tc ECD) SPECT under rest conditions, it was reported that PTSD patients demonstrated increased rCBF in dACC compared to healthy controls (Chung et al. 2006). A study that used identical twins as control subjects performed 2-deoxy-2-[fluorine-18] fluoro-D-glucose (^{18}F-FDG) PET to compare PTSD patients, trauma-exposed controls and healthy controls under rest conditions and reported that in the PTSD group, there was relatively increased activity in dACC (Shin et al. 2009). Mid- and dorsal anterior cingulate cortex was one of the regions most consistently hyperactivated in PTSD patients in a recent meta-analysis (Hayes et al. 2012), which identified dmPFC (including mid/dorsal ACC) as one of the several key salience network regions. Some symptom provocation studies have however reported deactivation (Shin et al. 1999; Gold et al. 2011) or equal activation (Phan et al. 2006) in dACC in PTSD patients compared to control groups.

Because PTSD is associated with memory problems, abnormal hippocampal function has frequently been considered in neuroimaging studies. This structure ordinarily provides information about the context of a situation through its role in explicit memory, and dysfunction of the hippocampus may help explain memory problems in the disorder as well as deficits in identifying safe contexts (Bremner et al. 2005). Debate exists regarding possible mechanisms of purported hippocampal dysfunction, which include chronic stress of PTSD being toxic to the hippocampus, and variation in amygdalar influence on hippocampal function (Elzinga and Bremner 2002; Layton and Krikorian 2002). The nuclear neuroimaging literature regarding hippocampus in PTSD is controversial, reporting activations (Chung et al. 2006; Britton et al. 2005; Shin et al. 2004b; Yehuda et al. 2009), deactivations (Molina et al. 2010; Kim et al. 2012; Bremner et al. 1999a, 2003a, b) or no change (Rauch 1996) in hippocampal activity. A PTSD treatment study using ^{99m}Tc-ECD SPECT found hippocampal activation after psychotherapy (Peres et al. 2007). Meta-analysis of PET and fMRI studies reveals no change (Hayes et al. 2012). The variation in reported results may in part be related to chronicity of the disorder, in which hippocampal deactivation is a feature of chronic PTSD (Bremner et al. 2003a).

Limited nuclear neuroimaging research has specifically examined the relationship between hippocampal dysfunction and memory deficiencies in PTSD. A cognitive activation study to test verbal declarative memory performed using ^{15}O-water PET to scan patients with PTSD, trauma-exposed controls and healthy controls reported no significant differences in memory performance between the groups, but

it was found that the PTSD group demonstrated failure of activation of the left hippocampus during encoding (Bremner et al. 2003a). A study using ^{15}O-water PET to scan PTSD patients and healthy controls using a visuoverbal target detection task involving continuous updating (variable target condition) or no updating (fixed target condition) to examine verbal working memory in PTSD reported no hippocampal findings (Clark et al. 2003).

Located in the left inferior frontal cortex (BA 44, 45), Broca's area is the structure believed to be responsible for applying semantic representations to personal experience which allow communication or description of this experience (Hull 2002). Various groups have implicated deactivation of Broca's area to explain why PTSD patients struggle to cognitively restructure their traumatic experience (Rauch et al. 1996; Shin et al. 1997a, b, 1999; Osuch et al. 2001; Bremner et al. 2003a; Lindauer et al. 2004). Treatment studies using both non-pharmacologic (Lansing et al. 2005; Peres et al. 2007) and pharmacologic therapy (Fernandez et al. 2001) report activation of Broca's area in PTSD patients after therapy.

14.3 Neurochemistry of PTSD

There is a growing understanding of the neurochemistry of the stress response as well as of PTSD (Chrousos 2009). The hypothalamic-pituitary axis (HPA), the sympathetic adrenomedullary system and a range of other neurotransmitters play a key role. Receptor-radioligand imaging is one of the more promising means of assessing these systems although it is not without its limitations: altered binding of a radioligand may be explained by several different mechanisms which may be difficult to distinguish (reduced radioligand delivery, altered receptor affinity, altered number of receptors, altered concentrations of endogenous competing molecules or altered removal of radioligand from the receptor site). Currently, there are limited molecular imaging data available, but they are already assisting in understanding PTSD from a neurochemical perspective, and this work is likely to be key to improving our understanding of the neurobiology of PTSD in the future. In this section we will cover existing molecular imaging work on neurochemical/neuroreceptor systems implicated in PTSD.

14.3.1 Serotonergic System

Animal research has implicated the serotonin system in anxiety – specifically in the modulation of anxiety and fear. Inescapably shocked animals develop decreased levels of CNS serotonin (Valzelli 1982). In animal studies, low serotonin is related to an inability to modulate arousal (Gerson and Baldessarini 1980; Dupue and Spoont 1989) – an observation that may be relevant to the phenomenology of PTSD in humans (van Der Kolk 1994). Evidence for a role of the serotonergic system in PTSD is also to be found in the efficacy of selective serotonin reuptake inhibitors (SSRIs) in treating the symptoms of the disorder (Albucher and Liberzon 2002).

A study that used [technetium-99m]-D, L-hexamethyl-propyleneamine oxime (^{99m}Tc-HMPAO) SPECT to scan 11 patients with PTSD pre and post 8 weeks of treatment with citalopram (a SSRI) found that treatment with citalopram resulted in significant deactivation in the left medial temporal cortex (incorporating hippocampus and amygdala) irrespective of clinical response (Seedat et al. 2004). A significant correlation was found between PTSD symptom improvement and activation in the left paracingulate region (mPFC). These data are consistent with a model in which treatment of PTSD with a SSRI may extinguish learned fear responses by restoring the normal mPFC modulation of amygdala activity. The findings in the mPFC are supported by a study which used ^{15}O-water PET to measure rCBF in 13 PTSD patients before and after 12 weeks of treatment with paroxetine (SSRI) or placebo. Patients were scanned with neutral and trauma-related scripts at each time point. While both placebo and paroxetine treatment was associated with a significant increase in rCBF to the ACC in response to traumatic scripts (as well as improvement in symptoms), paroxetine treatment was associated with an additional increase in function of the OFC (a component of vmPFC) (Fani et al. 2011).

Mouse knockout models have demonstrated the role of serotonin type 1A (5-HT$_{1A}$) receptors in the regulation of anxiety responses (Parks et al. 1998; Ramboz et al. 1998). There is also evidence that the efficacy of SSRIs in treating anxiety is at least in part attributable of their binding to this inhibitory receptor (Varnas et al. 2004). This is growing evidence for the role of this receptor in anxiety (Akimova et al. 2009). Despite this evidence, a study using [fluorine-18]-trans-4-fluoro-N-2-[4-(2-methoxyphenyl) piperazin-1-yl]ethyl-N-(2-pyridyl) cyclohexanecarboxamide (^{18}F-FCWAY) to compare 5-HT$_{1A}$ binding in 12 patients with PTSD and 11 healthy controls during rest conditions found no differences in binding between the groups in a priori defined areas of interest (midbrain raphe, anterior temporopolar cortex, posterior cingulate, anterior insula, anterior cingulate and medial temporal cortex (hippocampus plus amygdala) (Bonne et al. 2005). Their findings suggest that other serotonin receptor deficits or alternative alterations in serotonergic function need to be sought in PTSD.

A study of serotonin type 1B receptor (5-HT$_{1B}$) expression has also been conducted by using [carbon-11]-P943 (^{11}C-P943) to scan 49 patients with PTSD, 20 trauma-exposed controls and 27 healthy controls (Murrough et al. 2011a). Again, no significant differences were found between the PTSD group and the trauma-exposed controls, although marked reductions in ligand binding in the caudate, the amygdala and the ACC were seen in PTSD and trauma-exposed individuals compared to healthy controls – a finding which may be related to trauma exposure rather than PTSD per se.

Animal research focusing on the serotonin transporter (5-HTT) has demonstrated altered morphology of basolateral amygdala in 5-HTT knockout mice (Wellman et al. 2007; Hariri and Holmes 2006), whereas overexpression of the human 5-HTT gene in transgenic mice resulted in a low-anxiety phenotype (Jennings et al. 2006). Genetic studies in humans have demonstrated that the short allele of the common repeat polymorphism in the promoter region of the gene coding for the serotonin transporter (5-HTTLPR) increases vulnerability of developing PTSD (Lee et al.

2005; Kilpatrick et al. 2007; Xie et al. 2009; Kolassa et al. 2010). A study examining serotonin transporter binding using [carbon-11]-2-[2-(dimethylaminomethyl) phenylthio]-5-fluoromethyl-phenylamine (^{11}C-AFM) in 15 patients with PTSD and 15 healthy controls found that ligand binding in the left amygdala was reduced in PTSD compared to the controls. Furthermore, amygdala ligand binding was inversely correlated with both anxiety and depression scores. No between-group differences for any other brain regions were detected (Murrough et al. 2011b). The group's findings support the role of the amygdala in PTSD and are consistent with evidence from animal research that 5-HT signalling within the amygdala regulates normal fear and threat responsiveness (Wellman et al. 2007; Muller et al. 2011; Zanoveli et al. 2009). It may be that altered 5-HTT function influences amygdala activity to enhance the acquisition of conditioned fear and/or decrease fear extinction and that this mediates a vulnerability to PTSD (Murrough et al. 2011b).

14.3.2 Noradrenergic System

Preclinical evidence for the role of the noradrenergic system in stress is well established (Chrousos and Gold 1992; Charney et al. 1993). Noradrenergic cell bodies in the brain are predominantly concentrated in the locus coeruleus from which there are projections to cortical and subcortical structures (e.g. Cedarbaum and Aghajanian 1978; Ashton-Jones and Bloom 1981). Noradrenergic models of stress in animals have demonstrated evidence of locus coeruleus hyperactivity and resultant increase in release of noradrenaline in multiple brain regions (Redmond 1979; Tanaka et al. 1982). There has long been evidence to suggest that PTSD patients have increased sympathetic nervous system activity (see, e.g. Kosten et al. 1987).

No nuclear neuroimaging studies have thus far examined adrenergic receptors in PTSD directly, though the development of novel radioligands may allow this in the future (e.g. Van der Mey et al. 2006; Logan et al. 2007). Indirect evidence supporting the role of the adrenergic system in PTSD is to be found in a study in which ten patients with PTSD and ten controls underwent scans using ^{18}F-FDG after yohimbine (an α_2-antagonist) and after placebo administration. Of the ten PTSD patients, six had a panic attack with yohimbine administration and three had a flashback. None of the controls experienced symptoms. Significant differences in the brain metabolic response to yohimbine were seen between PTSD and controls in orbitofrontal cortex, temporal cortex and prefrontal cortex. Metabolism tended to decrease in patients with PTSD and increase in healthy subjects following administration of yohimbine (Bremner et al. 1997). These findings suggest that in PTSD either there is increased noradrenaline in central brain structures, which affects metabolism (and presumably symptoms), or there are alterations in specific noradrenergic receptors.

14.3.3 Gamma-Aminobutyric Acid (GABA) System

The efficacy of benzodiazepines in the treatment of anxiety disorders has led to interest in their underlying mechanisms of action. It has been known for decades

(from animal research) that the $GABA_A$ receptor is the main target for the central actions of benzodiazepines (Costa et al. 1975; Haefely et al. 1975). Animal studies on benzodiazepine binding in conditions of inescapable stress have demonstrated reductions in the frontal cortex (e.g. Lippa et al. 1978; Weizman et al. 1989) and cerebral cortex (e.g. Medina et al. 1983), as well as (less consistently) in the hippocampus (e.g. Medina et al. 1983 vs. Weizman et al. 1989).

There is evidence that in PTSD there is reduced benzodiazepine binding in several brain regions. In a study using [iodine-123] iomazenil (^{123}I-iomazenil) SPECT to study benzodiazepine receptor density in 13 PTSD patients and 13 healthy controls, it was reported that benzodiazepine receptor binding was 41 % lower in PTSD (compared to controls) in the dorsolateral prefrontal cortex. No other differences were detected between the two groups. A positive correlation was also found between symptom severity in the PTSD group and decreased benzodiazepine binding in the dorsolateral prefrontal cortex (Bremner et al. 2000). Another study that used [carbon-11] flumazenil (^{11}C-flumazenil) dynamic PET to study benzodiazepine binding in nine patients with PTSD and seven trauma-exposed controls reported that PTSD subjects showed decreased ligand binding potential throughout the cortex, caudate nuclei, hippocampus, thalamus, left amygdala and left striatum in comparison to the control group (Geuze et al. 2008). The data may represent a difference in subunit composition of $GABA_A$-benzodiazepine receptors in PTSD, a lower expression of $GABA_A$ receptor in PTSD or a disease or trauma-induced modulation or downregulation of the of $GABA_A$-receptor complex (Geuze et al. 2008). Failure to demonstrate a global reduction in benzodiazepine-binding receptors by the former group may be due to differences in imaging modality. Nevertheless, not all data are consistent; a study that used ^{123}I-iomazenil to image benzodiazepine receptor density in 19 PTSD patients and 19 healthy controls found no significant differences in ligand binding in any brain regions, even after partial volume correction (Fujita et al. 2004).

14.3.4 Opioid System

In animal studies, the endogenous opioid system has been implicated in the modulation of fear (Good and Westbrook 1995) as well as anxiolysis (Kang et al. 2000). Abnormalities in this system in PTSD have been proposed by several groups (Glover 1993; Pitman et al. 1990). Several studies have shown that the μ-opioid system has an inhibitory role during negative emotional states. Trauma exposure or recall may result in an exaggerated release of endogenous opioids with subsequent downregulation of μ-opioid receptors. An inadequate initial opioid response or an inadequate subsequent downregulation could explain the study's findings. Alternatively, μ-opioid receptors could be located on inhibitory intraneurons, as has been demonstrated in the hippocampus (Drake and Milner 1999). Low binding could reflect less inhibition of interneurons and as a result, the development of a stronger capacity for inhibition during emotional stimulation.

A study that used [carbon-11] carfentanil (^{11}C-carfentanil) to image μ-opioid receptor binding in a priori regions of interest in 16 patients with PTSD, 14

trauma-exposed controls and 15 healthy controls found that both the trauma-exposed control group and PTSD group had lower μ-opioid receptor binding in extended amygdala, nucleus accumbens and dorsal frontal and insular cortex but had higher binding potential in the orbitofrontal cortex. PTSD patients exhibited reduced binding potential in ACC compared to both control groups. Mu-opioid receptor binding in trauma-exposed controls was lower in the amygdala but higher in orbitofrontal cortex compared with PTSD patients and healthy controls (Liberzon et al. 2007b). The authors suggest that trauma exposure leads to widespread changes in the function of the endogenous opioid system, possibly involving downregulation of the limbic forebrain, thalamus and associated cortical regions (insula, ACC, mPFC), along with upregulation of OFC and subgenual ACC receptors. Furthermore, the abnormal responses seen in PTSD may reflect an inability to adequately activate and subsequently downregulate μ-opioid receptors in the amygdala, thalamus and sublenticular extended amygdala and to adequately upregulate these receptors in the OFC and subgenual ACC. Given the role of OFC and subgenual ACC in reward and negative reinforcement and self-induced sadness, these abnormalities may contribute to the anhedonia and emotional numbing observed in PTSD.

14.3.5 Dopaminergic System

In animal models, overstimulation of the dopaminergic system is related to potentiation of fear conditioning (Morrow et al. 1996) and delayed extinction of fear (Borowski and Kokkinidis 1998). Higher levels of dopamine in a stressful situation may consolidate memories related to the traumatic event. Urinary dopamine levels are raised in combat veterans (Yehuda et al. 1992) and in at least some subgroups of children with PTSD (De Bellis et al. 1999). One group (Hamner and Diamond 1993) also demonstrated that patients with PTSD have higher plasma dopamine levels. Genetic studies by several groups have found associations between variants of D_2 receptor and PTSD (Comings et al. 1996; Young et al. 2002), between variations in the D_4 receptor gene and intensity of PTSD symptoms (Dragan and Oniszczenko 2009), and between variations of the dopamine transporter gene and the likelihood of developing PTSD when exposed to a natural disaster (Drury et al. 2009).

Based on the rationale of a disordered dopaminergic system in PTSD, a study imaging presynaptic dopamine transporter density was conducted using 2-[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo[3.2.1]oct-2-yl]methyl](2-mercaptoethyl)amino]ethyl]amino]-ethanethiolato(3-)-oxo-[1R-(exo-exo)]-[technetium-99m] (^{99m}Tc-TRODAT-1) SPECT in 21 patients with PTSD and 21 trauma-exposed control subjects. PTSD patients had a higher DAT binding potential in left and right striatum compared to the control group. No clear correlation was found with PTSD symptoms (Hoexter et al. 2012). The authors suggest that their findings support a hypothesis of dopaminergic hyperactivity in PTSD. The authors

propose that DAT density increases may not be specifically related to PTSD core symptoms, but rather to the general processing of salient events.

14.3.6 Nicotinic System

Nicotinic acetylcholine receptors (nAChRs) have been implicated in both memory dysfunction and dysregulation of arousal (Gotti et al. 1997; Levin et al. 2006). A study that used a ligand for β_2 nicotinic acetylcholine receptors [iodine-123]-5-IA-85380 ([^{123}I]5-IA) to perform SPECT imaging of ten PTSD patients and ten healthy controls reported that in examining a priori regions of interest, relative to never-smoking controls, never-smoking PTSD patients showed higher β_2-nAChR availability in the medial temporal cortex. The significance of this difference was weakened when people with prior nicotine exposure were included. A significant association was found between thalamic ligand binding and re-experiencing symptoms of PTSD (Czermak et al. 2008). The authors suggest that their findings support the involvement of β_2-nAChRs in PTSD and also speculate that β2-nAChRs contribute to re-experiencing symptoms in PTSD by modulating the sensory input to the cortex (via thalamus).

14.3.7 Hypothalamic-Pituitary-Adrenal (HPA) Axis

The HPA axis is also believed to play a role in PTSD. Through its action on glucocorticoid receptors, cortisol exerts negative feedback on pituitary, hypothalamus and other sites (De Kloet and Reul 1987; Jacobson and Sapolsky 1991), possibly including mPFC (Diorio et al. 1993; Kern et al. 2008). Once the acute stress has been removed and the amygdala is no longer activated by perception of external threat, it activates negative feedback inhibition of the HPA axis in tandem with the hippocampus (McEwen et al. 1987), restoring hormone levels to baseline conditions.

PTSD was initially hypothesised to represent a state of chronic hypercortisolism, but more recent evidence indicates that it is associated with hypocortisolism (Mason et al. 1986; Yehuda et al. 1990b, 1993, 1995a, b; Meewisse et al. 2007). Yehuda (2001) proposes that this low cortisol in PTSD is a downstream manifestation of enhanced negative feedback inhibition resulting from increased glucocorticoid receptor number and sensitivity in the pituitary gland. This is supported by evidence of exaggerated endogenous cortisol suppression with low-dose dexamethasone suppression test in PTSD (Yehuda et al. 1995b) and by the fact that blocking the negative feedback of cortisol on pituitary using metyrapone results in an exaggerated ACTH response in PTSD (Yehuda et al. 1996).

Neuroimaging research provides some support for altered glucocorticoid responsiveness in PTSD. A study that measured changes in brain glucose metabolism following hydrocortisone or placebo administration in 16 patients with PTSD and 16 trauma-exposed controls with ^{18}F-FDG PET found no differences in baseline

cortisol levels between the two groups. PTSD patients showed a decrease in activity in the ACC with hydrocortisone, whereas the controls showed an increase – presumably reflecting differences in central glucocorticoid responsiveness. The PTSD group also demonstrated increased metabolism in the right hippocampus and right ventral amygdala in response to hydrocortisone (Yehuda et al. 2009). They found that the net effect of hydrocortisone was to restore a normal inverse association between the ACC and amygdala in the PTSD group but to disrupt this neural network in the control group.

Both animal and human research suggests a role for cortisol in causing hippocampal dysfunction in PTSD, with evidence to suggest that hypercortisolism (Sapolsky et al. 1986, 1990; McEwen 1999) or low cortisol levels (Raison and Miller 2003) are detrimental to hippocampus function and result in volume loss. Alternatively or additionally, altered (increased or decreased) glucocorticoid receptor sensitivity might account for hippocampal damage (Yehuda et al. 2001b; Raison and Miller 2003). One study correlated HPA-axis function, hippocampal volume (measured by MRI), hippocampal function (measured using FDG) and memory tasks in 12 patients with PTSD and 8 trauma-exposed controls. In addition to baseline imaging and neuroendocrine measures, memory tasks and PET imaging were performed (together with ACTH and cortisol measurements) following placebo and hydrocortisone administration. Baseline urinary cortisol excretion was the same in both groups but there was an exaggerated suppression of cortisol with dexamethasone suppression test in the PTSD group. Baseline hippocampal volume asymmetry varied between PTSD and control groups. These differences at baseline were negatively associated with cortisol, ACTH and hemispheric differences in hippocampal metabolism and positively associated with retention, showing an association between structural and functional measures of hippocampal structure, neuroendocrine activity and memory performance. Following hydrocortisone administration, these associations were no longer present. When compared to placebo, the PTSD group demonstrated an increase in hippocampal activation in response to hydrocortisone, whereas the control group showed a decrease. In addition, the PTSD group demonstrated greater suppression of ACTH in response to hydrocortisone than controls. Hydrocortisone did not impact memory performance in PTSD but worsened memory task performance in the control group (Yehuda et al. 2010). The authors concluded that differences in brain metabolic responses may reflect differences in peripheral and central glucocorticoid responsiveness. An earlier study supports this (Yehuda et al. 2009). Nevertheless, not all data are consistent; one study found a negative correlation between endogenous cortisol levels and rCBF in a region most likely representing hippocampal perfusion (Bonne et al. 2003 – see below), and another study found no involvement of hippocampus in PTSD (Liberzon et al. 2007a).

A way of exploring the role of the HPA axis in PTSD is to correlate endogenous cortisol levels with SPECT or PET findings. This was examined in a study in which 11 patients with PTSD, 17 trauma-exposed controls and 11 healthy controls were scanned using ^{99m}Tc-HMPAO SPECT. No significant differences were detected between groups in baseline cortisol levels prior to scanning. The group reported a

negative correlation between cortisol level and rCBF to medial temporal lobes bilaterally and a positive correlation between cortisol level and fronto-cingulate transitional cortex perfusion in the PTSD group. In the trauma-exposed group, negative correlations between cortisol level and bilateral fronto-cingulate transitional cortex as well as bilateral vmPFC were reported (Bonne et al. 2003). The authors suggested that the contrasting pattern of correlation between cortisol and mPFC/fronto-cingulate transitional cortex in PTSD and trauma-exposed controls may be related to the inadequate shutoff of the stress response in PTSD, while the negative correlation between medial temporal lobe rCBF and cortisol indicates either increased hippocampal control of HPA-axis secretion or a negative effect of cortisol on hippocampal perfusion (since hippocampus is probably the major contributor to medial temporal cortex perfusion measurement).

Similarly, an elegant study conducted to explore the relationship between hypothalamic-pituitary-adrenal axis activity and cortisol release and rCBF, specifically tried to identify circuits that activate the HPA axis and structures that are modulated by cortisol release. The group examined 16 patients with combat-related PTSD, 15 volunteers with combat-exposure but no PTSD and 15 normal controls by performing ^{15}O-water PET imaging during autobiographical trauma-related or neutral event script reading as well as in response to emotional pictures from the International Affective Picture System (Lang and Cuthbert 1997). In the PTSD group there were positive correlations between rCBF and ACTH response in the right insula, rACC and right prefrontal cortex, and unlike trauma-exposed controls, PTSD subjects did not have positive correlations between rCBF and subsequent ACTH response in dmPFC and parahippocampal gyrus (Liberzon et al. 2007a). The implications of these data are that insula and rACC are dysfunctional in PTSD and increases in rCBF in these regions may represent activity in circuits that activate the HPA axis. It is possible that deficient activation of dmPFC (when compared to trauma-exposed controls) in PTSD represents a failure to recruit modulatory circuits. To investigate cortical regions through which cortisol might modulate subsequent cognitive/emotional processing, they examined the relationship between pre-stimulus cortisol level and subsequent cortical responses (rCBF) to traumatic stimulus. They found that only the PTSD group had a positive correlation between pre-stimulus cortisol and a subsequent rCBF response to traumatic stimulus in subgenual ACC, bilateral superior temporal gyrus and right temporal lobe. The authors speculate that this cortisol-rCBF covariation suggests that cortisol may potentially "prime" the circuits that detect emotional cues in auditory stimuli. A reanalysis of the data obtained in the study by Liberzon et al. (2007a) found that trauma recall elicited ACTH responses in some but not all participants, regardless of PTSD status, leading to the conclusion that HPA-axis pathology in PTSD cannot be ascribed solely to a failure of the ACTH response to stressful stimuli (King et al. 2009).

Intriguingly, there is evidence that HPA-axis dysfunction is present early (immediately after the inciting traumatic event) in individuals that go on to develop PTSD (McFarlane et al. 1997; Delahanty et al. 2000) and HPA-axis dysfunction may in fact precede the trauma, indicating that HPA-axis dysfunction may be a risk factor for PTSD rather than simply an effect of the disorder (Yehuda et al. 1998; Yehuda

1999; Seckl and Meaney 2006). No nuclear neuroimaging studies examining early posttrauma (or baseline) HPA disruption and subsequent development of PTSD have been conducted. Imaging research examining the HPA axis in PTSD has thus far been indirect, measuring changes in rCBF or regional metabolism and correlating these with either endogenous or administered glucocorticoids. A novel class of drugs – the corticotropin release factor (CRF) antagonists as well as (currently experimental) radioligand tracers that target glucocorticoid (Steiniger et al. 2008) or CRF receptors (Zuev et al. 2011) in the brain – have the potential to improve our understanding of HPA-axis dysfunction in PTSD.

Conclusion

Current understanding of the neurocircuitry of PTSD is derived from animal research on fear conditioning, extinction and sensitisation and supported by a range of neuroimaging research, including PET and SPECT. A contemporary model of PTSD emphasises that the amygdala (responsible for initial threat assessment and fear response) and (additional research suggests) insulae are hyperactive – leading to an exaggerated fear response. This is due to or exacerbated by inadequate top-down modulation by ventral/medial prefrontal cortex (vmPFC) (which includes the rostral anterior cingulate cortex (rACC), medial prefrontal cortex (mPFC), subcallosal cortex and orbitofrontal cortex) – potentially explaining deficient extinction in PTSD. In addition to the potential gating function of the rACC, subregional analysis has identified the dACC as important in PTSD – hyperactivity of this region in PTSD is related to a disordered vigilance and salience network. Hippocampal dysfunction has been implicated in explaining memory dysfunction in PTSD, though this has not been reproduced in several studies. Broca's area (responsible for applying semantic representations of traumatic experiences and enabling their communication) may be hypoactive in PTSD. Neuroconnectivity research has helped widen interest in a range of other structures. Further neuroconnectivity research is required to reliably identify these regions and the relationships between them.

Beyond neuroconnectivity work lies research investigating the underlying neurochemical deficits of PTSD. There is growing interest in using molecular imaging to understanding neurochemical alterations in these circuits. Although only a small number of studies have been done, PET and SPECT are ideally suited for this area of enquiry. As discussed above, key neurotransmitter systems worth exploring in future work include serotonergic, adrenergic and dopaminergic systems as well as inhibitory systems such as the endogenous opioid system and GABA. Dysfunction of the HPA axis, implicated in chronic stress, also has relevance to the neurobiology of PTSD and warrants further investigation.

In summary, nuclear neuroimaging plays a valuable role in the noninvasive testing of PTSD models (derived from animal research) in humans. While much work has focused on the individual structures involved in mediating PTSD, there is now growing interest in connectivity between these structures. Furthermore, there is growing knowledge of the various underlying neurochemical systems involved and how these respond to interventions. There is currently inconsis-

tency in the literature, and future research will need to pay attention to methodological issues in an attempt to reduce such variance. Nuclear imaging is expected to be particularly useful in future contributions to understanding the neurochemistry of PTSD.

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Neuroimaging in PTSD-Related Psychotherapies

15

Marco Pagani 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), neuronal volume and density (magnetic resonance imaging, MRI), and, more recently, brain electric signal (electroencephalography, EEG). However, to date the number of such studies is still far too limited since only a few psychotherapies have been investigated using SPECT and MRI. In this respect, a recent study designed to monitor psychotherapy-related neurobiological changes is expected to pave the way for a new concept in PTSD treatment investigations. 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 2012, to present a critical review and to analyze the reported pathophysiological changes.

M. Pagani (✉)
Institute of Cognitive Sciences and Technologies, CNR,
Via Palestro 32, Rome 00185, Italy

Department of Nuclear Medicine, Karolinska Hospital, Stockholm, Sweden
e-mail: marco_00198@yahoo.com

M. Cavallo
Department of Mental Health, "San Luigi Gonzaga" Hospital Medical School, University of Turin, Regione Gonzole 10, Turin 10043, Italy

Department of Translational Medicine, "Amedeo Avogadro" University of Eastern Piedmont, Novara, Italy

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_15, © Springer-Verlag Berlin Heidelberg 2014

15.1 Introduction

Posttraumatic 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 reexperience 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 a fear response, thus resulting in the body's emotional reactions of autonomic arousal. It is estimated that in the general population of the USA, 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). Drawing on such evidence, a large survey conducted in six European countries (Belgium, France, Germany, Italy, Spain, and the Netherlands) by way of face-to-face interviews administered to 21,425 participants showed that the general prevalence of PTSD was 1.1 % (95 % confidence interval = 1.0–1.3). 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. These alterations occur in those areas of the brain implicated in trauma psychology and in symptoms onset. As a result, metabolic and morphological changes in the brain can be identified during the symptomatic phase of the disease, and also that each area involved in the complex mechanism underlying the processing of emotions and psychological traumas can 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 (script) of the trauma. Most of these studies included in a review (Bremner 2007) led to the identification of metabolic and morphological changes occurring in the brain when the disease becomes symptomatic, thus helping to associate a function with each specific area involved in the processing of emotions and psychological traumas.

However, to date no functional neuroimaging study has succeeded in investigating PTSD and its related psychotherapies with accurate time resolution. The real-time firing of brain neurons responding to external psychotherapy-induced stimuli, along with the effects of such stimuli on brain activation/deactivation, was recorded 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 might potentially help to overcome the limiting

methodological factors is the 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.

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 into the neurobiology of emotions. It is worth noting that since the neutral script administered to the patient is experienced as a new procedure, stress levels can rise and/or attention levels can be below normal levels and, finally, that the resting state may differ from one investigation to the next. To some extent, the above factors are responsible for inconsistency across PTSD research results.

In the review by Francati et al. (2007), in which functional studies on PTSD were evaluated, it is worth noting that, in general, SPECT studies include a larger sample of patients (on average 16 compared with 9 for positron emission tomography, PET, and functional MRI, fMRI, studies) and a broader spectrum of traumatic events. In fact, of the reviewed ^{99m}Tc-HMPAO SPECT studies, four out of eight did not include combat-related or sexual abuse studies, whereas this was true for only 5 out of 30 PET and fMRI studies. The need for recruiting larger cohorts of subjects is partially due to the lower spatial and time resolution of SPECT as compared to PET and fMRI leading to the need for a larger number of investigated subjects to reach comparably reliable results. Moreover, 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 related more to daily life and social problems.

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), and the hippocampus. The amygdala appears to be involved when dealing with threat-related stimuli (Morris et al. 1998; Whalen et al. 1998; Davis and Whalen 2001) and plays a role in the process of fear conditioning (LeDoux 2000; Davis and Whalen 2001). As PTSD patients are very sensitive to potential threats from the surrounding environment and are prone to acquire conditioned fear (Orr et al. 2000; Peri et al. 2000), an amygdala hyperactivation has been suggested in this clinical condition. Another region of interest is the mPFC that is connected to the amygdala and is involved in the extinction of fear conditioning (Quirk et al. 2000; Milad and Quirk 2002). In fact, patients with PTSD show a significant response to fear in their everyday life and exhibit reduced extinction of conditioned fear (Orr et al. 2000; Rothbaum et al. 2001). Lastly, a further region of interest is the hippocampus, which is involved in memory processes (Eichenbaum 2000; Corcoran and Maren 2001). Interestingly, it has been demonstrated that PTSD is associated with memory impairment and abnormal hippocampal functions.

More specifically, amygdala hyperresponsivity in PTSD has been shown during the presentation of traumatic narratives (Rauch et al. 1996; Shin et al. 2004a) and combat sounds (Liberzon et al. 1999; Pissiota et al. 2002). In patients with PTSD, the amygdala also appears to show significant responses to affective material not strictly associated to personal traumas, such as fearful facial expressions. Interestingly, the activity of the amygdala is positively correlated with PTSD symptom severity (Shin et al. 2004a) and self-reported anxiety (Pissiota et al. 2002; Fredrikson and Furmark 2003). However, it is worth noting that some studies of PTSD failed to detect any amygdala activation during symptomatic states (Bremner et al. 1997). Failure to replicate this finding has been related to methodological divergences between studies and to scientific and technical limitations such as relatively poor spatial and temporal resolution (e.g., in SPECT), small sample sizes of patients and controls involved in the studies, and inappropriate paradigm to induce symptoms.

Various neuroimaging studies in PTSD consistently showed a decreased activation and/or a failure to activate the mPFC, including anterior cingulate cortex and medial frontal gyrus. Such evidence occurred when patients were listening to traumatic narratives (Lindauer et al. 2004; Shin et al. 2004a; Britton et al. 2005) and were exposed to combat pictures or sounds (Bremner et al. 1999b). Some studies have reported that mPFC activation is inversely related to PTSD symptom severity (Shin et al. 2004a; Britton et al. 2005). Although the majority of studies have shown a diminished activation of mPFC in PTSD, a few studies have shown different results, such as both increased and decreased activation in this region (Shin et al. 1997) or increased activation (Rauch et al. 1996; Zubieta et al. 1999; Sachinvala et al. 2000). Possible explanations for such discrepancies may depend on the specific technique used or on technical properties' heterogeneity. Another explanation accounts for the presence of a dissociative state of the participants during experiments.

Lastly, some neuroimaging studies focusing on hippocampal function in PTSD led to mixed results. Early studies reported lower activity in this region in the presence of symptoms (Bremner et al. 1999a; Shin et al. 1999), and cognitive activation studies showed a failure to recruit this neural structure during the recollection of emotional words (Bremner et al. 2003) and neutral words (Shin et al. 2004b). However, the latter study also found that blood flow in the hippocampus and parahippocampal gyri was significantly positively correlated with symptom severity.

In a recent functional connectivity study on rCBF changes during trauma versus neutral scripts (Osuch et al. 2008), the authors showed left amygdala coupling with right ACC and bilateral anterior insula, as well as coupling between the amygdala and contralateral hippocampus.

To summarize, during the last years a growing body of evidence has irrefutably demonstrated the existence of a neural model of PTSD encompassing the amygdala, the mPFC, and the hippocampus. These neural structures appear to be pathologically involved in PTSD (Shin et al. 2006). According to this model, the amygdala is typically hyperresponsive, implying an unexpected response to fear. By contrast, regions of the mPFC (including rostral anterior cingulate cortex and ventral medial frontal gyrus) are hyporesponsive, and this has been linked to a partial failure to appropriately inhibit the amygdala activity. In addition, it has been suggested that such

a hypofunction may also be related to reduced fear extinction. Lastly, hippocampal dysfunction may be associated to the declarative memory impairment typically showed in patients with PTSD. However, it is worth noting that 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 13 years (indexed in PubMed 1999–2012) regarding cerebral changes in patients diagnosed with PTSD for whom the neurobiological effects of various psychotherapies have been investigated by neuroimaging techniques and mostly by SPECT and structural MRI scans. A very recent EEG investigation will also be mentioned reinforcing the hypotheses suggested by previous functional neuroimaging studies.

15.2 Neuroimaging in PTSD Psychotherapies

Neuroimaging techniques have been used in an 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 it impossible to draw any well-structured conclusion. However, the studies under review were conducted on a variety of experimental paradigms, methodologies, and psychotherapies, but more 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 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). The outcome of the SPECT examination was described, 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 abovementioned inadequacy, this study paved the way for subsequent studies which demonstrated the feasibility of investigating brain physiology during the reliving of trauma.

Few years after, 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 the amygdalae.

By using structural magnetic resonance imaging, Bryant et al. (2008) 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 of CBT (8 sessions) and were then divided into two subgroups: 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, responders had an rACC volume comparable to that of controls. The authors interpreted this interesting pattern of results by stating that larger rACC volume may allow the patient 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, 2008, clinical studies; Pagani et al. 2005, 2007; Nardo et al. 2011, SPECT studies; Looi et al. 2008, 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 cognitive behavioral therapy (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

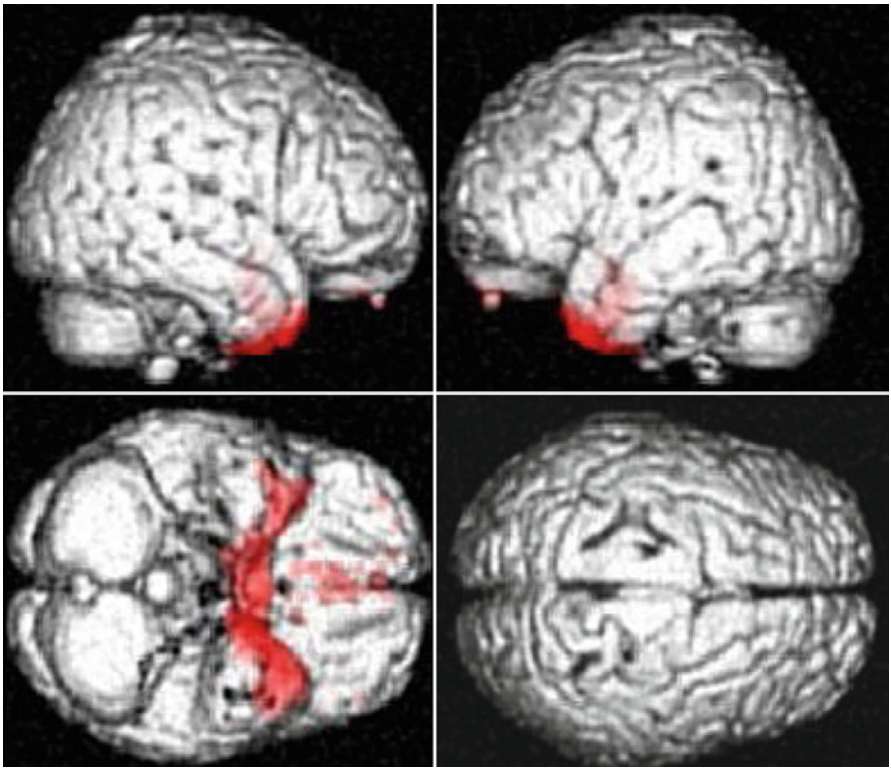

Fig. 15.1 Three-dimensional rendering of voxels reflecting higher tracer distribution in patients before EMDR ($n = 15$) as compared to controls ($n = 27$). The statistically significant differences are highlighted. The *first row* represents the lateral aspect of the right (on the left) and of the left (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)

and exposure therapies had a positive clinical outcome in the treatment of PTSD (Davidson and Parker 2001). Another study (Bradley et al. 2005) reported that in more than half of the patients who completed treatment with CBT or EMDR, overall symptoms improved. 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 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 psychotherapy (Nardo et al. 2011). Fifteen patients were scanned before and after therapeutic intervention, and in order to increase the reliability and robustness of the study, a control group of 22 nonsymptomatic subjects suffering from the same trauma was included in the study. This latter methodological caveat is of great relevance, since it minimizes any possible bias in the results due to psychological heterogeneity between the two groups. Furthermore, a very strict statistical threshold was applied

(false discovery rate correction at both voxel and cluster level) 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. 15.1) disappeared after treatment. Furthermore, following therapy the responders showed significant CBF normalization in the parieto-occipital lobes, visual cortex, and hippocampus and an increased CBF in the lateral prefrontal cortex. These results were confirmed 4 years later by an MRI study highlighting decreased gray matter density in roughly the same limbic and cortical structures in nonresponders before EMDR therapy (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 prefrontal cortex, which has been shown to inhibit the limbic system in response to pathological stimuli that resemble the traumatic event, recovered its inhibitory role, reducing amygdala hyperactivation and the corresponding cortical hyperarousal.

The latest SPECT EMDR study to date related to 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 ($p < 0.01$). 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 exposure to cognitive restructuring therapy and following successful psychotherapy, reported a higher activation in cortical (temporal, parietal, and prefrontal lobes) and subcortical (thalamus) regions in the left hemisphere during a script-driven provocation paradigm (Peres et al. 2007). This investigation was also performed using a low statistical threshold ($p < 0.001$ uncorrected for multiple comparisons) and the results should be viewed with caution.

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 PTSD scores, 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 the liberal level of $p < 0.01$ uncorrected for multiple comparisons at

voxel level. The same group published a MRI study in 2005 in which the same subjects showed a lack of volumetric changes following BET (Lindauer et al. 2005). However, the 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 the index traumas) or state (following the index trauma) characteristic has not yet been clarified. 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, during the past 13 years a body of research has been carried out on humans to evaluate psychotherapies' effectiveness, and a number of studies are focused on revealing their functional substrates despite difficulties arising from both time and spatial resolution of the selected 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 relatively low spatial resolution of SPECT, the increased blood flow found at 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. These findings are consistent with clinical improvements, including depression and general affective disorders, demonstrating that psychotherapies have a significant impact on brain function and that the emergent normalized pattern of brain activity is consistent with changes that may be mitigating posttraumatic and anxiety conditions.

In the last 2 years, a new and groundbreaking investigation has been carried out, based on online EEG monitoring of the functional response during psychotherapy (Pagani et al. 2011, 2012). A preliminary methodological validation report describing the methodology and feasibility of this approach (Pagani et al. 2011) was recently published. To allow the experiment to be as patient friendly as possible, the EEGs in a group of ten subjects with major psychic 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 both 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-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 in the frontoparietal cortex at the first EMDR session was also observed.

In our opinion, the importance of this latter study lies not only in the validation, through a different 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) which can occur in PET or SPECT (Mazard et al. 2002).

15.3 General Discussion

The main objective of the functional studies carried out over the last 13 years has been to broaden our knowledge concerning the neurobiological mechanisms underlying successful psychotherapy. This has been pursued utilizing various methodologies (neuropsychology, SPECT, PET, MRI, and EEG) in order to identify the neuronal changes upon psychotherapy occurring in human pathophysiology, i.e., neuropsychology, blood perfusion, neuronal density, and electrical activation, following psychotherapy. This exciting journey has helped to confirm the initially sparse evidence of 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 activations at the stage of symptom disappearance can be interpreted as a neurobiological correlate of clinical recovery. This supports the hypothesis of a shift of emotive attention 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 processing the experience.

In general, limbic hyperactivation in PTSD patients is paralleled by cortical hypofunction (Bremner et al. 1999a) resulting in a lack of inhibition of reaction to fear from the amygdala and lack of adequate attenuation of peripheral sympathetic and hormonal responses to stress. It has been proposed that such hyperperfusion and hyperactivity of limbic and paralimbic regions are related to stress-induced long-term potentiation between the amygdala and periaqueductal gray through the N-methyl-D-aspartate (NMDA)-mediated pathway, once a sufficient amount of glutamate is released following stressful events (Hull 2002).

It has been postulated that the critical involvement of the limbic system is connected with the emotional responsiveness to the retrieved traumatic experience elicited by symptom provocation. It is worth noting that chronic PTSD is often associated with long-term pharmacological treatment and/or alcohol and substance abuse which will further affect brain structure and function and confound the results of the investigations. In this respect, the choice of a control group is a critical factor in the global neuroimaging analysis. Subjects exposed to the same trauma as patients but not developing PTSD clinical symptoms are likely to be the best candidates to form a control group. In this case, CBF distribution differences following group comparisons will be entirely related to the disorder itself and will not be confused with possible group and trauma discrepancies nor biased by other variables.

Conclusions

In conclusion, functional and anatomical studies carried out during the last decade have yielded very promising results, supporting the evidence of neurobiological models and explaining the changes which take place following PTSD-related psychotherapies. These findings call for continued commitment to unravel the pathophysiological mechanisms underlying these effective treatments of posttraumatic stress disorder. In this respect, there is a shortage of properly controlled pre- and posttreatment neuroimaging studies investigating treatment effects in PTSD.

Acknowledgements The authors wish to thank Mrs Emanuela Enrico for assisting in English editing and EMDR Italy and the Departments of Nuclear Medicine, Karolinska Hospital, Stockholm, Sweden, and of Systems Medicine, University of Rome "Tor Vergata," Rome, Italy, for the valuable collaboration in our previous studies.

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16 Dissociative Identity Disorder and Fantasy Proneness: A Positron Emission Tomography Study of Authentic and Enacted Dissociative Identity States

A.A.T. Simone Reinders and Antoon T.M. Willemsen

Contents

Abstract

Dissociative identity disorder (DID) is a disputed psychiatric disorder. Research findings and clinical observations suggest that DID involves an authentic mental disorder related to factors such as traumatisation and disrupted attachment. A competing view indicates that DID is due to fantasy proneness, suggestibility, suggestion and role-playing. Here, we investigate whether dissociative identity state-dependent psychobiological features in DID can be induced in high- or low-fantasy-prone individuals by instructed and motivated role-playing and suggestion. Differences in neural activation patterns were found between

A.A.T.S. Reinders, PhD (✉)
Department of Psychosis Studies, King's College London, Institute of Psychiatry,
16 De Crespigny Park, PO 40, London SE5 8AF, UK
e-mail: a.a.t.s.reinders@gmail.com, a.a.t.s.reinders@kcl.ac.uk

A.T.M. Willemsen, PhD
Department of Nuclear Medicine and Molecular Imaging,
University Medical Center Groningen, University of Groningen,
Hanzeplein 1, Groningen 9713 GZ, The Netherlands

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_16, © Springer-Verlag Berlin Heidelberg 2014

the DID patients and both high- and low-fantasy-prone controls. That is, the identity states in DID were not convincingly enacted by DID simulating controls. The findings indicate that DID does not have a sociocultural (e.g. iatrogenic) origin.

16.1 Introduction

Despite its inclusion in the Diagnostic Manual of Mental Disorders (American Psychiatric Association 2000), the genuineness of dissociative identity disorder (DID) continues to be disputed. Supporters of the diametrically opposed trauma-related and non-trauma-related views have been engaged for decades in a passionate debate regarding its validity as a mental disorder and whether it is related to traumatisation or to fantasy proneness, suggestibility, suggestion, and simulation (Bremner 2010; Coons 2005; Fraser 2005; Giesbrecht et al. 2008, 2010; Piper and Merskey 2004a, b, 2005; Sar 2005).

The non-trauma-related position (Giesbrecht et al. 2008; Merckelbach and Muris 2001; Merckelbach et al. 2002; Piper and Merskey 2004a, b; Pope et al. 2006), also referred to as the sociocognitive model of DID (Lilienfeld et al. 1999; Spanos 1994, 1996), holds that DID is a simulation caused by high suggestibility and/or fantasy proneness (Giesbrecht and Merckelbach 2006; Giesbrecht et al. 2007; Merckelbach et al. 2000, 2001; Rassin et al. 2001), suggestive psychotherapy, and other suggestive sociocultural influences (e.g. the media and/or the church). According to this model, '[t]he rules for enacting the [DID] role […] are as follows: (a) Behave as if you are two (or more) separate people who inhabit the same body. (b) Act as if the you I have been addressing thus far is one of those people and as if the you I have been talking to is unaware of the other co-inhabitants. (c) When I provide a signal for contacting another co-inhabitant, act as though you are another person. To the extent that patients behave in terms of these rules, the "classic" symptoms [of DID] follow by implication and do not have to be taught through direct instruction or further suggestion' Spanos (p.239, (Spanos 1996)). Although fantasy proneness and suggestibility refer to different concepts, they are highly correlated (Braffman and Kirsch 1999; Levin and Spei 2004; Merckelbach et al. 2001; Poulsen and Matthews 2003; Silva and Kirsch 1992), and dissociative symptoms were found to be correlated with fantasy proneness, heightened suggestibility, and susceptibility to pseudomemories (Merckelbach and Muris 2001; Rauschenberger and Lynn 1995). Of note, people who argue against the DID trauma perspective do not solely talk about fantasy proneness but also suggest the possibility of mild cognitive impairment as an alternative explanation (Giesbrecht et al. 2008).

To date, the position that DID is caused by sociocultural factors such as fantasy proneness has not been tested in brain imaging studies involving DID patients, and evidence that the complex phenomenology and psychobiology of DID can be created and sustained over time by these factors is lacking (Brown et al. 1999; Gleaves 1996; Loewenstein 2007; Xiao et al. 2006). Despite this lack of empirical support,

the sociocognitive and fantasy-based model of DID is influential in contemporary psychiatry, and there have been proposals to prevent the inclusion of DID in the DSM-V (Gharaibeh and Merskey 2009).

The trauma-related perspective entails that DID is related to a combination of factors that include chronic emotional neglect as well as emotional, physical, and/or sexual abuse from early childhood, insufficient integrative capacity, attachment disorder, and lack of affect regulation by caretakers(Dell and O'Neil 2009; Gleaves 1996; van der Hart et al. 2006; Putnam 1992; Spiegel 2006). In this view DID is thought to be at the far end of the spectrum of trauma-related psychiatric disorders, i.e. being a severe form of post-traumatic stress disorder (PTSD) (van der Hart et al. 2006; Spiegel 1984).

Holders of the trauma-related view acknowledge that some features of dissociative identity states can be influenced by sociocultural factors (van der Hart et al. 2006), that false-positive cases of DID have evolved in a treatment setting and that some psychiatric patients imitate DID (Draijer and Boon 1999). However, they also note that there are differences between authentic and imitated DID and that there is no evidence that DID can (sub-)consciously be created by sociocultural factors (Gleaves 1996). Furthermore, even if DID symptoms can be created iatrogenically or can be enacted, this does not mean that genuine trauma-related DID does not exist (Elzinga et al. 1998).

According to the DSM-IV (American Psychiatric Association, APA, DSM-IV 2000), DID is characterised by, among others, the presence of two or more distinct 'identities' or 'personality states'. Different proposed labels include 'different emotional states', 'alters', 'dissociative parts of the personality' (van der Hart et al. 2006) and 'dissociative identity states'. Following previously used descriptions and terminology (Reinders et al. 2003, 2006), different types of dissociative identity states are indicated here as the neutral identity state (NIS) and trauma-related identity state (TIS). These indicators are derived from the terms 'apparently normal part of the personality (ANP)' and 'emotional part of the personality (EP)', respectively, which are used in the theory of structural dissociation (van der Hart et al. 2006; Nijenhuis et al. 2002). This theory defines dissociation as a division of personality into different types of subsystems, each with their own first-person perspective, that is, their own point of view as to who they are, what the world is like, and how they relate to that world (Nijenhuis and Van der Hart 2011). As NIS, DID patients concentrate on functioning in daily life, commonly try to hide their pathology, and have not sufficiently integrated (e.g. have partial or complete amnesia to) traumatic memories. That is, NIS fails to relate the trauma-related nature to its self (Reinders et al. 2003). In contrast, TIS does have conscious access to these memories, recalls them as personal experiences and is bodily and emotionally affected by them. That is, as TIS, the patients are fixated in traumatic memories and engage in defensive actions such as freeze and flight, when they are or feel threatened (Nijenhuis et al. 2002, 2004), thereby activating fast subcortical response routes in the brain (LeDoux 2000; Reinders et al. 2006). Patients, as TIS, either can engage in active kinds of physical defence (e.g. freeze, flight, fight), indicating a dominance of the sympathetic nervous system, or can

engage in total submission (i.e. playing dead) which would be primarily mediated by the dorsal vagal branch of the parasympathetic nervous system (Nijenhuis and Den Boer 2009).

16.1.1 Brain Imaging Studies in DID

Despite the fact that imaging neuroscience has been around for more than 20 years and is by now the predominant technique in behaviour and cognitive neuroscience (Friston 2009), only very few studies have been performed in patients with DID (Dalenberg et al. 2012; Reinders 2008). The first functional brain scan in one patient with DID was a PET scan of the brain resting state (Mathew et al. 1985). This study included three control subjects and revealed blood flow differences in the temporal cortex of the DID patient. Four more studies assessing the resting state of the DID brain have been reported, all four using the low spatial resolution imaging technique of single-photon emission computed tomography (SPECT). Two of these studies were case studies (Saxe et al. 1992; Sheehan et al. 2006) with no control groups. The remaining two SPECT studies were performed by the same research group and include the largest group of 21 DID patients (plus nine healthy controls) ever assessed using brain imaging techniques (Sar et al. 2001, 2007). These two latter studies consistently found bilateral frontal perfusion differences between patients and controls. Enhanced prefrontal cortex functioning was also found during a working-memory task (Elzinga et al. 2007) when comparing 16 DID patients to healthy controls, using functional magnetic resonance imaging (fMRI), a high temporal and spatial resolution imaging technique. Elzinga et al. found that dissociative patients recruited the left anterior prefrontal cortex (BA 10), the left dorsolateral prefrontal cortex (BA 9) and the left parietal cortex (BA 40) more than controls. The prefrontal areas were found to be activated independent of task difficulty, while the parietal cortex activation was task-load dependent.

Two other studies used fMRI but only involved case studies of a DID patient switching between different identity states (Savoy et al. 2012; Tsai et al. 1999). Interestingly, Savoy et al. found the dorsolateral prefrontal cortex (BA9), the anterior prefrontal cortex (BA10) as well as the orbitofrontal cortex (BA 11) to be involved in voluntary switching between identity states. In addition, bilateral activation was found in an area in the striatum, the nucleus accumbens. The study of Tsai et al. did not report the involvement of the prefrontal cortical areas but did report the hippocampal areas to be involved in switching between identity states as well as the parahippocampus, medial temporal structures, substantia nigra, and the global pallidus. The latter structure is part of the dorsal striatum.

The literature review above shows that functional alterations have been reported widespread throughout the brain, i.e. in the temporal (Mathew et al. 1985; Sar et al. 2001; Saxe et al. 1992; Sheehan et al. 2006; Tsai et al. 1999), frontal (Elzinga et al. 2007; Sar et al. 2001, 2007; Savoy et al. 2012), and occipital (Sar et al. 2007) cortices and the nucleus accumbens (Savoy et al. 2012) and the hippocampal and pallidum structures (Tsai et al. 1999). In a multi-subject PET study, Reinders et al.

(2006) reported that different dissociative identity states (i.e. NIS and TIS) in DID are associated with different brain activation patterns when confronted with trauma-related cues. They reported the involvement of mainly the cortical multimodal posterior association areas (PAA), the subcortical amygdala, and subparts of the dorsal striatum (i.e. the caudate and putamen) in the psychopathology of DID.

16.1.2 DID and Fantasy Proneness

Proponents of the sociocognitive view have argued that the different patterns of subjective, psychophysiological, and neural activity for NIS and TIS in response to a trauma-memory script that Reinders et al. (2003, 2006) documented might be due to fantasy proneness, suggestion, and role-playing and that they do not prove a traumagenic origin of DID. Obtaining independent proof of childhood traumatisation in adulthood is most difficult. However, the claim that the previously reported PET results constitute effects of fantasy proneness, suggestion, and role-playing is open to test. Here, we describe a neuroimaging study that involves a psychobiological comparison between NIS and TIS engaging in active kinds of physical defence in DID patients (i.e. the DID identity states from Reinders et al. (2003, 2006)) and simulated NIS and TIS in high- and low-fantasy-prone, mentally healthy women. The women in this control group did not report a trauma history and were instructed and motivated to role-play these different identity states (i.e. simulated identity states).

The a priori hypotheses of the current study are as follows: (i) important previously found neurobiological differences between NIS and TIS in DID patients (Reinders et al. 2003, 2006) are upheld when correcting for the response in the control group, (ii) the upheld neurobiological differences for NIS and TIS in DID patients include higher subcortical activity (e.g. the amygdala and caudate nucleus) for TIS in DID, and (iii) the cortical multimodal posterior association areas (e.g. the intraparietal sulcus and (pre-)cuneus) for NIS in DID patients are hyperactivated when listening to personal trauma scripts.

16.2 Methods

16.2.1 Participants

Twenty-nine subjects participated in the PET study: 11 patients with dissociative identity disorder (DID), 10 high-fantasy-prone DID simulating controls (CH), and 8 low-fantasy-prone DID simulating controls (CL). Controls were carefully matched for gender (all female) and age and differences in age were not significant (DID vs. CH: $F(1,18) = 0{,}499$ $p = 0.489$, n.s. and DID vs. CL: $F(1,16) = 0.153$; $p = 0.701$, n.s.). The study presented in this chapter has been published elsewhere (Reinders et al. 2012) and a detailed description of the controls and the DID enactment procedure can be found in that paper (Reinders et al. 2012). In sum, the controls were recruited by local newspaper advertisements, did not suffer from potentially traumatising

events such as physical abuse and emotional neglect and filled in the Creative Experiences Questionnaire (CEQ) (Merckelbach et al. 2001) which measures fantasy proneness. The controls were divided into two groups based on their CEQ scores resulting in a high-fantasy-prone group ($n = 10$, age 38.2 (SD 10.9), Traumatic Experience Checklist (TEC; Nijenhuis et al. 2002) 0.7 (SD 1.3), Somatoform Dissociation Questionnaire (SDQ-20; Nijenhuis et al. 1996) 22 (SD 2.4)) with CEQ 13.7 (SD 3.2) and a low-fantasy-prone group ($n = 8$, age 42.5 (SD 10.1), TEC 0.4 (SD 0.5), SDQ-20 20.9 (SD 1.5)) with CEQ 3.9 (SD 1.6). A CEQ cut-off for high fantasy proneness of ten was used, which the developers of the CEQ recommended for the current sample (Giesbrecht T and Merckelbach H, personal written email communication on the 11th of February, 2008). The controls received written and oral information on dissociative identity states and were instructed to enact the two DID identity states: a neutral identity state (NIS) and a trauma-related identity state (TIS). Controls were asked to provide their most painful memory to serve as an analogue for the patients' personal trauma memories, as well as a neutral personal episodic memory. Controls were subsequently instructed how to write the autobiographical analogue neutral and 'trauma' memory scripts. For the experiment they had to train themselves in being in a neutral state, the NIS who is unresponsive or under-responsive to the painful experience, and in being in a state in which they re-experience the painful memory, the TIS.

A detailed description of the DID patients can be found elsewhere (Reinders et al. 2003, 2006). In short, 11 patients (all female, age 41.0, SD 6.1) participated: (i) whose treatment had progressed to include therapeutic exposure to trauma-related memories; (ii) who met the criteria for DID, as operationalised in the Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D(Steinberg 1994)); (iii) who had at least one TIS and one NIS that they could activate on demand; and (iv) with whom the involved TIS had displayed signs of sympathetic nervous system dominance under perceived threat in clinical situations.

Cerebral blood flow PET (Siemens/CTI ECAT HR+) data and autonomic (systolic and diastolic blood pressure, discrete heart rate and heart rate variability (HRV)) and subjective (controls' subjective sensorimotor and emotional experiences) reactions were obtained (see for details: (Reinders et al. 2003, 2006, 2012)). DID patients as well as high-fantasy-prone and low-fantasy-prone controls were studied in the two different types of identity states during a memory script (MS)-driven (neutral or trauma-related autobiographical texts) imagery paradigm. Four conditions were obtained twice in patients and three times in controls: NISn, NISt, TISn, TISt, where the last minor character (n or t) denotes the content of the memory script (MS: neutral or trauma related).

16.2.2 Image Acquisition and Data Processing

Data acquisition, reconstruction, attenuation correction, spatial transformation, spatial smoothing (isotropic Gaussian kernel of 12 mm) and global normalisation were performed as usual (Reinders et al. 2012). The brain imaging data of the three

groups was preprocessed and statistically analysed in SPM5 (www.fil.ion.ucl.ac.uk/spm) in a three-by-two-by-two factorial design (see Intermezzo 1 with Fig. 16.1), which allows for the assessment of within- and between-identity state effects within and between the three groups.

Intermezzo: The Study's General Linear Model

The water-activation-PET data was analysed in an imaging-specific data-analysis program called *Statistical Parametric Mapping* (SPM: www.fil.ion.ucl.ac.uk/spm/). In SPM the variance in the data is modelled using the General Linear Model (GLM). The GLM (Friston 1997) estimates parameters 'β' to explain the measured regional cerebral blood flow (rCBF) 'x' in terms of a linear combination of 'K' explanatory variables 'g' plus an error term:

$$x_{ij} = g_{i1}\beta_{1j} + g_{i2}\beta_{2j} + \ldots + g_{iK}\beta_{Kj} + e_{ij}$$

Where

$i = 1, \ldots, I$ indexes the observations, i.e. all the scan of all the subjects.

$j = 1, \ldots, J$ indexes the voxel j of the images.

$k = 1, \ldots, K$ indexes the number of explanatory variables.

This can also be written in matrix form as $X = G\beta + e$

with

X the observation matrix

G the design matrix

β the parameter matrix

With every additional explanatory variable, the GLM will fit the variance in the data better as it has more degrees of freedom to do so. But using additional degrees of freedom will weaken the statistical power and therefore the possibility to find a significant result.

PET data has a limited number of observations and is therefore directly modelled via the 'Basic models' option. The data in the current study was modelled in SPM5 using a three-by-two-by-two factorial design representing three groups, two identity states, and two memory scripts. To this end, we first defined the default factor 'Subject' with the assumption of independent measures and, considering that multiple measurements were obtained for each subject, the error variance was assumed to be equal for this factor. Then the 'Group' factor (DID, CH, and CL) was set with the assumption of independent measures and with unequal variance since the groups were independent. The Identity and Script factors were combined in the 'Condition' factor representing the (simulated) identity NIS and TIS and the scripts t and n. Considering that multiple measurements were obtained for each condition within one subject, the error variance was assumed to be equal for this factor but the measurements are not independent. The GLM consisted of the three

factor main effects: subject, group and conditions, and a group by condition interaction.

Objective measures were obtained at the end of each two-minute PET scan (blood pressure (systolic and diastolic) and heart rate (discrete and variability)). In addition, six subjective emotional measures were obtained (fear, sorrow, sadness, anger, shame, and disgust) and ten sensorimotor experiences (visual, kinaesthetic, auditory, olfactory + gustatory reactions, pain, physical numbness, body stiffening, paralysis, and restlessness). Including all these measures in the GLM to explain variance induced by autonomic reactions and suggestibility/simulation would absorb too many degrees of freedom. Therefore these measures were submitted to a Principal Component (PC) analysis, which 'categorises' variance into different components, i.e. eigenvectors. We used a cut-off of one for the eigenvalues. The variance in the subjective ratings could be described with the first two, six and five PC for the DID, high- and low-fantasy-prone groups, respectively, explaining 64, 68 and 72 % of the variance. The variance in the autonomic reactions could be described with the first three PC for each of the DID, high- and low-fantasy-prone groups, explaining 85, 82 and 87 % of the variance, respectively. These subjective and autonomic PC reactions were included as group-specific covariates of interest (mean padded). Finally, the global cerebral blood flow (CBF) was included as a nuisance covariate (AnCova by subject).

The full design matrix is presented in Fig. 16.1. From left to right the parameters included in the GLM can be read. The first factor 'Subject' allocates 27 columns and consists of the ten patients, the nine CH, and the

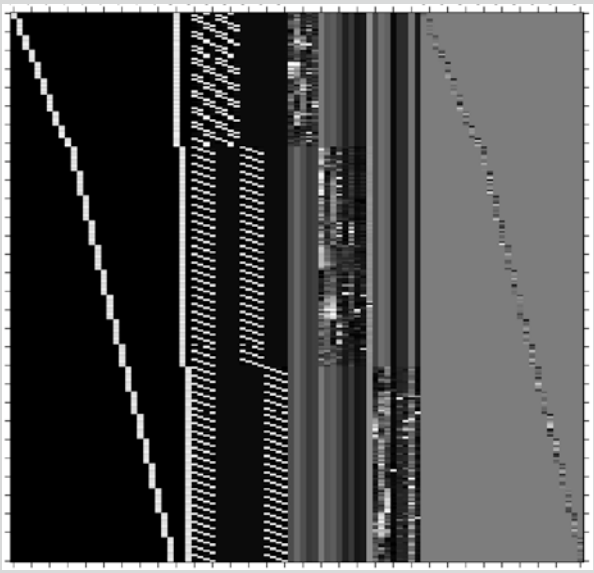

Fig. 16.1 The study-specific general linear model as created in SPM

eight CL and accounts for the subject specific variance. The next three columns define the second factor 'Group' consisting of the three groups and explain variance *common* to all groups. The factor 'Condition' consists of four columns and explains variance *common* to all four conditions: NISn, NISt, TISn, and TISt. The next 12 columns are the effects of interest as they account for the variance in the data that belongs to the Interaction of group × condition. The subtraction analyses described in this chapter are performed by setting the contrasts on these 12 columns. The next columns are the two sets of group-dependent physiologic and subjective measures covariates as created by the principal component analyses: DID two and three, CH three and six, and CL five and three. The last 27 columns accommodate variance due to differences in global cerebral blood flow (CBF), which was included as a nuisance covariate (AnCova by subject). Of note, alternatively a reduced design matrix can be used including only subjects, group × condition interaction, covariates, and the subject × gCBF (see also the tutorial at https://www.jiscmail.ac.uk/cgi-bin/webadmin?A2=spm;bbc7faf8.0805). This, however, does not change the results.

Reference

Friston KJ (1997) Analyzing brain images: principles and overview. In: Frackowiak RSJ, Friston KJ, Frith C, Dolan R, Mazziotta JC (eds) Human brain function. Academic Press, London, pp 25–41

16.2.3 Statistical Inference and Reporting

Our a priori hypothesis was that earlier findings would still hold after the correction for non-trauma-related factors. Both whole-brain and a priori region of interest (ROI) multiple comparisons correction were performed on the basis of false discovery rate statistics (Genovese et al. 2002). If an a priori hypothesised brain area did not survive whole-brain multiple comparison correction, i.e. only survived an uncorrected threshold of $p<0.001$, multiple comparison correction was performed within the a priori region of interest (ROI) (Reinders et al. 2012). Note: In line with previously used statistical thresholds (Reinders et al. 2006), voxels surviving significant levels only uncorrected for multiple testing for the whole brain, i.e. $p<0.001$, were reported as well, but for comparison purposes only. Only clusters larger than eight voxels are reported taking into account the spatial resolution of the PET camera. In contrast to the earlier publication (Reinders et al. 2012), here, only the most significant peak voxels in a brain region is reported for simplicity. Brain regions and Brodmann areas (BA) were defined using both the Talairach atlas (Talairach and Tournoux 1988) and Deamon (Lancaster et al. 2000). Activations in sulci were defined using Brain Tutor (www.brainvoyager.com).

16.3 Results

16.3.1 Comparing Simulated and Pathological Identity States

The comparison of different conditions in different groups is not always straightforward to understand. It can also be described as a between-group comparison of within-group differences. For clarification this is depicted in Fig. 16.2. The easiest approach is to think of this by starting with the within-group comparisons which can be performed for each group separately, as shown at the top of Fig. 16.2. Figure 16.2 shows a simplified graphical representation of the statistical comparison process and uses the conditions 'NIS' and 'TIS' as example conditions. These conditions can be replaced by, for example, TISt and NISt to clarify the between-identity state comparisons or by TISt and TISn to understand the within-identity state

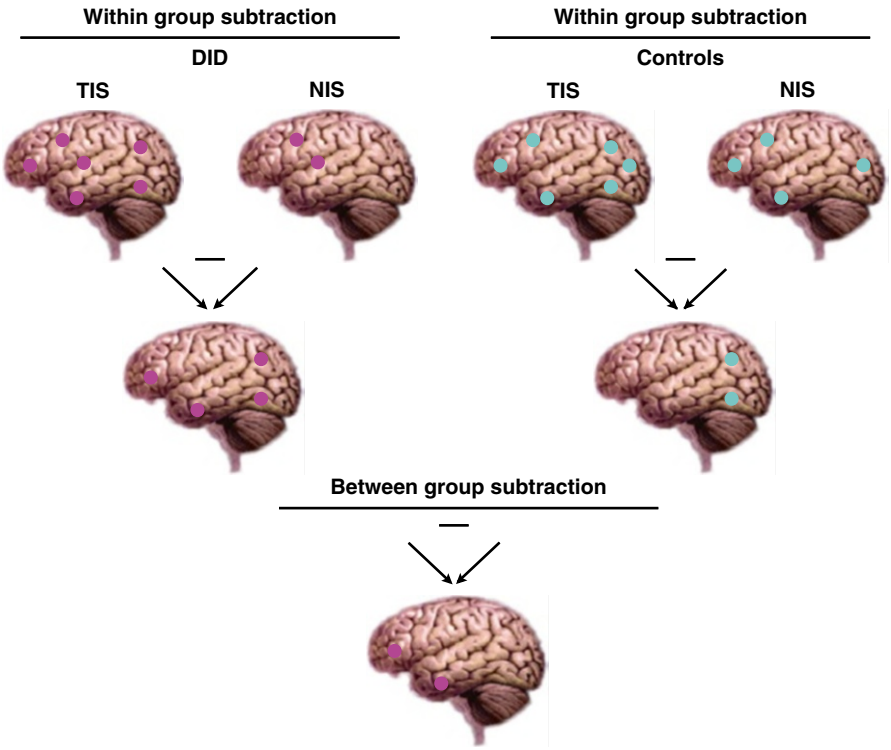

Fig. 16.2 A between-group comparison of within-group differences. This figure depicts two conditions in two groups (DID and Controls) at the *top row*. The middle row shows the within-group differences of two conditions per group (DID or Controls). The bottom row depicts the between-group differential brain activation patterns. Note that SPM does not calculate each step separately; the figure is for clarification only

comparisons. The top row of Fig. 16.2 shows the two conditions in two groups. The middle row shows the result of the simple subtraction analyses between the two conditions within each group. The middle row therefore represents the within-group brain activation maps of the difference between the two conditions. These two differential maps are now compared to each other to obtain the between-group differential brain activation map, which is depicted on the bottom row. It is important to realise that the statistical model *must* start with a within-group comparison. Thus it is not possible to obtain meaningful results when directly comparing a single condition between groups. For example, we cannot investigate the difference for the NISt condition between the DID and control subjects.

16.3.1.1 Within-Identity State Trauma-Related Memory Script Effects

Trauma-related MS effects within both TIS and NIS are given in Table 16.1. TIS showed significant regionally specific increases and decreases in cerebral blood flow, when processing the trauma-related MS as compared to the neutral MS, between the DID and both the high- and low-fantasy-prone control groups. These findings are depicted in Fig. 16.3.

16.3.1.2 Between-Identity State Trauma-Related Memory Script Effects

Trauma-related MS effects between NIS and TIS are given in Table 16.2. Different rCBF patterns were found for NIS and TIS, when processing the trauma-related MS, between the DID and both the high- and low-fantasy-prone control groups. These differential rCBF patterns are shown in Fig. 16.4.

Table 16.1 Memory script effects within dissociative identity state

			Within group	Between group	
	L/R	Brain region[a] = a priori	DID only	DID-CH	DID-CL
TISt-TISn					
Cortical areas	L	Insula[a]	+	+[c]	+[c]
	L	Parietal operculum[a]	+	–	+[c]
	R	Postcentral gyrus	–	–	+
	R	I. temporal gyrus	–	+	–
	L	S. temporal gyrus	–	–	+
Subcortical areas	L	Amygdala[a]	+	+[c]	–
	L	Caudate nucleus (dorsal part)[a]	–	–	+[c]
	R	Caudate nucleus (dorsal part)[a]	+	+[c]	+[c]
	L	Caudate nucleus (tail)[a]	+	+[c]	–
	R	Caudate nucleus (tail)	+	–	–
	L	Putamen	–	+	+
Cerebellum	L	Cerebellar tonsil (nodule)[a]	+	–	–

(continued)

Table 16.1 (continued)

			Within group	Between group	
	L/R	Brain region[a] = a priori	DID only	DID-CH	DID-CL
TISn-TISt					
Cortical areas	R	Angular gyrus	−	−	+
	L	Anterior cingulate gyrus	+	−	−
	L	Posterior cingulate gyrus[a]	+	−	−
	R	Cingulate sulcus[a,c]	+	−	+[b]
	L	Cuneus[a]	+	+[b]	−
	R	Cuneus	+	−	−
	R	I. frontal gyrus	+	−	−
	R	Fusiform gyrus[a]	+	−	+
	L	Lingual gyrus	−	−	+
	R	Lingual gyrus	−	−	+
	L	S. occipital gyrus/angular gyrus[a]	+	−	+
	R	S. occipital gyrus[a]	+	−	−
	R	S. occipital sulcus/cuneus[a]	+	−	−
	R	Occipitotemporal sulcus[a]	+	+	+[b]
	L	Parahippocampal gyrus	−	−	+
	L	Intraparietal sulcus[a]	+	−	−
	R	Intraparietal sulcus[a]	+	+[b]	+[b]
	L	Rostral I. parietal lobule[a,d]	+	−	−
	R	S. parietal lobule/precuneus[a]	+	−	+[b]
	L	Precentral sulcus[a]	+	−	−
	L	Precuneus	+	+	+
	R	(Pre-)cuneus/parieto-occipital sulcus	+	−	−
	R	M. temporal gyrus[a]	+	+	−
Cerebellum	L	Cerebellum (anterior lobe)	+	−	+

Overview of brain areas with statistically significant cerebral blood flow changes when comparing DID patients to high or low DID simulating controls (CH and CL, respectively) for the trauma-related memory script effects within dissociative identity states

DID dissociative identity disorder patient group, *CH* high-fantasy-prone DID simulating control group, *CL* low-fantasy-prone DID simulating control group, *L/R* left/right, *TISn* trauma-related identity state exposed to the neutral memory script, *TISt* trauma-related identity state exposed to the trauma-related memory script, *I* inferior, *M* middle, *S* superior

[a]A priori brain areas based on Reinders et al. (2006)

[b]Region of interest multiple comparison correction ($p < 0.05$)

[c]Callosomarginal sulcus (SCM) (= cingulate sulcus)

[d]Supramarginal gyrus (rostral I. parietal lobule)

16.4 Discussion

The present study was performed to examine whether earlier reported results (Reinders et al. 2003, 2006) for DID hold after correcting for potential iatrogenic effects. To this end, we tested whether these findings can be simulated by motivated role enactment and/or is facilitated by a high level of fantasy proneness (Merckelbach

et al. 2001) by reinvestigating the patient population from Reinders et al. (2006). Neither high- nor low-fantasy-prone healthy controls, instructed and motivated to simulate two different types of dissociative identity states in DID (i.e. NIS and TIS), mimicked previously observed psychophysiological and neural reactions that are associated with these identity states in DID (Reinders et al. 2006), which is supportive of our first a priori hypothesis.

From results shown in Figs. 16.3 and 16.4, a first impression of the (dis)similarities between DID patients and controls can be obtained. Figures 16.3 and 16.4 show that most of the original DID rCBF patterns remain present when comparing them to the high- or low-fantasy-prone groups. This clearly demonstrates that neither high- nor low-fantasy-prone controls are able to reliably simulate the DID patients' rCBF patterns. As patients and controls were scanned in a highly similar experimental setting and because controls were highly motivated to simulate DID, the found commonalities in brain activation between patients and controls were expected. Despite this overlap in brain activation between patients and controls, important previously found psychophysiological

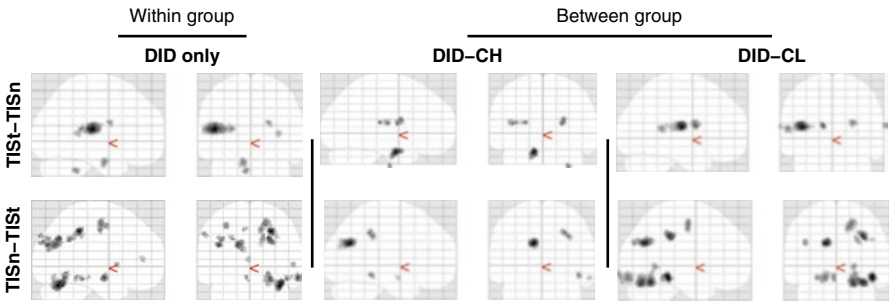

Fig. 16.3 'Glass brain' renderings showing differences in the processing of the trauma-related text (indicated with a small 't') and the neutral text (indicated with a small 'n') within the trauma-related identity state (*TIS*). Differences in regional cerebral blood flow patterns for the dissociative identity disorder (*DID*) group (*left*) and the comparison of this group to the high- (*middle*) and low (*right*)-fantasy-prone DID simulating controls (CH and CL, respectively) are depicted. See Table 16.1 for the specific areas

Table 16.2 Memory script effects between dissociative identity states

			Within group	Between group	
	L/R	Brain region[a] = a priori	DID only	DID-CH	DID-CL
TISt-NISt					
Cortical areas	L	Insula	+	–	+[b]
	R	Insula	–	–	+
	L	Orbitofrontal cortex	–	+	–
	R	Parietal operculum	–	–	+
	R	Postcentral gyrus[a]	+	+	+[b]
	R	Precentral gyrus	–	–	+
	L	S. temporal gyrus	–	–	+

(continued)

Table 16.2 (continued)

			Within group	Between group	
	L/R	Brain region[a] = a priori	DID only	DID-CH	DID-CL
Subcortical areas	L	Amygdala[a]	+	+[c]	–
	R	Caudate nucleus (caudal part)[a]	+	+[c]	–
	L	Caudate nucleus (dorsal part)[a]	+	+[c]	+[b]
	R	Caudate nucleus (dorsal part)[a]	+	+[c]	+[b]
	L	Caudate nucleus (tail)[a]	+	–	–
	L	Putamen[a]	–	+[c]	–
	R	Putamen	–	–	+
Cerebellum	L	Cerebellar tonsil (nodule)[a]	+	+	–
	L	Cerebellum (lateral part)[a]	+	–	–
NISt-TISt					
Cortical areas	R	Angular gyrus	+[b]	+	+
	X	Anterior cingulate gyrus[a]	+[b]	–	–
	L	Cingulate gyrus[a]	+[b]	–	–
	R	Cingulate gyrus[a]	+[b]	+[c]	–
	L	Cingulate sulcus/cingulate gyrus[a]	+[b]	–	–
	R	Cingulate sulcus[d]	+[b]	–	+
	L	Posterior cingulate gyrus	–	+	–
	L	Cuneus[a]	+[b]	+[c]	+[c]
	R	Cuneus[a]	+[b]	+[c]	–
	X	Cuneus	+[b]	–	–
	L	I. frontal gyrus	–	–	+
	R	S. frontal gyrus[a]	+[b]	–	–
	R	S./medial Frontal gyrus[a]	+[b]	–	–
	L	S. frontal sulcus[a]	+[b]	–	+
	R	S. frontal sulcus[a]	+[b]	+[c]	+[c]
	L	Fusiform gyrus	–	–	+
	R	Fusiform gyrus[a]	+[b]	–	+[b]
	L	Lingual gyrus	–	–	+[b]
	R	Lingual gyrus	+[b]	–	+
	L	M. occipital gyrus	+[b]	–	–
	L	S. occipital gyrus/angular gyrus[a]	+[b]	+[b]	+[b]
	R	S. occipital gyrus	+[b]	–	–
	R	S. occipital sulcus/cuneus	+[b]	–	–
	R	Occipitotemporal sulcus[a]	+[b]	+[c]	+[b]
	L	Parahippocampal gyrus[a]	+[b]	+	+[b]
	R	Parahippocampal gyrus[a]	+[b]	+[c]	+[b]
	L	Intraparietal sulcus[a]	+[b]	+[c]	–
	R	Intraparietal sulcus[a]	+[b]	+[c]	+
	L	Rostral I. parietal lobule[a,e]	+[b]	–	–
	R	S. parietal lobule/precuneus[a]	+[b]	+[c]	+[b]
	L	Precuneus	+[b]	+	+
	R	Precuneus	–	+	–
	X	Rectal gyrus	–	–	+[b]
	L	M. temporal gyrus	–	–	+[b]
	R	M. temporal gyrus[a]	+[b]	+	+[b]

Table 16.2 (continued)

			Within group	Between group	
	L/R	Brain region[a] = a priori	DID only	DID-CH	DID-CL
Subcortical areas	L	Caudatus nucleus (head)[a]	+[b]	–	–
	R	Globus pallidus[a]	+[b]	–	+[b]
Cerebellum	L	Cerebellum (anterior lobe)	+[b]	–	+[b]

Overview of brain areas with statistically significant cerebral blood flow changes when comparing DID patients to high or low DID simulating controls (CH and CL, respectively) for the trauma-related memory script effects between dissociative identity states

DID dissociative identity disorder patient group, *CH* high-fantasy-prone DID simulating control group, *CL* low-fantasy-prone DID simulating control group, *L/R* left/right, *NISt* neutral identity state exposed to the trauma-related memory script, *TISt* trauma-related identity state exposed to the trauma-related memory script, *I* inferior, *M* middle, *S* superior

[a]A priori brain areas based on Reinders et al. (2006)

[b]Whole-brain multiple comparison correction ($p < 0.05$)

[c]Region of interest multiple comparison correction ($p < 0.05$)

[d]Callosomarginal sulcus (SCM) (= cingulate sulcus)

[e]Supramarginal gyrus (rostral I. parietal lobule)

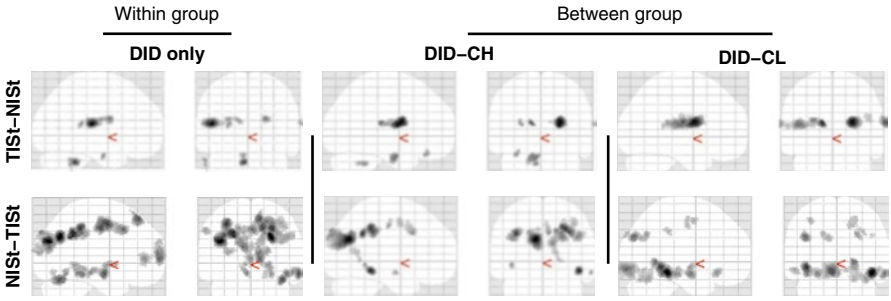

Fig. 16.4 'Glass brain' renderings showing differences in the processing of the trauma-related text (indicated with a small 't') between the trauma-related identity state (TIS) and the neutral identity state (NIS). Differences in regional cerebral blood flow patterns for the dissociative identity disorder (*DID*) group (*left*) and the comparison of this group to the high- (*middle*) and low (*right*)-fantasy-prone DID simulating controls (CH and CL, respectively) are depicted. See Table 16.2 for the specific areas

and neurobiological differences between NIS and TIS in DID patients were upheld when controlling for fantasy proneness, suggestion, and instructed and motivated role-playing, which is supportive of our first a priori hypothesis. It should be noted that, in addition to not having DID, the control group was non-traumatised as measured with the TEC. Therefore, it could be argued that both groups essentially did not complete the same task, i.e. one group was thinking about a traumatic event and one was thinking about a painful experience, and

therefore it might be of less work for the controls than the experimental group. This also could lead to the argument that it is trauma itself that caused the results instead of dissociation, i.e. the results do not indicate compartmentalised autobiographical memory retrieval but instead differential emotional reactivity. However, as the sociocognitive model (Spanos 1994) assumes that DID can easily be simulated, we feel that the current study provides important information to the aetiology discussion concerning DID. Nevertheless, we do recommend that future research include a traumatised group without dissociation, for example, PTSD, and/or the inclusion of additional control condition for patients consisting of a non-autobiographical 'trauma' (i.e. negative event).

The activated areas seem to be subdivided in two distinct neural networks, where the NIS activates areas in the cerebral cortex, while the TIS mainly activates subcortical areas (e.g. see Table 16.2 and Fig. 16.4). The tables show a detailed listing of all the brain areas involved. Brain areas that disappear after comparison to a control group are brain areas non-specific to DID, i.e. these areas share commonalities between patients and controls. Other brain areas are specific to DID.

Our findings support the cortico-limbic inhibition model of trauma-related dissociative disorders (Lanius et al. 2010; Nijenhuis et al. 2002). Results of both the NISt-TISt comparison and the main effect of NIS show significant overlap with the activated network of brain regions during emotional memory suppression of unwanted memories in mentally healthy individuals (Anderson et al. 2004), for example, in frontal areas (BA 4/6/8/10/47), cingulate cortex (BA 32), and intraparietal sulcus (BA 7/40). Anderson et al. (2004) did not find all of these brain areas. There is significant overlap between our study and their study, but in our patient population more brain areas were involved in the modulation of access to trauma-related memory. This might be an indication that, when DID patients are functioning as NIS, different cortical processes are involved that modulate conscious and subconscious perception of trauma-related information. These areas, e.g. (pre-) cuneus (BA 7/39, 18/19), fusiform gyrus (BA 18/19/37), lingual gyrus (BA 18), occipital gyrus (BA 18/19/37), and the parahippocampal gyrus (BA 35/36), are located in the posterior association areas (PAA), and there are indications that these areas are involved in multimodal (Driver and Vuilleumier 2001) somatosensory integration (Lanius et al. 2004; Simeon et al. 2000) of information, especially in relation to attention and perceptual awareness. Hyperactivation of cortical multimodal association areas for NIS in DID when listening to personal trauma scripts constituted our third a priori hypothesis. We thus propose that for emotional memory suppression, or NIS' mental avoidance (Nijenhuis et al. 2002), of unwanted memories in DID the PAA fulfils a pivotal role.

There are notable similarities in the patterns of brain activation for DID patients (see Table 16.1) and mentally healthy individuals unsuppressed memory retrieval (Anderson et al. 2004). Both groups have increased activation of the insula (BA 13) and parietal operculum (BA 40/43). We did not find the hippocampus to play a role in memory retrieval in DID patients, despite the fact that this area has been indicated in memory processing in mentally healthy individuals. Instead we found that the caudate nucleus was activated when DID patients listened to the trauma-memory

scripts as TIS. Acute stress can be associated with a shift from hippocampal involvement to caudate nucleus involvement (Schwabe et al. 2008; White 2009). Thus, acute stress is linked with a caudate nucleus-dependent stimulus response at the expense of hippocampal-dependent spatial learning and memory. According to the theory of structural dissociation (van der Hart et al. 2006; Nijenhuis and Den Boer 2009), listening to a description of a personal traumatic memory in an experimental setting constitutes a consciously experienced acute stressor for TIS, because dissociative identity state DID patients do not manage to mentally avoid the relevant memory. An alternative explanation for increased caudate and amygdala activation in DID patients as compared to controls is based on the finding that the dorsal striatum (caudate, putamen, and pallidum) correlates negatively with trait dissociation during stress-induced analgesia (Mickleborough et al. 2011). Thus, we could speculate that the dorsal striatum is involved in dissociation (Mickleborough et al. 2011) and switching between identity states (Tsai et al. 1999) as well as maintaining identity states in DID (Reinders et al. 2006, 2012). In a single subject functional MRI study, Savoy et al. (2012) reported the involvement of the ventral striatum (i.e. the accumbens area) during identity state switching. Furthermore, findings of studies in patients with focal lesions in the dorsal striatum indicate the involvement of this structure in task switching and inhibition of irrelevant information (Yehene et al. 2005, 2008). Taking both the switching and memory hypotheses together, in DID the dorsal striatum is involved in the regulation of memory access by modulating the presence of neutral or trauma-related identity states. This finding is consistent with the TIS as the type of alternate identity that recognises, relates, and emotionally responds to the traumatic past as personal autobiographical information (van der Hart et al. 2006). We could speculate that the caudate plays an important role in DID patients' ability to recognise trauma-related, emotional information as autobiographical. These findings for TIS are supportive of our second a priori hypothesis.

To date, experimental research of inter-identity amnesia in DID has produced mixed results. One study (Elzinga et al. 2003) demonstrated evidence for inter-identity amnesia, which is in line with the current findings. Other studies (Huntjens et al. 2003, 2005a, b, 2006, 2007) found inter-identity transfer of newly learned non-autobiographical stimuli, even though the 'amnestic' identity reported subjective amnesia for these stimuli. Several principles might explain the inconsistent findings: (i) Inter-identity amnesia may only exist for stimuli that have personal relevance for the 'amnestic' identity. In the cited studies, it was not assessed if or to what degree the applied stimuli had autobiographical meaning for the tested 'amnestic' and 'mnestic' dissociative identities. Our study included traumatic memories that were subjectively autobiographical for TIS but not for NIS and found that NIS and TIS had different subjective, psychophysiological, and neural reactions to a description of the involved traumatic memories. We also found that as an NIS, DID patients did not relate these traumatic memories to themselves (Reinders et al. 2003). These results indicate the importance of using autobiographical information when investigating inter-identity amnesia in DID. (ii) Inter-identity amnesia may predominantly exist between different types of dissociative identities, particularly between neural and trauma-related identity states. This has been clinically observed,

theoretically proposed (van der Hart et al. 2006) and is in line with our results. Unfortunately, in most studies it was not assessed what types of dissociative identities participated, e.g. NIS or TIS. Therefore, we strongly recommend that in future research in DID the types of dissociative identities are verified and reported and that test material is used that is subjectively autobiographical for one dissociative identity, but not for another.

The sociocognitive view of DID entails the idea that this disorder can be easily and readily created in motivated suggestible individuals and that few suggestions would suffice to generate the symptoms of DID (Spanos 1996). However, this is not supported by our study. Still, one might argue that the short practice period of DID simulation is insufficient to simulate the psychobiological profiles of NIS and TIS. However, even if years of practice could generate these profiles, our findings show that our controls do not activate many brain areas found in DID patients and it seems unlikely that this will change with practice.

For the first time, it is shown using brain imaging that neither high- nor low-fantasy-prone healthy women, who enacted two different types of dissociative identity states, were able to substantially simulate these identity states in psychobiological terms. We feel that our study provides an important contribution to the aetiology discussion for DID as the results do not support the idea of an iatrogenic origin for DID.

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OCD: Serotonergic Mechanisms

17

Jennifer I. Lissemore, Marco Leyton, Paul Gravel, Debbie Sookman, Thomas E. Nordahl, and Chawki Benkelfat

Contents

J.I. Lissemore, BSc
Department of Psychiatry, McGill University,
1033 Pine Ave West, Montreal, QC H3A 1A1, Canada

M. Leyton, PhD • P. Gravel, MSc • C. Benkelfat, MD, DERBH (✉)
Department of Psychiatry, McGill University,
1033 Pine Ave West, Montreal, QC H3A 1A1, Canada

Department of Neurology and Neurosurgery, McConnell Brain Imaging Center,
Montreal Neurological Institute, McGill University, Montreal, QC, Canada
e-mail: chawki.benkelfat@mcgill.ca

D. Sookman, PhD
Department of Psychiatry, McGill University,
1033 Pine Ave West, Montreal, QC, H3A 1A1, Canada

Department of Psychology, Obsessive-Compulsive Disorder Clinic,
McGill University Health Center, Montreal, QC, Canada

T.E. Nordahl, MD, PhD
Department of Psychiatry and Behavioral Sciences,
University of California at Davis School
of Medicine, UC Davis Medical Center, 2230 Stockton Boulevard,
Sacramento, CA 95817, USA

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_17, © Springer-Verlag Berlin Heidelberg 2014

Abstract

Obsessive-compulsive disorder (OCD) is typically treated with selective serotonin-reuptake inhibitors (SSRIs), cognitive behavioral therapy (CBT), or both. The neurobiological effects of these treatments that are associated with symptom improvement, however, remain unclear. The neurotransmitter serotonin has been implicated in OCD pathology, including in brain circuits contained in cortico-striato-thalamic loops; yet, there is no consensus in the literature over a particular underlying serotonergic mechanism in OCD.

Recent studies have used the α-[^{11}C]methyl-L-tryptophan tracer coupled with positron emission tomography (PET) to estimate brain regional serotonin synthesis capacity in OCD patients in vivo. Regions that exhibited elevated serotonin synthesis in symptomatic OCD, relative to healthy controls, demonstrated a paradoxical and further increase during *treatment* with CBT or SSRI, parallel to symptomatic improvement. This suggests that serotonin *engagement* may be an attempt at inhibiting symptoms at baseline, albeit unsuccessfully, and that "braking" or "resistance" might gradually become more effective, and eventually successful, with the help of adapted behavioral interventions and/or SSRIs.

17.1 Overview

Characterized by frequent and persistent obsessive thoughts and/or compulsive behaviours, obsessive-compulsive disorder (OCD) can cause significant distress and disability in an individual's life. OCD is prevalent, affecting upwards of 3.5 % of the general population according to DSM-IV criteria (Fineberg et al. 2012). Yet, OCD currently lacks a universally effective treatment avenue, leading many cases to be misleadingly labelled "treatment refractory". This term falsely implies that nonresponders to available treatments are inherently less treatable, rather than communicating that a reliable treatment may not yet be available to these patients. Currently, drug therapy with selective serotonin reuptake inhibitors (SSRIs) and specialty cognitive behaviour therapy (CBT) have demonstrated efficacy in the treatment of OCD. However, roughly only 25 % of patients show clinically significant symptom reduction or remission to one or both of these treatments, 35 % of patients show partial response and 40 % do not show significant improvement in symptom severity, depending on a number of factors including the definition of a satisfactory response (Pallanti et al. 2002; Rasmussen and Eisen 2002). Research that aims to increase our understanding of the pathophysiology underlying OCD symptom presentations is crucial to inform development and refinement of effective treatment strategies.

OCD is widely recognized to include a variety of symptom profiles, adding to the complexity of the disorder (McKay et al. 2004; Sookman et al. 2005). Types of obsessions include intrusive thoughts, mental images, impulses and fears, and types of compulsions include mental rituals such as counting and behavioural rituals such as checking or washing. This diversity has led many researchers to investigate the categorization of OCD subtypes. For example, early-onset and late-onset subtypes

have been proposed (Geller et al. 1998), as have subtypes based on the presence or absence of various comorbid disorders, including Tourette's syndrome (Leckman et al. 2000), depression and other anxiety disorders (Nestadt et al. 2003). Each subtype may be due to different underlying neurobiological mechanisms, thus emphasizing the clinical importance of addressing the heterogeneous nature of this disorder.

17.1.1 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. Intriguingly, most patients with OCD are aware of the irrationality of their own thoughts and behaviours, yet their symptoms persist to a maladaptive extent. A central inhibition system designed to mediate these symptoms may come into play, but the patient's perceived failure to regain control perseveres, 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 behavioural and drug therapies strengthen these inhibitory mechanisms with the support needed to successfully mediate OCD symptoms. Our understanding of the pathways and neurotransmitters involved in this hypothesized neural system, however, is primitive.

17.2 Neurobiology

17.2.1 Brain Circuits

Over the past few decades, multiple studies have provided evidence of abnormalities in the cortico-striato-thalamo-cortical (CSTC) circuit in OCD. Brain regions involved in this circuit that have been hypothesized to play a role in OCD include the orbitofrontal cortex (OFC), the caudate, and the anterior cingulate gyrus (ACG) (Aouizerate et al. 2004; Menzies et al. 2008). PET imaging studies have identified, to variable degrees, evidence of increased brain activity, as measured by glucose metabolic rates, in each of these brain regions in OCD patients (Baxter et al. 1987; Brody et al. 1998; Nordahl et al. 1989). Accordingly, both SSRI and CBT treatments have been shown to significantly reduce glucose metabolism or cerebral blood flow in the caudate and OFC of OCD patients that respond to treatment (Baxter et al. 1992; Benkelfat et al. 1990). Although hypoactivation of these regions in OCD has also been found (Busatto et al. 2000; Rubin et al. 1992), the current literature largely suggests that dysfunction within these circuits helps drive OCD symptoms. Antidepressants and CBT help diminish this dysfunction, possibly by supporting neurobiological mechanisms already mediating these circuits. However, our understanding of the neurobiological processes contributing to dysfunction within these circuits, as well as those helping to control this dysfunction, is still in its nascency.

17.2.2 Neurochemistry

Although a wide variety of neurotransmitters have been implicated in OCD, including glutamate and oxytocin, this chapter will focus on the widely implicated neurotransmitter serotonin. The role of the neurotransmitter dopamine in OCD will also be briefly examined, given its intimate relationship with serotonin. Whereas the study of serotonergic and dopaminergic mechanisms offers crucial insight into OCD neuropathology, the likely involvement of additional neurotransmitter systems should not be discounted.

17.2.2.1 Serotonin

The neurotransmitter serotonin, also known as 5-hydroxytryptamine (5-HT), contributes to communication within the CSTC circuit, and neurons of the serotonergic raphe nuclei project to each of these regions (Graybiel and Ragsdale 1983; Jacobs 1994). The serotonergic system has received particular focus in the study of OCD largely based upon the relative effectiveness of SSRIs (fluvoxamine, sertraline, fluoxetine, paroxetine, and citalopram) and the tricyclic antidepressant clomipramine in reducing obsessive-compulsive (OC) symptoms. These antidepressants inhibit serotonin reuptake by blocking the binding of 5-HT to the serotonin transporter (SERT) and have been shown to successfully treat some cases of OCD (Jackson et al. 1994; Kronig et al. 1999; McDonough and Kennedy 2002; Montgomery et al. 2001). Furthermore, 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), suggesting a specific serotonergic mechanism involved in OCD, possibly within CSTC circuits. The link between the clinical benefit of SSRIs and abnormalities underlying OCD symptoms is, however, indirect and does not causally implicate serotonergic mechanisms in OCD pathology. Whether maladaptive obsessions and compulsions are elicited by a central serotonergic dysfunction or whether 5-HT plays a role in mediating other underlying dysfunctions in OCD has yet to be established. Thus, the clinical success of the SSRIs merits further exploration into how they influence obsessions and compulsions. The somewhat similar efficacy of CBT raises the possibility of an overlapping effect on the serotonergic system, but there is a paucity of studies examining the influence of CBT on OCD neurobiology. Thus, although SSRIs and CBT are the treatments of choice for OCD, the exact means by which 5-HT plays a role in their ability to alleviate OCD symptoms remain unknown.

To address this, early studies investigated peripheral measures of 5-HT and 5-HT metabolites, such as 5-hydroxyindoleacetic acid (5-HIAA), in the cerebral spinal fluid (CSF) of OCD patients. In 1980, Thorén et al. reported that after 3 weeks of clomipramine treatment, a significant improvement in symptoms correlated strongly with a greater decrease in CSF 5-HIAA concentrations. Additionally, patients who responded to treatment showed significantly higher pretreatment CSF 5-HIAA levels than nonresponders and healthy controls. These findings provided direct evidence implicating 5-HT in OCD. However, later studies were unable to reliably identify abnormal baseline measures of 5-HIAA and peripheral 5-HT in OCD (Insel

et al. 1985; Leckman et al. 1995). Further indication of a serotonergic dysfunction in OCD came from pharmacological challenge studies that found that the non-specific 5-HT receptor agonist meta-chlorophenylpiperazine (mCPP) and the 5-HT_{1D} receptor-specific agonist sumatriptan could worsen OC symptoms (Gross-Isseroff et al. 2004; Zohar et al. 1987). Additionally, prior treatment with clomipramine was reported to eliminate mCPP's exacerbation of symptoms (Zohar et al. 1988). These findings, however, have also not been reliably replicated in the literature (Goodman et al. 1995; Ho Pian et al. 1998; Stein et al. 1999). Although 5-HT is ubiquitous throughout the brain, 5-HT elicits a complex array of excitatory and inhibitory influences, and the role of serotonin in OCD is likely to involve specific serotonergic mechanisms 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 elucidate any pathway-specific serotonergic mechanisms related to the successful treatment of OC symptoms. And further, Berney et al. (2006), in a 5-HT depletion study, found evidence that risk for relapse of OCD symptoms most likely does not depend solely on short-term changes in presynaptic 5-HT availability.

Since Thorén's promising findings in 1980, the study of OCD has expanded to examine various aspects of the disorder, and the techniques for studying serotonergic mechanisms in the brain have improved significantly. New neuroimaging technologies allow 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. Despite some progress, no clear explanation of serotonin's role in OCD has emerged.

PET and SPECT imaging techniques, among others, are useful tools for investigating components of the serotonergic system, such as SERT and 5-HT receptor availability in vivo, in specific parts of patients' brains. In accordance with Thorén et al.'s (1980) original finding, Zitterl et al. (2008) indicated that clomipramine treatment decreased SERT availability in the thalamus and hypothalamus of OCD patients, and higher SERT availability before treatment was associated with a better treatment response. However, PET and SPECT studies imaging SERT availability in the brain have produced variable results. SERT binding has been reported to be increased (Pogarell et al. 2003) or normal (Simpson et al. 2003) in OCD patients compared to healthy controls, and a slightly larger cohort of studies have found SERT binding to be decreased in brain regions previously implicated in OCD (Hesse et al. 2005; Reimold et al. 2007; Stengler-Wenzke et al. 2004; Zitterl et al. 2006). For instance, Matsumoto et al. (2010) found reduced SERT binding in the insular cortex, and putatively the OFC, using PET with [^{11}C]DASB, a tracer that is more specific to SERT than those previously used tracers such as [^{11}C]McN 5652 in PET (Simpson et al. 2003) and [^{123}I]β-CIT in SPECT (Hesse et al. 2005; Pogarell et al. 2003; Stengler-Wenzke et al. 2004; Zitterl et al. 2006). The interpretation of many of these findings, however, is restricted by the inclusion of heterogeneous, non-drug-naïve samples of OCD patients. A recent study by Hesse et al. (2011) investigated a group of drug-naïve patients using the [^{11}C]DASB ligand, taking age of onset and a variety of other factors into account. SERT binding was reduced only in patients with late-onset OCD in limbic areas, including the striatum,

hippocampus and amygdala. More studies that consider these important heterogeneities between patients are needed to help clarify the inconsistent findings to date.

Serotonin receptor distribution has also been investigated using PET and SPECT imaging, with similarly conflicting results. One study showed reduced 5-HT_{2A} postsynaptic receptor availability in OCD patients compared to healthy controls using the [^{11}C]MDL100907 radioligand, and these reductions were associated with an increase in symptom severity (Perani et al. 2008). Yet another study investigating the same receptor found no such significant differences between patients and controls (Simpson et al. 2011). Additionally, animal models of compulsive behaviour have implicated the 5-HT_{2C} receptor system in compulsion-like rituals in rodents. Although abnormalities in certain 5-HT receptors have been suggested in OCD, the precise mechanisms underlying these potential abnormalities are unclear.

17.2.2.2 Dopamine

Despite the abundance of literature focusing exclusively on the role of serotonin in OCD, neurotransmitter systems rarely act in isolation. In particular, one other monoamine neurotransmitter, dopamine (DA), is also believed to play a role in OC symptoms via CSTC circuits, likely in conjunction with 5-HT (Goodman et al. 1992; Goodman et al. 1990a). Although inconsistencies also exist in the DA literature, current findings suggest that DA neurotransmission may be overactive in the basal ganglia of OCD patients (Denys et al. 2004a). For example, some PET and SPECT studies have found abnormally high DA transporter binding ratios in the basal ganglia (Kim et al. 2003; van der Wee et al. 2004) and abnormally low dopamine receptor binding in the caudate (Denys et al. 2004b), suggesting that in these areas there is an overall elevated level of DA in the synapse of OCD patients. 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 relatively 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). This suggests that DA may act synergistically with 5-HT, consequently affecting the aetiology and/or treatment of OCD. However, the exact mechanism(s) by which this conjunction of effects is made *operative* is not known, motivating further study.

17.3 Dimensions vs Category

Whereas studies associating dysfunctional circuits and neurotransmitter systems with a diagnosis of OCD offer some direction, the complex array of symptom profiles requires that the study of OCD be further broken down. Given current inconsistencies in the literature, it is likely that some "core" symptoms may be more common between OCD patients, whereas others may be specific to

different presentations of OCD. As such, our understanding of OCD aetiology may benefit from the disorder's decomposition into a broad array of OCD dimensions. Each OCD subtype likely comprises a complex subset of dimensions, such as impaired inhibition, maladaptive perseveration, dysfunctional habit formation, and rigid monitoring and control. 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 OFC and striatum have been found in OCD, the relationship between activity in these areas and OCD pathology 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 forms, interpretations of findings that relate specific dimensions to specific neurobiological mechanisms should be made with caution. Still, this approach can be useful for elucidating the complex pathways participating in OCD symptomatology that have thus far led us to the plethora of inconsistent findings. A large body of functional neuroimaging studies examining the aetiology of various OCD dimensions has therefore been accumulating in recent years.

In particular, deficits in behavioural and cognitive flexibility, thought to involve the OFC, striatum, and serotonergic system, have been speculated in OCD, and a variety of studies have examined neuropathology in this dimension using reversal learning tasks (Ghahremani et al. 2010; Tsuchida et al. 2010). Given the rigidity of behaviours in some OCD subjects, those very patients may have difficulty shifting their responses or learned associations in changing contexts. For the most part, findings have indicated decreased OFC and striatal activity in OCD patients compared with controls during reversal learning (Chamberlain et al. 2008; Remijnse et al. 2006). Additionally, it was shown in animals models that 5-HT, but not DA, was crucial to the OFC's role in reversal learning, and that DA, but not 5-HT, was more relevant to the caudate's role in reversal learning (Clarke et al. 2011). Although it is unlikely that OCD consists solely of a reversal learning deficit, the study of this potential dimension has helped educate clinicians and researchers about the complexities of fronto-striatal, 5-HT, and DA mechanisms that might underlie some behavioural *dimension*(*s*) in OCD.

Multiple other dimensions have been studied in a similar manner (e.g. Flaisher-Grinberg et al. 2008), and help to parse out the specific processes underlying symptoms. Findings in OCD patients, such as 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), are only some illustrations of specific brain dysfunctions associated with particular OCD dimensions. To date, the nature of human brain imaging techniques used to document brain correlates during performance (e.g. fMRI) requires a lot of interpretation. It is thus hardly possible to conclude that those putative brain dysfunctions are primary events, etiologically related to the disorder examined and predating the emergence of core symptoms, or secondary events, occurring in the context of the performance.

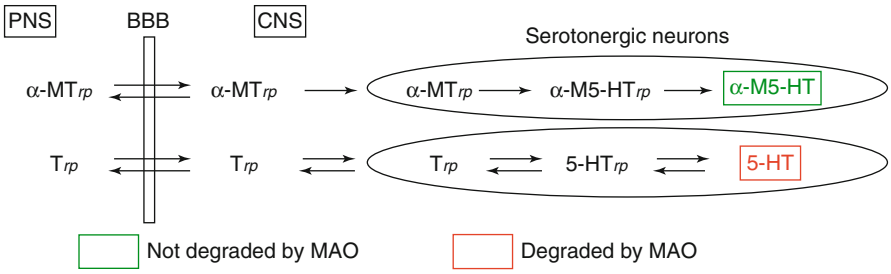

Fig. 17.1 A schematic of the similar metabolic pathways of the 5-HT precursor tryptophan and the analogous radioisotope α-[^{11}C]MTrp. *PNS* peripheral nervous system, *CNS* central nervous system, *BBB* blood-brain barrier, *α-[^{11}C]MTrp* α-[^{11}C]methyl-L-tryptophan, *Trp* tryptophan, *α-M5-HTrp* α-methyl-5-hydroxytryptophan, *α-M5-HT* α-methylserotonin, *5-HTrp* 5-hydroxytryptophan, *5-HT* serotonin, *MAO* monoamine oxidase

17.3.1 α-[^{11}C]MTrp

A relatively new and valuable PET tracer, α-[^{11}C]methyl-L-tryptophan (α-[^{11}C]MTrp), has been used in recent years to study regional serotonin synthesis in a variety of patient populations (Chugani et al. 1999; Chugani et al. 2001; Pfund et al. 2002). During serotonin synthesis, the 5-HT precursor tryptophan (Trp) is converted into 5-hydroxytryptophan (5-HTrp), which is then metabolized into 5-HT. It has been shown that levels of Trp correlate with levels of 5-HT (Cohen et al. 1995) and that increasing the level of Trp 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 accurately reflect rates of 5-HT synthesis (Chugani and Muzik 2000). An overview of the pathway of Trp in comparison to that of α-[^{11}C]MTrp is illustrated in Fig. 17.1. 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 BBB 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. This tracer has been utilized in a number of studies of different disorders. For instance, abnormally low K^* values have been reported in areas such as the temporal cortex and ACG in depression (Rosa-Neto et al. 2004), as well as in the medial frontal gyrus, ACG, temporal gyrus, and striatum of borderline personality disorder (Leyton et al. 2001) and the OFC and medial prefrontal cortex of suicide attempters (Leyton et al. 2006).

Table 17.1 The demographics of both OCD patients and healthy controls in a recent 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	15 M/6 F	15 M/6 F
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 Concentration, nmol/l	8.4 (3.7)	8.9 (3.8)

OCD obsessive-compulsive disorder, *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

17.3.2 Baseline Measurements of Serotonin Synthesis in OCD

A recent α-[^{11}C]MTrp study of OCD patients identified a pattern of effects that was opposite to that seen in the previously tested patient groups. Berney et al. (2011) compared regional K^* values of unmedicated OCD patients ($n=21$) with those of age- and gender-matched healthy controls ($n=21$). All patients were without current comorbid disorders and reported never having used the alleged SERT-inhibiting neurotoxic substances 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyamphetamine (MDA). Patients with a past history of depression secondary to OCD were included in this study, 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 included cortical areas such as the OFC and ACG and subcortical areas such as the caudate, based on previous implications of these regions in OCD pathology. 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. The larger subgroup of male patients also showed significantly higher K^* values in the caudate nucleus bilaterally. Furthermore, estimates of 5-HT synthesis in the temporal cortex and right caudate correlated positively with symptom severity (Table 17.1).

These findings suggest that OCD patients, as a group, relative to non-symptomatic healthy volunteers, may have abnormally 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 connote the failed attempt by the inhibitory system to regain control. This interpretation was deemed plausible and emphasized.

17.3.3 The Effects of Treatment on Serotonin Synthesis in OCD

Extending the findings of Berney et al. (2011), a recent unpublished study by our group has investigated the change in brain regional 5-HT synthesis rates after behavioural and drug therapy for OCD. By also using PET in combination with the α-[^{11}C] MTrp tracer, brain 5-HT synthesis was estimated before and after CBT or sertraline treatment. Participating patients were randomly assigned to 12 weeks of either biweekly CBT sessions ($n=6$) or daily doses of sertraline ($n=6$). CBT included cognitive therapy for symptom-related difficulties such as dysfunctional beliefs and tolerance of distress, and exposure and response prevention 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 daily dose received was 133 mg/day (SD = 52 mg/day). Both SPM8 and volume of interest analyses were performed, and Yale-Brown Obsessive Compulsive Scale (Y-BOCS), BDI, and Go/NoGo task scores were assessed prior to and following treatment. Although a total of 16 patients were recruited, the preliminary PET analyses presented here are limited to a subset of 12 patients. As such, the following results are preliminary, and the proposed interpretations, based upon the intriguing patterns that have emerged thus far, are *provocative and must be considered speculative*. Significant improvement in symptom severity was observed in both treatment modalities (see Fig. 17.2), with four patients in the sertraline group and five in the CBT group showing a minimum 30 % decrease in Y-BOCS scores, classifying them as responders to treatment (Table 17.2).

Interestingly, in both treatment modalities, there was a significant positive correlation between symptom improvement and K^* value change in the right striatum, right hippocampus, and cerebellum ($p<.05$). That is, both CBT and sertraline treatment appear to have increased α-[^{11}C]MTrp trapping in regions previously found to have abnormally high α-[^{11}C]MTrp trapping in unmedicated OCD patients (Berney et al. 2011). These findings suggest that a modulation of central serotonergic neurotransmission could contribute to further coping, thus providing the support needed to effectively control OC symptoms. The direction of change in K^* values suggested that the response seen here was associated with a further enhancement of 5-HT synthesis, in essence allowing any inhibitory influence to achieve full potential and act effectively as a brake against obsessions and compulsions. Additionally, tracer trapping (K^*) at baseline correlated positively with treatment response, independently of the nature of treatment. The higher the 5-HT synthesis in the pons before treatment, the more patients benefitted from either CBT or sertraline treatment (see Fig. 17.3). The ability of K^* values at baseline to predict response to treatment is consistent with the proposed braking system hypothesis.

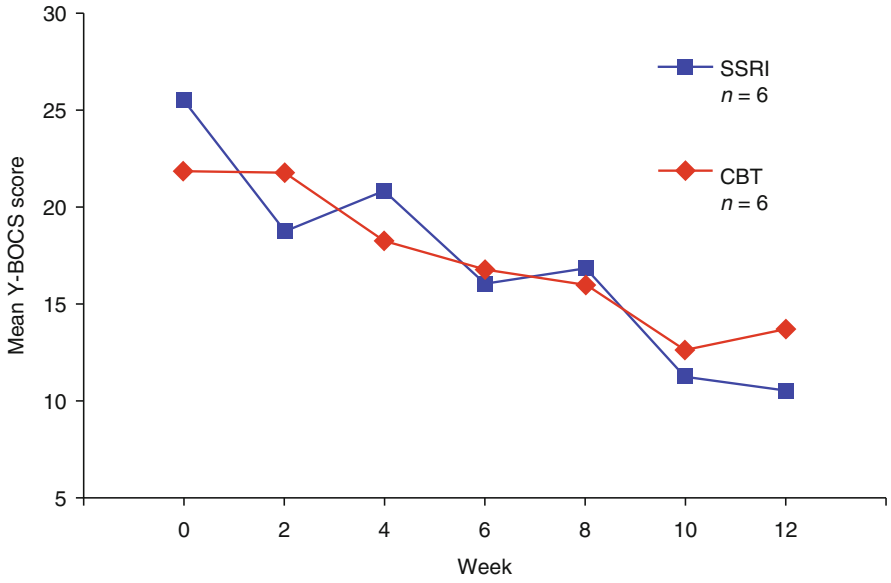

Fig. 17.2 Significant decreases in symptom severity were observed in OCD patients treated with 12 weeks of either cognitive behaviour therapy (*CBT*) or the selective serotonin reuptake inhibitor (*SSRI*) sertraline

Table 17.2 The demographics of OCD patients treated with either SSRI or CBT

Characteristics	**SSRI group (n = 6)**		**CBT group (n = 6)**	
Age in years				
Mean (SD)	33.5 (10.0)		37.0 (11.1)	
Range	18–45		26–53	
Gender	4 M/2 F		4 M/2 F	
Early-onset OCD	3		5	
Predominant compulsion				
Washing	3		1	
Checking	3		5	
History of mood disorder	2		2	
History of substance abuse	0		0	
Past SSRI treatment	1		0	
	Pre	**Post**	**Pre**	**Post**
Mean Y-BOCS score (SD)	25.5 (3.4)	15.7 (9.4)	21.8 (4.5)	14.6 (6.0)
Mean BDI score (SD)	16.8 (11.8)	8.8 (10.7)	9.7 (5.3)	6.4 (5.9)
Mean plasma free Trp Concentration, nmol/l	9.9 (2.1)	10.0 (2.1)	10.8 (2.8)	8.6 (1.3)

SSRI selective serotonin reuptake inhibitor, *CBT* cognitive behaviour therapy, *OCD* obsessive-compulsive disorder, *Y-BOCS* Yale-Brown Obsessive Compulsive Scale, *BDI* Beck Depression Inventory, *Trp* tryptophan

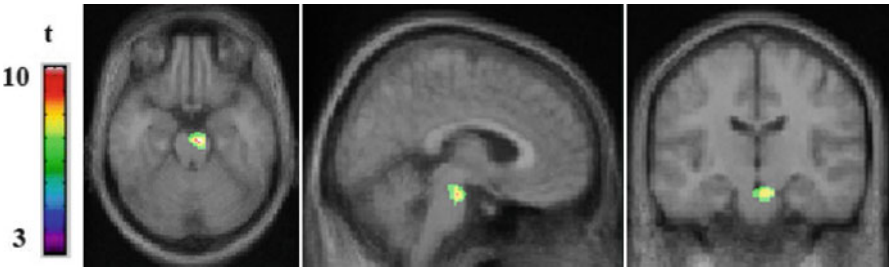

Fig. 17.3 Statistical parametric maps (SPM8) demonstrating a positive correlation between pre-treatment *K** values in the pons and symptom improvement after CBT or SSRI treatment

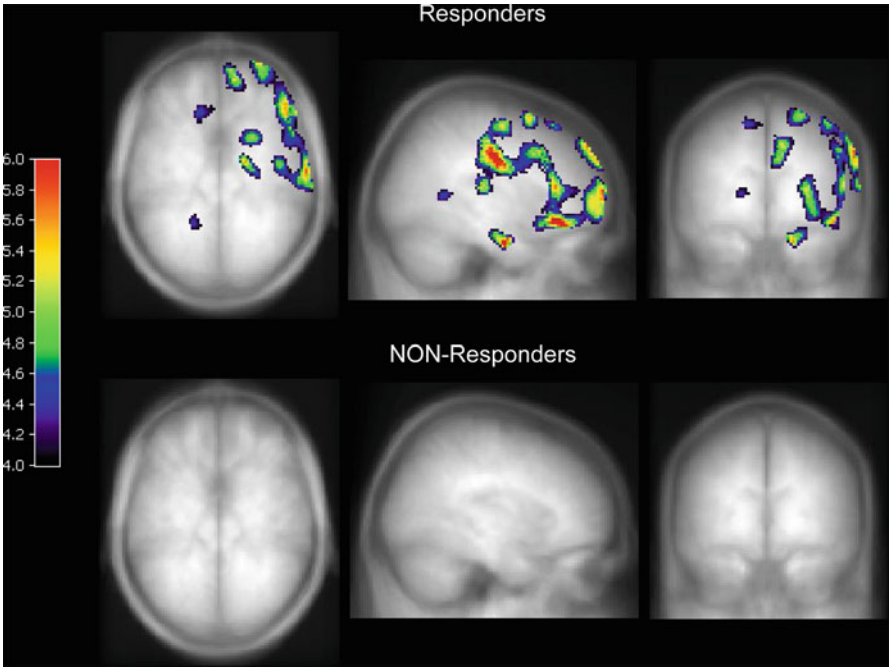

Fig. 17.4 Maximum intensity projection of the *t*-values (SPM8: $p<0.005$ and $k=50$ voxels) for the non-normalized *K** difference between the post- and pretreatment conditions. *TOP*: OCD patients that responded to either SSRI treatment or CBT (>30 % decrease in Y-BOCS scores). *Bottom*: OCD patients that did not respond to either treatment (no significant voxel)

Furthermore, responders showed substantial increases in unidirectional α-[^{11}C] MTrp trapping, suggesting that these changes were not merely a regression towards the mean, as shown in Fig. 17.4. These increases in regional 5-HT synthesis appear 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 "disappear" with a larger sample studied for a longer time. Those responders whose baseline *K**

values in the temporal cortex, frontal cortex, and cerebellum were below the average control K^* values in these regions of healthy controls from a study by Berney et al. (2011) showed increases in K^* values well above mean control K^* values. Similarly, responders whose K^* values in the striatum and hippocampus were already above mean control K^* values at baseline also showed a substantial increase in regional 5-HT synthesis. The marked increases in α-[^{11}C]MTrp trapping were not observed in nonresponders, thus suggesting that dysfunction in the nonresponders may well be differentially mediated.

17.4 Concluding Remarks

In spite of numerous findings, some of which were reviewed herein, one must recognize that those very many contributions to our understanding of OCD cannot fully elucidate the details within the multiple OCD aetiologies. Several aetiological pathways and mechanisms, responsible for the many diverse phenotypic expressions, are likely to be encountered. Additionally, longer-term CBT is required for many patients to optimize symptom reduction (offered following this study). Further research could usefully examine results following additional treatment duration.

One intriguing observation that can be made, though, is the link between memory and OCD. In particular, it has often been speculated that OCD patients with predominantly checking compulsions (referred to as "checkers") may have altered meta-memory (van den Hout and Kindt 2003). It has been reported that for individuals performing an experiment with disinformation distractors, those with reduced memory confidence exhibited a greater amount of checking (Alcolado and Radomsky 2011; Cuttler et al. 2013; Radomsky and Alcolado 2010). OCD checkers may exhibit dysfunctional memory self-monitoring; that is they have decreased confidence in their memory ability, yet they actually have higher standards for the reliability of their memory (Macdonald et al. 1997). Interestingly, then, OCD patients showed, at baseline, abnormal α-[^{11}C]MTrp trapping in the temporal cortex, which is a structure with important roles in memory formation and preservation (Bayley et al. 2005).

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 in a good portion of OCD patients. Accordingly, clinical improvement as a result of either behavioural or drug therapy may arise from a stimulation of serotonergic neurotransmission that ultimately allows this system to control symptoms effectively, thus producing a therapeutic response. As the system is progressively engaged, and further *overactivity* of the serotonergic system gains traction, effective inhibition may take place.

Acknowledgments Alexandre Berney, MD; Igor Sibon, MD, PhD; Amir Barsoum, MD; Gilbert Pinard, MD; Akio Nakai, MD, PhD; Mirko Diksic, PhD

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Part IV

Psychosis and Cognitive Disorders

Molecular Imaging in Schizophrenia Spectrum Disorders

18

Hans C. Klein, Janine Doorduin, and Bart N. van Berckel

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-IV 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).

H.C. Klein, MD, PhD
Program for Geriatric Psychiatry, University Center Psychiatry, Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, CC44, Hanzeplein 1, Groningen 9713 GZ, The Netherlands

J. Doorduin, PhD
Department of Nuclear Medicine and Molecular Imaging, University of Groningen, University Medical Center Groningen, Hanzeplein 1, Groningen 9713 GZ, The Netherlands

B.N. van Berckel (✉)
Department of Radiology and Nuclear Medicine, VU University Medical Center, De Boelelaan 1117, Amsterdam 1081 HV, The Netherlands
e-mail: b.berckel@vumc.nl

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_18, © Springer-Verlag Berlin Heidelberg 2014

The notion that the so-called typical antipsychotics bind to dopamine D_2 and D_3 receptors (Creese et al. 1976; Seeman et al. 1976) is one of the cornerstones of the dopamine hypothesis of schizophrenia (Davis et al. 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 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 receptor. In one of the first human studies with [^{11}C]-raclopride, Farde et al. (1986) described that an occupancy of 70–80 % of the D_2/D_3 receptor 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. 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 "atypical" antipsychotics still bind for a large proportion to dopamine D_2/D_3 receptors, which contributes significantly to their antipsychotic efficacy (Nord and Farde 2011). 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 paths 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.

18.1 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 lost 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 are currently designated as positive symptoms, such as delusions, hallucinations, and increased power of (bizarre) associations. 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 in females a second peak around 40 years of age occurs. The disease has features of a waxing and waning course, with psychoses at 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 newer transmitters like glutamate and its receptors like the N-methyl-D asparate receptor (NMDA) 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 still to be met by other drugs than clozapine.

18.2 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 by 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 hyper-availability of dopamine and/or receptor hypersensitivity as cause of (part) of the disease. But the abovementioned observations do not explain the temporary effects of D_2-blocking

and dopamine-releasing drugs versus the protracted course of psychosis and schizophrenia. In addition they do not explain why negative and cognitive symptoms do not respond (Davis et al. 1991).

In the past decade, 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 been granted a revival. Major genetic studies with GWAS (genome-wide association scans) show an association between MHC (major histocompatibility complex) antigen-presenting phenotypes and schizophrenia. But also an increased activity of resident immune cells (microglia) in the brain is possibly associated with schizophrenia.

18.3 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 indicated that there is indeed a small increase in D_2/D_3 receptors 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. 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.

The D_2/D_3receptor tracer [^{11}C]-raclopride and [^{123}I]-IBZM can also be used to probe dopamine release in vivo (Laruelle 1998). The key mechanism behind this is that 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 (Abi-Dargham et al. 1998; Breier et al. 1997; Laruelle et al. 1996).

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 much 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. Currently, there are no studies available that quantified glutamate receptors in vivo in patients with schizophrenia mainly due to lack of tracers for this purpose. Recently it has become 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 disease. Several human proof-of-concept studies with this tracer are already available, and the tracer kinetic model for its analysis has been validated. In addition, several new PET tracers for the N-methyl-D-aspartate (NMDA) receptors are currently being tested in humans. 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 temporal and frontal cortex of patients with chronic schizophrenia. Activated microglia can be quantified in vivo with the PET tracer [^{11}C]-(R)-PK11195. In two independent imaging 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). The presence of activated microglia in schizophrenia has recently been replicated using the new-generation PET tracer [^{11}C]-PBR28 (Kreisl et al. 2013).

Activated microglia may play an important role in the neurodegeneration associated with schizophrenia. Indeed, in a hypothetical model, an unknown trigger may cause activated microglia, which by itself can induce neurodegeneration which can cause more neuroinflammation and more microglia activation. As such, activated microglia is a new therapeutic target for the treatment of schizophrenia.

18.4 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 mechanism involved in schizophrenia hampers 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 different molecular mechanisms, such as dopaminergic and glutamatergic neurotransmission, in a single animal longitudinally and can be easily combined with behavioral analysis. Furthermore, many of the PET and SPECT tracers that are used in small animals can 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 in the brain.

There are numerous animal models of schizophrenia in which mice or rats display schizophrenic-like behavior. In this paragraph the models described in literature are attributed to drug-induced, neurodevelopmental, 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, injection of these antagonists in rodents, both acute and chronic, results 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 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).

Rat pups that were treated with the NMDA antagonist CGP40116 on a total of 8 days up until postnatal day 21 show 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 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 was found to have effect 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 caesarean 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 D_1-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 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 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.

The abovementioned studies are only a selection of the studies performed in animal models of schizophrenia. They are examples to show the work that has been done on dopamine and glutamate receptors using radiolabeled molecules. In the majority of the studies in the animal models of schizophrenia, changes in dopamine and glutamate receptors are found. 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 new insights in 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 neurotransmission in patients with schizophrenia. In addition, imaging of neuroinflammation provides a very different view on the pathophysiology of schizophrenia, enabling new treatment strategies. Molecular imaging also makes it 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 animal models indicate to be affected by the disease. This is an area

academic and industrial partners should collaborate, and indeed this already has provided new tracers. Only with such a joint approach we can come up with new targets that will eventually lead to a radical other way of treatment of patients with schizophrenia.

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Neuroimaging of Delirium

19

Arjen J.C. Slooter and Jan-Cees de Groot

Contents

Abstract

Delirium is an acute change of consciousness and cognition that is associated with poor outcome. The arsenal to treat delirium is limited due to the poor understanding of the pathophysiology of the underlying encephalopathy. Neuroimaging can be used to elucidate possible neural mechanisms. In delirium, however, neuroimaging is still in its infancy. Despite concerns about the feasibility of neuroimaging in delirious patients, several investigations have been performed. Most structural imaging studies suggest that delirium is associated with more brain atrophy and focal abnormalities, such as infarcts and white matter disruption. Functional imaging studies suggest perfusion abnormalities and altered functional connectivity. More advanced imaging techniques may provide new insight in the pathophysiology of delirium.

A.J.C. Slooter, MD, PhD (✉)
Department of Intensive Care Medicine, University Medical Center Utrecht, University of Utrecht, Heidelberglaan 100, Utrecht 3584 CX, The Netherlands
e-mail: a.slooter-3@umcutrecht.nl

J.-C. de Groot, MD, PhD
Department of Radiology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, Groningen 9713 GZ, The Netherlands

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_19,

Abbreviations

ASL	Arterial Spin labelling
CBF	Cerebral Blood Flow
CT	Computed Tomography
DIR	Double Inversion Recovery
DSM-IV-R	Diagnostic and Statistical Manual of Mental disorders, fourth revised edition
DTI	Diffusion Tensor Imaging
fMRI	Functional Magnetic Resonance Imaging
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
PET	Positron Emission Tomography
SPECT	Single Photon Emission Computed Tomography

19.1 Introduction

Delirium is a common condition in elderly patients, particularly in those with pre-existing cognitive impairment and in critically ill patients. It can be defined according to the *Diagnostic and Statistical Manual of Mental Disorders* (fourth revised edition, DSM-IV-R) (American Psychiatric Association 2000) as a disturbance of consciousness and a change in cognition that develops over a short period of time and tends to fluctuate during the day. Of all cognitive domains, attention is particularly affected in delirium (Blazer and van Nieuwenhuizen 2012). Other common features are sleep-wake cycle disturbances, memory problems, perceptual disturbances and hallucinations, language disturbances, thought process abnormalities and affective disorders (Inouye 2006; Blazer and van Nieuwenhuizen 2012). Delirium is present in hyperactive, hypoactive and mixed forms. However, patients may rapidly switch from one type to another (Inouye 2006; Blazer and van Nieuwenhuizen 2012).

Delirium is associated with an increased risk of death, institutionalization and dementia, independent of important confounders, such as age, co-morbidity, illness severity and pre-existing cognitive impairment (Witlox et al. 2010). In addition, delirium increases hospital length of stay and medical costs (Inouye 2006). Despite its frequency and consequences, delirium is ill recognized by general physicians (Van Eijk et al. 2009).

The development of delirium involves the complex interrelationship between predisposing factors, including advanced age and exposure to precipitating factors, such as an infectious disease or dehydration (Inouye 2006). Delirium is a manifestation of encephalopathy with altered function of neural networks. The pathophysiology of the underlying encephalopathy is incompletely known and may involve neurotransmitter alterations, especially acetylcholine and dopamine, inflammatory pathways and an aberrant stress response (Hughes et al. 2012).

A multicomponent, non-pharmacological approach may prevent delirium. Once delirium develops, symptomatic treatment with antipsychotics is usually started

(Zaal and Slooter 2012). Atypical antipsychotics may have less side effects but seem not to be more effective than haloperidol. However, the effectiveness of antipsychotics in delirium has not been proven in a large-scale, placebo-controlled randomized clinical trial (Zaal and Slooter 2012). One reason for the limited therapeutic arsenal is the poor understanding of the pathophysiology. Neuroimaging may be used to elucidate possible neural mechanisms underlying delirium.

19.2 Neuroimaging

Neuroimaging techniques have provided numerous new insights in the pathogenesis of a variety of neuropsychiatric disorders, particularly dementia, schizophrenia and mood disorders. In delirium, however, neuroimaging is still in its infancy. Neuroimaging can be used to clarify structural or functional predictors, correlates or consequences of delirium. This includes the use of Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Single Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET).

19.2.1 Feasibility

An important concern though is the feasibility of neuroimaging in delirious patients. Attention deficits, clouding of consciousness, restlessness and agitation may seriously hamper procedures that require the subject to lay still in a supine position for quite some time. This is particularly important in MRI where additional discomfort might be induced by the head coil, needed to obtain adequate signal. Motion artefacts can be prevented by sedating the patient. Although the use of sedatives will not affect structural imaging, it may seriously interfere with functional imaging. Functional MRI (fMRI) resting-state studies have shown that sedation reduces default mode network connectivity, the network that has been linked to self-related processes (Heine et al. 2012). Most previous neuroimaging studies in delirium, however, do not report on the proportion of dropout patients due to motion artefacts.

19.2.2 CT

Most previous CT studies showed that delirious patients had larger ventricles and wider sulci than non-delirious controls, suggesting more cortical and subcortical atrophy (Soiza et al. 2008). In addition, delirium was found to be associated with focal abnormalities, such as cerebral infarcts (Soiza et al. 2008).

In one study, xenon-enhanced CT was used to measure cerebral blood flow (CBF) in ten patients during and after delirium (Yokota et al. 2003). Delirium was found to be associated with bilateral reductions in global CBF, in particular the caudate head, thalamus and lenticular nuclei. With recovery from delirium, there

was an increase of regional CBF to normal values for each of these regions. These findings suggest that cerebral hypoperfusion may contribute to the pathogenesis of delirium, although it cannot be excluded that hypoperfusion may be a consequence of microcirculatory alterations due to the underlying encephalopathy.

It should, however, be noted that the methodological quality of previous CT studies in delirium was low, with small and heterogeneous groups of patients, confounded by age and use of nonvalidated outcome measures. Yet, from these studies it may be concluded that structural brain abnormalities such as atrophy may predispose to delirium.

19.2.3 MRI: Structural Imaging

Structural imaging using MRI confirmed CT studies, in showing that delirium appears to be associated with cortical and subcortical atrophy as well as an increased proportion of structural lesions (Soiza et al. 2008). These studies showed in particular an increased frequency of periventricular and deep white matter hyperintensities, possibly with a predominance of the basal ganglia (Soiza et al. 2008). In a combined CT/MRI study in stroke patients, a higher proportion of cerebral hemisphere (as opposed to brainstem or cerebellum) stroke was found in delirious patients, as compared to non-delirious controls (Caeiro et al. 2004). Several case reports have been published on delirium in response to a variety of focal lesions (Alsop et al. 2006). However, in a large combined CT/MRI study ($n=235$), abnormal brain scans were not predictive for delirium (Kishi et al. 1995). The relationship between cerebral lesions and the occurrence of delirium seems therefore not to be strong.

Three recent larger studies deserve more attention. In a study in 116 patients undergoing cardiac surgery, Diffusion Tensor Imaging (DTI) was used to study whether microstructural white matter abnormalities predispose patients to develop postoperative delirium (Shioiri et al. 2010). Fractional anisotropy values of the white matter in the left frontal lobe and left thalamus were significantly lower (i.e. more white matter disorganization, possibly disruption) in patients who developed delirium than in patients who did not (Shioiri et al. 2010).

In 47 patients after critical illness, 3 T MRI was performed both at hospital discharge and 3-month follow-up (Morandi et al. 2012). Fractional anisotropy was calculated quantitatively using DTI. Greater duration of delirium was associated with lower fractional anisotropy in the corpus callosum and anterior limb of the internal capsule at hospital discharge. These associations persisted at 3 months for the corpus callosum. A lower fractional anisotropy score was associated with worse cognitive scores up to 12 months later (Morandi et al. 2012).

In the same cohort, brain volumes were evaluated in relation to the duration of delirium (Gunther et al. 2012). Longer duration of delirium was associated with greater ventricle to brain ratios, both at hospital discharge and at 3 months. The areas with greatest volume loss were the hippocampus and the superior frontal lobe, areas that play an important role in declarative memory, respectively, executive function. Greater brain atrophy at 3 months was associated with worse cognitive

performances at 12 months. Smaller superior frontal lobes, thalamus and cerebellar volumes at 3 months were associated with worse executive functioning and visual attention at 12 months (Gunther et al. 2012). These latter two studies may thus offer insight in a structural correlate of the association between delirium and long-term cognitive impairment (Morandi et al. 2012; Gunther et al. 2012).

In conclusion, these findings suggest that patients with delirium have more brain atrophy and reduced white matter integrity. However, the association of structural lesions with delirium seems to be relatively weak (Alsop et al. 2006).

19.2.4 MRI: Functional Imaging

There is currently only one publication on resting-state functional connectivity in patients with delirium (Choi et al. 2012). In this study, 22 patients underwent functional MRI during and after delirium as well as a heterogeneous, age- and sex-matched control group. Functional connectivity was assessed using the seed region of the posterior cingulate cortex and functional connectivity strengths between a priori selected subcortical regions related to acetylcholine and dopamine. Dorsolateral prefrontal cortex activity and posterior cingulate cortex activity were inversely correlated in controls but strongly correlated in patients during an episode of delirium as indicated by increased functional connectivity between the two regions. Functional connectivity strengths of the intralaminar thalamic and caudate nuclei with other subcortical regions were reduced during an episode of delirium but recovered after resolution of delirium. These findings suggest that the disruption in reciprocity of the dorsolateral prefrontal cortex with the posterior cingulate cortex and reversible reduction of functional connectivity of subcortical regions may play a role in the development of delirium (Choi et al. 2012).

Another exciting MRI technique is Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) that has been applied in a few investigations on delirium. The largest study on delirium has been performed in 14 haematological cancer patients after bone marrow transplantation and ten age- and sex-matched, healthy controls (Yager et al. 2011). In delirious patients, elevated choline and reduced N-acetyl aspartate levels were found compared to normal controls and patients without delirium. This could indicate inflammatory processes, white matter damage and/or neuronal loss. Alternatively, these findings could be related to the treatment of cancer in these patients (Yager et al. 2011).

19.2.5 SPECT

Several articles on SPECT in delirium have been published, albeit mostly case reports or case series (Alsop et al. 2006). Although there is wide variety in these publications with regard to the aetiology of delirium, radioactive isotope used and processing of scans, several articles suggest that delirium is associated with a decrease in CBF, particularly of parietal and frontal regions (Alsop et al. 2006).

A limitation of most SPECT studies is that absolute measurement of blood flow was not performed.

In a larger study on 22 delirious patients, 99mTc HMPAO SPECT was used to study cerebral perfusion (Fong et al. 2006). Compared with healthy age-matched controls, CBF was reduced in the left inferior frontal, right temporal, right occipital and pontine regions in 11 of 22 delirium patients (Fong et al. 2006). In cases with scans during and after resolution of delirium ($n=6$), reversible abnormalities were found in three participants, with decreased right parietal perfusion in two subjects and increased left parietal perfusion in one patient. Regional perfusion abnormalities may thus occur during delirium (Fong et al. 2006).

19.3 Methodological Issues and Recommendations for Future Investigations

It should be noted that neuroimaging studies on delirium are currently scarce. Moreover, in these few studies, there is a great diversity of designs, patient populations, neuroimaging techniques and types of measurement. Few investigations applied serial imaging. In addition, many studies were subject to methodological weaknesses, precluding firm conclusions. These weaknesses include small sample sizes and unsophisticated methods of imaging and analysis.

Future studies should use standard diagnostic criteria and describe recruitment of patients in more detail. Delirium of different aetiologies should be compared. These investigations should be adequately powered to detect realistic effect sizes, which may be small to moderate. Preferably, these studies should apply sequential imaging before, during and/or after episodes of delirium. When case–control designs are applied, control subjects should be of similar ages and have similar co-morbidities.

Recently, numerous imaging techniques have been developed with great potential to offer insight in the pathophysiology of delirium. With regard to structural MRI, high-field (7 T) MRI may reveal encephalopathy-related alterations that may be undetected on conventional (1.5 T) MRI, such as microinfarcts and microbleeds (Theysohn et al. 2011). Double-inversion recovery techniques (3D-DIR) may be used to investigate cortical lesions.

With regard to functional MRI, (selective) arterial spin labelling (ASL) is a promising technique to assess cerebral perfusion. As it can quantify modulations of flow over seconds, ASL may assess the effect of pharmacological interventions (Hendrikse et al. 2012). Given the recent insight in the functional architecture of the brain, it is interesting to use resting-state fMRI to unravel which cerebral networks are affected in delirium. Further, MRS studies may be used to measure brain metabolites, which could lead to a better understanding of the pathophysiology of the encephalopathy that underlies delirium.

Advanced PET and SPECT imaging offer various exciting opportunities to study delirium and its underlying encephalopathy. PET scanning using [^{11}C]-6-OH-BTA-1, also known as Pittsburgh compound B, allows in vivo investigation of β amyloid metabolism (Mori et al. 2012). This technique could be used to study

whether prolonged delirium is associated with increased amyloid deposition, which may explain the occurrence or acceleration of dementia after delirium. Increased neuroinflammation and alterations in neurotransmitter activity, particularly acetylcholine and dopamine, are presumed to play an important role in the pathogenesis of the encephalopathy that underlies delirium (Hughes et al. 2012). Neuroinflammation is associated with activated microglia, which may be visualized with PET imaging (Politis et al. 2012). Brain cholinergic function can be estimated by measuring acetylcholinesterase activity in the brain with PET and radiolabelled acetylcholine analogues (Mori et al. 2012). Different steps in the process of dopaminergic neurotransmission can be investigated with numerous PET and SPECT radiotracers (Shen et al. 2012). However, many new tracers require special chemistry or cyclotron facilities as well as considerable preparation time and expense, which may make studies of acute delirium impractical in the near term.

Conclusion

In summary, most structural imaging studies suggest that delirium is associated with more brain atrophy and focal abnormalities, such as infarcts and white matter disruption. Functional imaging studies suggest perfusion abnormalities and reduced functional connectivity. It should, however, be noted that these associations may not demonstrate necessary causal relationships. Instead, these findings may simply indicate contributing pathways or, in other words, a more vulnerable brain. More advanced imaging techniques and serial scanning may provide new insight in the pathophysiology of delirium.

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PET and SPECT Findings in Patients with Hallucinations

20

Matthijs G. Bossong and Paul Allen

Contents

Abstract

Hallucinations remain one of the most intriguing phenomena in psychopathology. The development of neuroimaging techniques has enabled investigators to examine the neural underpinnings of hallucinatory symptoms present in schizophrenia and other disorders. Here we provide an overview of positron emission tomography (PET) and single-photon emission computed tomography (SPECT) neuroimaging studies in patients with hallucinations. The majority of these studies have been in schizophrenia patients with auditory verbal hallucinations, and show increased metabolism or blood flow in auditory cortex and speech perception areas. A number of studies also implicate non-sensory brain regions such as the anterior cingulate cortex that may be involved in top-down attentional and speech monitoring processes. In patients with neurological disorders who experience visual hallucinations reduced activation in the ventral visual pathway is reported, again implicating a fundamental role for the modality-specific sensory cortex. In conclusion, findings from PET and SPECT neuroimaging studies

M.G. Bossong • P. Allen, PhD (✉)
Department of Psychosis Studies, Institute of Psychiatry, King's College London, 16 De Crespigny Park, London SE5 8AF, UK
e-mail: p.allen@kcl.ac.uk

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_20, © Springer-Verlag Berlin Heidelberg 2014

might suggest that 'imbalances' between bottom-up sensory activation and top-down attentional modulation are the primary neurocognitive dysfunction that underpins the hallucinating brain.

20.1 Introduction

Hallucinations are intriguing phenomena. They can be defined as any perceptual experience in the absence of external stimuli and must be sufficiently compelling to be considered a true perception. Hallucinations can occur in any sensory modality, although auditory and visual hallucinations are most common in psychiatric disorders. Auditory verbal hallucinations (AVH) or 'hearing voices' are a characteristic symptom of psychosis, occurring in 60–80 % of affected individuals, and are one of the main clinical features of schizophrenia (Diagnostic and Statistical Manual IV, 1994). They are often distressing and abusive (Nayani and David 1996) and are also reported in a significant minority of the general population (~5 %) (Tien 1991). Hallucinations are also present in other psychiatric or neurological disorders such as Parkinson's disease or dementia with Lewy bodies (DLB), where patients often report visual hallucinations (Diederich et al. 2009).

The development of neuroimaging techniques has allowed investigators to examine the neural underpinning of hallucinatory symptoms seen in schizophrenia and other disorders. The aim of this chapter is to provide an overview of positron emission tomography (PET) and single-photon emission computed tomography (SPECT) neuroimaging studies in patients with hallucinations. These studies are concerned with changes in blood flow and metabolism associated with the occurrence of hallucinations. This includes both studies that correlated clinical features with brain function during resting states as well as studies that have directly compared brain activity between patients when they are experiencing hallucinations and when they are not. A small number of case reports in patients with various hallucination types are also included in this chapter. Furthermore, studies that have compared patients with and without hallucinations on cognitive tasks, presumed to measure trait-like cognitive processes underlying the disposition to hallucinate, and studies that examined neurochemistry underlying hallucinations will be reviewed. Findings are critically discussed and compared with later functional magnetic resonance imaging (fMRI) findings in patients with hallucinations. The emphasis of this chapter will be on AVH in schizophrenia patients as most have been concerned with this group. However, we will also pay attention to imaging studies with schizophrenia patients who experience hallucinations in other sensory modalities (visual, tactile), as well as studies examining hallucinations in neurological conditions.

20.2 Brain Activity in Patients Prone to Hallucinations

Early studies in patients with schizophrenia used PET and SPECT scans that measured regional cerebral blood flow or metabolism during resting states and then correlated this with clinical features (Table 20.1). Using [^{11}C]-deoxy-D-glucose and

Table 20.1 PET and SPECT studies that measured brain activity in patients prone to hallucinations

Author	Subjects	Modality	Activation pattern associated with hallucinations
Schizophrenia			
Volkow et al. (1987)	18 patients with AVH	[^{11}C] DG-PET	Hallucinations ↑, temporal lobe R ↑
Liddle et al. (1992)	30 patients with AVH	^{15}O-PET	Hallucinations/delusions ↑, medial temporal lobe L ↑
Gordon et al. (1994)	10 patients with AVH	SPECT	Hallucinations/delusions ↑, temporal lobe L ↓
Gur et al. (1995)	42 patients with AVH	FDG-PET	Hallucinations ↑, superior temporal lobe ↓
Sabri et al. (1997)	24 patients with AVH	SPECT	Hallucinations ↑, thalamus L ↓
Lahti et al. (2006)	32 patients with AVH 23 patients with AVH	$H_2{}^{15}$O-PET	Positive symptoms ↑, anterior cingulate ↑, parahippocampus L ↓
Kopecek et al. (2007)	15 patients with AVH 15 patients without AVH	FDG-PET	Prefrontal cortex R ↑ in hallucinators Hallucinations ↑, prefrontal cortex R ↑
Horacek et al. (2007)	12 patients with AVH	FDG-PET	Hallucinations ↑, prefrontal cortex R, inferior temporal gyrus L ↑ After rTMS on temporoparietal cortex L, activity inferior temporal gyrus L ↓, temporoparietal cortex R, frontal lobes LR ↑
Klirova et al. (2013)	15 patients with AVH	FDG-PET	rTMS based on peak activity more effective than standard rTMS on temporoparietal cortex L
Neurological disorders			
Nagano-Saito et al. (2004)	8 PD patients with visual hallucinations 11 PD patients without visual hallucinations	SPECT	Superior frontal gyrus L ↑ in hallucinators
Oishi et al. (2005)	24 PD patients with visual hallucinations 41 PD patients without visual hallucinations	SPECT	Fusiform gyrus R ↓ in hallucinators
Matsui et al. (2006a)	31 PD patients with visual hallucinations 39 PD patients without visual hallucinations	SPECT	Inferior parietal lobule LR, inferior temporal gyrus LR, precuneus LR, occipital cortex LR ↓ in hallucinators
Matsui et al. (2006b)	11 PD patients with AVH and visual hallucinations 17 PD patients with visual hallucinations	SPECT	Prefrontal cortex LR, superior temporal gyrus R ↓ in patients with AVH and visual hallucinations
Boecker et al. (2007)	8 PD patients with visual hallucinations 11 PD patients without visual hallucinations	FDG-PET	Parietal lobe LR, precuneus LR, middle temporal gyrus L, posterior cingulate R, lingual gyrus L ↓ in hallucinators

(continued)

Table 20.1 (continued)

Author	Subjects	Modality	Activation pattern associated with hallucinations
(Perneczky et al. 2008)	14 DLB patients with visual hallucinations 7 DLB patients without visual hallucinations 16 healthy controls	FDG-PET	Occipitotemporal junction R, middle frontal gyrus R ↓ in hallucinators vs non-hallucinators
Nagahama et al. (2010)	100 DLB patients with visual hallucinations	SPECT	Hallucinations ↑, ventral occipital gyrus L, parietal lobe LR ↓

AVH auditory verbal hallucinations, *[11C]DG* [11C]-deoxy-D-glucose, *DLB* dementia with Lewy bodies, *FDG* [18F]-fluorodeoxyglucose, *L* left, *PD* Parkinson's disease, *PET* positron emission tomography, *R* right, *rTMS* repetitive transcranial magnetic stimulation, *SPECT* single-photon emission computed tomography

PET, Volkow and colleagues (1987) examined brain metabolism in 18 patients with chronic schizophrenia and demonstrated a positive correlation between hallucinations and activity in the right temporal lobe (Volkow et al. 1987). Liddle et al. (1992) were the first to directly investigate the association between symptoms and brain activity in patients with schizophrenia. Using the $^{15}O_2$ inhalation technique and PET, they showed that different symptom clusters (psychomotor poverty, disorganisation, and reality distortion) were positively associated with different patterns of cerebral blood flow in a group of 30 patients. In particular, reality distortions (hallucinations and delusions) were correlated with resting state perfusion in the left medial temporal lobe (involved in auditory perception and memory processes) (Liddle et al. 1992). Gordon and colleagues found that lower cerebral blood flow in the left temporal lobe as measured with SPECT correlated with the presence of positive symptoms (hallucinations and delusions) (Gordon et al. 1994). Gur et al. (1995) also observed a negative correlation between severity of hallucinations and superior temporal lobe metabolism in a group of 42 medication-free schizophrenia patients who were studied with [18F]-fluorodeoxyglucose (FDG) PET (Gur et al. 1995). Using SPECT, Sabri and colleagues demonstrated that hallucinations were negatively correlated with blood flow in the left thalamus in 24 never-treated patients with acute schizophrenia. After treatment, this correlation was no longer present (Sabri et al. 1997). More recently, Lahti et al. (2006) conducted a similar $H_2{}^{15}O$-PET study with two cohorts of medication-free schizophrenia patients and performed a voxel-wise whole brain regression analysis between symptoms and cerebral blood flow. Positive symptoms correlated positively with resting state activity in the anterior cingulate cortex and negatively in the left parahippocampus (Lahti et al. 2006). In a series of FDG-PET studies, the group of Horacek and colleagues investigated glucose metabolism changes in patients with AVH and the effect of repetitive transcranial magnetic stimulation (rTMS), as a potential treatment, on brain metabolism and symptoms. In the first study, Kopecek et al. (2007) observed increased activity in the right prefrontal cortex of 15 patients with prominent AVH when compared to 15 non-hallucinating schizophrenia patients. Metabolism in this area showed a significant correlation with the intensity of hallucinations (Kopecek et al. 2007). In a second study with 12 treatment-resistant patients, hallucination scores correlated

positively with metabolism in the left inferior temporal gyrus and right prefrontal cortex. After treatment with rTMS applied to the left temporoparietal cortex (Wernicke's area, the main brain region involved in the comprehension of language), metabolism in the left inferior temporal gyrus decreased, with a corresponding increase in the contralateral temporoparietal cortex and bilateral frontal lobes. A decline in symptom scores after rTMS was predicted by higher pretreatment activity in the left inferior temporal and parahippocampal gyrus and the right precentral gyrus (Horacek et al. 2007). Klirova et al. (2013) showed that individualised rTMS that was administered according to the local maxima of glucose metabolism of the left temporoparietal cortex had even better treatment effects on AVH than standard positioning of rTMS (Klirova et al. 2013). Altogether, results of these studies suggest involvement of the temporal lobe in AVH, although the direction of the correlation between temporal lobe activity and the severity of hallucinations remains equivocal, with three studies showing a positive and three studies showing a negative relationship. Possibly, increased activity in Wernicke's area is particularly related to the occurrence of AVH, as studies that applied rTMS to this area have shown beneficial effects on hallucinatory behaviour (Hoffman et al. 2000; Aleman et al. 2007; Horacek et al. 2007). However, rTMS guided by individual maxima of hallucinatory activity may be even more effective, suggesting that other (temporal) areas are also involved (Sommer et al. 2007; Klirova et al. 2013). Differences in findings could be explained by the fact that most studies do not report if patients were actively hallucinating at the time of the scans, thereby possibly conflating trait and state factors. In addition, some studies did not report the specific relationship between activity and hallucinations, but included a broader spectrum of positive symptoms including hallucinations (e.g. Gordon et al. 1994; Lahti et al. 2006).

Psychotic symptoms are also present in non-schizophrenia illnesses such as Parkinson's disease or dementia with Lewy bodies (DLB), where patients often report visual hallucinations. (Perneczky et al. 2008) measured glucose metabolism with FDG-PET in 14 DLB patients with visual hallucinations, 7 DLB patients without visual hallucinations, and 16 healthy controls. Direct comparison between the two patient groups revealed a significant decrease in metabolism in the right occipitotemporal junction and right middle frontal gyrus of patients with hallucinations (Perneczky et al. 2008). Nagahama and colleagues (2010) found in a SPECT study with 100 DLB patients that visual hallucinations were associated with decreased perfusion in the left ventral occipital gyrus and bilateral parietal areas (Nagahama et al. 2010). Performing a SPECT study with patients with Parkinson's disease, Nagano-Saito and colleagues (2004) demonstrated a significant increase in glucose metabolism in the left superior frontal gyrus of patients with a recent history of visual hallucination ($n=8$) compared to those without hallucinations ($n=11$) (Nagano-Saito et al. 2004). In a larger sample, Oishi et al. (2005) compared 24 patients with Parkinson's disease who had visual hallucinations and 41 patients who had never experienced visual hallucinations using SPECT. They reported decreased perfusion of the right fusiform gyrus (involved in processing of colour information and face and body recognition) in hallucinators with Parkinson's disease (Oishi et al. 2005). This finding was in part replicated by Matsui and colleagues (2006a), who found with SPECT that hallucinating patients with Parkinson's disease ($n=31$) exhibit decreased perfusion in several brain regions

involved in visual processing, including the bilateral inferior parietal lobule, inferior temporal gyrus, precuneus, and occipital cortex, when compared to non-hallucinators ($n=39$) (Matsui et al. 2006a). Using FDG-PET, Boecker et al. (2007) reported a decline in metabolism in 8 patients with Parkinson's disease and visual hallucinations compared to 11 patients without visual hallucinations in similar occipito-temporo-parietal areas, including bilateral inferior and superior parietal lobes and precuneus, as well as left middle temporal gyrus, right posterior cingulate, left parahippocampal gyrus, and left lingual gyrus (Boecker et al. 2007). Finally, another SPECT study by Matsui and colleagues (2006b) showed that patients with Parkinson's disease with both verbal and visual hallucinations ($n=11$) exhibited significantly decreased perfusion in the bilateral prefrontal cortex and right superior temporal gyrus compared to patients with visual hallucinations only ($n=17$) (Matsui et al. 2006b). Altogether, results of these studies convincingly suggest a role for the ventral visual pathway (involved in the recognition, identification, and categorisation of visual stimuli) in visual hallucinations, as five of the six studies showed decreased activity related with hallucinations in brain areas associated with the ventral visual pathway, such as occipitoparietal areas, fusiform gyrus, and precuneus.

20.3 Brain Activity During Hallucinations

A number of PET and SPECT studies have directly compared brain activity between schizophrenia patients when they are experiencing hallucinations and when they are not (Table 20.2). In general, patients in these studies were symptomatic and using

Table 20.2 PET and SPECT studies that measured brain activity during hallucinations

Author	Subjects	Modality	Activation pattern during hallucinations
Schizophrenia			
Musalek et al. (1988)	17 patients with AVH 28 healthy controls	SPECT	Medial temporal region LR, anterior basal ganglia LR ↑, frontal cortical areas LR ↓
Musalek et al. (1989)	11 patients with tactile hallucinations 28 healthy controls	SPECT	Inferior temporal regions LR ↓
Cleghorn et al. (1990)	9 patients with AVH 10 patients recovered from AVH 10 healthy controls	FDG-PET	AVH associated with highly correlated activity pattern in Broca's area, Broca's homologue, anterior cingulate, superior temporal gyrus L
Walter et al. (1990)	17 patients with AVH 10 controls with musical hallucinations while hypnotised	SPECT	Medial temporal region LR ↑, frontal lobes LR, thalamus LR ↓
Cleghorn et al. (1992)	12 patients with AVH 10 patients without AVH	FDG-PET	Posterior superior temporal gyrus LR ↓ Hallucinations ↑, striatum, anterior cingulate cortex ↑

Table 20.2 (continued)

Author	Subjects	Modality	Activation pattern during hallucinations
McGuire et al. (1993)	13 patients with AVH (scans were compared when patients were symptomatic and remitted)	SPECT	Broca's area, temporal cortex L, anterior cingulate ↑
Suzuki et al. (1993)	5 patients with AVH (scans were compared when patients were symptomatic and remitted)	SPECT	Temporal lobe L, anterior cingulate ↑
Silbersweig et al. (1995)	5 patients with AVH (scans were compared for periods when AVH were present and absent)	$H_2{}^{15}O$-PET	Parahippocampal gyrus LR, thalamus LR, caudate R, putamen R, anterior cingulate ↑
Szechtman et al. (1998)	8 subjects hallucinating under hypnosis 6 subjects not hallucinating under hypnosis	$H_2{}^{15}O$-PET	Anterior cingulate ↑
Copolov et al. (2003)	8 patients with AVH (scans were compared for periods when AVH were present and absent)	$H_2{}^{15}O$-PET	Medial frontal and prefrontal regions R, medial temporal gyrus R, superior temporal gyrus L, parahippocampal gyrus L, posterior cingulate ↑
Parellada et al. (2008)	8 patients with AVH (scans were compared when patients were symptomatic and remitted)	FDG-PET	Supplementary motor area LR, anterior cingulate, medial and superior frontal lobes, cerebellum, superior temporal pole R, orbitofrontal cortex R ↑
Horga et al. (2011)	9 patients with AVH	FDG-PET	Superior and middle temporal region L, superior medial frontal cortex LR, caudate L ↑, hippocampal complex LR, cerebellum LR , parietal cortex LR ↓
	7 patients without AVH		Hallucinations ↑, superior temporal cortex R, cerebellum ↑
Neurological disorders			
Adachi et al. (2000)	5 CBS patients with visual hallucinations	SPECT	Thalamus L ↑ for all patients individually
Matsui et al. (2007)	4 PD patients with AVH 77 PD patients without AVH	SPECT	Thalamus R ↑

AVH auditory verbal hallucinations, *CBS* Charles Bonnet syndrome, *FDG* [^{18}F]-fluorodeoxyglucose, *L* left, *PD* Parkinson's disease, *PET* positron emission tomography, *R* right, *SPECT* single-photon emission computed tomography

antipsychotic medication at the time of scanning. In a series of SPECT studies, the group of Musalek and colleagues compared cerebral blood flow between 17 schizophrenia patients with chronic, treatment-resistant AVH and healthy controls. Auditory hallucinations were associated with increased blood flow in the anterior basal ganglia and the medial temporal region bilaterally, as well as reductions in blood flow in frontal cortical areas when compared to 28 non-hallucinating control subjects (Musalek et al. 1988, 1989). A comparison between the same group of

schizophrenia patients with AVH and a control group who reported musical hallucinations only while hypnotised ($n = 10$) demonstrated increased activity in the medial temporal region and decreased activity in the frontal lobes and thalamus bilaterally of patients (Walter et al. 1990). However, the substantial age difference between patients and control groups could be a serious confounder in the interpretation of the results of these studies as cerebral blood flow is known to decline with age (e.g. Melamed et al. 1980). Cleghorn and colleagues evaluated auditory hallucinations using FDG-PET in two different studies. The first study found no differences in regional glucose uptake between nine schizophrenia patients with AVH, ten schizophrenia patients who had recovered from AVH, and ten control subjects. Interestingly, auditory hallucinations were associated with a highly correlated pattern of activity in specific language centres, including Broca's area and its right hemisphere homologue (involved in speech production), anterior cingulate, and left superior temporal gyrus (Cleghorn et al. 1990). In a second study, using the same imaging technique, a group of 12 medication-free schizophrenia patients who were experiencing auditory hallucinations during scanning demonstrated lower relative metabolism in the bilateral posterior superior temporal gyrus when compared to ten medication-free schizophrenia patients who did not hallucinate during imaging. The intensity of reported hallucinations was significantly correlated with glucose metabolism in the striatum and anterior cingulate cortex (involved in attentional processes) (Cleghorn et al. 1992). McGuire et al. (1993) scanned 13 schizophrenia patients using SPECT during an episode of their illness in which they regularly experienced auditory hallucinations. They were scanned again on a second occasion, during a remission period, when the hallucinations were absent. When the scans were compared, brain activity associated with hallucinations was observed in language-related regions, especially Broca's area. To a lesser extent, activity was also found in the anterior cingulate and left temporal cortex (McGuire et al. 1993). Using a similar approach, comparable results were reported by Suzuki et al. (1993), who demonstrated with SPECT an increase in cerebral blood flow in the left temporal lobe (auditory association cortex) and anterior cingulate cortex in five hallucinating patients. Blood flow patterns were normalised after clinical improvement (Suzuki et al. 1993). Silbersweig and colleagues (1995) again used patients as their own control subjects, but measured cerebral blood flow during hallucinations and quiescent periods in the same scanning session with $H_2{}^{15}O$-PET. Five patients pushed a button to indicate the duration of the auditory verbal hallucination while they were scanned. Activation during hallucinations was shown in subcortical structures (bilateral thalamus, right putamen, and caudate), bilateral parahippocampal gyrus, right anterior cingulate, and left orbitofrontal cortex (areas involved in emotion regulation). The authors suggest that activity in deep brain structures might generate or modulate hallucinations, whereas cortical activity may affect the specific perceptual content of the hallucinations (Silbersweig et al. 1995). An $H_2{}^{15}O$-PET study of auditory hallucinations performed by Szechtman et al. (1998) did not include schizophrenia patients but compared brain activity in highly hypnotisable volunteers during different experimental conditions: hearing, imagining, and hallucinating. Eight of these volunteers were able to hallucinate under hypnosis (these were termed hallucinators), whereas six lacked this ability (control group). A region in the right anterior

cingulate cortex was activated in the group of hallucinators when they heard an auditory stimulus and when they hallucinated hearing it, but not when they merely imagined hearing it. The same experimental conditions did not yield such activation in the control group. The investigators suggest that the anterior cingulate activation 'tags' an auditory event as originating from the external world. Thus, in hallucinations, such activation may reflect a mismatch between externally directed attention and internally generated events. They propose that the involvement of rostral anterior cingulate cortex (which has been implicated in modulating affect) may imply that the attention of hallucinators is more affect-laden than that of non-hallucinators, and speculate that when attention is more affect-laden, self-generation of the expected auditory event is more likely to occur (Szechtman et al. 1998). A major problem, however, is that no anterior cingulate activation was observed in the hearing versus baseline condition for the non-hallucinators. If anterior cingulate activation tags an auditory event as originating from the external world, one would expect such activation also in the control group. Similar to Silbersweig et al. (1995), eight schizophrenia patients scanned with $H_2{}^{15}O$-PET by Copolov and colleagues (2003) indicated their AVH episodes by a button press. During hallucinations, a network of cortical regions was activated, including right medial frontal and prefrontal regions, right medial temporal gyrus, left superior temporal gyrus, left parahippocampal gyrus, and left posterior cingulate (Copolov et al. 2003). Parellada and colleagues (2008) performed three consecutive FDG-PET scans of nine first-episode schizophrenia patients with prominent AVH. Scans were obtained during hallucinations, after medication-induced remission, and in remission during a linguistic activation task, respectively. Patients demonstrated significantly increased activity in bilateral supplementary motor area, anterior cingulate cortex, medial and superior frontal lobes, and cerebellum during auditory verbal hallucinations compared to the remission scan. Activation was also observed in the right superior temporal pole and right orbitofrontal cortex. During linguistic activation, higher activity was observed in bilateral middle and superior temporal cortex and left parahippocampus compared to the remission scan. The authors suggest that the different patterns of glucose metabolism between hallucinations and physiological auditory activation indicate that frontal cortical regions implicated in the generation of inner speech rather than auditory-linguistic pathways may be involved in auditory verbal hallucinations of acute schizophrenia patients (Parellada et al. 2008). Horga et al. (2011) investigated differences in glucose metabolism with FDG-PET between antipsychotic-naïve first-episode schizophrenia patients with ($n=9$) and without ($n=7$) AVH during scanning. Hallucinators exhibited significantly increased activity in the left superior and middle temporal region, bilateral superior medial frontal cortex, and left caudate and decreased activity in the hippocampal complex, cerebellum, and parietal cortex compared to patients without hallucinations during the scan. The severity of hallucinations showed a positive correlation with metabolic rate in the right superior temporal cortex and cerebellum (Horga et al. 2011).

Altogether, results of these studies convincingly suggest a role for the temporal lobe in AVH, as seven of the 11 studies showed significantly increased temporal lobe activity during hallucinations (three bilateral and four left lateralised). In addition, several studies report the involvement of cortical and subcortical areas in the

experience of hallucinations, such as anterior cingulate cortex, Broca's area, and basal ganglia. Although the exact role of these regions is not yet clear, a possible hypothesis is that activity in subcortical areas and modality-specific association cortices account for the conscious perceptual experience of hallucinations. Inappropriate anterior cingulate activation may reflect impairments in the monitoring of speech and erroneously tags internally generated imagery as originating from an external source. An alternative explanation could be that increased temporal activation drives cingulate activation, which then results in greater attention being directed towards the sensory cortex (Hunter et al. 2006). What is clear however is that studies have consistently observed activity in either language-production areas or in the primary auditory cortex during auditory hallucinations. This strongly implicates the temporal lobe, more specifically the middle or superior temporal gyri.

Neuroimaging studies have also been performed with schizophrenia patients who experienced hallucinations in other sensory modalities and with other groups of patients with hallucinations. For example, one SPECT study examined cerebral blood flow of schizophrenia patients while they were having tactile hallucinations (feeling imagined bugs). A comparison between 11 patients with only tactile hallucinations and a group of 28 non-hallucinating control patients with schizophrenia revealed a significant reduction in blood flow in the inferior temporal regions (Musalek et al. 1989). Furthermore, although visual hallucinations are being reported more often than auditory hallucinations in patients with Parkinson's disease, Matsui and colleagues (2007) examined brain perfusion with SPECT in patients with Parkinson's disease during the occurrence of AVH. They found that those with AVH ($n=4$) showed significantly higher perfusion of the right thalamus during AVH than patients without these symptoms ($n=77$) (Matsui et al. 2007). In a SPECT study with five patients with Charles Bonnet syndrome (CBS), a condition in which psychologically healthy people with significant visual loss experience recurrent complex visual hallucinations, Adachi et al. (2000) showed increased perfusion in the left thalamus of all individual patients. However, the authors did not perform a group analysis in which they examined brain regions showing significantly different activity levels in their patient group.

20.4 Case Reports

Several interesting case studies in which brain function was assessed while patients experienced hallucinations have been reported. The first study used SPECT to evaluate a 45-year-old alcohol-dependent male with AVH. Images obtained while the subject was actively hallucinating showed the highest degree of radioactive accumulation in the left superior temporal lobe, an area corresponding to primary and secondary auditory cortex (Matsuda et al. 1988). Unfortunately, the patient was not imaged again while not hallucinating. Notardonato and colleagues scanned a 41-year-old female schizophrenia patient with a 4-year history of auditory hallucinations with SPECT before and after pharmacological treatment. Hallucinations were associated with increased activity in the basal ganglia and right temporal lobe. Abnormalities in brain activity resolved with clinical improvement after treatment

(Notardonato et al. 1989). In a study of a 70-year-old female with a 1-month history of 'seeing ghosts' following a left hemispheric stroke, increased cerebral blood flow was demonstrated with SPECT in the bilateral parietooccipital lobes. Once again, resolution of the hallucinatory phenomenon correlated with a normalisation of parietooccipital activity (Kim et al. 1993). A 23-year-old male, drug-naïve schizophrenia patient who experienced both visual and auditory verbal hallucinations, was scanned with $H_2{}^{15}O$-PET while he indicated the presence of hallucinations with a button press. Hallucinations were associated with activity in visual areas (lingual, fusiform, and occipital gyri) and in the superior and middle temporal cortex (Silbersweig et al. 1995). Kasai and colleagues (1999) examined cerebral blood flow with SPECT in a cognitively intact 88-year-old woman during musical hallucinations and in their absence and compared both states with a group of 18 elderly controls. Activity was increased in the right superior temporal and inferior frontal gyri during the occurrence of hallucinations (Kasai et al. 1999). Izumi et al. (2002) obtained three SPECT scans of a 51-year-old male during musical hallucinations, during verbal hallucinations, and in the absence of hallucinations, respectively. They found evidence of differing patterns of regional cerebral blood flow during musical hallucinations and verbal hallucinations, with increased activity in the bilateral lower frontal area and basal ganglia during musical hallucinations, and increased activity in the left lower temporal area, right lower frontal area, and left basal ganglia during verbal hallucinations (Izumi et al. 2002). Using SPECT, Mori et al. (2006) observed increased regional cerebral blood flow in left temporal regions and left angular gyrus in a patient with Alzheimer's disease who experienced musical hallucinations when compared to nine patients without hallucinations (Mori et al. 2006). Finally, Godani and colleagues (2012) examined glucose metabolism in a 67-year-old woman with auditory hallucinations after right parietal haemorrhagic stroke and compared it to a normal control database. They demonstrated significantly increased metabolism in the middle and posterior areas of corpus callosum as well as in the precuneus and cuneus cortex (Godani et al. 2012).

Altogether, findings of these case reports confirm results from group studies during hallucinations as they show altered function in both the temporal lobe and non-sensory regions thought to be involved in language and speech monitoring processes. Increased glucose metabolism during hallucinations in corpus callosum, as described by Godani et al. (2012) in relation to haemorrhagic stroke, has also been reported in unmedicated schizophrenia patients (Buchsbaum et al. 2007) and could be associated with inefficiency in brain circuitry or defects in white matter leading to enhanced energy need.

20.5 Brain Activity During Performance of Cognitive Tasks

A small number of studies have applied cognitive paradigms to patients with and without hallucinations in an attempt to uncover specific abnormalities in cognitive or trait factors associated with the predisposition to hallucinate. Cognitive models have proposed that AVH arise through the misattribution to an external source of thoughts or inner speech due to defective source or self-monitoring (for reviews see

Allen et al. 2007; Waters et al. 2012). Inner speech models propose that AVH occur when thoughts are not recognised as being self-generated and are misattributed to an external agent. A possible mechanism by which this misrecognition could occur was proposed by Frith and colleagues and involved a breakdown in the monitoring of inner speech (Frith and Done 1988). McGuire and colleagues (1996a) investigated the hypothesis of defective verbal self-monitoring in a $H_2{}^{15}O$-PET study by examining the neural correlates of inner speech and verbal imagery in schizophrenia patients with and without AVH ($n=6$ in each group). In the inner speech task, volunteers were asked to imagine speaking particular sentences. In the verbal imagery task, they were asked to imagine sentences spoken in another person's voice, which, according to the authors, entails the monitoring of inner speech. During the verbal imagery task, hallucinators showed reduced activation in the left medial temporal gyrus and the rostral supplementary motor area, regions that were strongly activated by both normal volunteers and non-hallucinating patients. The authors concluded that a predisposition to verbal hallucinations in schizophrenia is associated with a failure to activate areas implicated in the normal monitoring of inner speech (McGuire et al. 1996a). This finding has in part been replicated by Stephane et al. (2006), who used $H_2{}^{15}O$-PET to scan 18 patients with schizophrenia and 12 healthy volunteers while reading single nouns. The subset of patients with AVH ($n=8$) showed reversed laterality in the supplementary motor area compared to the control groups (greater in the right hemisphere). The authors interpreted their findings within a defective speech monitoring model and concluded that abnormal laterality of the supplementary motor area activity may account for the failure to attribute speech generated by one's own brain to one's self (Stephane et al. 2006).

Altogether, results of both studies suggest that AVH in schizophrenia patients are associated with the inefficient recruitment of brain areas involved in speech monitoring. This is further supported by two subsequent functional MRI studies by Shergill and colleagues. The first experiment compared the functional anatomy of auditory verbal imagery between schizophrenia patients with AVH and controls. Patients showed an attenuated response during auditory verbal imagery in the posterior cerebellar cortex, hippocampi, and lenticular nuclei bilaterally and the right thalamus, middle and superior temporal cortex, and left nucleus accumbens (Shergill et al. 2000a). In a second study, a parametric design was used and participants were trained to vary their rate of inner speech generation. When the rate of inner speech generation was increased, schizophrenia patients showed a relatively attenuated response in the right temporal, parietal, parahippocampal, and cerebellar cortex (Shergill et al. 2003). These results complement earlier PET studies by implicating the involvement of a more distributed network of cerebellar and subcortical areas in defective self-monitoring of inner speech in patients experiencing hallucinations. However, although these studies imply a role for these areas in the monitoring of inner speech, they do not directly test if areas are involved in the misattribution of speech or thoughts to an external source.

According to the self-monitoring model, a sensory outcome of an action can be calculated on the basis of the motor commands issued to generate that action. If the speech signal predicted on the basis of the motor output matches what is actually perceived, then there is no change in activation in the areas that mediate the sensory

processing of speech (the lateral temporal cortices; Frith 1992). McGuire and colleagues (1996b) investigated this hypothesis in a $H_2{}^{15}O$-PET study with healthy volunteers who performed a verbal self-monitoring task. In the first condition volunteers were shown words and asked to read them aloud. In the second condition volunteers were asked to read the word silently but heard the investigator saying the word instead of themselves. On half the trials, the speech that the volunteers heard was distorted by elevating the pitch. Distortion of the volunteers' speech while they read aloud led to a bilateral activation of the lateral temporal cortex. Similar auditory cortex activation was seen when participants read aloud, but heard the voice of someone else. These findings suggest that the temporal cortex is involved in speech monitoring and is activated to a greater extent when there is a mismatch between perceived and expected speech. A subsequent fMRI study by Fu and colleagues (2006) using the same task in a healthy control group confirmed these results and also showed that correct source attributions for self-speech were associated with greater temporal activation than misattributions (Fu et al. 2006).

20.6 Neurochemistry Underlying Hallucinations

Many SPECT and PET neuroimaging studies indicate increased dopamine neurotransmission and elevated dopamine synthesis capacity in the striatum of patients with schizophrenia (see for reviews Abi-Dargham 2004; Howes et al. 2009). For example, using SPECT, the dopamine D2 receptor radiotracer [^{123}I]IBZM and an amphetamine challenge (which causes dopamine to be released in the synapse), it has been shown that amphetamine-induced displacement of [^{123}I]IBZM in the striatum, which indicates dopamine transmission in this region, is significantly increased in schizophrenia patients (Laruelle et al. 1996; Abi-Dargham et al. 1998). Higher [^{123}I]IBZM displacement was significantly correlated with worsening of positive symptoms, suggesting that the striatal dopamine system is involved in delusions and hallucinations experienced by schizophrenia patients (Laruelle et al. 1996, 1999; Abi-Dargham et al. 1998).

Recently, Howes and colleagues (2013) have performed the first study to directly examine dopaminergic function in relation to auditory hallucinations. Using [^{18}F]-DOPA PET, they examined striatal dopamine function in a sample of 16 healthy, well-functioning people, who heard non-distressing voices at least once per hour for several minutes in the absence of medication confounds (Howes et al. 2013). The study reports no significant difference in dopamine synthesis capacity in the striatum or its functional subdivisions between non-patient hallucinators and controls, and no relationship between subclinical psychotic symptom severity and dopamine synthesis capacity in the auditory hallucinations group. This finding suggests that altered dopamine synthesis capacity is unlikely to underlie subclinical auditory hallucinations (Howes et al. 2013). However, the exact relationship between dopaminergic function and auditory hallucinations in schizophrenia patients remains to be elucidated.

PET and SPECT studies have also been conducted in the context of neurological conditions such as DLB and Parkinson's disease. In a [^{123}I]-FP-CIT SPECT study with 18 DBL patients, Roselli and colleagues (2009) investigated the level of dopamine transporters in the striatum in relation to the severity of neuropsychiatric

symptoms, including visual hallucinations. Higher levels of striatal dopamine transporters were significantly correlated with lower severity of visual hallucinations, both for the overall striatum and separate caudate and putamen measures. Striatal dopamine transporter levels were not associated with other symptoms. This suggests involvement of the striatal dopamine system in visual hallucinations of DBL patients (Roselli et al. 2009). Ballanger et al. (2010) examined serotonin 2_A receptor binding in a [^{18}F]-setoperone PET study with seven patients with Parkinson's disease and visual hallucinations and seven non-hallucinating control patients. Patients with hallucinations exhibited increased serotonin 2_A receptor binding in brain regions involved in visual processing, including the bilateral inferior occipital gyrus, right fusiform gyrus, and right inferior temporal gyrus, as well as the bilateral dorsolateral prefrontal cortex, medial orbitofrontal cortex, and insula. These findings suggest a role for serotonin 2_A receptors in mediating visual hallucinations in Parkinson's disease via brain regions associated with the ventral visual pathway (Ballanger et al. 2010). Interestingly, the serotonin 2_A receptor is the major site of action of hallucinogens such as lysergic acid diethylamide (LSD) and psilocybin (Nichols 2004).

20.7 Discussion

This chapter summarises PET and SPECT neuroimaging studies that have investigated the neural underpinning of hallucinations seen in patients with a psychiatric or neurological disorder. Altogether, these studies provide insufficient neuroimaging evidence to fully understand the neurobiological substrate of hallucinations. However, imaging techniques have allowed us to begin to understand what is happening in the brain of those who experience hallucinations at physiological and neurochemical levels.

Both studies that correlated hallucinatory symptoms with resting state activity and studies that measured blood flow or metabolism while schizophrenia patients were experiencing auditory hallucinations consistently reported altered function in sensory regions, mainly in the middle and superior temporal gyrus. The superior temporal gyrus contains the primary and secondary auditory cortex and is crucial for perception and processing of sounds, whereas the middle temporal gyrus is involved in a number of cognitive processes, including language, semantic memory, and the integration of information from different senses. Elevated activity in these brain regions, as reported in schizophrenia patients with AVH, might lead to the experience of vivid perceptions in the absence of sensory stimuli. One possibility is that AVH arise through externalised thoughts or inner speech due to defective source or self-monitoring (Allen et al. 2007; Waters et al. 2012), as suggested by reports of reduced or altered activation during processes associated with speech monitoring in the medial temporal lobe and supplementary motor area of schizophrenia patients with AVH (McGuire et al. 1996a; Shergill et al. 2000a, 2003; Stephane et al. 2006). However, the involvement of these regions in inner speech monitoring is only implied by these studies and not experimentally tested (with the exception of McGuire et al. (1996b), although this study only reports findings in healthy controls and not in patients).

Several studies reported the involvement of other cortical and subcortical areas in the experience of hallucinations, such as anterior cingulate cortex, Broca's area, orbitofrontal gyrus, parahippocampal gyrus, and basal ganglia. Although the exact role of these regions is not yet clear, a possible hypothesis is that activity in subcortical areas and modality-specific association cortices account for the conscious perceptual experience of hallucinations. In particular, activation of the anterior cingulate is reported in several studies (Cleghorn et al. 1992; McGuire et al. 1993; Suzuki et al. 1993; Silbersweig et al. 1995; Szechtman et al. 1998; Lahti et al. 2006; Parellada et al. 2008). An fMRI study by Hunter et al. (2006) shows that in healthy volunteers, spontaneous auditory cortex activation is highly correlated with spontaneous activation in the anterior cingulate cortex. Possibly, this strong pattern of co-activation between these regions results in attention being drawn towards aberrant activation in the auditory cortex that is experienced as hallucinations. However, this model has not yet been tested in patients with hallucinations. Overall, it would seem that the altered or reduced activation in non-sensory regions that is reported in patients with AVH reflects deficits in apparent top-down control of sensory and perceptual mechanisms (Allen et al. 2008).

Reassuringly, findings of PET and SPECT studies that have examined brain activity during AVH of schizophrenia patients have largely been confirmed by a number of subsequent functional MRI studies (Dierks et al. 1999; Shergill et al. 2000b; van de Ven et al. 2005; Sommer et al. 2008) and a coordinate-based meta-analysis of the hallucinatory state (Jardri et al. 2011). In addition, two recent fMRI studies suggest that a very similar cortical network is involved in the experience of AVH in schizophrenia patients and non-patient hallucinators (Linden et al. 2011; Diederen et al. 2012).

A number of PET and SPECT studies have examined blood flow or metabolism associated with visual hallucinations in neurological disorders such as Parkinson's disease or dementia with Lewy bodies (DLB), where patients often report visual hallucinations. Results of these studies suggest decreased activity related with hallucinations in brain areas associated with the ventral visual pathway, such as occipitoparietal areas, fusiform gyrus, and precuneus (Oishi et al. 2005; Matsui et al. 2006a; Boecker et al. 2007; Perneczky et al. 2008; Nagahama et al. 2010). Reduced activity in sensory cortices of neurological patients with visual hallucinations is contrary to most studies in schizophrenia patients with AVH, which showed increased activity in the auditory cortex and speech perception areas. One possible explanation is that decreased activity in visual areas is involved in trait factors, while increased activity is related to state effects, as none of the studies with neurological patients examined brain activity during hallucinations. This is supported by an fMRI study by Ffytche et al. (1998), who demonstrated increased activity in the ventral occipital lobe of patients with Charles Bonnet syndrome while they were experiencing visual hallucinations. Furthermore, it was shown that the content of the hallucinations reflected the functional specialisations of the activated regions. Thus, in patients who hallucinated in colour, activity was found in the colour centre (V4), whereas in the only patient who hallucinated in black and white, the activity was outside this region (Ffytche et al. 1998).

In conclusion, PET and SPECT imaging studies were the first to examine what was happening in the brain of patients who experience hallucinations. The majority of these studies have been in schizophrenia patients and show increased metabolism or blood flow in auditory cortex and speech perception areas. A number of studies also implicate non-sensory brain regions that may be involved in top-down attentional and speech monitoring processes. These findings have largely been confirmed by later fMRI studies. However, no PET or SPECT studies have employed an experimental design that has convincingly probed the role of these non-sensory regions in patients with AVH and as such their function is largely speculative. In patients with neurological disorders who experience visual hallucinations, reduced activation in the ventral visual pathway is reported, again implicating a fundamental role for the modality-specific sensory cortex. However, no PET or SPECT studies have directly compared brain activity between these patients when they are experiencing hallucinations and when they are not. Overall, findings from neuroimaging studies discussed in this chapter might suggest that 'imbalances' between bottom-up sensory activation and top-down attentional modulation are the primary neurocognitive dysfunction that underpins the hallucinating brain.

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Part V

Impulse Control and Related Disorders

PET and SPECT in Personality Disorders

21

M. Mercedes Perez-Rodriguez, Luis H. Ripoll, Larry J. Siever, and Antonia S. New

Contents

Abstract

While neurobiological studies have focused primarily on DSM-IV Axis I disorders, there is an emerging 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.

M.M. Perez-Rodriguez • L.J. Siever • A.S. New (✉)
The Mental Health Patient Care Center and the Mental Illness Research Education and Clinical Center, James J. Peters Veterans Affairs Medical Center, 130 West Kingsbridge Road, Bronx, NY 10468, USA

Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: antonia.new@mssm.edu

L.H. Ripoll
Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_21, © Springer-Verlag Berlin Heidelberg 2014

21.1 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 initiative, RDoC) (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 comprised 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 amygdala as regulated by prefrontal regions including 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 PDs and have the largest empirical evidence of clinical utility and validity (Skodol et al. 2011). Since the neurobiological underpinnings of other DSM-IV 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 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.

21.2 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 present in a variety of contexts, as indicated by at least five of nine DSM-IV-TR criteria (APA 2000). 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 21.1 for a summary of all studies reviewed) (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 anterior cingulate cortex (ACC) are 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 (Soloff et al. 2003). Using script-driven imagery during PET, Schmahl et al. (2003, 2004) found that women with BPD failed to activate 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 dorsolateral prefrontal cortex 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 (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 (Goethals et al. 2005; Juengling et al. 2003; New et al. 2009). 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 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 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 OFC and amygdala associated with aggression in a PET study. The tight coupling of metabolic activity between 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 recent pilot study using SPECT on a very small sample ($n=5$) showed that BPD patients had hyperperfusion at rest in 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 the

Table 21.1 PET and SPECT studies in BPD

	Study	Method	Sample size (patients-controls)	Subjects state	Main results
1.	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
2.	De la Fuente et al. (1997)	FDG PET	10 BPD – 15 HC	Auditory cortical activation task vs resting state	Hypometabolism in premotor area, PFC, ACC, thalamus, caudate, and lenticular nuclei
3.	Frankle et al. (2005)	SERT radiotracer [11C]McN 5652 PET	10 (7 BPD + IED, 3 IED) – 10 HC	Resting state	Reduced SERT availability in the ACC
4.	Goethals et al. (2005)	99mTc-ECD brain perfusion SPECT	37 BPD and/or ASPD – 34 HC	Resting state	Hypoperfusion in temporal cortex and PFC
5.	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
6.	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
7.	Koch et al. (2007)	SERT specific ligand [I-123] 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
8.	Lai et al. (2007)	SPECT	5 BPD – 5HC	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

9.	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
10.	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-[11C]MTrp trapping in corticostriatal pathways, including superior temporal gyrus and ACC, negatively correlated with impulsivity scores
11.	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
12.	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
13.	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 right OFC and ventral amygdala seen in HC with dorsoventral differences in amygdala circuitry was not present in IED + BPD patients

(continued)

Table 21.1 (continued)

	Study	Method	Sample size (patients-controls)	Subjects state	Main results
14.	New et al. (2009)	FDG PET	38 IED + BPD – 36 HC	Aggression provocation task (PSAP), two conditions: 1. Provocation; 2. Non-provocation	BPD + IED patients increased metabolism in 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
15.	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 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
16.	Perez-Rodriguez et al. (2012)	FDG PET	38 IED + BPD – 36 HC	Aggression provocation task (PSAP), two conditions: 1. Provocation 2. Non-provocation	Male IED + BPD patients had significantly lower striatal metabolism than all other groups during both conditions

17.	Prossin et al. (2010)	Mu-opioid receptor radiotracer [11C] 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
18.	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 cingulus, occipital lobe, temporal pole, left superior parietal gyrus, and right superior frontal gyrus
19.	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 OFC, adjacent ventral medial and cingulate cortex
20.	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 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
21.	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

(continued)

Table 21.1 (continued)

	Study	Method	Sample size (patients-controls)	Subjects state	Main results
22.	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
23.	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
24.	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 nonsignificant the gender differences

Abbreviations: *[11C]McN 5652* [11C](+)-6β-(4-methylthiophenyl)-1,2,3,5,6α,10β-hexahydropyrrolo [2,1-a]isoquinoline, *FDG* 2-deoxy-2-[18F]fluoro-D-glucose, *alpha-[(11)C]MTrp* alpha-[(11)C]methyl-L-tryptophan, *ACC* Anterior Cingulate Cortex *ASPD* antisocial personality disorder, *BPD* borderline personality disorder, *[I-123] ADAM* [I-123] (2-([2-([dimethylamino]methyl)phenyl]thio)), *ECD* Ethylcysteinate dimer, *IED* intermittent explosive disorder, *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, *SERT* serotonin transporter, *SPECT* single photon emission computed tomography

stress condition. According to the authors, the lack of frontal activation under the stress condition (as opposed to the basal condition) could represent the absence of frontal modulation of the emotional response under the stress condition. After 16 months of psychodynamic psychotherapy, the posttreatment neural pattern in two treated BPD patients under the stress condition was different from their pretreatment pattern, and it was similar to their pattern in the 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 the 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 hyperrespond 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). 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).

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 hyperreactivity) 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 hyperresponsivity 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 (E. 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 recent PET study using the ligand [11C]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 ([I-123] ADAM (2-([2-([dimethylamino]methyl)phenyl]thio)-5-I-123-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). Both the 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 hyperresponsivity. 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 one recent imaging study has 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). 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 theoretically very attractive model, and current research is underway to provide more robust empirical evidence for it.

21.3 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.

SPD is characterized according to the DSM-IV-TR as "a pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships as well as by cognitive or perceptual distortions and eccentricities of behavior, beginning by early adulthood and present in a variety of contexts" (APA 2000). Psychoticism and cognitive deficits are core dimensions of SPD.

Psychotic-like symptoms are a key feature of SPD patients. 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 schizophrenia patients. The authors hypothesized that the dopaminergic dysregulation seen in schizophrenia spectrum disorders might have a trait component, present in remitted schizophrenia 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 D2/3 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 [18F]6-fluoro-l-dopa PET, in the whole striatum and its associative and sensorimotor subdivisions (Howes et al. 2011). Using PET and [11C]raclopride, Soliman et al. reported that patients with negative symptom schizotypy show greater striatal dopamine release than healthy controls in response to stress (Soliman et al. 2008).

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. 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 schizophrenia 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). 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). 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 not activated in healthy controls (Table 21.2).

Table 21.2 PET and SPECT studies in SPD

	Study	Method	Sample size (patients-controls)	Subjects state	Main results
1.	Abi-Dargham et al. (2004)	DA D2/3 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)	99 m 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 D2/3 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
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)	[18F]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

(continued)

Table 21.2 (continued)

Study	Method	Sample size (patients-controls)	Subjects state	Main results
8. Shihabuddin et al. (2001)	FDG PET	16 SPD – 27 SCZ – 32 HC	Verbal learning task	SPD patients showed increase metabolism in the ventral putamen
9. Soliman et al. (2008)	DA tracer [11C] raclopride PET	16 SPD – 10 HC	Psychological stress task and sensorimotor 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

Abbreviations: *IBZM* [123I]iodobenzamide, *FDG* 2-deoxy-2-[18F]fluoro-D-glucose, *DA* dopamine, *SPD* schizotypal personality disorder, *PET* positron emission tomography, *PFC* prefrontal cortex, *SCZ* schizophrenic, *SPQ* schizotypal personality Questionnaire, *SPECT* single photon emission computed tomography, *99 m Tc-HMPAO* technetium-99 m-d,l-hexamethylpropylene amine oxime, *SMT* symbol matching test, *WCST* Wisconsin Card Sort test

21.4 Antisocial Personality Disorder (ASPD)

ASPD is characterized in the DSM-IV-TR 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, irresponsibility, deceitfulness, indifference to the welfare of others, recklessness, a failure to plan ahead, and irritability and aggressiveness (APA 2000).

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). 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; 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 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). 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 frontal-temporal 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 frontal-temporal 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 OFC, adjacent ventral medial frontal cortex, and cingulate cortex (Siever et al. 1999).

Of note, the heterogeneity of the ASPD diagnosis itself and of the samples and control groups analyzed (e.g., different demographic groups, psychiatric comorbidities) 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 (Table 21.3).

Table 21.3 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. 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
4. 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 frontal-temporal hypoperfusion than in those with posterior temporal-parietal hypoperfusion
5. Mychack et al. (2001)	^{133}X and ^{99m}Tc brain perfusion HMPAO SPECT	12 FTD with right-sided frontal-temporal hypoperfusion – 19 FTD with left-sided frontal-temporal hypoperfusion	Resting state	Higher rate of undesirable social behaviors in subjects with right-sided frontal-temporal hypoperfusion than in those with left-sided frontal-temporal hypoperfusion
6. 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-[18F]fluoro-D-glucose, *AD* Alzheimer's disease, *ASPD* antisocial personality disorder, *ECD* Ethylcysteinate dimer, *HMPAO* Hexamethyl-propyl-eneamine-oxime, *FTD* Frontal-temporal dementia, *OFC* orbital frontal cortex, *PET* positron emission tomography, *SPECT* Single photon emission computed tomography

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Molecular Imaging Studies in Stimulant Addiction: A Cross-Species Perspective

22

Jeffrey W. Dalley and Bruce Russell

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 non-invasive neuroimaging techniques, positron emission tomography (PET), and single-photon emission computerised tomography (SPECT). Based on the seminal discovery of

J.W. Dalley (✉)
Behavioural and Clinical Neuroscience Institute,
University of Cambridge, Cambridge CB2 3EB, UK

Department of Psychology, University of Cambridge,
Downing Street, Cambridge CB2 3EB, UK

Department of Psychiatry, Addenbrooke's Hospital,
University of Cambridge, Cambridge CB2 2QQ, UK
e-mail: jwd20@cam.ac.uk

B. Russell
School of Pharmacy, University of Auckland,
85 Park Road, Grafton, Auckland, New Zealand

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_22, © Springer-Verlag Berlin Heidelberg 2014

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). 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). 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-Lopez et al. 2012)) and parallel advances in neuroimaging techniques and behavioural assessment in experimental animals (Nader et al. 2006; 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 persuasive evidence that dopamine (DA) and various DA-innervated structures, in particular the nucleus accumbens (NAcb) and prefrontal cortex (PFC) which 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

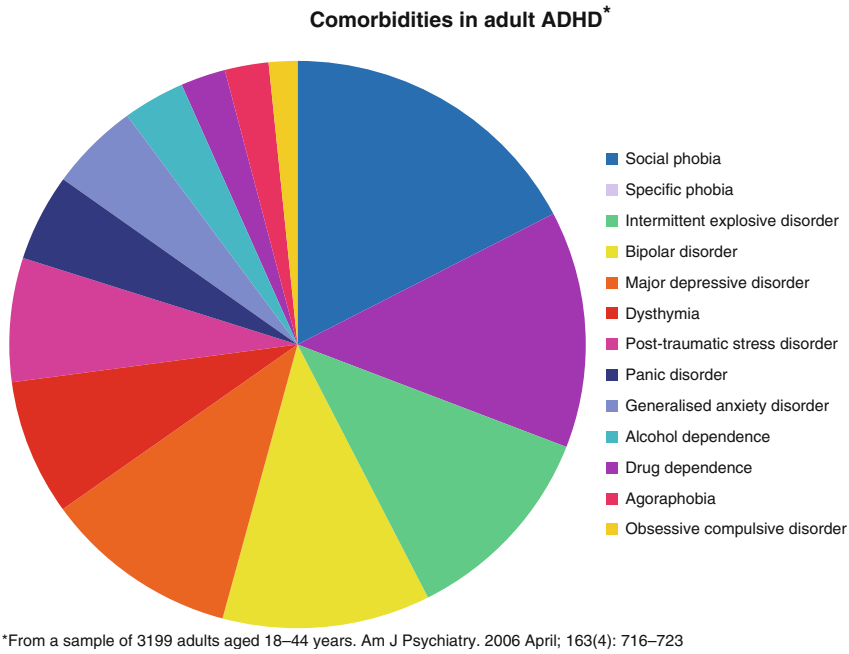

Fig. 22.1 Schematic illustration showing the major co-morbidities associated with adult attention deficit hyperactivity disorder, including alcohol and drug dependence (From Kessler et al. (2006))

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-Garcia et al. 2008; Ersche et al. 2010). Moreover, the balance of research findings indicates that impulsivity, in particular, may be a pre-existing vulnerability marker for addiction (Verdejo-Garcia et al. 2008). 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 2012), 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 evidence of shared neural mechanisms between ADHD and addiction and interrelate these findings in addicts and experimental animals.

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,

co-morbidities, 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 poly-drug 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 (Imperato and Di Chiara 1988a; 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), 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). 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}]-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 adolescent rats treated with methylphenidate (Thanos et al. 2009). 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) 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.

Consistent with this view, compelling evidence indicates that personality traits that encompass novelty/sensation seeking and impulsivity can predispose to drug

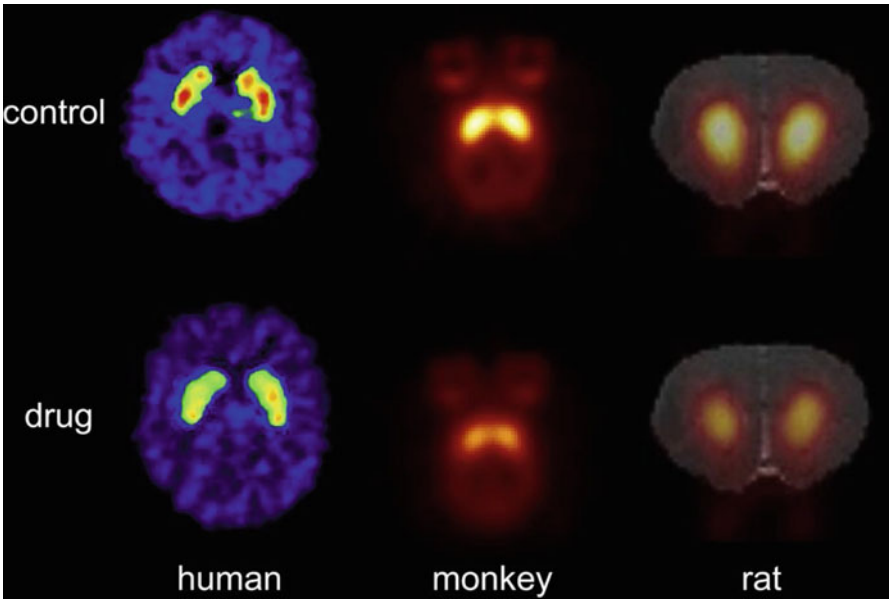

Fig. 22.2 Positron emission tomography scans showing reduced $D_{2/3}$ receptor availability in the striatum of a recently abstinent cocaine addict (Volkow et al. 2002), a rhesus macaque monkey exposed to 3-month intravenous cocaine self-administration (Nader et al. 2006), and a Lister-hooded rat exposed to prior intravenous amphetamine self-administration (Dalley et al. 2009) (From Dalley et al. (2011). Reprinted with permission from Cell Press)

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; Verdejo-Garcia 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 and colleagues (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).

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 5-choice serial reaction time task, a computerised operant test of sustained visual attention and impulsivity (Robbins 2002). The impulsive phenotype is 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), a region acknowledged to mediate primary drug reinforcement (Everitt and Robbins 2005).

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) and for habitual smokers but 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

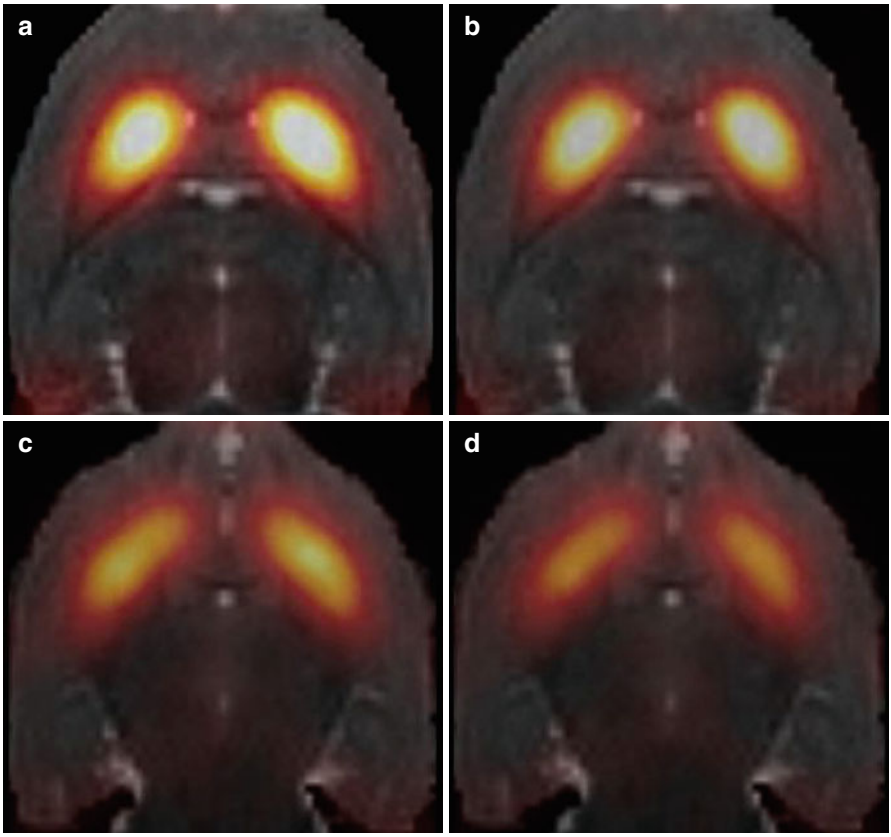

Fig. 22.3 Horizontal MR-co-registered PET scans showing reduced uptake of the high-affinity $D_{2/3}$ receptor antagonist [18F]-fallypride in the ventral, but not dorsal, striatum of high-impulsive rats. The scans show, respectively, $D_{2/3}$ receptor binding in the dorsal and ventral striatum of low (**a**, **c**)- and high (**b**, **d**)-impulsive rats (From Dalley et al. (2007). Reprinted with permission from AAAS)

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). In addition, high psychosocial stress levels 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).

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; Sekine et al. 2003). In contrast, a longitudinal PET study using [^{11}C]-d-threo-methylphenidate during both short (<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. 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). 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). 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).

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). 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). The authors concluded that D_3 receptors are upregulated in the brain of MA abusers. Thus, D_3 receptor antagonism may be a viable strategy to reduce the risk of relapse by curbing impulsive behaviour. Although this was the first study to specifically examine D_3 receptor density in MA addiction, all subjects were poly-drug users having reported the use of cocaine, MDMA, benzodiazepines,

opiates, THC, and ketamine. Moreover, 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 that 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 versus 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 Johanson and co-workers found that VMAT-2 density was decreased in abstinent MA abusers compared with control subjects (Johanson et al. 2006). Surprisingly, however, 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 perturbation that correlated inversely with the number of lifetime MDMA exposures (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 5-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.

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). 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-naıve 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 density was also compared in 9 treatment-naïve children with ADHD and 6 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). 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-naive 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 6 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 Fougere et al. 2006).

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 (Imperato and Di Chiara 1988a, b), and (3) behavioural traits such as impulsivity and novelty/sensation seeking (Piazza et al. 1989; Dalley et al. 2007; Buckholtz et al. 2010). Additionally, co-morbid brain disorders such as ADHD, which critically appear to influence disease progression (Verdejo-Garcia 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). This important study suggests that methylphenidate treatment per se is not a risk factor for addiction. However, further studies will be needed to investigate the effects of this, and related compounds, in animals pre-selected for trait-like impulsivity, especially as ADHD is accompanied by reduced $D_{2/3}$ receptor availability in the striatum (Volkow et al. 2009), just as in addiction (Sect. 22.2.2).

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). 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 non-invasive imaging of neurotransmitter systems other than the biogenic amines. Corresponding methods for ionotropic glutamatergic receptors are poorly developed and have yet to yield useful agents (Sobrio et al. 2010). However, promising PET ligands have been developed for mGluR1 and mGluR5 receptors (Hostetler et al. 2011; Simeon et al. 2012), 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). In a similar vein, research is needed to exploit established and novel tracers for $GABA_A$ and $GABA_B$ receptors (Moran et al. 2012), given the evidence of increased $GABA_A$ receptor availability in smokers (Stokes et al. 2012), and GABA dysfunction in humans with

rash impulsivity (Boy et al. 2011). 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). 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), these 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).

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). 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).

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.

Acknowledgements The authors acknowledge funding support from the UK Medical Research Council (G0701500) and a joint award from the MRC and Wellcome Trust in support of the Behavioural and Clinical Neuroscience Institute at Cambridge University. The authors also acknowledge funding within the MRC Imperial College, Cambridge University, and Manchester University (ICCAM) strategic addiction cluster.

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Abnormalities in Reward Processing in Drug Addiction: Lessons from Neuropsychology and Neuroimaging Studies

23

Rita Z. Goldstein

Contents

R.Z. Goldstein
Department of Psychiatry and Department of Neuroscience,
Friedman Brain Institute, Icahn School of Medicine at Mount Sinai,
The Leon and Norma Hess Center for Science and Medicine,
10th Floor 1470 Madison Ave, New York, NY 10029, USA
e-mail: rita.goldstein@mssm.edu

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_23, © Springer-Verlag Berlin Heidelberg 2014

Abstract

Drug addiction is characterized by compulsive drug use despite detrimental consequences to the individual's functioning as associated with increased salience attributed to the drug and drug-related cues at the expense of nondrug-related reinforcers. Underlying mechanisms include neuroadaptations of the dopaminergic striato-prefrontal circuit to intermittent and chronic supraphysiological stimulation by drugs that increase reward thresholds and decrease sensitivity to reward. This chapter summarizes behavioral and neurobiological evidence for decreased valuation of nondrug reinforcers and cues in individuals with chronic drug use or addiction. It is recommended that future research directly compares between responses to drug and nondrug-related stimuli in addicted individuals. The goal is to devise novel strategies to normalize reward processing, thereby decreasing anhedonia and increasing the motivation to attain alternative nondrug reinforcers, in addicted individuals.

23.1 Short Account of the Phenomenology and Neurobiology of Drug Addiction

Drug addiction is a chronically relapsing disorder characterized by repeated periods of drug craving, intoxication, bingeing, and withdrawal (American-Psychiatric-Association 1994). This cycle culminates in the escalated preoccupation with the attainment and consumption of – or recovery from – the substance, which replaces engagement with other rewarding experiences. This pattern continues despite attempts of the addicted individual to stop or curtail drug use, in the face of detrimental consequences to the individual's functioning (encompassing physical health and other personal, social, and occupational goals) and even when the rewarding experiences from the drug are markedly reduced. A putative mechanism is summarized by the Impaired Response Inhibition and Salience Attribution (iRISA) model where a disproportionate salience, or value, is attributed to drugs with a concomitant decrease in the value attributed to other primary and secondary reinforcers as associated with decreased self-control (Goldstein and Volkow 2002, 2011).

Drugs of abuse exert their reinforcing and addictive effects by activating the brain's reward system, consisting of the mesolimbic and mesocortical dopamine (DA) fibers, which originate in the ventral tegmental area (in the mesencephalon) and terminate in the ventral striatum (VStr, which encompasses the nucleus accumbens), ventral pallidum, amygdala, hippocampus, and prefrontal cortex (PFC). All addictive substances increase DA in the mesolimbic brain regions (Volkow et al. 1997b) as associated with their reinforcing effects (e.g., self-reports of "high" and "euphoria") (Laruelle et al. 1995; Volkow et al. 2002a). Importantly, drugs of abuse induce supraphysiological DA increases that do not habituate (Bassareo et al. 2002) and that encode for motivation to procure the drug irrespective of whether the drug is pleasurable or not (McClure et al. 2003). In contrast, nondrug primary ("natural") reinforcers induce DA increases within the physiological range that habituate with repeated consumption or decrease

with satiety and that mark reward prediction rather than the reward itself (Koob and Bloom 1988; Pontieri et al. 1996, 1998; Schultz et al. 2000).

Adaptations of the reward circuit to these intermittent and chronic supraphysiological stimulations by drugs include reward threshold elevations and reward sensitivity decreases (Ahmed et al. 2002; Ahmed and Koob 1998), an allostatic process similar to tolerance. Stated differently, frequent and high-dose drug use leads to compensatory brain changes that limit appetitive hedonic and motivational processes ("reward"), instead strengthening aversive (opponent or "anti-reward") systems (Koob and Le Moal 2001) where negative reinforcement (e.g., withdrawal) prevails over positive reinforcement (e.g., drug-induced high) (Solomon and Corbit 1973, 1974). Anhedonia is indeed a defining characteristic of drug dependence (Russell 1976) and criteria for major depressive disorder, which includes anhedonia as core symptom, are met by many drug-addicted individuals [e.g., 50 % of cocaine-addicted individuals (Gold 1997)]. In this state of reward deficiency (Blum et al. 2000), by increasing (or even normalizing) DA in the VStr, drugs may be processed as uniquely salient stimuli that will inherently motivate further procurement of more drug (regardless of whether the drug is consciously perceived as pleasurable or not) in susceptible individuals (Volkow et al. 2004a). Therefore, because addicted individuals may be self-administering drugs to compensate for the decreased stimulation of DA-regulated reward pathways by nondrug rewards, the goal of this chapter is to review human neuropsychological and neuroimaging studies that explored processing of nondrug reinforcers or that compared them to drug reinforcers in drug-addicted individuals.

23.2 Behavioral Evidence Suggesting Enhanced Processing of Drug as Compared to Nondrug Cues

23.2.1 Subjective Self-Reports

An impressive body of research has documented the subjective overpowering effects of drugs of abuse (Fox et al. 2005; Gawin 1991; Lasagna et al. 1955; Leyton et al. 2005; Von Felsinger et al. 1955), suggesting that conditioned drug-related responses trigger an intense desire for the drug, possibly exceeding desire for other nondrug reinforcers. The influential incentive motivation model suggests an important distinction between the desire for the drug, or drug wanting, and drug liking: as the incentive value of drugs and drug-related cues intensifies, drugs are increasingly "wanted" – but not necessarily "liked" – as associated with progressively more compulsive patterns of drug-seeking and drug-taking behavior (Robinson and Berridge 1993, 2001, 2003). We developed a brief self-report measure (Sensitivity to Reinforcement of Addictive and other Primary Rewards, STRAP-R) that dissociates "liking" from "wanting" of expected "drug" rewards as compared to "food" and "sex" while respondents report about three different situations (Goldstein et al. 2010b). Results in 20 cocaine-addicted individuals revealed that the reinforcers' relative subjective value changed such that "drug" was rated higher than "food" (otherwise "drug" < "food") when reporting about the last time one was "under drug

influence." This relative paling of other rewards in the environment was highest in the individuals with the youngest age of cocaine use onset, suggesting this subjective value shift (that included food, a primary reinforcer needed for survival) may represent a cumulative effect of drug use or it may predispose individuals to more intense early drug experimentation and subsequent development of addiction. Lack of such an effect when reporting about the other two situations ("current" lab situation and hypothetical "in general") points to the potential effectiveness of interventions administered during nondrug-related situations.

23.2.2 Objective Choice Behavior

Although essential, self-reports are limited due to their potential modulation by extraneous factors encompassing demand characteristics (and social desirability) as well as limited awareness of one's own mental processes [which may be all the more pronounced in drug addiction (Goldstein et al. 2009b)]. To overcome these limitations, experimental paradigms have tested the somewhat more objective choice behavior. Here, juxtaposing choice for drug against choice for competing reinforcers, studies have shown that previously drug-exposed animals choose cocaine over novelty (Reichel and Bevins 2008), adequate maternal behavior (Mattson et al. 2001), and even food (Aigner and Balster 1978; Woolverton and Anderson 2006; Zombeck et al. 2008). Parallel human studies use the multiple-choice procedure that provides an index of the relative reinforcing value of a drug vs. alternative reinforcers (Griffiths et al. 1993, 1996). Here, studies show that drug-addicted individuals routinely choose their drug of choice over money (Donny et al. 2003); Hart et al. 2000; Martinez et al. 2007). This effect is modulated by drug dose: choice for immediate alcohol (vs. 1-week delayed monetary delivery) increased with alcohol dose (12, 24, or 36 oz) in 27 young binge drinkers (>5 drinks at one sitting twice a week) (Benson et al. 2009). Interestingly, at the highest alcohol dose, alcohol choice was enhanced even in the immediate monetary payment condition (Benson et al. 2009). It would be important to test whether increasing monetary amounts would decrease the choice for alcohol or other drugs as indeed suggested naturalistically [e.g., decreases in cigarette smoking rates with pack price increases (Centers for Disease Control and Prevention 2011)]. We developed a picture choice task to provide an opportunity for testing choice for drug-related reinforcers as compared to competing reinforcers (pleasant and unpleasant pictures) outside of an acute drug administration paradigm, therefore suitable for use even when direct drug administration is not feasible or ethical (e.g., in abstaining or treatment-seeking drug-addicted individuals) (Moeller et al. 2009). Results showed that cocaine-addicted individuals selected more, and worked more for, viewing cocaine pictures than matched healthy control subjects (Moeller et al. 2009) and that this pattern was most pronounced in cocaine urine-positive (current users) as compared to cocaine urine-negative (longer abstinence, treatment-seeking status) addicted individuals (Moeller et al. 2010). Importantly, higher choice for viewing cocaine pictures, especially when directly compared to selections of the other positively valued and reportedly more pleasant pictures, correlated with higher frequency of actual cocaine use (Moeller et al. 2009) and higher degree of impaired insight in the abstinent cocaine-addicted individuals (Moeller et al. 2010) as possibly indicative of higher drug

Fig. 23.1 Drug fluency: a 1-min marker of processing bias in addiction. Subjects were asked to "call to mind and name as many drug-related words as possible for 1 min." These could be "names of drugs, people, places, or states of mind related to getting, using, or recovering from drugs" (Goldstein et al. 2007d). While healthy controls (*left*) produced a mean of 14 correct words, cocaine-addicted individuals (current users: cocaine urine positive) (*right*) produced 17 words. In addition, qualitative differences were noted such that the addicted individuals reported more words related to paraphernalia and drug administration via smoking, while the control subjects reported more words related to nonaddictive prescription drugs (Image created from TagCrowd.com)

addiction severity. Recent results further suggest that this choice, which prospectively predicts drug use after 6-month follow-up (Moeller et al. 2013), can be predicted using event-related potential (ERP) recordings in cocaine-addicted individuals with impaired insight (while self-reported arousal ratings predict choice in those whose insight is intact) (Moeller et al. 2012b). Given that, on average, the choice for viewing pleasant images was highest, it remains to be determined whether cocaine viewing choice (a proxy of actual cocaine use) can be reduced by exposure to pleasant images or other positive reinforcers, especially during craving, bingeing, or withdrawal.

23.2.3 Cognitive Processes

Cognitive studies similarly demonstrate that drug-related cues elicit a unique pattern of response in drug-addicted individuals. For instance, exposure to drug-related stimuli (e.g., pictures, paraphernalia) in drug-addicted individuals impacts classical neuropsychological measures of cognitive interference (e.g., the Stroop effect) (Carter and Tiffany 1999; Duka and Townshend 2004; Franken et al. 2000; Hester et al. 2006; Mogg and Bradley 2002). Similarly tailoring other neuropsychological measures to specifically target drug addiction also shows promising results. For example, drug-addicted as compared to control subjects name more drug-related words, while there are no group differences on the standard semantic fluency test (naming animals and fruits or vegetables) (Goldstein et al. 2007d) (Fig. 23.1). In addition to attention bias, the mechanisms underlying such automatic cue reactivity may include overlearning of drug-predictive cues (Redish 2004), "fresher" memory traces of drug effects (Lee et al. 2006), and heightened arousal/autonomic reactions evidenced in addicted

individuals in response to these drug-related cues (Carter and Tiffany 1999; Ehrman et al. 1992; Glautier and Drummond 1994; Margolin et al. 1994; Sinha et al. 2000). An open question in these studies is whether this bias to drug-related processing is associated with decreases in efficiency of nondrug-related processing, which would be evidenced by a cognitive compromise under a neutral context, as indeed suggested using classical neuropsychological studies in addiction [e.g., (Goldstein et al. 2004; Woicik et al. 2009, 2011)]. We speculate that this cognitive compromise in addicted individuals is not fully driven by a neutral (i.e., not motivating) context and that even under high levels of motivation, compromised neurocognitive functioning could be detected as suggested by results of neuroimaging studies as reviewed next.

23.3 Use of Money in Neuroimaging Studies in Drug-Addicted Individuals

Bar some exceptions, functional magnetic resonance imaging (fMRI) studies report that compared to controls, drug-addicted individuals show enhanced fMRI blood oxygenation level-dependent responses in the PFC (and subcortical regions) to drug-related cues relative to control cues (Goldstein and Volkow 2011). Such cue-induced PFC responses correlate with craving (Brody et al. 2002) and severity of drug use (Yalachkov et al. 2009) and predict both subsequent performance on a primed emotion recognition task (Artiges et al. 2009) and drug use 3 months later (Grusser et al. 2004), indicating that these measures have clinical significance. Comparisons between these drug-related stimuli with the processing of nondrug reinforcers have not been frequently inspected. Given the conditioning between monetary availability and drug procurement, using money as a reinforcer in drug addiction research is particularly important. If processing of this secondary generalizable reinforcer is compromised in addicted individuals, it is possible that for this population, only more immediate drug-related cues [e.g., pictures or a video; see (Garavan et al. 2000)] or the drug itself could activate this circuit at a comparable level with that induced by a nondrug-related reward in the nondrug-addicted individual. Importantly, because money is an effective reinforcer that acquires its value by social interaction, its compromised processing would suggest a socially disadvantageous emotional learning mechanism in addiction. Such a deficit, all the more distinct given the strong motivational and arousal value that is normally associated with this reward, would corroborate the notion that in addiction, brain reward circuits are "hijacked" by drugs, although the possibility for a preexisting deficit in reward processing also cannot be ruled out.

We used fMRI to investigate how cocaine-addicted individuals and controls responded to receiving monetary reward for correct performance on a sustained attention/forced-choice task (Goldstein et al. 2007a). In controls, sustained monetary reward (gain that did not vary within task blocks and that was fully predictable) was associated with a robust and complex neuronal activation pattern: there was a trend for the left orbitofrontal (OFC) to respond in a graded fashion (high money > low money > no money), the lateral and medial PFC (including anterior cingulate cortex) responded instead to the two conditions of monetary value equally (high = low > no money), while the mesencephalon displayed a third pattern of sensitivity to the

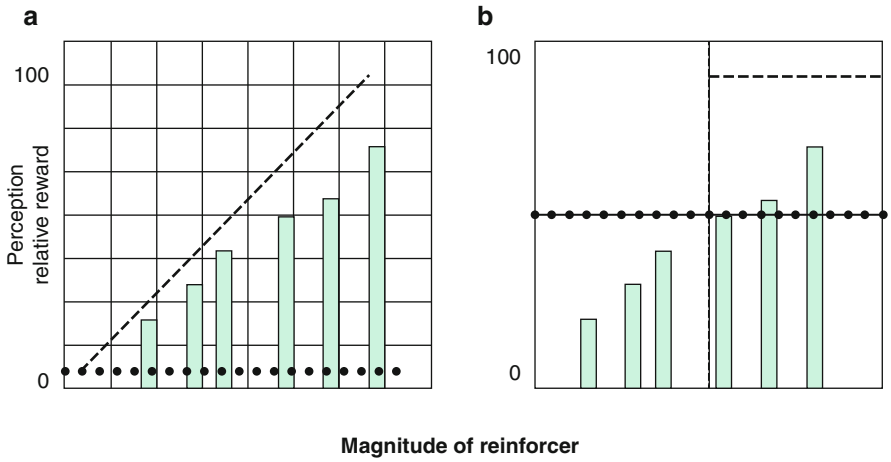

Fig. 23.2 Diagrammatic representation of the changes in relative and absolute reward in addiction. *Dotted lines* reflect the threshold for a stimulus to be perceived as reinforcing: the threshold is lower in the nonaddicted (**a**) and higher in the drug-addicted (**b**) individual. *Dashed lines* reflect the function that describes the perception of a stimulus as subjectively valuable. The high sensitivity to the reinforcers (*small squares*, **a**) allows the detection of small reinforcers and differences in magnitude between reinforcers in control subjects (*monotonically positive function*). The low sensitivity in cocaine abusers (*large squares*, **b**) does not permit the distinction between stimuli of different gradations but rather identify only those that reach the threshold required for the stimulus to be perceived as reinforcing (*step function*) (With permission from Goldstein et al. (2007b) Figure #4)

highest available reward only (high > low = no money). In general, these results were consistent with role of the (a) OFC in relative reward processing in the primate (Tremblay and Schultz 1999) and in healthy human subjects (Breiter et al. 2001; Elliott et al. 2003; Knutson et al. 2000; Kringelbach et al. 2003; O'Doherty et al. 2001), (b) PFC in the control of attention (Hornak et al. 2004) possibly irrespective of reward magnitude (Watanabe 1989), and (c) mesencephalon in an all-or-nothing reward processing in the primate (Tobler et al. 2005) and in healthy human subjects (Elliott et al. 2003). The cocaine-addicted subjects did not display this complex pattern of activation to monetary reward, demonstrating instead reduced fMRI signals in the left OFC for high gain compared to controls and showing less sensitivity to differences between the monetary rewards in the left OFC and in the dorsolateral PFC. Remarkably, more than half of the cocaine-addicted subjects rated the value of all monetary amounts equally (i.e., $10 = $1,000) (Goldstein et al. 2007b). Eighty-five percent of the variance in these ratings could be attributed to the lateral OFC and medial frontal gyrus (and amygdala) responses to monetary reward in the addicted subjects. Although these findings need to be replicated in a larger sample size and with more sensitive tasks, they nonetheless suggest that some cocaine-addicted individuals may have reduced sensitivity to relative differences in the value of rewards. Such "flattening" of the perceived reinforcer gradient (Fig. 23.2) may underlie overvaluation or bias toward immediate rewards (such as an available drug) (Roesch et al. 2006) and the discounting of greater but delayed rewards (Kirby and Petry 2004; Monterosso et al. 2007), therefore reducing sustained motivational drive.

Using the same sustained attention task and monetary reward quantities for the high, low, and no gains (45 1, and 0¢) while recording ERPs, we replicated the impact of monetary reward on neural responses (measured here with the P300 ERP component) in healthy young adults (Goldstein et al. 2006). This result was consistent with a large body of literature implicating the P300 in processing reward magnitude and valence [e.g., (Yeung and Sanfey 2004)]. Importantly, we subsequently replicated these results in 18 healthy individuals matched on age and other demographic factors to 18 cocaine-addicted individuals (abstinence 0–4 days) (Goldstein et al. 2008): while in the control subjects the amplitude of the P300 component was higher in the 45¢ condition than the 0¢ condition, a similar P300 response to money was not significant in the cocaine-addicted subjects. In parallel, only the control subjects reacted faster to the highest monetary condition (45¢) as compared to the neutral cue (0¢). Importantly, only in the control subjects these P300 amplitude differentials were directly intercorrelated with the respective behavioral adjustments to the monetary incentive (45¢>0¢ with accuracy and 1¢>0¢ with reaction time); in the cocaine-addicted subjects, the better the accuracy adjustment for the high monetary condition, the less frequent the cocaine use during the year preceding the study. Our most recent results show that such compromised P300 responses to money characterize both cocaine urine-positive (current users, shorter abstinence) and cocaine urine-negative (longer abstinence) addicted individuals, who show the most compromised P300 amplitudes (Parvaz et al. 2012) as potentially driven by structural integrity of the PFC (Parvaz et al. 2011).

These results may be therapeutically relevant as monetary reinforcement in well-supervised environments has been shown to enhance drug abstinence (Kampman 2010) and may also be relevant in predicting clinical outcomes. Indeed, in a similar population of subjects, the degree of midcingulate hypoactivation in a task where correct performance was monetarily remunerated correlated with frequency of cocaine use, whereas the degree of rostroventral cingulate cortical hypoactivation correlated with task-induced craving (Goldstein et al. 2009a). There was also an inverse association between these PFC regions of interest with cue reactivity in the mesencephalon in cocaine-addicted but not in control subjects, which implicates these cingulate subdivisions in the regulation of automatic drug responses (Goldstein et al. 2009c). It remains to be determined whether treatment could normalize these neural responses to money as potentially associated with better clinical outcome. Promising lines of evidence indicate an association between the lowest self-reported alcohol craving with the highest VStr monetary gain activations in abstinent alcoholics (Wrase et al. 2007). Because this region is important for reward *anticipation* [e.g., (Knutson et al. 2005)] and for processing both gains and losses (gain > loss) (Wrase et al. 2007) in healthy control subjects, its normalization may be consequential for the processing of numerous reinforcers.

23.4 Other Nonmonetary Reward

Studies of neural responses to drug-related vs. nondrug-related cues (including potential reinforcers) in addicted vs. nonaddicted individuals have generally utilized electrophysiological recordings while subjects view drug-related, pleasant, unpleasant,

and neutral pictures. Including nondrug emotional stimuli, in addition to the usual drug-related vs. neutral pictures, is important for emotional neuroscience studies in drug addiction (Aguilar de Arcos et al. 2005; Verdejo-Garcia et al. 2006). For example, we used an ERP component, the late positive potential (LPP), as a psychophysiological measure of automatic (Hajcak et al. 2007) or bottom-up (Ferrari et al. 2008) motivated attention bias elicited by drug-related stimuli in 55 cocaine-addicted individuals (27 abstinent and 28 current users) as compared to 29 matched controls (Dunning et al. 2011). Results showed that the LPPs elicited by cocaine pictures were similar to LPPs elicited by the other emotional pictures only in the addicted individuals; in the controls, LPPs elicited by the cocaine pictures were instead comparable to LPPs elicited by the neutral pictures, and both were significantly smaller than LPPs elicited by the other emotional pictures. These findings suggest that for the cocaine-addicted subjects, but not controls, cocaine stimuli automatically increase attention. This study also supports a relatively early attention bias to cocaine stimuli in the cocaine-addicted individuals, further suggesting that recent cocaine use may be associated with deficient sustained processing of any emotional stimuli. As mentioned above, a follow-up study showed these LPPs predict prospective choice (drug > pleasant for both) in cocaine-addicted individuals whose insight is compromised, of relevance to developing new intervention and prevention efforts (Moeller et al. 2012b). A study in active heroin-addicted individuals (24 h abstinence) reported similar drug-related P300 enhancements (Lubman et al. 2009) as correlated with baseline craving (Lubman et al. 2008). The more recent study (Lubman et al. 2009) also showed lack of the typical P300 reward enhancement to pleasant vs. neutral or drug pictures, consistent with inhibited responding to nondrug reinforcers in addicted individuals.

Compromised responsiveness to pleasant pictures in heroin-addicted individuals was similarly reported in an fMRI study, where the bilateral dorsolateral PFC was activated to pleasant pictures in 18 healthy controls but not in 16 abstinent (1–24 weeks) inpatient male heroin-addicted individuals (Zijlstra et al. 2009). Interestingly, in initially detoxified alcoholic subjects, VStr (and thalamic) response to pleasant vs. neutral stimuli predicted drinking days and alcohol intake within a 6-month follow-up period (Heinz et al. 2007). Taken together, the preserved responding to nondrug reinforcers may characterize individuals with less pronounced illness severity or reflect a protective factor in drug-addicted individuals. Indeed, offspring of alcoholics with higher striatal DA D2 receptor availability may be protected against developing alcoholism through more adaptive recruitment of corticolimbic circuits (including the OFC) needed for emotion regulation (Volkow et al. 2006).

23.5 The Underlying Mechanism for a Possible Reward Value Shift in Drug Addiction

Dopamine is an essential neurotransmitter in processing reward and reward prediction errors (McClure et al. 2004; Schultz 2006; Volkow et al. 1993) and in salience enhancement (Volkow et al. 2002b, 2004b). Positron emission tomography studies have documented that with chronic drug use striatal DA D2 receptor availability is

reduced (Nader and Czoty 2005; Nader et al. 2006; Volkow et al. 1990, 1997b) as associated with blunted responses to drug rewards (e.g., intravenous methylphenidate) (Volkow et al. 1997a) and altered function in dopaminergically innervated corticolimbic areas (encompassing in the PFC the OFC and anterior cingulate cortex) that mediate processing of reward salience and motivation (McClure et al. 2004; Schultz 2006; Volkow et al. 1993).

The abnormalities in reward processing in drug addiction are therefore not surprising and are consistent with similar compromises in other dopaminergically mediated psychopathologies. For example, monetary incentives do not modulate grip force in patients with bilateral striatal-pallidal damage (Schmidt et al. 2008), and Parkinson's disease patients are less proficient in learning the predictive value of monetary reward cues, displaying diminished functional connectivity of the mesencephalon and VStr (Schott et al. 2007). In healthy individuals, a preliminary pharmacological fMRI study suggested that a dopaminergic agent (0.25 mg/kg oral dextroamphetamine vs. placebo) modulated VStr responses during anticipation of gains such that responses were blunted in peak amplitude but extended in duration (Knutson et al. 2004). The association between DA and reward processing is thus not linear, and potentially modulated by baseline DA levels. For example, higher baseline striatal DA synthesis is associated with better reward learning but worse learning with further dopaminergic intervention (with bromocriptine) in healthy controls; in contrast, lower baseline striatal DA synthesis is associated with better punishment learning and DA enhancement improves reward learning (Cools et al. 2009). It is therefore possible that DA agonists could be used to improve reward processing in selected subgroups of drug-addicted individuals. Suggestive of the success of such an intervention, preliminary results in our laboratory showed a correlation between baseline DA receptor availability (measured with positron emission tomography with C^{11} raclopride) and thalamic and medial PFC response to money (measured with fMRI) in seven cocaine-addicted individuals (Asensio et al. 2009).

More direct evidence for the role of DA in the modified reward valuation in addicted individuals derives from another positron emission tomography study where blunted amphetamine-induced DA release in the VStr (and dorsal striatum) was predictive of actual choice for cocaine over money (and not of positive subjective drug effects) in 24 cocaine-addicted individuals (14 days abstinence) as compared to 24 controls (Martinez et al. 2007). These results were all the more compelling as subjects could choose to receive $5 or self-administer smoked cocaine (6 or 12 mg) with street value <$5. Although results of this study need to be validated using a more immediate monetary gain (the $5 gain was delayed, given as a merchandise voucher redeemable at local stores and paid upon discharge from the study), choice on this self-administration paradigm may model relapse (drug choice followed a priming dose/drug cue). In fact, the authors interpreted these results to indicate that the cocaine-addicted individuals who are most vulnerable to relapse are those with the lowest presynaptic DA function because their DA levels may be insufficient to provide the signal that could shift habitual behavior (drug choice, lesser reward) to a more advantageous behavior (monetary choice, greater reward). A follow-up fMRI study used a similar paradigm in cigarette smokers, where

subjects could win cigarettes or money. Occasional smokers were more motivated to obtain money than cigarettes, whereas dependent smokers made similar efforts to win money or cigarettes (Buhler et al. 2010). A similar group by reward interaction was observed in the right OFC, bilateral dorsolateral PFC, and left anterior cingulate cortex, such that in the occasional smokers these regions showed higher activity to stimuli predicting an increasing monetary reward than to stimuli predicting a cigarette reward, whereas the dependent smokers showed no significant differences in such anticipatory brain activity. These regions also showed higher activation to money in the occasional than dependent smokers (Buhler et al. 2010). Dopaminergic agonists may reverse these abnormalities as remains to be studied.

23.6 Conflicting Results

Throughout most of this chapter, results have generally pointed to decreased valuation of nondrug reward in addiction. Indeed animal research suggests that after chronic drug administration, the value of saccharin is decreased (Grigson and Twining 2002). Similarly, human cocaine-addicted subjects but not controls showed reduced activation of corticolimbic brain areas when viewing an erotic video than when exposed to a cocaine video (Garavan et al. 2000). Yet evidence from animal studies also suggests that drug sensitization can *increase* the incentive value of other rewards, such as sucrose or other foods, a sexually receptive female (for male rats), and conditioned stimuli for such rewards (Fiorino and Phillips 1999a, b; Nocjar and Panksepp 2002; Taylor and Horger 1999; Wyvell and Berridge 2001). Similarly, in human addicted individuals, evidence suggests that some cocaine-addicted individuals are hypersexual (Washton and Stone-Washton 1993) and some substance-dependent individuals may be hyperresponsive to money rewards (Bechara et al. 2002). These latter lines of evidence are consistent with the notion of a generally drug-sensitized brain reward circuit where heightened drug motivation may "spillover" to nondrug rewards (Robinson and Berridge 2003). A resolution of this apparent conflict may reside in a better demarcation of the role different brain regions carry within the reward circuit [e.g., different brain regions may show the opposite patterns of response to reward (Konova et al. 2012)], types of drugs used (e.g., cocaine vs. heroin), or in other individual differences (e.g., severity of addiction, impulsivity) as remains to be studied.

23.7 Summary and Conclusions

Evidence for a modified valuation of monetary and other nondrug-related reward in drug-addicted individuals was reviewed. The selective diversion of motivational resources away from conventional rewards and toward drug rewards in addicted individuals offers strong support for the hypothesis that the value of drug-related cues overpowers that of nondrug-related cues in addicted individuals. These abnormalities may contribute to the deficits in controlling drug-taking behavior in

drug-addicted individuals. For example, restricted range of subjective valuation of reward may play a mediating role in the ability to use internal cues and feedback from the environment to inhibit inappropriate (drug-escalated) behavior. Moreover, a "flattened" sensitivity to gradients in reward may predispose individuals to disadvantageous decisions (e.g., trading a car for a couple of cocaine hits). Without a relative context, drug use and its intense effects (craving and high) could become all the more overpowering.

Taken together, these results contribute to our understanding of how relative reward preferences may change in addiction, such that preference for the drug competes with (and sometimes exceeds) preference for other reinforcers, with a concomitant decrease in the ability to assign relative values to nondrug-related rewards. Insofar as emotions are defined as "states elicited by reinforcers" (Rolls 2000), such reward valuation abnormalities may contribute to pervasive disruptions in emotional processing in drug-addicted individuals, encompassing empathy (Kim et al. 2010), self-awareness and awareness of disease severity, and need of treatment (Goldstein et al. 2009b). Because reinforcement is crucial in most types of learning, these disruptions may also contribute to cognitive dysfunction spanning attention, working memory, decision-making, and inhibitory control (Goldstein et al. 2011), together threatening sustained abstinence (Garavan and Hester 2007), increasing attrition from treatment (Aharonovich et al. 2003, 2006), or even predisposing individuals to develop drug addiction (Moffitt et al. 2011; Tarter et al. 2003).

23.8 Future Directions

A lingering question is whether altered sensitivity to nondrug reinforcers in addicted individuals also applies to negative reinforcers such as money loss. Studies in animals show that "addicted" subjects manifest persistent drug seeking even if the drug is associated with receiving an electric shock (Deroche-Gamonet et al. 2004). In humans, hypoactivation in the right ventrolateral PFC in smokers during monetary loss, and in gamblers during monetary gain, has been reported (de Ruiter et al. 2009). Although more studies are clearly needed, the implication of reduced sensitivity to negative reinforcers in addiction has practical implications as, in addition to positive reinforcers (such as vouchers and privileges), negative reinforcers (such as incarceration) are increasingly being used in the management of drug abusers.

Future studies could also help to ascertain whether addicted individuals may resort to taking drugs because they are easily bored, frustrated, angry or fearful, perhaps as a result of altered reward valuation. Low threshold for experiencing any of these emotions, or the inability to sustain goal-directed behavior (e.g., complete a boring task) especially when experiencing these emotions, may be associated with impaired inhibitory control (i.e., enhanced impulsivity). In cocaine-addicted individuals, PFC activity habituates prematurely to repeated presentation of an incentive-sustained attention task (Goldstein et al. 2007c), in the absence of a compensatory response in the dopaminergic midbrain during such mental fatigue

(Moeller et al. 2012c), which could be indicative of compromised sustainability of effort and may result in inadequate engagement in treatment activities and relapse.

Future studies need to identify the drug-addicted individuals who evidence a compromised sensitivity to nondrug reward for tailored interventions to improve associated cognitive-emotional skills (e.g., attention, response shifting, learning and memory, general value estimations) with the goal of modulating choice behavior such that nondrug rewards would be chosen over drug use. In this quest, one could explore promising new approaches that have been shown to modify behavior and decision-making [e.g., virtual environments and computer games that can acquire persistent motivational properties (McCabe et al. 2009)]. Direct brain stimulation or pharmacological enhancement of the dopaminergically innervated corticolimbic brain regions may also be beneficial, especially if combined with targeted cognitive-behavioral exercises (Goldstein et al. 2010a; Moeller et al. 2012a, c) or in a more sustained fashion during resting state (Konova et al. 2013), for neural rehabilitation purposes (Vinogradov et al. 2011).

Time dedicated to working on this chapter was supported by grants from the National Institute on Drug Abuse (1R01DA023579).

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SPECT and PET in Eating Disorders

24

Aren van Waarde, Kurt Audenaert, Geraldo F. Busatto, Carlos Buchpiguel, and Rudi A.J.O. Dierckx

Contents

A. van Waarde (✉)
Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713GZ Groningen, The Netherlands
e-mail: a.van.waarde@umcg.nl

K. Audenaert
Department of Psychiatry and Medical Psychology, University Hospital, Ghent University, De Pintelaan 185, 9000 Ghent, Belgium
e-mail: kurt.audenaert@ugent.be

G.F. Busatto
Department of Psychiatry, Faculty of Medicine, University of São Paulo, Rua Ovídio Pires de Campos s/n, 05403-010 São Paulo, Brazil
e-mail: geraldo.busatto@gmail.com

C. Buchpiguel
Nuclear Medicine Service, Department of Nuclear Medicine, Clinical Hospital, School of Medicine, University of São Paulo, Rua Ovídio Pires de Campos s/n, 05403-010 São Paulo, Brazil
e-mail: buch@usp.br

R.A.J.O. Dierckx
Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713GZ Groningen, The Netherlands

University of Ghent, Ghent, Belgium
e-mail: r.a.dierckx@umcg.nl

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_24, © Springer-Verlag Berlin Heidelberg 2014

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, and cannabinoid CB1), stimulant-induced dopamine release, 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.

24.1 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).

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, 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).

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).

Medical imaging techniques such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) can provide insight in 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 (Frank 2012; Frank and Kaye 2012; Jauregui-Lobera 2011; Kaye 2008).

24.2 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 7 female AN patients (age 19 ± 5 years) and 5 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 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 10 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 9 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 of a persistent eating disorder. Thus, rCBF at initial presentation seems to predict neuropsychological status at 4-year follow-up (Frampton et al. 2012).

In conclusion, most studies suggest that AN is associated with hypoperfusion in several brain areas (Table 24.1). 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).

24.3 Bulimia and Brain Perfusion

An initial ^{99m}Tc-HMPAO-SPECT study in bulimia nervosa compared rCBF in 5 patients with bulimia (age 21.0 ± 2.9 years), 8 patients with anorexia (age 24.1 ± 7.8 years), and 9 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).

Table 24.1 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)
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)
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. (2007b)

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

A subsequent study examined rCBF in 9 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 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. 2007b). 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 3 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 towards 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 24.2). 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.

24.4 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 ten 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

Table 24.2 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

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 towards 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. 1997b). 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. 1997a). 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. 1997b, 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 distribute 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 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 distribute 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 mediodorsal thalamus, ventral pontine nuclei, and cerebellum. Brain metabolism in cingulate and the surrounding motor and somatosensory cortex were 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 recent study evaluated how cerebral glucose metabolism correlates with clinical improvement after deep brain stimulation (DBS) 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).

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 24.3). 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.

24.5 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

Table 24.3 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. (1997b)
Dep uw, control	Only 1 session	^{18}F-FDG	↓ in uw group	–	Delvenne et al. (1997a)
AN, control	Pre-/post-therapy	^{18}F-FDG	↓ in AN ctx areas	Normalization	Miller et al. (2004)
AN, BN, control	Only 1 session	^{18}F-FDG	Rel ↓ par ctx, rel ↑ cau nuc AN, BN	–	Delvenne et al. (1997b, 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

Table 24.4 Studies of CMRglucose (activation paradigm)

Study groups	Study moment	Stimulus	Tracer	Findings	After therapy	Reference
BN, control	Only 1 session	Visual task	$^{18F\text{-}FDG}$	Asymmetry in controls No right activation in BN	–	Wu et al. (1990)
BN, MAD, control	Only 1 session	Visual task	$^{18F\text{-}FDG}$	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

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 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 24.3). However, data from FDG studies using an activation paradigm suggest that the processing of visual tasks may be impaired in BN (Table 24.4).

24.6 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 24.5; reviewed in Bailer and Kaye 2011; Barbarich et al. 2003; Kasper et al. 2002; Kaye et al. 2005a, b).

Table 24.5 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-ß-CIT	↓	–	Tauscher et al. (2001)
ob BN, ob control	Only 1 session	^{123}I-ß-CIT	↓ midbr	–	Kuikka et al. (2001)
ob BN, ob control	Pre-/post-therapy	^{123}I-ß-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)
			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 1session	^{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. (2007a)
			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, *le* left, *med* medial, *midbr* midbrain, *mpc* medial parietal cortex, MPPF 2′-methoxyphenyl-(*N*-2′-pyridinyl)-*p-fluoro-benzamidoethyipiperazine*, *ob* obese, *occ* occipital, *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

An initial study used the tracer [^{123}I]-2ß-carbomethoxy-3ß-(4-iodophenyl)tropane (ß-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 reported in a Finnish study using the same approach. Obese binge-eating women showed a significantly (28 %) reduced ß-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 ß-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 ß-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 midbrain (containing the dorsal raphe), superior and inferior cingulate, and higher binding potential in 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).

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 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 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-fluoro-phenoxy)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. 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 in the patient groups (Goethals et al. 2007a).

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]WAY100635 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 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]WAY100635 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 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 later 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.

24.7 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 24.6). An early study included 10 women who had recovered from anorexia nervosa and 12 healthy control subjects. The patient 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 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 recent 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,

Table 24.6 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)
			μ-Opioid binding		
BN, control	Only 1 session	^{11}C-carfentanil	↓ le ins ctx	–	Bencherif et al. (2005)
			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 Relative ↑ ins AN, BN	–	Gerard et al. (2011)

am amygdala, *AN* anorexia nervosa, *ant* anterior, *BN* bulimia nervosa, *BP-AN* binge/purge type of anorexia nervosa, *cau* caudate, *CIT* carbomethoxy-3β-(4-iodophenyl)tropane, *ctx* cortex, *ins* insula, *le* left, *nuc* nucleus, *R-AN* restrictive type of anorexia nervosa, *str* striatum, *ven* ventral

food-related dopamine release produces anxiety in patients with AN, whereas feeding is pleasurable in healthy subjects.

A very recent 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 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.

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 amygdala, hippocampus, medial prefrontal cortex, orbitofrontal cortex, and temporal cortex. Anorexia patients showed even higher binding potential in 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 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.

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, 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.

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Impulsivity Imaging

25

Mariza Vorster, Nozipho Nyakale, and Mike Sathekge

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 dysfunction and dysregulation 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 pathophysiology of impulsivity. Thus individual variation in limbic striatal D_2/D_3 receptor availability, diminished functioning of the highly diverse serotonergic

M. Vorster, MD (✉) • N. Nyakale, MD • M. Sathekge, MD, PhD (✉)
Nuclear Medicine Department, Steve Biko Academic Hospital, University of Pretoria, Voortrekkers Road and Malan Street, Capital Park, Pretoria, South Africa
e-mail: mike.sathekge@up.ac.za

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_25, © Springer-Verlag Berlin Heidelberg 2014

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 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.

25.1 Overview

25.1.1 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 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 behavioral inhibition as a type of temperament in the child that presents a unique combination of behavioral and physiological responses to novelty. Furthermore, he believed this temperament was associated with future development of anxiety disorders in adulthood. From a behavioral

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, Barratt, Dougherty, Schmitz and Swann (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 the cluster B personality disorders).

25.1.2 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).

25.1.3 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 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 three 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 25.1).

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 and Coskunpinar (2011). Other methodological problems with the study of impulsivity

Table 25.1 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	Color words are presented in different ink colors (e.g., *green* is printed in red ink). Participants are required to name the word color 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 nonplanning impulsiveness (lack of "futuring" or forethought).

Aichert et al. (2012)

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.

25.1.4 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, orbito-frontal, 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, current emphasis appears to have shifted to the importance of the dopaminergic and noradrenergic systems.

25.1.5 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 (vast majority of tracers used) and do not illicit pharmacological effects due to the very low (tracer) doses used.

25.1.6 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.

25.1.6.1 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

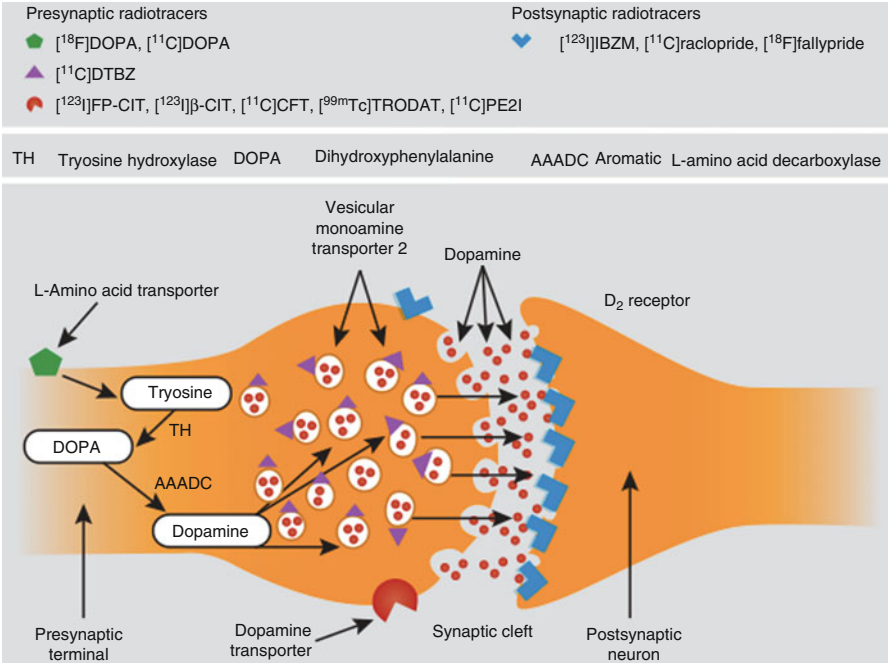

Fig 25.1 The dopaminergic synapse (Taken from Fusar-Poli et al. (2012)

reuptake of free dopamine from the synaptic cleft mediated by a macromolecular transporter located in the axonal membrane (DAT).

The majority of neuropsychiatric disease 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 25.1 below provides an overview of the most important functional imaging targets and some of the more commonly used SPECT and PET tracers (Fusar-Poli et al. 2012).

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 integration of motivational and reward-based processing (Cardinal et al. 2004).

There has been 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 recent 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 exist. 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).

25.1.6.2 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 (Asberg et al. 1976) (Fig. 25.2).

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. Tryptophan hydroxylase (TPH) plays an important role in the synthesis of serotonin by synthesizing L-tryptophan to 5-hydroxy-L-tryptophan, which in turn is synthesized 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)

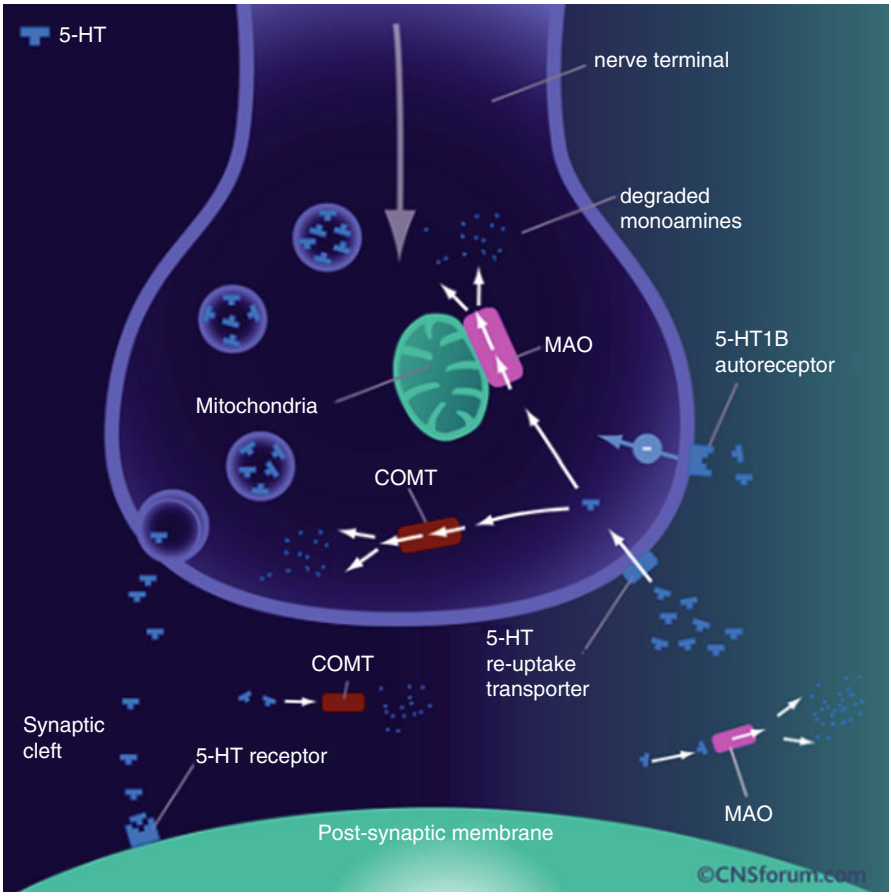

Fig 25.2 5-HT neurotransmission

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 in charge of degrading serotonin, and the resulting aldehyde is oxidized by aldehyde dehydrogenase to 5-hydroxyindoleacetic acid (5-HIAA).

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. The following table has been taken from their paper and provides a nice summary of the imaging options and studies so far (Paterson et al. 2013) (Table 25.2).

Saulin et al. (2012) published a review, which summarizes 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 advances in in vivo quantification of these different receptors and

Table 25.2 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[a]	2	1[a]	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[b]	1990	3	36	7
	[^{18}F]altanserin	1994	5	51	10
	[^{18}F]deuteroaltanserin	1998	2[a]	5[a]	1
	[^{11}C]MDL100907	1998	5	6	5
5-HT_4	[^{11}C]SB207145	2008	3[a]	3[a]	2
5-HT_6	[^{11}C]GSK215083	2008	1	2	1
SERT	Beta-[^{123}I]CIT[b]	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[c]	17[d]	2
Synthesis	[^{11}C]-HTP	1991[a-d]	4	10	3

Paterson et al. (2013)

enzymes that are part of the serotonergic system using PET. A summary from their publication can be found below (Saulin et al. 2011) (Table 25.3).

Saulin and co-workers (2011) mention the following in their review, which relates to impulsivity.

In 5-HT_{1B} knockout mice, an increase in impulsive behaviour and defective regulation of impulsivity was observed (Meneses 2007; Meneses and Perez-Garcia 2007).

The 5-HT_{1B} receptor has been implicated in various 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 orbitofrontal cortex, anterior cingulate, frontal cortex and other regions of the brain (Haugbøl et al. 2007).

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} in deliberate self-harm patients was significantly reduced in the frontal cortex (after correction for age) when compared

Table 25.3 Overview of 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 [^{11}C]WAY100635	[^{18}F]MefWAY (primate) [^{11}C]CUMI-101, (baboon, *Papio anubis*, human)	Wooten et al. (2011) Milak et al. (2008, 2010, 2011)
5-HT_{1B}	[^{11}C]AZ10419369 [^{11}C]P943	–	Varnäs et al. (2011a) Murrough et al. (2011)
5-HT_{1C}	–	–	–
5-ht_{1E}	–	–	–
5-HT_{1F}	–	–	–
5-HT_{2A}	[^{18}F]altanserin [^{11}C]MDL100,907	[^{11}C]CIMBI-36 (pig) (R)-[^{18}F]MH.MZ (rodent)	Ettrup et al. (2011) 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 [^{11}C]MADAM	[^{18}F]FPBM (rat) [^{18}F]ADAM (rat, monkey)	Wang et al. (2010) Huang et al. (2010)
VMAT2	[^{11}C]DTBZ [^{11}C]MTBZ	[^{18}F]AV133 (mouse, human)	Zhu et al. (2010) Okamura et al. (2010)
MAO-A	[^{11}C]harmine [^{11}C]clorgyline [^{11}C]befloxatone	[^{11}C]RS 2360 (mouse)	Soliman et al. (2011) Fowler et al. (2005) Bottlaender et al. (2003) De Bruyne et al. (2010)
5-HT synthesis	[^{11}C]AMT [^{11}C]5-HTP	–	Visser et al. (2011)
Endogenous 5-HT	[^{18}F]MPPF	–	Derry et al. (2006) Yatham et al. (2001) Varnäs et al. (2011b)

Saulin et al. (2011)

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).

Abnormalities of 5-HT$_2$ receptors in the brain cortex are viewed as representative of 5-HT$_{2A}$ receptors in 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 para-hippocampal 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). 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 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 had previously had a serious suicide attempt and their matched healthy controls. SPECT imaging demonstrated a correlation between

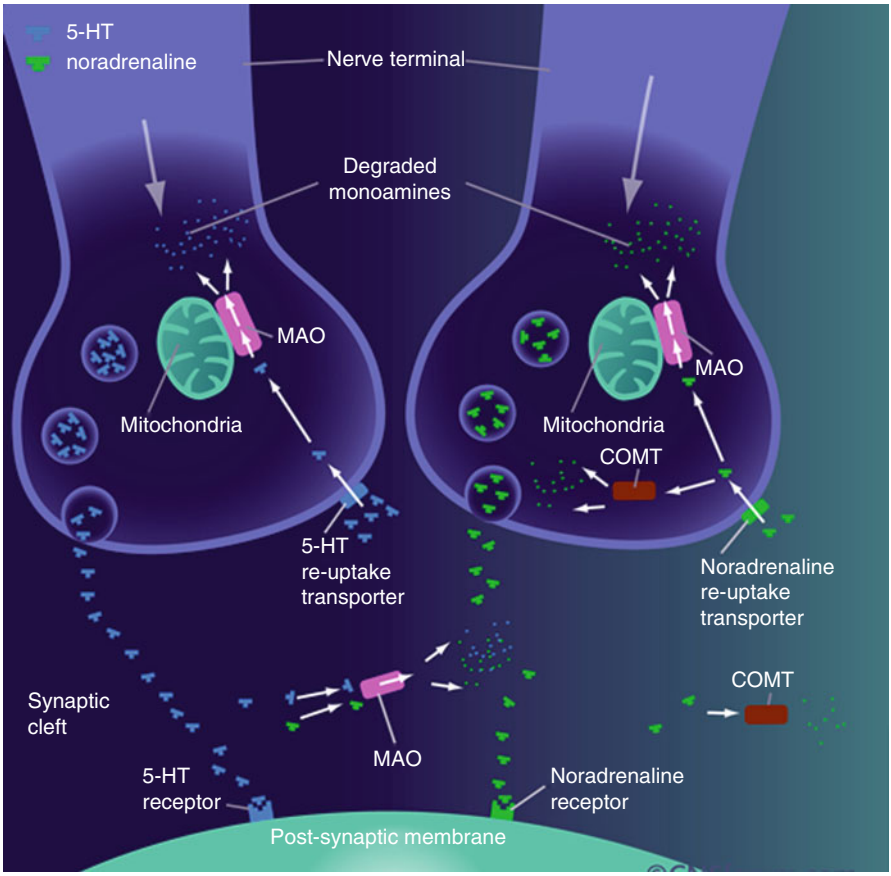

Fig 25.3 Noradrenergic neurotransmission

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).

25.1.6.3 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 throughout the cerebral cortex, whereas low levels are found in cerebellum and striatum.

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 (Fig. 25.3).

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 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 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 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.

25.1.6.4 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 more 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 these 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-naive 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).

25.2 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.

25.2.1 Neurology

25.2.1.1 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 (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.

25.2.1.2 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 recent 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 25.4):

The following observations were made (Fig. 25.4):

- 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 increased 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).

Table 25.4 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-naive, 1 drug-free	1.00
ADHD			9	3	41	11		
Comparison			9	3	41	11		
Cheon et al. (2004)	[^{123}I]IPT	SPECT					Drug-naive	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-naive, 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-naive	1.06[a]
ADHD			20	11	35	7		
Comparison			20	11	32	8		

(continued)

Table 25.4 (continued)

Study and group	Radiotracer	Technique	*N*		Age (years)		ADHD treatment status	ADHD/comparison ratio of dopamine transporters
			Total	Female	Mean	SD		
Spencer et al. (2007)	[^{11}C]altropane	PET					Drug-naive	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-naive	0.80[a]
ADHD			53	26	32	8		
Comparison			44	14	31	6		
Hesse et al. (2009)	[^{123}I]FP-CIT	SPECT					Drug-naive	0.81[a]
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

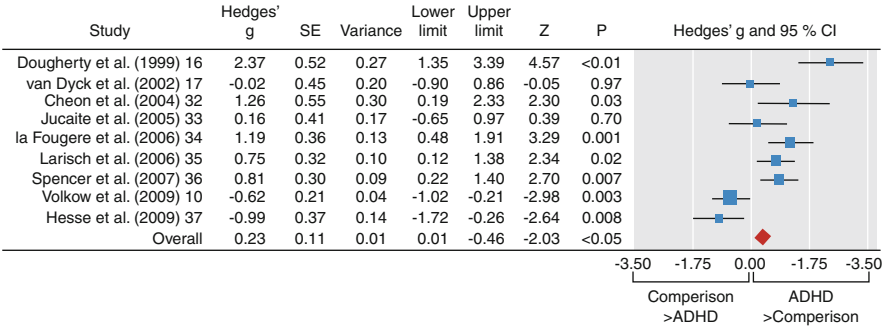

Fig. 25.4 Meta-analysis of striatal dopamine transporter density in ADHD patients and healthy comparison subjects employing random-effects models (Fusar-Poli et al. (2012))

25.2.1.3 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-naive 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).

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).

25.2.1.4 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).

Genetics 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 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).

Sarah Durston (2010) reviewed what is known on the subject so far, which is summarized in the following tables (Durston 2010) (Table 25.5):

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).

25.2.1.5 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).

Table 25.5 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) 57 NC (17.6 ± 9.1 yrs) Mixed ethnicity; US study	Structural MRI (1.5 T); semi-automated volumes of TB, cerebellum, PFC; manual volumes of CN, PAL DRD4 VNTR exon 3; 7R-car vs not: 17 ADHD-7R; 22 NC-7R	No genotype effects No group × genotype interactions
Bobb et al. (2005)	163 ADHD (86 M; 9.0 ± 2.2 yrs; meds not reported) 129 NC (74 M; 16.0 ± 8.1 years) Mixed ethnicity; US study	Structural MRI (1.5 T); fully automated volumes of TB, lobes, BG, cerebellum DRD1; rs4532 C-car vs not: 64 ADHD C-car and 36 NC C-car; rs265981 T-car vs not: and 62 ADHD T-car; 36 NC T-car 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	No genotype effects No group × genotype interactions
Durston et al. (2005)	26 ADHD (30 M; 12.1 ± 2.5 yrs; all MPH) 26 unaffected siblings (30 M; 11.6 ± 3.2 years) 20 NC (30 M; 10.7 ± 1.9 yrs) Caucasian sample; Dutch study	Structural MRI (1.5 T); automated volume of PFC GM; manual volume of CN DRD4 VNTR exon 3; 4R/4R vs not: 34 4R/4R DAT1 3′ VNTR; 10R/10R vs carrier 9R: 40 10R/10R	Main effects: DAT1 on CN: 9R > 10R DRD4 on PFC GM: 4R < car variant alleles
Shaw et al. (2007)	105 ADHD (50 M; 10.1 ± 2.8 yrs; 85 stimulant meds) 103 NC (58 M; 10.0 ± 2.9 yrs) Mixed ethnicity; US study	Structural MRI (1.5 T); longitudinal; Automated cortical thickness DRD4 VNTR exon 3; 7R-car vs not: 43 ADHD 7R and 35 NC 7R	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
Monuteaux et al. (2008)	24 ADHD (12 M; 38.1 ± 10.8 yrs; meds not reported) 19 ADHD and BD (13 M; 35.8 ± 14.1 yrs) 20 NC (13 M; 33.2 ± 10.0 yrs) Mixed ethnicity; US study	sMRI (1.5 T) volumes of sup frontal, mid frontal, ACG, cerebellar cortices DRD4 VNTR exon 3; 7R-car vs not: 6 ADHD; 7 ADHD and BD; 6 NC 7R	Main effect genotype in frontal and cerebellar cortex for ADHD only: 7R-car < not

(continued)

Table 25.5 (continued)

Authors	Participants	Modality and methods	Results
Brain chemistry			
Cheon et al. (2005)	11 ADHD (9 M; 9.8 ± 1.3 yrs; all med naïve) Pharmacogenetics study: 8 wk MPH treatment Ethnicity not reported; Korean study	I[123I]IPT SPECT (to assess DAT availability) DAT1 3′ VNTR; 9R-car vs 10R/10R: 4 10R/10R	Striatal DAT availability: 10R >9R 10R associated with poorer MPH response
Krause et al. (2006)	29 ADHD (19 M; 37.6 ± 10 yrs; all med naïve) Caucasian sample; German study	[(99 m)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
Brain function			
Rohde et al. (2003)	8 ADHD (8 M; range 8–12 yrs; all MPH-naïve) Pharmacogenetics study: 4-day MPH treatment Ethnicity not reported; Brazilian study	99mTc-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: 10R/10R >carrier 9R
Loo et al. (2003)	27 ADHD (18 M; 10.1 ± 1.5 yrs; 48 hr med washout) Pharmacogenetics study: single dose MPH Ethnicity not reported; US study	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 Carriers 9R: reverse pattern
Szobot et al. (2005)	34 ADHD (34 M; 11.6 ± 2.5 yrs; all med naïve) Ethnicity not reported; Brazilian study	99mTc-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
Baehne et al. (2009)	122 ADHD (72 M; 34.7 ± 9.6 yrs; all med free but not necessarily naïve) 84 NC (44 M; 34.8 ± 10.3 years) Ethnicity not reported; German study	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: Homozygotes risk alleles at both TPH2 loci <non-homozygotes

Durston et al. (2008)	10 ADHD (10M; 14.6 ± 2.6 yrs; 1 med naïve; 24 hr meds washout) 10 unaffected sibs (10M; 14.8 ± 2.3 yrs) 9 NC (9 M; 15.3 ± 2.1 yrs) Caucasian sample; Dutch study	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: 9R & Uparrow; activation in CN 9R & Downarrow; activation in vermis Group × genotype interaction: Effect in CN related to ADHD and unaffected siblings – not NC
Brown et al. (2010)	42 ADHD (20M; 35.2 ± 13.5 yrs; 16 med naïve; 24 hr meds washout) Caucasian sample; US study	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
Bédard et al. (2010)	33 ADHD (24 M; 11.1 ± 2.5 yrs; 21 med naïve; 2 wk meds washout) Mixed ethnicity; US study	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

Sarah Durston (2010)

Legend: *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* gray 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 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 C^{11}-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 to healthy age-matched controls. The authors enrolled eight patients with pathological gambling (as a prototype of ICD) and found differences in 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).

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).

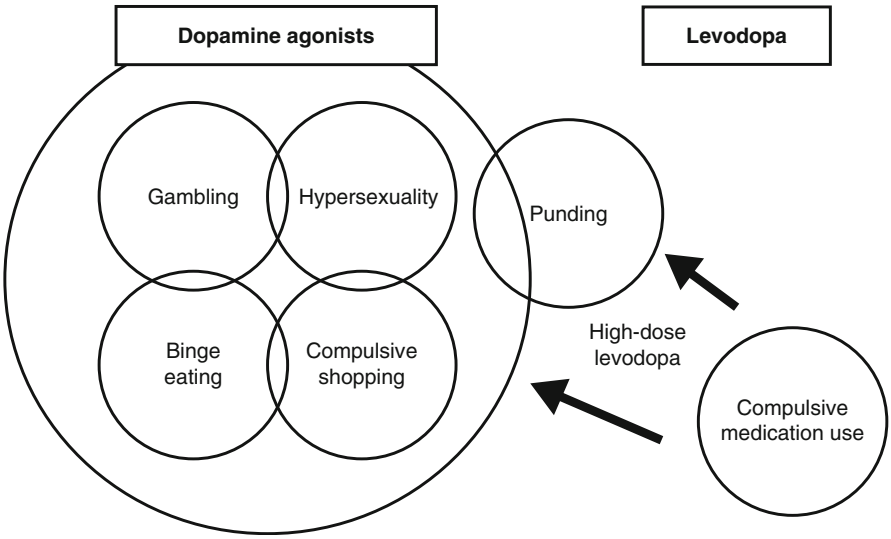

Fig 25.5 Conceptualization of impulse control behaviour in Parkinson's disease as it relates to treatment (Voon and Fox 2007)

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, no clear consensus or definite evidence to support such practices exists. Also, a significant proportion of these patients may experience a debilitating withdrawal syndrome upon dose reductions or discontinuation (Fig. 25.5).

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.

25.2.2 Psychiatry

25.2.2.1 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 (DSc 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 (DSc 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 2006a, b; 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 includes part of the cingulate (ACC; BA 24) and the dorsolateral prefrontal cortex (BA 9, 10 and 46) and ventromedial prefrontal cortex (VMPF) (including 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 cortex (VMPF) 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 super-high-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 1,000-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 glucose significantly increased metabolism in patients with BPD compared to controls in the anterior cingulate, the superior frontal gyrus bilaterally, the right inferior frontal gyrus and the opercular part of the right precentral gyrus. 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 F-18-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 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 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 cingulated cortex of the group with IA compared to the healthy group and concluded that the serotonergic innervations in the anterior cingulated cortex was 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) groups. Those with 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 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).

25.2.2.2 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 the 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 understimulation 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 this 2003 review, Volkow et al. explore 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. 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 by Lee et al. using ^{11}C-raclopride (Lee et al. 2009).

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 assessment of response to treatment in alcoholic patients (Volkow et al. 2003).

Conclusion

Functional imaging has an emerging, potentially important role in the evaluation and study of impulsivity. From the literature available and the continuing work being done in this field, the molecular and genetic base of this technology will help in patient management through provision of a clearer understanding of the pathophysiology of the disease processes. 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 Impulsive-Aggressive Dog

26

Kathelijne Peremans, Simon Vermeire, Tim Waelbers, Eva Vandermeulen, André Dobbeleir, Bart De Spiegeleer, and Kurt Audenaert

Contents

K. Peremans (✉) • S. Vermeire • T. Waelbers • E. Vandermeulen • A. Dobbeleir
Department of Veterinary Medical Imaging and Small Animal Orthopaedics, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, B-9820 Merelbeke, Belgium
e-mail: kathelijne.peremans@ugent.be

B. De Spiegeleer
Drug Quality and Registration, Faculty of Pharmaceutical Sciences, Ghent University, Harelbekestraat, B-9000 Gent, Belgium

K. Audenaert
Department of Psychiatry and Medical Psychology, University Hospital, Ghent University, De Pintelaan 185, B-9000 Gent, Belgium

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_26,

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 given on the use of functional brain imaging in dogs suffering from impulsive aggression.

26.1 History of Behavioural Brain Research in Animal Models

Dogs have been loyal allies to man since 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 recording of behavioural changes; others were based on test performance in challenge tasks, such as go/no-go tasks. Although, in retrospect, some of these techniques were animal unfriendly and are not welcome anymore in this era, they provided an invaluable contribution to the knowledge of brain function and behaviour today. Detailed reviews on the evolution of research concerning animal neuropsychology are given by Fuster (1997) and Joseph (1996) proving the link between the frontal cortex and the limbic system with behaviour (Fuster 1997; Joseph 1996).

26.2 Studies on Canine Brain Pathophysiology

The availability of non-invasive functional imaging methods in the investigation of behavioural pathophysiology is an important advantage in the living animal. Moreover, since radioprotective measurements are not as stringent compared to man, multiple longitudinal studies are possible. Using the appropriate tracers, both perfusion and metabolism can be visualised using SPECT or PET. On the other hand, 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 keep of these animals is not obvious. Second, they 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 high 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. 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.

26.2.1 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). Recently 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

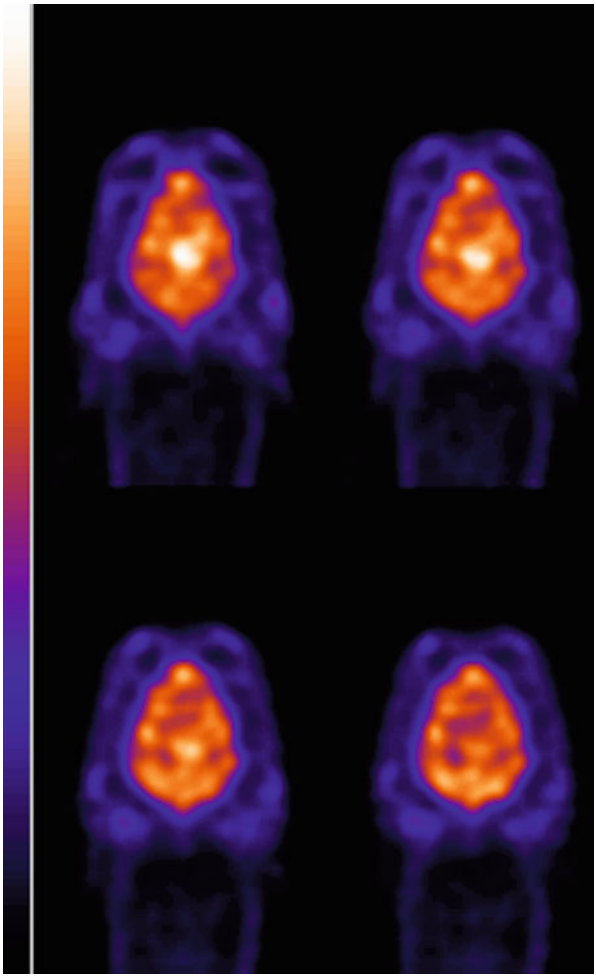

Fig. 26.1 Brain perfusion SPECT in a normal dog (horizontal/transverse slices). The colour scale gives information on the intensity of radioactivity registered in different areas: highest uptake is related with the colours at the top of the scale, low uptake with those at the bottom. The areas with highest radioactivity represent neuronal tracer uptake in the cortical and subcortical areas

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. 26.1) and the serotonin 2A (5-HT_{2A}) receptor radioligand binding were compared with a group of

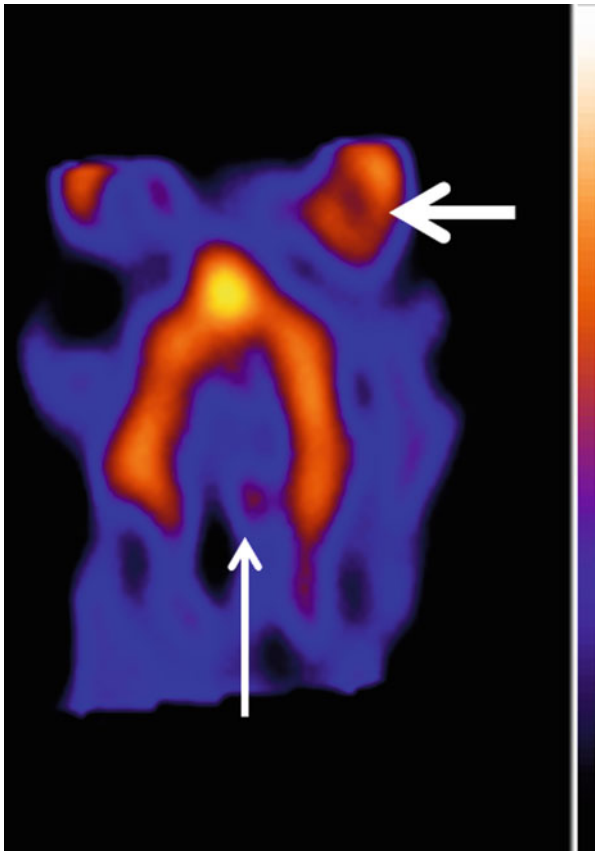

Fig. 26.2 A typical image of the distribution of the 5-HT_{2A} receptor radioligand in the cortical areas (horizontal/transverse slices). Note the lack of activity in the cerebellar area, a region void of 5-HT_{2A} receptors and used as a reference region for semiquantification (*arrow*). Note also the high physiological periorbital uptake (*thick arrow*)

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. 26.2). 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 et al. 1995). The optimal scanning time, the time when pseudo-equilibral 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.

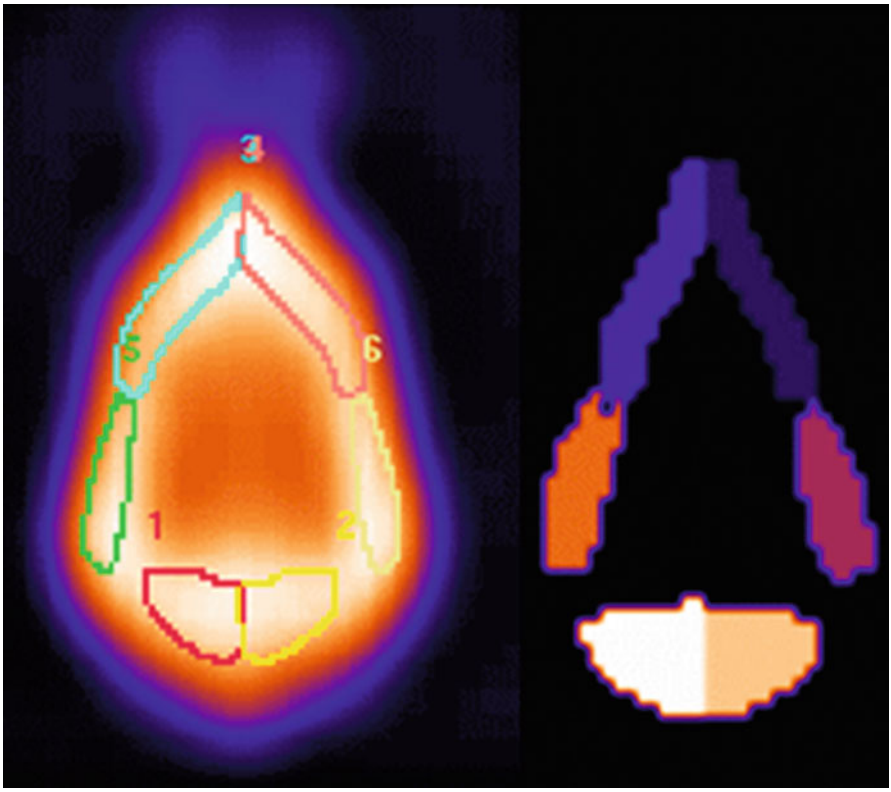

Fig. 26.3 Semiquantification of perfusion data is performed with BRASS software (Hermes, NUD) (normalisation to total brain counts). A template is created from the data of the group of normal dogs (*left panel*). A manually drawn Volume of Interest (VOI) map is created on this template (*right panel*) 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

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. 26.3). 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. 26.4). The cerebellum was 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

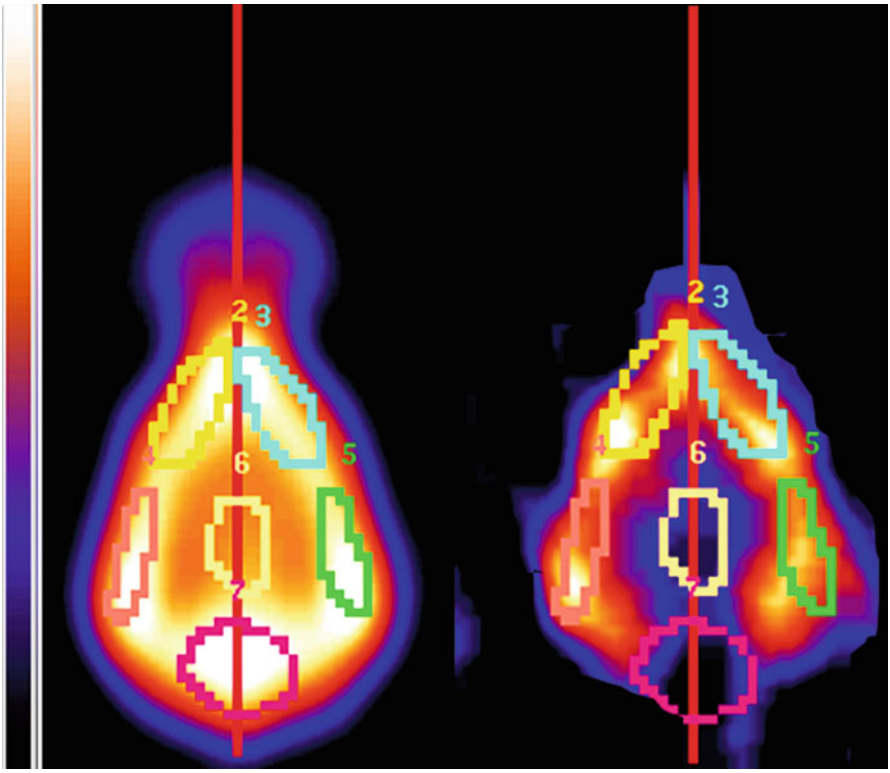

Fig. 26.4 The perfusion images of the same individual are used to define the VOIs on the serotonin-2A receptor radioligand data. Radioligand data are fused with the perfusion data and the VOIs defined on the perfusion data are automatically applied to the radioligand images. The cerebellar area is used 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

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. 26.5). 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 post-mortem findings in the brain of suicide victims (Arango et al. 1990; Arora and Meltzer 1989; Stanley et al. 1983).

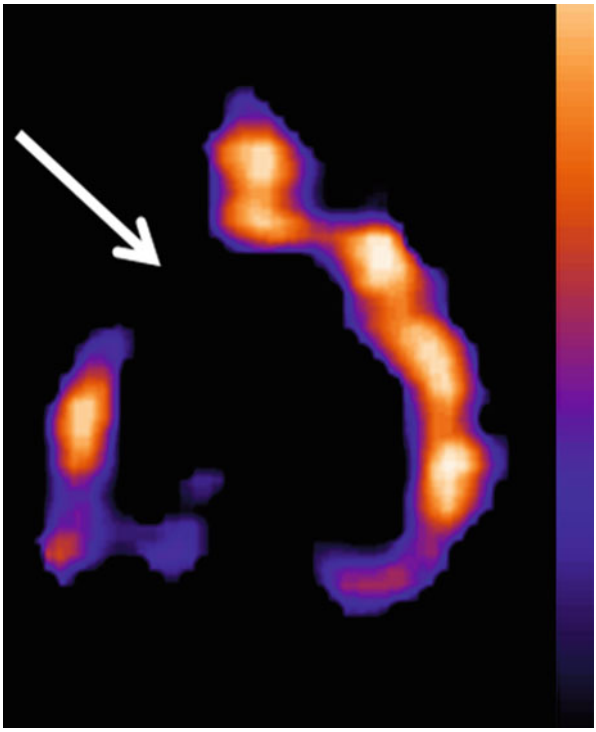

Fig. 26.5 A 5-HT_{2A} receptor SPECT in an aging dog (10 years). Note the decreased (*arrow*) radioactivity in the frontal cortex compared to the distribution of radioactivity in Fig. 26.2

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 up-regulation 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 serotonergic system in particular. As an example, up-regulation 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).

26.2.2 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.

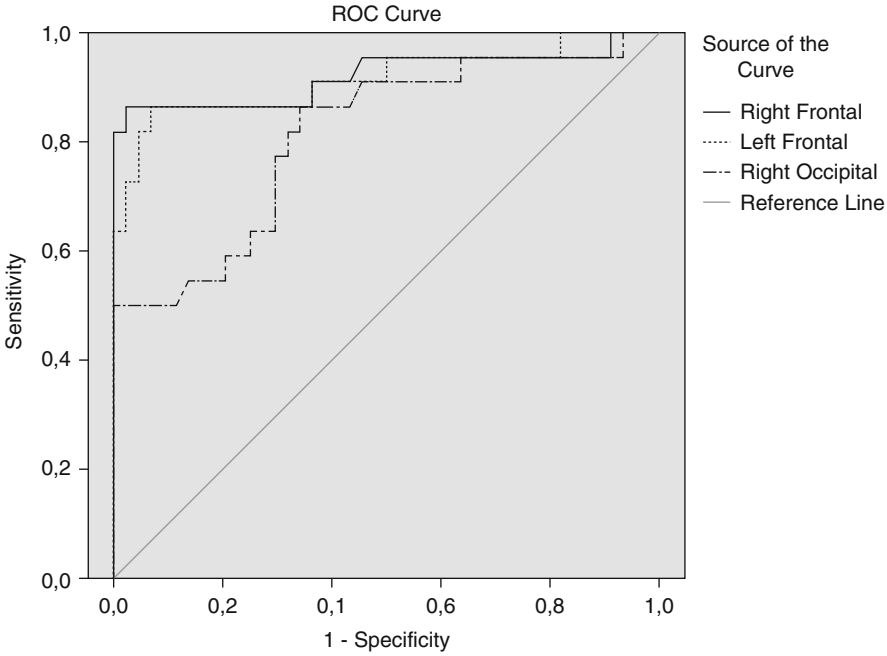

Fig. 26.6 Receiver operating curves (*ROC*) are shown for the group of impulsive-aggressive dogs. The sensitivity (true-positives) is plotted against (1-specificity) (the false-positives) across a range of cut-off values. The reference curve represents the characteristics of a test that is unable to differentiate the two groups. The curve of the ideal test would go straight up to a sensitivity of 1 (*left top corner*) before moving to the right (*right top corner*). 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

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. 26.6), 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).

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.

26.3 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. 26.7a, 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 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

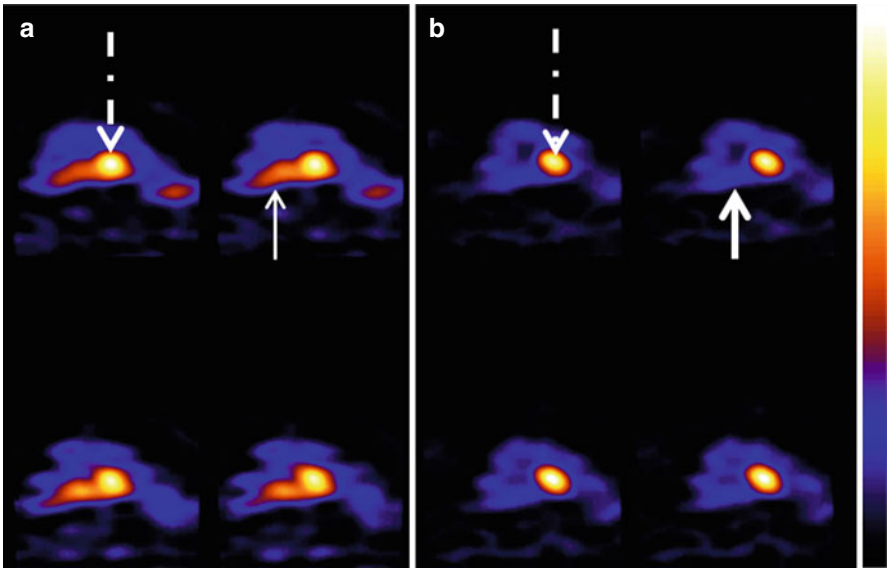

Fig. 26.7 SERT and DAT imaging with ^{123}I-β-CIT in a normal dog before (**a**) and after (**b**) administration of the SSRI Cipramil. Note the decreased activity in the area of the raphe nuclei where SERT are abundantly present (*thin arrow*). After blockade of the SERT by Cipramil, radiopharmaceutical 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

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.

26.4 Confounding Factors in Canine Functional Brain Imaging Studies

26.4.1 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 et al. 2012, 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 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.

26.4.2 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 not possible. 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 (6 multi-focused holes, 3 mm ∅)). Co-registration with MRI images then also allows localisation of the small subcortical areas, such as the basal

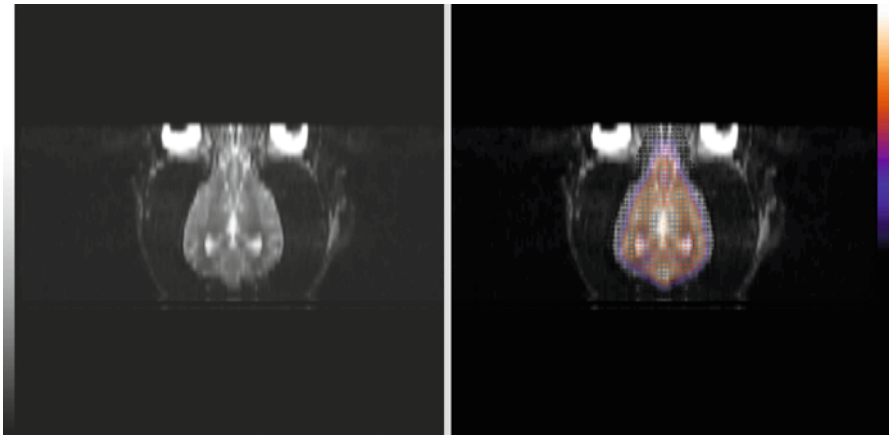

Fig. 26.8 Micro-SPECT perfusion images in a dog fitted to MRI data (*right panel*) to obtain anatomical reference for the delineation of the cortical and subcortical structures. Similar to conventional perfusion data, a VOI map can be created for the perfusion data based on the delineated regions on the MRI and used in the BRASS software program

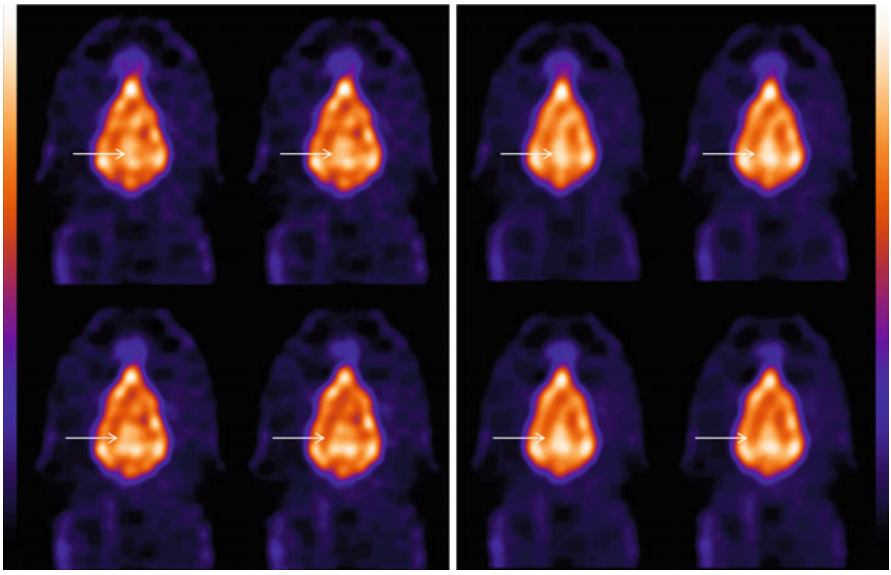

Fig. 26.9 An alternative solution to increase resolution is the use of resolution recovery software. Note the improved visualisation of the subcortical structures (*left panel*, *arrows*) compared to images obtained with conventional reconstruction (*right panel*, *arrows*). Filtering is the same in both reconstructions

ganglia and the thalamus (Fig. 26.8). An alternative is provided by resolution recovery software, available from several 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. 26.9).

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 analogue behavioural conditions 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).

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Obesity an Addiction? Imaging of Neurotransmitter Systems in Obesity

27

Elsmarieke van de Giessen, Silja McIlwrick, Dick Veltman, Wim van den Brink, and Jan Booij

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 and compares the findings to the available knowledge of animal research and to the literature on addiction and eating disorders.

E. van de Giessen (✉) • J. Booij
Department of Nuclear Medicine (F2N), Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
e-mail: elsmarieke@gmail.com

S. McIlwrick
Cognitive Science Center, University of Amsterdam, Plantage Muidergracht 22-24, 1018 TV Amsterdam, The Netherlands

D. Veltman • W. van den Brink
Department of Psychiatry, Amsterdam Institute for Addiction Research, Academic Medical Center, University of Amsterdam, Meibergdreef 5, 1105 AZ Amsterdam, The Netherlands

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_27, © Springer-Verlag Berlin Heidelberg 2014

Presently, only the dopaminergic and serotonergic system have been studied with molecular imaging techniques in obese humans, and results show that both systems are involved. The major findings are that the striatal dopamine $D_{2/3}$ receptor ($DRD_{2/3}$) availability is lower in obese subjects compared to normal-weight controls, that striatal dopamine transporter (DAT) availability is not different in obese compared to normal-weight subjects, and that 5-HT_{2A} receptor availability in cortical regions is positively correlated with body mass index (BMI).

The finding of lower striatal $DRD_{2/3}$ availability in obesity is similar to findings in drug addiction, but for the other findings, the similarities with drug addiction are less clear. Moreover, it is still a question whether the dopaminergic and serotonergic differences are a cause or a consequence of the obese state. Furthermore, there are other neurotransmitter systems that have not yet been studied and seem to be involved in eating behavior, e.g., the cannabinoid and the opioid system. Therefore, future molecular imaging studies are needed to better understand the pathophysiology of obesity and to determine the extent of overlap with addiction, which has the potential to aid in development of new anti-obesity drugs.

27.1 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 etiology of obesity and a possible target for prevention and treatment. Many brain structures participate in food intake regulation (Berthoud 2004, 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 as a consequence of 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 behavioral and neuropharmacological similarities have been hypothesized (Volkow and Wise 2005). A summary of the publications on molecular imaging in obesity reviewed in this section can be found in Table 1.

27.2 Imaging Findings on Neurotransmitter Systems in Obesity

27.2.1 The Dopaminergic System

The majority of the neuroimaging studies on the 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 10 morbidly obese subjects (BMI >40 kg/m^2) and 10 age-matched controls (BMI <30 kg/m^2). They showed that $DRD_{2/3}$ binding was lower in the striatum of obese participants and also 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). Recently, 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 and overweight/

Table 27.1 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
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
Dunn et al.	(2010)	[^{11}C]raclopride PET	5 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	(2012a)	[^{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
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	$5\text{-}HT_{2A}$ receptor availability
Erritzoe et al.	(2009)	[^{18F}]altanserin PET	136 subjects, BMI 18.4–42.8	$5\text{-}HT_{2A}$ receptor availability
Haahr et al.	(2012)	[^{11}C]SB207145 PET	28 subjects, BMI 20.5–40.0	$5\text{-}HT_4$ 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
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

[a]Sample overlap with Wang et al. (2001)
[b]Sample overlap with Kuikka et al. (2001)
PET positron emission tomography, *SPECT* single-photon emission computed tomography, *OB* obese (BMI >30 kg/m2), *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, *5-HT* serotonin, *SERT* serotonin transporter

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. Finally, 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. Overall, four out of the five studies reviewed here indicated that the striatal level of free synaptic $DRD_{2/3}$ is decreased in obesity. Therewith it seems a well-established finding.

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 though between BMI and dopamine release. Overall, studies failed to show a significant relationship between striatal dopamine release and BMI, but increased dopamine release might be associated with binge eating.

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. Recently, two small studies have tried to answer the question whether dopaminergic neurotransmission and $DRD_{2/3}$ availability might 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 actually 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 5 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). The results of Steele et al. (2010) and Dunn et al. (2010) clearly contradict each other. It is possible that this is partly due to the use of different tracers, i.e., [^{18}F]fallypride in Dunn's study, compared to [^{11}C]raclopride in the study by Steele. The small sample sizes of both studies preclude firm conclusions about the effect of weight loss on $DRD_{2/3}$ availability.

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. (2012a) found that there was 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. Overall, three out of four studies found no association between BMI and striatal DAT availability, which suggests that striatal DAT levels are not different at high BMI.

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, 3 subjects with BMI >30 kg/m^2) using the ligand 6-[^{18F}]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 towards a downregulation mechanism that limits the available striatal dopamine production in response to overeating.

27.2.2 The Serotonergic System

Apart from the dopaminergic system, only the serotonergic system has been studied in obese humans using molecular imaging methods. 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). This time 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).

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 two studies investigating the association between BMI and the serotonin transporter (SERT), which regulates synaptic serotonin levels. The largest study was performed by 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. The significance of this finding appeared to be based on differences within the female twin pairs, while there was no significant difference in SERT binding within the male twin pairs between the heavier and the leaner twin. 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 went together with an increase of SERT availability in the midbrain (Tammela et al. 2003). This suggests that obese women with binge eating disorder have aberrant midbrain SERT availability which could normalize after treatment. Together, the reviewed studies on SERT binding indicate that a dysregulation of subcortical and cortical SERT levels is associated with a high BMI, but more studies are needed to elucidate the exact direction of the associations and to discover how it is regulated in obesity.

27.3 Discussion

Several independent research groups have shown that the dopaminergic and serotonergic 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 the striatal $DRD_{2/3}$ availability is lower in obese subjects compared to normal-weight controls, that striatal DAT availability is not different, and that 5-HT_{2A} receptor binding in cortical regions correlates positively with BMI.

27.3.1 Discussion of Findings on the Dopaminergic System

The lower striatal $DRD_{2/3}$ availability in obesity is supported by animal research: Decreased $DRD_{2/3}$ levels were found in the nucleus accumbens (NAc) and dorsal striatum in genetically obese rodent models and in diet-induced obese rodent models (van de Giessen et al. 2012b; 2013; Hamdi et al. 1992; Hajnal et al. 2008; Davis et al. 2009; Thanos et al. 2008; Johnson and Kenny 2010), although one study reported an increase in $DRD_{2/3}$ levels in the dorsal striatum of diet-induced obese mice (South and Huang 2008). The lower striatal $DRD_{2/3}$ availability has been linked to reward deficiency. It has been postulated that a decrease in $DRD_{2/3}$ availability results in a decreased sensitivity of the reward circuit to food, which subsequently leads to increased food intake to temporarily reach the desired reward level (Volkow et al. 2011). The role of this system has been compared to its role in substance use disorders. In this respect, it is important to notice that the studies with morbidly obese subjects found striatal $DRD_{2/3}$ binding reduction of a magnitude

(17.4 % (Wang et al. 2001) and 13.4 % (Volkow et al. 2008)) very similar to those observed in alcohol (Volkow et al. 1996a), methamphetamine (Volkow et al. 2001a), and opiate abusers (Wang et al. 1997). However, in obese subjects, lower $DRD_{2/3}$ availability has not yet been linked to eating behavior or other behavioral parameters. Apart from that, there is increasing evidence that glucose homeostasis can directly affect the striatal dopaminergic system (Morris et al. 2011). The obese state might therefore affect striatal $DRD_{2/3}$ availability via imbalances in metabolic systems, and a focus on eating behavior alone would be too narrow.

Whether a lower striatal $DRD_{2/3}$ availability in obesity is a predisposing condition or a result of the obese state and/or metabolic changes has not yet been determined. Carriers of the Taq1A allele in the gene encoding $DRD_{2/3}$ show decreased $DRD_{2/3}$ expression (Pohjalainen et al. 1998) and have a higher chance of being obese than noncarriers (Noble 2003; Epstein et al. 2007; Blum et al. 1996). This suggests that a lower $DRD_{2/3}$ expression is a preexisting and predisposing condition that increases the risk of developing obesity (and substance use disorders). However, in a recent animal study, Johnson and Kenney (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. A combination of both, i.e., cause and consequence, is also a possibility: a predisposing low level of striatal $DRD_{2/3}$, which is then further decreased by the obese state. This combination has previously been found for cocaine dependence in nonhuman primates, where low striatal $DRD_{2/3}$ availability predisposed to high levels of cocaine self-administration and was further reduced after chronic cocaine self-administration (Nader et al. 2006). The studies on striatal $DRD_{2/3}$ availability after acute weight loss by bariatric surgery do not yet answer the question in how far a change in body weight or eating behavior is linked to $DRD_{2/3}$ levels. There is no evidence yet that the striatal $DRD_{2/3}$ availability increases by significant weight loss, which would suggest some form of reversibility. Studies investigating this issue could determine whether striatal $DRD_{2/3}$ availability follows weight changes, suggesting that obesity induces low striatal $DRD_{2/3}$ availability, or whether low striatal $DRD_{2/3}$ availability is independent of weight changes, suggesting a possible predisposing condition. In cocaine-dependent nonhuman primates, $DRD_{2/3}$ availability seems to return to normal levels during abstinence though (Beveridge et al. 2009), which indicates reversibility in substance use disorders. The results of the available studies in obesity are still conflicting and the samples are too small (Dunn et al. 2010; Steele et al. 2010). More information on these effects would help to better understand the link between body weight or eating behavior and $DRD_{2/3}$ availability and the flexibility of the system.

Apart from the lower striatal $DRD_{2/3}$ availability, it has also 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. To date, a dopamine release after food intake in healthy humans has been demonstrated only once after a meal (Small et al. 2003) and once 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 ten 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 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 is surprising in the context that binge eating has been referred to as a form of food addiction (Ziauddeen et al. 2012). As the authors did not find a correlation between BMI and dopamine release, this study shows that it is probably the (pathological) eating pattern that is related to the dopamine release, whereas there is not yet evidence for a direct relation with the obese status. The question still remains whether the responsiveness of the striatal dopaminergic system is different between obese and normal-weight humans.

With regard to the presynaptic side of the dopaminergic system, imaging results suggest that striatal DAT availability is not changed in obesity. This would mean that there is an imbalance in the striatal dopamine system. The previously described lower striatal $DRD_{2/3}$ availability in obesity reflects a lower signal transduction capacity, which does not seem to be compensated by an increase in synaptic dopamine due to lower DAT availability, i.e., lower capacity transporting synaptic dopamine back into the cell. As a consequence, the system is out of balance and the dopamine signal is less efficiently transmitted in obesity, which could lead to impaired reward experiences. However, based on the imaging results so far, we cannot conclusively exclude that there is a slightly lower DAT availability in obesity. Animal studies demonstrate that rodents on a high-fat diet for obesity induction show a significant decrease in DAT density on the cell surface in the striatum (Speed et al. 2011; South and Huang 2008), although one animal study shows 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 drugs abusers: lower DAT levels for methamphetamine (Volkow et al. 2001b; Sekine et al. 2001) and nicotine users (Yang et al. 2008; Newberg et al. 2007), lower levels or no change for alcohol users (Volkow et al. 1996a; 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 provide further evidence for a similar mechanism in obesity and substance use disorders. Given the more outspoken findings for lower DAT levels in substance use disorders compared to obesity, these findings suggest that this mechanism is less outspoken in obesity than in substance use disorders.

Concerning the role of dopamine in obesity, many important questions have been addressed. Apart from the finding of lower striatal $DRD_{2/3}$ availability, most issues are not yet resolved and need further evidence. One aspect that has not been studied yet is whether endogenous synaptic dopamine levels are also lower in obesity. Given the finding of reduced dopamine production in the striatum in obesity, synaptic dopamine levels may also be lower, similar to what has been shown in cocaine addiction (Martinez et al. 2009). 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 test this hypothesis.

27.3.2 Discussion of Findings on the Serotonergic System

Regarding the serotonergic system, the positive correlation of BMI and cortical $5\text{-}HT_{2A}$ 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). It is (partly) supported by animal work, which also shows that there are significantly higher $5\text{-}HT_{2A}$ 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 $5\text{-}HT_{2A}$ 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 $5\text{-}HT_{2A}$ 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 $5\text{-}HT_{2A}$ receptor availability.

Furthermore, the (non-replicated) finding of a positive correlation between BMI and $5\text{-}HT_4$ receptor availability shows that also subcortical, reward-related parts of the serotonergic system are involved in obesity (Haahr et al. 2012). Indeed, the $5\text{-}HT_4$ receptor has been implicated in food intake regulation and food-related reward (Ratner et al. 2012; Francis et al. 2011). Possibly, this positive correlation is also a reflection of an upregulation of $5\text{-}HT_4$ receptors due to a widespread decrease in serotonin levels throughout the brain, as previously described for the $5\text{-}HT_{2A}$ receptors.

Research on SERT in obesity is still inconclusive. An inverse correlation of SERT binding with BMI has been found in both cortical and subcortical regions (Erritzoe et al. 2010), which opposed the finding in female twins that SERT availability was higher in the heavier twin (Koskela et al. 2008). There is one study in patients with Parkinson's disease (PD), which shows that patients with a large change in BMI in the past year have higher SERT availability (in rostral raphe nuclei, hypothalamus, caudate nucleus, and ventral striatum) than PD patients with a stable BMI (Politis et al. 2011). However, it is difficult to directly apply this

finding to obesity, in particular, because PD itself has an effect on SERT levels, i.e., lower binding compared to controls (Politis et al. 2011). A negative correlation between SERT and BMI is not directly confirmed by animal studies, which found that only mice that were resistant to diet-induced obesity had decreased SERT binding in the nucleus accumbens, amygdaloid nucleus, and olfactory tubercle and not the obesity-prone mice (Huang et al. 2004b). On the other hand, female SERT knockout mice have increased abdominal fat, although the males have not (Homberg et al. 2010). 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, Lundgren et al. 2009;). On the other hand, in bulimia nervosa patients SERT availability was decreased in 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. To better understand the relation between brain SERT and BMI, replications of the studies of Erritzoe et al. (2010) or Koskela et al. (2008) are necessary, as well as studies involving eating behavior and metabolic data to further disentangle the relation between the serotonin system and obesity.

27.3.3 Conclusion

In conclusion, the results of the imaging studies on neurotransmitter systems in obesity have clearly shown that both the dopaminergic and serotonergic systems are affected. The finding of lower striatal $DRD_{2/3}$ availability is similar to the findings in substance use disorders, but for the other findings, the similarities are less clear. Furthermore, it is still a question whether the dopaminergic and serotonergic differences are a cause or a consequence of the obese state, and several findings still need replication. Some studies also indicated that obese subjects with eating binges might be a subgroup within the obese population with specific differences in the dopaminergic and serotonergic systems. Finally, there are other neurotransmitter systems that are clearly involved in eating and in addictive behavior, but that have not yet been studied. With radioligands available for among others the cannabinoid type 1 receptor, the μ-opioid receptor, and dopamine D_1 receptor and with high specificity for the dopamine D_3 receptor, future molecular imaging studies can still contribute largely to our insight in the pathophysiological mechanisms in obesity and potentially to the development of new anti-obesity drugs.

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Neuroimaging Studies of Psychopathy

28

Maia Pujara 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

This chapter reproduces portions of the previously published article:
Koenigs M, Baskin-Sommers A, Zeier J, and Newman J. (2011) Investigating the neural correlates of psychopathy: A critical review. Molecular Psychiatry, 16, 792–799.

M. Pujara • M. Koenigs (✉)
Department of Psychiatry, University of Wisconsin-Madison,
6001 Research Park Boulevard, Madison, WI 53719, USA
e-mail: mrkoenigs@wisc.edu

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_28, © Springer-Verlag Berlin Heidelberg 2014

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.

Human brain imaging techniques, such as magnetic resonance imaging (MRI), have become an indispensible 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 28.1). 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 (Barkataki et al. 2006; Raine et al. 2000), 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 recent 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 (e.g., 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/

Table 28.1 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
Birbaumer	(2005)	Deficient fear conditioning in *psychopathy*: a functional magnetic resonance imaging study	F	BG	15	24.9	10
Bjork	(2012)	*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
	(2010)	Abnormal hippocampal shape in offenders with *psychopathy*	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
Craig	(2009)	Altered connections on the road to *psychopathy*	S	BG, C/R	25	28.4	9
de Oliveira-Souza	(2008)	*Psychopathy* as a disorder of the moral brain: fronto-temporo-limbic gray matter reductions demonstrated by voxel-based morphometry	S	BG, C/R	n/a	n/a	15
Deeley	(2006)	Facial emotion processing in criminal *psychopathy*. Preliminary functional magnetic resonance imaging study	F	BG	25	29.3	6
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
Glenn	(2009)	The neural correlates of moral decision-making in *psychopathy*	F	C/R	n/a	n/a	n/a
	(2010b)	No volumetric differences in the anterior cingulate of *psychopathic* individuals	S	BG, C/R	23	28.0	24
	(2010a)	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

(continued)

Table 28.1 (continued)

First author	Year	Title	Type of imaging	Type of analysis	PCL-R cutoff for P	Mean PCL-R for Ps	P sample size
Harenski	(2009)	Neuroticism and *psychopathy* predict brain activation during moral and nonmoral emotion regulation	F	C/R	n/a	n/a	n/a
	(2010)	Aberrant neural processing of moral violations in criminal *psychopaths*	F	BG, C/R	30	31.8	16
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
	(2004)	Temporal lobe abnormalities in semantic processing by criminal *psychopaths* as revealed by functional magnetic resonance imaging	F	BG	29	32.8	8
Laakso	(2001)	*Psychopathy* and the posterior hippocampus	S	C/R	n/a	n/a	n/a
Ly	(2012)	Cortical thinning in *psychopathy*	F, S	BG	30	31.8	21
Marsh	(2012 in press)	When *psychopathy* impairs moral judgments: neural responses during judgments causing fear	F	BG	n/a	n/a	n/a
Motzkin	(2011)	Reduced prefrontal connectivity in *psychopathy*	F, S	BG	30	31.9	20
Muller	(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
	(2008a)	Gray matter changes in right superior temporal gyrus in criminal *psychopaths*. Evidence from voxel-based morphometry	S	BG	28	33.4	17
	(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 noncriminal population	F	C/R	n/a	n/a	n/a
Pujara	(2013 in press)	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
Raine	(2003)	Corpus callosum abnormalities in *psychopathic* antisocial individuals	S	BG, C/R	23	30.3	15
	(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 noncooperation as a function of *psychopathy*	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
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
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
Yang	(2005b)	Volume reduction in prefrontal gray matter in unsuccessful criminal *psychopaths*	S	BG, C/R	23	28.4	29
	(2009)	Localization of deformations within the amygdala in individuals with *psychopathy*	S	BG, C/R	23	28.0	27
	(2010)	Morphological alterations in the prefrontal cortex and the amygdala in unsuccessful *psychopaths*	S	BG	23	n/a	26
	(2011)	Abnormal structural correlates of response perseveration in individuals with *psychopathy*	S	BG, C/R	23	n/a	27
	(2012)	Frontal information flow and connectivity in *psychopathy*	S	BG	n/a	n/a	55

P psychopathy, *S* structural, *F* functional, *C/R* correlation or regression analysis, *BG* between-group analysis, *n/a* not applicable or data not available

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 recent review on neuroimaging findings related to antisocial behavior in children, see Crowe and Blair 2008.)

28.1 Neuroimaging Data on Psychopathy: Summary of Results

The neuroimaging studies of psychopathy can be divided into "structural" studies, which assess brain morphology, and "functional" studies, which assess brain activity (Table 28.1). Structural neuroimaging studies associate psychopathy with a host of morphological brain abnormalities: reduced volumes of the amygdala, (Boccardi et al. 2011; Ermer et al. 2012; Yang et al. 2009, 2010); reduced volume of the basolateral nucleus of the amygdala and increased volumes of the central and lateral nuclei of the amygdala (Boccardi et al. 2011); reduced gray matter volumes in frontal cortex, especially the orbitofrontal cortex, the frontopolar cortex, the anterior rostral prefrontal cortex, and right inferior frontal gyrus (Boccardi et al. 2011; de Oliveira-Souza et al. 2008; Ermer et al. 2012; Gregory et al. 2012; Ly et al. 2012; Muller et al. 2008a; Yang et al. 2005b, 2010, 2011); reduced volume of the dorsal anterior cingulate cortex and bilateral precentral gyri (Ly et al. 2012); reduced volumes in temporal cortex, especially right superior temporal gyrus, anterior temporal cortices, superior temporal sulcus, and bilateral temporal pole (de Oliveira-Souza et al. 2008; Ermer et al. 2012; Gregory et al. 2012; Ly et al. 2012; Muller et al. 2008a; Yang et al. 2011); 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 (Glenn et al. 2010a); increased volume of the left nucleus accumbens (Pujara et al. 2013); increased volume of the corpus callosum (Raine et al. 2003); reduced volume of posterior hippocampus (Laakso et al. 2001); normal volume but abnormal shape of the hippocampus (Boccardi et al. 2010); reduced volume in 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); 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), viewing facial expressions of emotion (Carré et al. 2013; Deeley et al. 2006; Gordon et al. 2004), emotion attribution (Sommer et al. 2010), moral decision-making (Glenn et al. 2009; Harenski et al. 2009, 2010; Pujol et al. 2012), 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 (Muller et al. 2003, 2008b), social cooperation (Rilling et al. 2007), anticipation and/or receipt of reward (Bjork et al. 2012; Buckholtz et al. 2010; Carré et al. 2013; Pujara et al. 2013), and punishment administration (Veit et al. 2010). 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; Glenn et al. 2009; Gordon et al. 2004; Kiehl et al. 2001; Rilling et al. 2007). 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 amygdala (Birbaumer et al. 2005; Carré et al. 2013; Glenn et al. 2009; Kiehl et al. 2001; Rilling et al. 2007), hippocampus and parahippocampal gyri (Kiehl et al. 2001; Muller et al. 2003), anterior and posterior cingulate cortex (Birbaumer et al. 2005; Kiehl et al. 2001; Muller et al. 2003; Rilling et al. 2007), ventral striatum (Kiehl et al. 2001), and insula (Birbaumer et al. 2005). 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; Muller et al. 2003, 2008b; Rilling et al. 2007) as well as sensory areas, such as posterior visual cortices (Deeley et al. 2006; Muller et al. 2003) and parietal somatosensory cortex (Birbaumer et al. 2005; Deeley et al. 2006), and motor structures such as cerebellum (Deeley et al. 2006) and primary motor cortex (Deeley et al. 2006). Increased activity has been observed in frontal and temporal cortices (Intrator et al. 1997; Kiehl et al. 2001; Muller et al. 2003), nucleus accumbens (Bjork et al. 2012; Buckholtz et al. 2010), as well as areas of parietal lobe, occipital lobe, cerebellum, cingulate cortex, and amygdala (Muller 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 (Juárez 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). 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, amygdala activity was abnormally low during fear conditioning (Birbaumer et al. 2005), 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 (Muller et al. 2003) and facial expressions of anger (Carré et al. 2013). Similarly, 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. 2012; Buckholtz et al. 2010). 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 task and stimuli.

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.

28.2 Methodological Issues

28.2.1 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; Karpman 1946; Lykken 1957). In studies employing this usage, the data analysis strategy typically involves between-group comparisons of neuroimaging data (i.e., psychopaths vs. non-psychopaths; see Table 28.1). 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 28.1). 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. 2008; Walters et al. 2007)—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 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 ventromedial prefrontal cortex (adjacent to 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 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 ventral striatum among the psychopaths. 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 ventral striatum in the anticipation of reward. Another study found a similar association between

[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 heterogeneity of results regarding the neural correlates of psychopathy.

"psychopathic" traits and ventral striatum activity in response to the anticipation of reward (Bjork et al. 2012). 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. However, a recent 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. 2013). 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.

28.2.2 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. 2010a; 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 28.1), we found that this recommendation was followed in only a few studies of psychopathy (Boccardi et al. 2011; Harenski et al. 2010; Juárez et al. 2013; Motzkin et al. 2011; Muller et al. 2003; Pujara et al. 2013). Instead, researchers have routinely employed a variety of minimum PCL-R total scores to define psychopathy. In fact, cutoff scores in the mid-20s (or even lower) are fairly common

[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 (44).

(Birbaumer et al. 2005; Craig et al. 2009; Deeley et al. 2006; Glenn et al. 2010a; Gregory et al. 2012; Intrator et al. 1997; Kiehl et al. 2001; Ly et al. 2012; Raine et al. 2003; Yang et al. 2009, 2010). 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 cutoff 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, 12 had mean PCL-R scores below 30 (see Table 28.1).

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 (Muller et al. 2003). Muller et al. classified subjects as psychopaths if their PCL-R scores were greater than 30; Deeley et al. used a more liberal threshold of 25 or greater. The imaging results differed considerably. Deeley et al. found between-group differences in cerebellum, fusiform gyrus, and postcentral gyrus. 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, Muller et al. found that psychopaths had greater levels of activity in widespread areas of the brain, including medial temporal lobe, occipital and parietal cortex, precentral gyrus, superior temporal gyrus, inferior and medial frontal gyri, anterior cingulate, and amygdala. 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 28 imaging studies that define a group of psychopaths (regardless of inclusion criteria), eight have samples of $n = 10$ psychopaths or less (Table 28.1). The seven imaging studies that use the advised PCL-R cutoff score (30 or greater) have psychopathic sample sizes ranging from $n = 6$ to $n = 21$, 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.

28.2.3 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 (Arnett et al. 1993, 1997; Lykken 1957; 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 one neuroimaging study of psychopathy has employed this subtyping strategy (Motzkin et al. 2011).

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. 1999, 2000). 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.

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).

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

[3] In addition to proposing dysfunction in areas preferentially involved in affective processing, Kiehl's "paralimbic hypothesis" also proposes dysfunction in spatially distributed areas involved in language and attentional orienting.

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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Neurobiology of Aggression: Neuroimaging Findings

29

Michael Soyka

Contents

Abstract

Aggression is a difficult phenotype to study. With respect to psychiatric diagnoses, it is often related to psychopathy, antisocial behaviour, personality disorder, and schizophrenia. PET and to a much lesser extent SPECT data correspond with structural brain imaging and indicate that the frontal/prefrontal lobe and temporal lobe or limbic system are involved in the development of aggression, possibly through misinterpretation of emotional stimuli or impaired control. Few neuroimaging studies have addressed neurotransmitters issues. There is some evidence for serotonergic and dopaminergic dysfunction in aggressive individuals. Neuroimaging data indicate that there is no simple association of a serotonergic dysfunction and aggression.

M. Soyka, MD
Department of Psychiatry, Psychiatric Hospital, Ludwig Maximilian University, Nussbaumstr. 7, 80336 Munich, Germany

Privatklinik Meiringen, Willigen, PF 612, CH-3860 Meiringen, Switzerland
e-mail: michael.soyka@privatklinik-meiringen.ch

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_29, © Springer-Verlag Berlin Heidelberg 2014

In patients with schizophrenia and aggression, data from the few neuroimaging studies performed to date indicate frontal and temporal lobe abnormalities. PET and SPECT data further suggest deficits in the orbitofrontal and temporal cortex. Some fMRI studies found a negative association of violent behaviour with frontal and right-sided inferior parietal activity.

29.1 Introduction

Aggression and violence are common problems in all societies and have a complex background. There are different definitions and classifications of aggression, for example, concerning the target, mode, and cause of aggression (for review, see Siever 2008). From a methodological perspective, there are significant differences between studying patients with a criminal history or violent offenders from forensic settings and studying individuals who may score high on an aggression or psychopathy scale or have some form of state or trait aggression but no clinical history of aggression. Related clinical phenotypes are psychopathy, antisocial personality, and impulsivity, among others.

In addition, the role of psychiatric disorders in the development of aggression must be emphasized. Not all but some psychiatric disorders – especially substance use disorders, personality disorders including antisocial personality, bipolar disorder, and schizophrenia – are associated with aggression and the risk of violence.

29.2 Neurobiology of Aggression

29.2.1 Genetics of Aggression

A range of findings indicate that aggression and criminal behaviour are to some extent genetically inherited (Cadoret et al. 1995). To date, no genome-wide association studies have been published on aggression and violence. The candidate genes being studied in this context include those associated with the personality trait "novelty seeking," impulsivity or hostility, and also ADHD. Serotonin has been postulated as the major neurotransmitter in the regulation of aggression (Siever 2008), but enhancement of central dopaminergic or noradrenergic function is also of relevance (Comai et al. 2012). Since the serotonin system plays an important role in anxiety, impulsivity, and aggression on the genetic level, polymorphic genetic variants of the serotonergic system have been studied as possible genetic vulnerability markers for aggression (Beitchman et al. 2004). Among these variants are functional polymorphisms in monoamine oxidase A (MAO A) and the serotonin transporter (5-HTT) (Brunner et al. 1993; Fresan et al. 2007), for a review of the genetic determinants of aggression, see (Pavlov et al. 2012).

Catechol-*O*-methyltransferase (COMT) is one of the key enzymes in this area and involved in the degradation of dopamine, especially in the prefrontal cortex (Shehzad et al. 2012). In contrast to enzymes coded for by other candidate genes

(e.g., monoamine oxidase), COMT metabolizes dopamine, noradrenalin, and adrenalin, but not serotonin. COMT has a functional polymorphism resulting from a single amino acid exchange in which valine (Val) is replaced by methionine (Met). The polymorphism is relatively common and was first reported at the beginning of the 1980s. Val/Met and Met/Met carriers have four- to fivefold lower COMT activity than Val/Val homozygotes (Lachman et al. 1996; Strous et al. 1997, 2003).

A recent meta-analysis of the Val158Met polymorphism and violent behaviour in schizophrenia for individuals with Met/Met genotype when compared to Val/Val genotype carriers suggests a trend association of Met/Met homozygosity and violence in men (Singh et al. 2012), also confirmed by another meta-analysis (Bhatka et al. 2012). In addition, a recent study in children suggests an association of the COMT gene with high aggression (Hirata et al. 2012).

29.2.2 Brain Function

A dysfunction of certain neural circuits responsible for emotional and impulse control and self-regulation is believed to be part of the neurobiological basis of aggression. Key structures include the anterior cingulate cortex, the limbic structures, the amygdala, and the prefrontal cortex.

There are a number of theories on the brain structures, abnormalities, and neuromodulators underlying aggression. On the cortical level, lesions in certain areas, a decreased cortical volume – possibly linked to developmental disorders – and an orbitofrontal/cingulated cortex processing inefficiency have been discussed, together with a reduced serotonergic and enhanced dopamine/norepinephrine activity (Siever 2008). On the limbic level, a hyperactivity of the amygdala or other limbic structures, a reduced amygdalar volume, the role of hypersensitivity and kindling phenomena, a reduced GABA, and enhanced glutamate and acetylcholine activity have been proposed (Siever 2008). A prefrontal dysfunction has especially been linked to impulsive aggression (Brower and Price 2001). Hyperactivity of the limbic system in response to negative or provocative stimuli was shown in particular in antisocial and borderline patients (Herpetz et al. 2001; Donegan et al. 2003; Schmahl et al. 2003, 2004; Minzenberg et al. 2007) and is discussed also as an important mechanism underlying impulsive aggression (Palijan et al. 2010).

29.2.3 Structural Imaging

(For a review, see Wahlund and Kristiansson 2009; Dolan 2010; Anderson and Kiehl 2012).

Structural imaging has shown reductions in prefrontal grey matter (Raine et al. 2000; Narayan et al. 2007; Müller et al. 2008; Glenn et al. 2010; Yang et al. 2005, 2009; de Oliveira-Souza et al. 2008; Tiihonen et al. 2008), although some results are conflicting (Laakso et al. 2002; Dolan et al. 2002; Barkataki et al. 2006). In addition, volume reductions in the left frontal cortex and right anterior cingulated cortex

and the temporolimbic cortex, including the hippocampus, were found (Glenn et al. 2010; Yang et al. 2009; de Oliveira-Souza et al. 2008; Dolan et al. 2002; Barkataki et al. 2006; Hazlett et al. 2005; Raine et al. 2004; Matsuo et al. 2008; Antonuci et al. 2006). Tiihonen et al. (2008) studied a group of persistently violent offenders and found larger white matter volumes in various brain regions and reduced grey matter volume in the postcentral gyri, frontopolar cortex, and orbitofrontal cortex. The authors discussed whether the larger volumes in posterior brain areas may reflect atypical neurodevelopmental processes that underlie early-onset persistent antisocial and aggressive behaviour.

An excellent study on this topic was recently published by Schiffer et al. (2011) who examined patients from forensic settings and controlled for substance use disorders. Compared to nonoffenders, violent offenders presented with a larger grey matter volume in the amygdala bilaterally, the left nucleus accumbens, and the right caudate head and less grey matter volume in the left insula. Men with substance use disorders exhibited a smaller grey matter volume in the orbitofrontal cortex, ventromedial prefrontal cortex, and premotor cortex than patients without substance use. Regression analysis showed that the alterations in grey matter volume that distinguished the violent offenders from nonoffenders were associated with psychopathy scores and scores for lifelong aggressive behaviour. The grey matter volumes of the orbitofrontal and prefrontal cortex that distinguished the men with substance use from those without were correlated with scores for response inhibition. The authors concluded that a greater grey matter volume in the mesolimbic reward system may be associated with violent behaviour and that reduced grey matter volumes in the prefrontal cortex, orbitofrontal cortex, and premotor area characterize men with substance use disorders.

29.2.4 PET/SPECT Findings

Data on functional neuroimaging are largely restricted to PET studies, mostly using FDG-PET, in part with challenge tests, and very few SPECT data are available. In the field of aggression and violence, PET and SPECT are only used for research and scientific purposes, not for clinical diagnosis or psychiatric or forensic assessment.

In general, far fewer data are available from functional imaging studies than from structural imaging studies. Early studies using FDG-PET revealed decreased glucose metabolism in the temporal and frontal cortices of patients with violent behaviour (Volkow et al. 1995). A resting FDG-PET study in borderline patients revealed an inverse correlation between lifetime aggression and metabolism in the orbitofrontal cortex (Goyer et al. 1994). Later on these findings were replicated in murderers (Raine et al. 1994, 1997, 1998). In an FDG-PET study, George et al. (2004) reported a decreased glucose metabolism in the right hypothalamus and reduced relationships between cortical and subcortical brain structures in perpetrators of domestic violence. Another PET study in a small sample of borderline patients revealed an inverse relationship between a history of impulsive aggressive

behaviour and glucose metabolism in the prefrontal cortex, Brodmann's area 46 (Goyer et al. 1994). A challenge study with mCPP in patients with a history of physical aggression showed decrements in the lateral, medial, and frontal cortices at baseline (New et al. 2007). Another PET study on laboratory-induced aggression in patients from the same group with borderline personality disorder (New et al. 2009) showed an increased relative glucose metabolism in the orbital frontal cortex and amygdala in borderline patients with aggression, compared to controls. In contrast, an increased glucose metabolism was found in the anterior, medial, and dorsolateral prefrontal regions during provocation in healthy controls compared to borderline patients. The authors concluded that aggressive patients showed increased glucose metabolism in "emotional" brain areas and not in those areas associated with cognitive control of aggression.

Other studies used laboratory-induced aggression or challenge tests as a model to understand the anatomy of aggression. An experimental imaging study in healthy volunteers imagining aggressive behaviour showed blood flow reductions in the orbital frontal cortex (Pietrini et al. 2000). Another study on laboratory-induced aggression in patients with borderline personality disorder showed diminished responses to provocation in the medial frontal cortex and the anterior frontal cortex but greater responses in the orbitofrontal cortex compared to controls (New et al. 2006). Previously, two functional imaging studies showed an association of anger induction and activation of the orbitofrontal cortex in healthy adults (Dougherty et al. 1999; Kimbrell et al. 1999). Taken together, these neuroimaging findings give further evidence for the contribution of the ventromedial cortex, limbic system, amygdala, and thalamus to impulsivity control and aggression, which was previously shown in individual's brain damage in these regions (Berlin et al. 2004; Grafman et al. 1996; Bechara et al. 1999).

A number of other neuroimaging studies were performed not on aggression per se but on psychopathy, a related phenotype (for a review see Anderson and Kiehl (2012) and Yang and Raine 2009), mostly challenge tasks using psychological tests to study emotional responses to different scenarios. In sum, these studies also suggest that the hypoactive prefrontal cortex is involved in mediating the clinical features of psychopathy.

29.2.5 Serotonin and Dopamine in Aggression

Very few imaging studies have been performed on neurotransmitter function in aggressive individuals, some in healthy individuals.

MAO A is an enzyme involved in the release and degradation of dopamine and serotonin. MAO A genotype may be associated with aggression, as shown in some studies (Meyer-Lindenberg et al. 2006; Kim-Cohen et al. 2006; Newman et al. 2005). Caspi et al. (2002) demonstrated that low MAO genotype predicts high trait aggression in men with childhood trauma and MAO A genotype is one of the possible genetic determinants of aggression and impulsivity (Pavlov et al. 2012).

A PET study measuring trait aggression using clogyline labelled with carbon 11 as the radioligand in healthy males ($N=27$) found an inverse correlation between the measured amount of aggression and the multidimensional personality questionnaire (Alia-Klein et al. 2008). These data are not derived from patients with aggression or from forensic samples but are nevertheless interesting and suggest that lower MAO A activity in cortical and subcortical brain regions may predict aggressive or antisocial behaviour.

The relationship between MAO A binding and maladaptive personality traits has also been studied by Soliman et al. (2011). The group studied healthy nonsmokers using [^{11}C] harmine PET in prefrontal regions. In addition, personality traits were measured. Prefrontal MAO A binding correlated negatively with anger-hostility and positively with deliberation. In a two-factor regression model, these factors explained 35% of variance in prefrontal MAO A binding.

Other PET studies focused on serotonergic transmission or a serotonergic deficiency and its relationship with aggression. 5-HT (1a) and 5-HT (1B) receptors are very probably linked to aggression (De Boer and Koolhaas 2005). Correspondingly, Witte et al. (2009) studied 33 healthy volunteers using the radioligand (carbonyl-(11) C)WAY-100635 to quantify 5-HT (1A) binding potentials in the prefrontal cortex, limbic areas, and midbrain. In addition, testosterone and other hormone levels were measured. Statistical analysis revealed higher 5-HT (1A) receptor binding in subjects exhibiting higher aggression scores in prefrontal and anterior cingulated cortices. The authors discussed a reduced downstream control due to higher activity of frontal 5-HT (1A) receptors in more aggressive subjects, presumably modulated by sex hormones.

Since there is robust evidence from postmortem, in vivo imaging and genetic studies that the serotonin transmitter system is involved in the regulation of impulsive aggression PET studies have addressed this system. Da Cunha-Bang et al. (2013) studied trait aggression and impulsivity in healthy individuals. Trait aggression and impulsivity were assessed with the Buss-Perry Aggression Questionnaire and the Barratt Impulsiveness Scale. The 5T2A receptor binding was measured in a PET study. 94 individuals were included. Contrary to the hypothesis, results revealed no significant associations with 5-HT2AR and the psychopathology scales.

An interesting study has been published by Booij et al. (2010). The group studied the brain serotonin synthesis in a 21-year longitudinal study in individuals with a childhood-limited physical aggression ($N=8$) and with normal level of aggression ($N=18$) in a PET study using the tracer [^{11}C]methyl-L-tryptophan (^{11}C-AMT). Individuals with a history of aggression had significantly lower trapping of $^{11C\text{-}AMT}$ bilaterally in the orbitofrontal cortex and self-reported impulsiveness. Despite this, in adulthood there were no group differences in plasma tryptophan levels, genotyping, aggression, emotional intelligence, working memory, computerized measures of impulsivity, psychosocial functioning/adjustment, and personal and family history of mood and substance use disorders. The authors concluded that these results force a re-examination of the low 5-HT hypothesis as central in the biology of violence.

29.3 Aggression in Schizophrenia

Apart from "psychopathy" the only disorder studied in more detail in the context of aggression is schizophrenia. This is not surprising since numerous studies have indicated that aggression and homicide are more frequent in schizophrenia than in the general population (Fazel et al. 2009a, b; Soyka et al. 2007). A 7–12-year follow-up study of 1,662 former schizophrenic inpatients in Germany indicated that 169 patients (10.7%) were later convicted of a crime, in 94 cases a violent crime (Soyka et al. 2007).

Aggression and violence in schizophrenia can be explained by psychopathological symptoms such as delusions or hallucinations, comorbid substance use, social deterioration, cognitive deficits (Naudts and Hodgins 2006; Serper et al. 2008), or other clinical symptoms, but distinct neurobiological mechanisms may also play a role. Few studies have addressed the neurobiology of aggression and violence in schizophrenia.

29.3.1 Neuroimaging Studies

The amount of data from neuroimaging studies is limited (for a review see Soyka 2011). Two previous reviews identified about 50 articles indicating a connection between dysfunctional parts of the frontal and temporal lobes and violent antisocial behaviour and psychopathy (Wahlund and Kristiansson 2009; (Hoptman and Antonius 2011; Hoptman et al. 2010)) pointed at the amygdalofrontal functional disconnectivity and aggression in schizophrenia.

29.3.1.1 MRI Studies

Structural abnormalities have been repeatedly shown in violent and aggressive schizophrenia patients. Barkataki et al. (2006) reported that men with a history of violence showed reduced whole brain and hippocampus volumes. Hoptman et al. (2002) found indications of disturbed connectivity between the orbitofrontal cortex and the amygdala, and Wong et al. (1997) also reported structural abnormalities in the amygdala. Kumari et al. (2006) found that impulsiveness correlated negatively with reduced orbitofrontal grey matter volume and discussed whether dysfunctional, but not functional, impulsivity is elevated in patients with schizophrenia with a propensity for repetitive violence. Furthermore, the propensity for repetitive violence appeared to be associated with reduced volumes of both the orbitofrontal grey matter and the hippocampus. There is also some evidence for white matter abnormalities in this patient group. Hoptman et al. (2002) reported an association between measured aggression and increased diffusivity in the inferior frontal white matter.

Hoptman et al. (2005) published a quantitative MRI study of the orbitofrontal cortex in patients with chronic schizophrenia or schizoaffective disorder. Psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS) and Overt Aggression Scale (OAS). In this study, larger volumes of the right orbitofrontal cortex were associated with worse neuropsychological

performance. Larger grey matter volumes in the left orbitofrontal cortex and larger white matter volumes in the orbitofrontal cortex were found to be associated with a higher degree of aggression. Hoptman et al. (2010) discussed these somewhat surprising findings as indicating that larger volumes also may represent a reduced neuronal density or other pathophysiological processes.

Puri et al. (2008) reported results of an MRI study that compared structural changes in schizophrenia patients with and without violence. Schizophrenia patients with violence were found to have reduced grey matter volumes. Significant disturbances were found in the cerebellum, among other areas, which may be of relevance for input from ventrolateral prefrontal cortex and parietal regions. The findings were interpreted as showing that there may be disturbances in neuronal processes and, in particular, in parietotemporal connections, which may be particularly relevant for nonverbal working memory.

One of the most relevant confounding factors possibly explaining some of the variance is the effect of medication, especially in older studies. First-generation neuroleptics may have a profound effect on neurons and volumetric measures.

29.3.1.2 SPECT and PET Studies

Interesting data have arisen from functional imaging studies. Wong et al. (1997) used FDG-PET to study 31 patients with schizophrenia or schizoaffective disorder at a maximum security psychiatric hospital. Patients with a history of one act of violence showed reduced absorption of radioactively labelled glucose in the inferior, anterior, and temporal cortex of both hemispheres, while patients with a history of multiple acts of violence showed decreased FDG absorption in the anterior, inferior, and temporal cortex of the left hemisphere. This study did not find a selective reduction of glucose utilization in the prefrontal cortex. Spalletta et al. (2001) used SPECT to study the association between the function of the prefrontal cortex and aggression in 15 schizophrenia patients. In resting conditions, there were no differences between violent and non-violent patients. However, under neuropsychological stress (Wisconsin Card Sorting Test), prefrontal function was significantly reduced in the violent patients. Finally, Naudts and Hodgins (2006) stated that schizophrenia patients with aggression in comparison to nonaggressive schizophrenia patients show rather better neuropsychological performance, particularly in executive functions, but more impairments in the area of the orbitofrontal cortex. In addition, structural abnormalities in the amygdala-orbitofrontal system and in the prefrontal cortex and hippocampus may be involved.

Conclusion

Wahlund and Kristiansson (2009) in their fairly recent review on aggression and brain imaging reviewed 48 articles and concluded that the articles indicate a rather strong consensus on the connection between dysfunctional parts of the frontal and temporal lobes and violent antisocial behaviour but that there are fewer data on the limbic system. A hypoactive prefrontal cortex and a misinterpretation of emotional stimuli have been discussed as key issues. A previous review on this issue came to similar conclusions (Bufkin and Luttrell 2005). In

addition one may add that there is just a handful study on neurotransmitter dysfunction, although there are clear concepts (Comai et al. 2012). The lack of SPECT studies in this context is puzzling. PET studies indicate an increased glucose metabolism in the orbital frontal cortex and amygdale in patients with aggression, among others. Functional neuroimaging studies are especially of relevance to understand the interrelationship of neurotransmitter dysfunction and (impulsive) aggression. For the future, research may rather focus on the violent offenders or individuals with impulsive aggression as defined phenotype.

Acknowledgement This review was supported by the federal grants DFG SO 257/9-1 and So 257/9-2. The author thanks Jacquie Klesing, ELS, for editing assistance with the manuscript.

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Part VI

Miscellaneous Subjects

Application of PET and SPECT to the Study of Autism Spectrum Disorders

30

Diane C. Chugani

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 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

D.C. Chugani, PhD
Division of Clinical Pharmacology and Toxicology, Carman and Ann Adams Department of Pediatrics and the Department of Radiology,
Children's Hospital of Michigan, Detroit Medical Center,
Wayne State University School of Medicine,
3901 Beaubien Blvd, Detroit, MI 48201, USA
e-mail: dchugani@pet.wayne.edu

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_30, © Springer-Verlag Berlin Heidelberg 2014

synthesis 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.

Autism spectrum disorders are defined by a triad of behavioral impairments involving social interaction, communication, and restrictive repetitive stereotyped behaviors (APA 1994). 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 new genetic studies (Bill and Geschwind 2009). This chapter will include studies of cerebral blood flow, glucose metabolism, and protein synthesis, 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.

30.1 Focal and Global Brain Alterations in Glucose Metabolism

30.1.1 Increased Global Brain Glucose Metabolism in Autism

The measurement of 2-deoxy-2-[F-18]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; DeVolder et al. 1987; Seigel 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, Seigel 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 DeVolder study, since glucose metabolism shows marked changes with age (Chugani et al. 1987).

30.1.2 Regional Brain Glucose Metabolism Alterations in Autism and Related Disorders

30.1.2.1 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 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). Seigel 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 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. 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.

30.1.2.2 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 hippocampus (Bauman and Kemper 1994), but also because recent studies using volumetric MRI in patients with fragile X syndrome have found abnormalities in hippocampus (increased volume) and superior temporal gyrus (decreased volume) (Reiss et al. 1994). More recently, Dilber et al. (2013) studied a series 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.

30.1.2.3 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.

30.2 Focal and Global Brain alterations Cerebral Blood Flow

30.2.1 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 10 children (4–8 years) with autism and mental retardation, Gupta and Ratnam (2009) found generalized hypoperfusion in all 10 cases compared to 5 age-matched controls.

Zilbovicius et al. (1992) measured regional cerebral blood flow with SPECT and 133Xenon 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 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) were 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 was 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 were not statistically significant in children using 133Xenon 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 8 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 99mTc-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 99mTc-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 prefrontal cortex, medial frontal cortex, anterior cingulated cortex, medial parietal cortex, and anterior temporal cortex. There were two subgroups recognized based upon pattern of hypoperfusion, the medial-cingulate type and the temporal type, but these groups did not show any relationship with clinical symptoms. Also using ^{99}mTc-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 frontal, temporal, and parietal cortex and in 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 3–37 years. They reported prefrontal hypometabolism in all cases with autism, with further decreased metabolism in 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 99mTc-HMPAO brain SPECT. Visual and semiquantitative evaluations revealed hypoperfusion in the right posterior parietal cortex in 3 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 [1-11C] 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 eleven children with autism (7 males, 4 females; 6–7 years) before and 3 months after treatment with risperidone with 99mTc-HMPAO SPECT. There was a significant increase in cerebral perfusion following risperidone treatment bilaterally in 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 %.

30.2.2 Blood Flow Changes During the Performance of Tasks

In a functional mapping study using [O-15]-water PET, Happé 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 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 [O-15]water activation paradigm. Scans were performed at rest, while subjects listened to tones, listened to short sentences, repeated short sentences, and generated sentences. Analyses of peak activations revealed reduced or reversed dominance for language perception in 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 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 left frontal cortex and right dentate nucleus in the autistic subjects than the control group. These data suggest that 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.

30.3 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.

30.4 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, and acetylcholine.

30.4.1 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 [F-18]-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 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 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 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.

30.4.2 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, 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 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 right cortical, left cortical, and absence of abnormal asymmetry. Groups of autistic children, defined by 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-b-CIT, labeling both the dopamine and serotonin transporter described above, reported reduced serotonin transporter binding capacity in 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 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.

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 anterior and posterior cortices, as well as 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 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-HT2) 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 [11C]MDL 100907 in a group of 17 adults with Asperger's disorder (mean age 34.3) compared to 17 healthy matched adults.

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 measured using PET and SPECT and different tracers in small groups of children and adults with autism compared to age-matched controls.

30.4.3 $GABA_A$ 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 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 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 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 recent 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).

30.4.4 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*-[11C]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.

30.5 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, 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

31

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 ADHD. Investigations of cerebral perfusion and glucose metabolism during resting conditions and specific tasks have led ADHD to be associated with reduced

G.N. Stormezand
Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713 GZ, Groningen, The Netherlands

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_31,

functionality of the prefrontal cortex and the anterior cingulate cortex, as well as the basal ganglia, cerebellum and the 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.

31.1 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 focussed 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, efforts 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. 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).

31.2 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 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 et al. 1995) and dopamine receptor D4 gene (DRD4) (Faraone et al. 2001) with ADHD, in particular the 10-repeat allele at the DAT1 gene and the 7-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 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 in 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).

31.3 Neuroanatomy

In studies using nuclear imaging techniques, frontal and striatal structures have often been implicated in the brain localization of ADHD-related deficits (Table 31.1). Increasing evidence has come to suggest 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 the frontostriatal circuitry in predicting *what* will happen in a given context and the frontoneocerebellar circuitry in *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 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).

31.4 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 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).

31.5 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 behaviour 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 critical to develop insight into the neural bases 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 focussed 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 31.1 summarizes 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.

Table 31.1 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 and in 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_2	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)

(continued)

Table 31.1 (continued)

Series	*N* and clinical diagnosis	Technique and radiotracer	Study design	Findings	Specifications
Ernst et al. (1997)	10 ADHD 11 NC	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 8/10 ADHD patients received prior MPH treatment ROI-based analysis
Sieg et al. (1995)	10 ADHD 6 MC	SPECT and [I]-123 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 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 50 NC	PET and [^{18}F]-FDG	Cross-sectional	Lower global absolute CMRglc in ADHD and in 30 of 60 ROIS	Participants were adults Patients were stimulant naïve ROI-based analysis ($p<0.05$ uncorrected)
Lou et al. (1990)	9 ADHD 15 NC	SPET and [Xe]-133	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 Prior stimulant use not specified ROI-based analysis ($p<0.05$ uncorrected)

NC normal controls, *MC* mixed control group

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 frontal and temporal regions using voxel-based ^{99}mTc-ECD SPECT in prepubescent boys with ADHD who had 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).

31.6 Task-Related Functional Imaging

It can be seen from Table 31.1 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 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 usage of 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_2 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 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 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 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 (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 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.

31.7 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.

31.8 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 have 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).

31.9 Dopaminergic System

The dopamine system has been extensively investigated in ADHD. Most compelling evidence for its involvement in ADHD is the clinical benefit a substantial part of ADHD patients experiences during methylphenidate (MPH) treatment, although MPH mediates its effects though 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 31.2), suggesting 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 significant 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 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 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 that no response in all 5 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 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).

31.10 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 -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. Currently, no studies have yet been performed in ADHD to *directly* assess the neuroepinephrine system using PET or SPECT as a suitable tracer has been lacking. However, recent results with (S,S)-[^{11}C] methylreboxetine PET are promising, in that these results provide evidence of a dose-dependent uptake of tracer in areas proven to be NET-rich, such as the locus coeruleus, hypothalamus, thalamus and raphe nuclei (Hannestad et al. 2010).

31.11 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 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).

31.12 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 10-repeat allele polymorphism at DAT1 gene and the 7-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 gray matter volume (Durston et al. 2005). In vivo imaging of the DAT receptor with ^{123}I-IPT SPECT has linked homozygosity of the 10-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 7-repeat allele and homozygosity for the 10-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).

31.12.1 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 31.2 provides an overview, including studies assessing perfusion and glucose metabolism as well as neurotransmitter systems.

Table 31.2 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
Jucaite et al. (2005)	12 ADHD 10 NC	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) 3/12 patients were not stimulant naive

Ernst et al. (2003)	10 ADHD 12 NC	PET and [^{15}O]-H_2	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 2/10 received prior stimulant treatment Voxel-based analysis of a priori set ROIs
Kaya et al. (2002)	13 ADHD 17 NC	SPECT and ^{99m}Tc-HMPAO	Cross-sectional	Negative correlation (r=−.071) between teachers Du Paul rating scale and perfusion of the right medial temporal cortex in ADHD	All participants were children 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 naive 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

31.13 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 is 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 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.

31.14 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

32

Jacques Darcourt, Renaud David,
Renaud Guignard, and Philippe Robert

Contents

Abstract

Apathy is a frequent behavioural syndrome which is now characterised by precise criteria. It can be found in various neurological diseases. In Alzheimer's disease in particular, it is present at all stages and, in MCI patients, is a risk factor for conversion.

Anterior cingulate-subcortical circuit which originates from the anterior cingulate cortex in Brodmann's areas (BA) 24 and 32 and projects to the limbic striatum, globus pallidus and thalamus is the 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

J. Darcourt (✉) • R. Guignard
Nuclear Medicine Department, Centre Antoine Lacassagne. UMR CEA TIRO,
Université de Nice Sophia Antipolis, 33 Avenue de Valombrose, 06189 Nice, France
e-mail: darcourt@unice.fr

R. David • P. Robert
Memory Center CMRR – CHU Nice, Université de Nice Sophia Antipolis,
4 Avenue Reine Victoria, 06003 Nice, France

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_32, © Springer-Verlag Berlin Heidelberg 2014

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.

More neurotransmission imaging studies are necessary to complete the understanding of the pathophysiology of this syndrome and to participate to specific treatment developments.

Imaging findings in degenerative diseases such as Alzheimer's disease (AD) using single-photon emission tomography (SPECT) brain perfusion studies or 18-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) are mainly related to cognitive dysfunctions. However, noncognitive behavioural symptoms may also influence the imaging results. Apathy is recognised as one of the most frequent associated behavioural syndrome in degenerative and vascular brain diseases. It is an important issue on many aspects 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 region 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 on this syndrome and the related imaging findings.

32.1 What Is Apathy?

Apathy is now well recognised as an important behavioural syndrome in Alzheimer's disease (AD) and in several neuropsychiatric disorders (Starkstein and Leentjens 2008).

Marin was the first to present apathy as a motivation disorder (Marin 1990, 1991). Most of the current descriptions acknowledge this point and consider apathy in terms of lack of goal-directed motivation expressing itself in the cognitive, behavioural or emotional fields of human life (Marin et al. 1995; Brown and Pluck 2000; Starkstein et al. 2001; Levy and Dubois 2005).

A consensus conference was organised in 2009 to propose a set of diagnostic criteria for apathy (Table 32.1) (Robert et al. 2009). Apathy is now defined as a motivation disorder persisting over time which meets the following requirements. Firstly, the core feature of apathy, i.e. diminished motivation, must be present for at least 4 weeks; secondly, impairment in at least two among the three dimensions of apathy (i.e. reduced goal-directed behaviour, goal-directed cognitive activity and emotions) must also be present; thirdly, there should be identifiable functional impairments attributable to apathy. Finally, exclusion criteria are specified to exclude symptoms and conditions mimicking apathy.

In AD, apathy is the most frequently encountered symptom at all stages of the disease (Robert et al. 2005). In the REAL-FR cohort study, the prevalence of apathy and hyperactivity symptoms increased significantly during the 4-year follow-up

Table 32.1 Diagnostic criteria of apathy

For a diagnosis of Apathy the patient should fulfil the criteria (A), (B), (C) and (D)
(A) Loss of or diminished motivation in comparison to the patient's previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others
(B) Presence of at least one symptom in at least two of the three following domains for a period of at least four weeks and present most of the time *Domain B1*: Loss of, or diminished, goal-directed behaviour as evidenced by at least one of the following: Loss of self-initiated behaviour (e.g., starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices) Loss of environment-stimulated behaviour (e.g., responding to conversation, participating in social activities) *Domain B2*: Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following: Loss of spontaneous ideas and curiosity for routine and new events (i.e., challenging tasks, recent news, social opportunities, personal/family and social affairs) Loss of environment-stimulated ideas and curiosity for routine and new events (i.e., in the person's residence, neighbourhood or community) *Domain B3*: Loss of, or diminished, emotion as evidenced by at least one of the following: Loss of spontaneous emotion, observed or self-reported (e.g., subjective feeling of weak or absent emotions, or observation by others of a blunted affect) Loss of emotional responsiveness to positive or negative stimuli or events (e.g., observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotion-laden news)
(C) These symptoms (A–B) cause clinically significant impairment in personal, social, occupational or other important areas of functioning
(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 diminished level of consciousness or to the direct physiological effects of a substance (e.g., drug of abuse, a medication)

period, whereas the prevalence of affective and psychotic symptoms did not (Gonfrier et al. 2012). Overall, the prevalence is estimated to be in the order of 60 % of AD outpatients (van Reekum et al. 2005). Several studies have also indicated that apathy explained at least partially the loss of autonomy in daily life activities (Lechowski et al. 2009).

Furthermore, several studies have shown that in addition to the impairment of cognitive performances, neuropsychiatric symptoms are present very early in the AD process. Apathy and depressive symptoms are the most frequent neuropsychiatric symptoms in mild cognitive impairment (MCI) (Feldman et al. 2004; Gabryelewicz et al. 2004; Lopez et al. 2005). In a prospective study on predictive factors for AD, Robert et al. (2006) reported that the presence of mild signs of apathy in MCI patients was cross-sectionally associated with a higher degree of memory impairment. The same study also examined the influence of apathy dimensions on the risk of developing AD in 214 patients with MCI during a 3-year follow-up. Anxiety, depression and apathy assessment were included in the battery of neuropsychiatric tests. 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 (Vicini Chilovi et al. 2009). In a 2-year follow-up study, the rates of conversion to dementia were 24 % for MCI without depression or apathy, 7.9 % for depressed MCI, 19 % for depressed-apathetic MCI and 60 % for apathetic MCI. It is important to recall that, although apathy and depression have substantial overlap in key symptoms, there are different syndromes with different neurobiological correlates (Tagariello et al. 2009).

Apathy can be also diagnosed in other neurological diseases. For example, a multicenter study aimed at validating the apathy diagnostic criteria in daily clinical practice showed that apathy was present in 55 % of the AD patients, 70 % of the mixed dementia patients, 43 % of the MCI patients, 27 % of the Parkinson's disease patients, 53 % of the schizophrenic patients and 94 % of the major depressive episode patients (Mulin et al. 2011). Interestingly, apathy is seen with a general prevalence of roughly 60 % in diseases involving directly the cortex areas and, in average, in 40 % of diseases affecting subcortical structures like in most post-stroke situations, for example (van Reekum et al. 2005).

32.2 What Is Known About Its Anatomical Bases?

Alexander (Cummings 1997) first described a series of parallel frontal-subcortical circuits that link the frontal cortex to the striatum, globus pallidus and thalamus. Cummings further developed this concept which greatly helped in understanding the physiology of behaviour and neuropsychiatric changes occurring with lesions involving these circuits.

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 (Tekin and Cummings 2002).

Motivated behaviour is supported by the anterior cingulate-subcortical circuit which originates from the anterior cingulate cortex in Brodmann's areas (BA) 24 and 32. The corresponding neurons project to the ventral striatum called "limbic striatum", then to the ventral pallidum and the substantia nigra before reaching the anterior thalamus. A projection from the anterior thalamus back to the cingulated cortex closes this circuit (Fig. 32.1).

Lesions affecting this circuit produce a decrease in motivation also called anterior cingulated 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-stroke apathy in particular is observed roughly in 35 % of the patients (van Reekum et al. 2005) and is difficult to separate from depression (Hama et al. 2007). 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

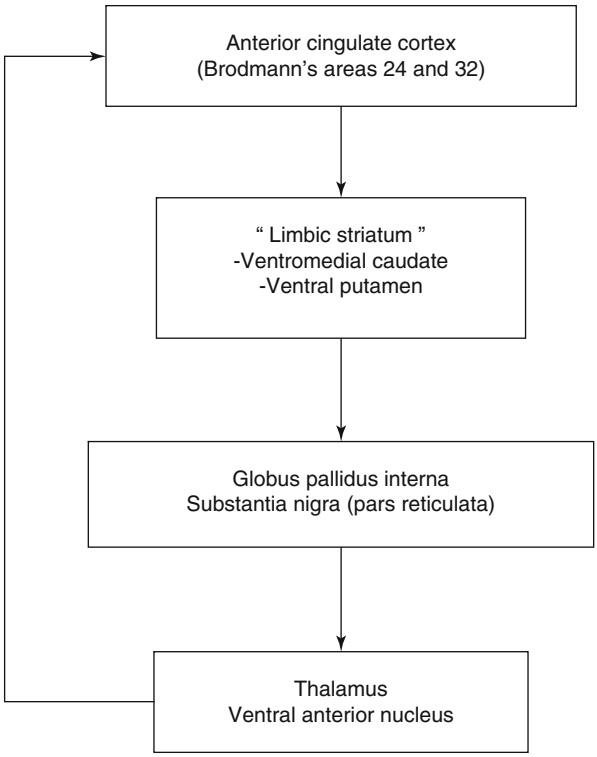

Fig. 32.1 The anterior cingulated-subcortical circuit

(Starkstein et al. 1993; Murakami et al. 2013). In general, the prevalence of apathy in diseases involving the basal ganglia is reported to be around 40 %.

In summary, apathy can be observed in various neurological diseases as long as they affect the anterior cingulated-subcortical circuit. In AD, this is due to cortical involvement, while after stroke it is more likely to be related to subcortical lesions.

From the neurobiological point of view, the projections from the frontal cortex to the striatum are mediated by glutaminergic neurotransmission as well as the projections from the thalamus to the cortex. The connections between the striatum and the globus pallidus externa-substantia nigra are mediated by γ-aminobutyric acid (GABA) as well as the connections between the latter and the thalamus (Tekin and Cummings 2002). However, these circuits are modulated by other neurotransmitter systems. The dopaminergic neurons projecting from the substantia nigra pars condensa to the striatum can affect the cingulate-subcortical circuit. Apathy is frequently observed in Parkinson's disease (Aarsland et al. 2007). Murakami et al. (2013) studying 149 post-stroke patients found that apathetic patients had lesions mostly located in the brain stem and in the striatum on MRI and suggested that apathy symptoms were associated with serotoninergic and dopaminergic dysfunction. A significant correlation between dopamine striatal activity measured using 11C-raclopride and anterior cingulated metabolism was demonstrated in the context of age-related decline (Volkow et al. 2000). David et al. (2008) found a significant

correlation between lack of initiative and striatal dopamine transporter levels, measured with SPECT independently of motor activity, in a small group of patients presenting either AD or Lewy body dementia. The neurotransmission systems implicated by the results of the specific apathy treatment effects include dopamine, acetylcholine, serotonin and norepinephrine (van Reekum et al. 2005).

32.3 How Does Apathy Reflect on 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 on using 18-fluorodeoxyglucose PET metabolic imaging.

32.3.1 SPECT Studies

The first study was published by Craig et al. (1996). They studied 31 AD patients using the Neuropsychiatric Inventory (NPI) (Cummings 1997) and perfusion SPECT. Perfusion SPECT data were obtained using a 133Xe calibrated 99mTc-HMPAO method which combined the spatial resolution of HMPAO with the absolute quantification of regional cerebral blood flow provided by 133Xe. With this method, rCBF could be expressed in millilitres per hundred grams and per minute (Darcourt et al. 1993). 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 anterior frontal regions – including the anterior cingulate area – 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, this work was the first in vivo imaging study demonstrating the relationship between anterior cingulated cerebral blood flow and apathy using region of interest analysis (ROI) and absolute quantification.

Benoit et al. (1999) studying the "behavioural 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-ECD SPECT images, they demonstrated a negative correlation between the NPI apathy score and the perfusion of the right anterior cingulate.

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 anterior cingulate gyrus 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 99mTc-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 anterior cingulated

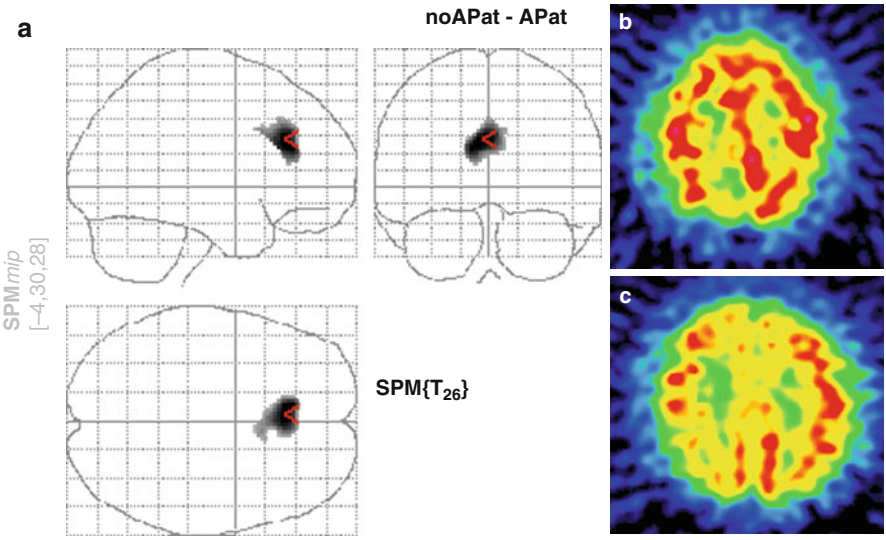

Fig. 32.2 99mTc-SPECT demonstration of anterior cingulate involvement in apathy (Adapted from Migneco et al. (2001)). (**a**) SPM analysis comparing apathetic and non-apathetic patients showing a very specific difference in anterior cingulated area (BA 24). (**b**) Transaxial cut involving the anterior cingulated cortex in a normal subject. (**c**) Same level of transaxial cut in an apathetic patient showing hypoperfusion in the anterior cingulate region

BA 24 (Fig. 32.2). 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 99mTc-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 the 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 anterior cingulated 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 cingulated involvement is more specifically related to the lack of initiative.

More recently Kang et al. (2012) used brain SPECT perfusion to address the relationship between apathy and depression. They used SPM analysis of 99mTc-HMPAO scans. Among 81 AD patients, they compared 9 patients only apathetic (nondepressed) A+ to 9 patients only depressed D+ (non-apathetic). They showed that different regions were involved in A+ and D+ patients. A+ patients had lower perfusion than A− in the right amygdala, temporal, posterior cingulate, right superior frontal, postcentral and left superior temporal gyri, whereas D+ patients had significantly lower perfusion in the right orbitofrontal and inferior frontal gyri than

D– patients. These results are in line with the involvement of different circuits for apathy and depression. However, they did not relate apathy to the same cortical areas as the previous studies.

In studies addressing post-stroke apathy, the results are different. For example, Onoda et al. (2011) studied 102 post-stroke patients using 123I-IMP rCBF SPECT and showed that apathy was present in 37 % of the patients and related to basal ganglia hypoperfusion.

32.3.2 PET Studies

Marshall et al. (2007) investigated 41 patients with probable AD. Fourteen of them were considered as apathetic based on the Scale for the Assessment of Negative Symptoms in Alzheimer's Disease (SANS-AD) (Reichman et al. 1996). Images were obtained using 18F-FDG PET and analysed by SPM. This study also found significantly reduced metabolism in the anterior cingulated 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 anterior cingulated involvement related to apathy (Fig. 32.3) described on perfusion SPECT.

More recently Schroeter et al. (2011) investigated 54 patients including 19 probable AD, 13 FLTD and 10 "other dementias". Fifty per cent of the patients exhibited apathy on the NPI. They were all studied using 18F-FDG PET and data were analysed using SPM. Apathy correlated with hypometabolism in the anterior cingulated cortex. Additional hypometabolism correlating with apathy was found in midcingulate, subcallosal 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.

Holthoff et al. (2005) studied the correlations between neuropsychiatric symptoms and 18F-FDG brain metabolism in 53 AD patients. They used NPI for symptoms evaluation and SPM for 18F-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 inferiorly. 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 anterior cingulate cortex but also with other areas such as inferior temporal pole and laterofrontal areas. In a recent study addressing a selected population of Parkinson's disease patients without dementia or depression, Robert et al. (2012) demonstrated a correlation between hypometabolism of the cerebellum and apathy.

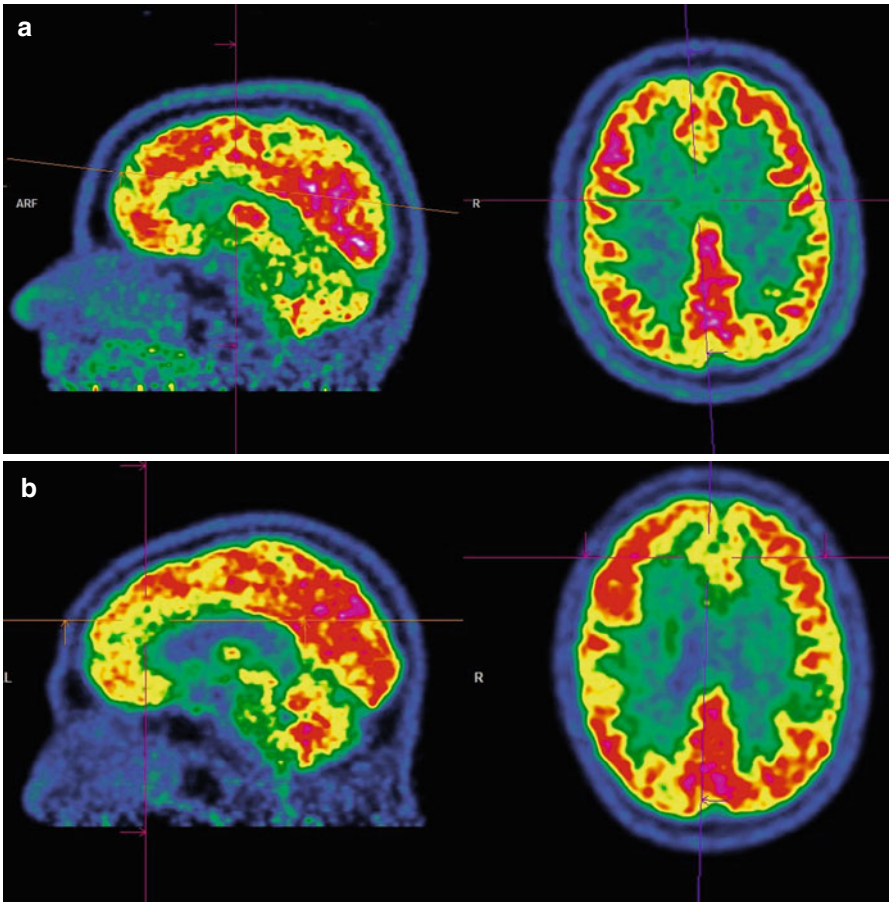

Fig. 32.3 Pattern of apathy on 18F-FDG-PET images. (**a**) Patient with no apathy. (**b**) Patient with apathy showing hypometabolism involving the anterior cingulate area

Conclusion

Hypoperfusion or hypometabolism in the anterior cingulate related to apathy is a robust finding in cortical degenerative diseases which can be observed on perfusion SPECT as well as on 18F-FDG PET. This finding is a recognisable pattern for clinical reading of images. SPECT and PET studies confirmed that apathy and related anterior cingulated hypoperfusion/hypometabolism is a neuropsychological independent behavioural syndrome which is independent from the underlying pathology as well as from clinical characteristics such as depression.

In other clinical settings than in cortical degenerative diseases like in stroke patients, the same anterior cingulated-subcortical circuit is involved, but the primary lesion usually lies at the subcortical level.

Both situations are in line with the anterior cingulate fronto-subcortical circuit model hypothesis of apathy advocated by J. Cummings.

However, hypoperfusion and hypometabolism can be found in areas which are not directly related to this system raising new hypotheses which need further developments such as the various dimensions of apathy which may involve different cortico-subcortical circuits. Neurotransmission imaging should also play a more important role in apathy understanding to help develop specific pharmacological interventions.

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PET and SPECT Studies in the Chronic Fatigue Syndrome/Myalgic Encephalomyelitis

33

Andor W.J.M. Glaudemans

Contents

Abstract

Chronic fatigue syndrome (CFS) or myalgic encephalitis (ME) comprises a group of disorders generally defined by persistent fatigue accompanied by a range of other symptoms that may fluctuate in intensity and severity and with great variability in the symptoms between individual persons.

The underlying pathophysiology is still not fully explained, but literature continues to demonstrate an involvement of the central nervous system. This book chapter reviews all SPECT and PET studies in patients with CFS/ME that have been published. No corresponding findings were found in all these studies. Some

A.W.J.M.Glaudemans, MD
Department of Nuclear Medicine and Molecular Imaging,
University Medical Center Groningen, University of Groningen,
Hanzeplein 1, Groningen, The Netherlands
e-mail: a.w.j.m.glaudemans@umcg.nl

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_33, © Springer-Verlag Berlin Heidelberg 2014

papers mention a global cerebral hypoperfusion and some hypoperfusion of the brainstem; others did not find any differences compared with healthy controls or found hyperperfusion of a certain brain region. However, for the future, there are several possibilities in which nuclear medicine may help to solve the problem of the aetiology of CFS/ME. Imaging the serotonergic system, targeted imaging of specific molecules and cytokines involved in this disease and imaging the role of neuroinflammation are areas that may be worthwhile to investigate.

33.1 Introduction

33.1.1 What Is Chronic Fatigue Syndrome?

Chronic fatigue syndrome (CFS), also called myalgic encephalomyelitis (ME), comprises a group of disorders generally defined by persistent fatigue accompanied by a range of other symptoms for a minimum of at least 6 months. Other symptoms include malaise, headaches, sleep disturbances, widespread muscle and joint pain, difficulties with concentration and other characteristic symptoms in a previously healthy and active person.

Symptoms in an individual person may fluctuate in intensity and severity, and there is also great variability in the symptoms between different persons. Many different potential aetiologies for CSF/ME have been investigated, including infectious, neurological, endocrine, immunologic, psychiatric, environmental and genetic aetiologies. 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 aetiology and the effectiveness of 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 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.

33.1.2 Classification of Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis

Several diagnostic criteria in CFS were developed after the introduction of the label CSF in 1988. 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 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).

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 CFS/ME 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).

For the diagnosis CFS/ME, 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

33.1.3 Nuclear Medicine Studies in CFS/ME

For diagnostic purposes, SPECT and PET imaging play no role as currently the exact pathophysiology of the development of CSF/ME is unknown. Nuclear medicine is not able to tell whether a person has CFS/ME or not. Neither is any other imaging technique.

However, recent research progress has been made in pathophysiology and several studies continue to demonstrate the involvement of the central nervous system (CNS). For further elucidation of the CNS involvement, nuclear medicine can offer unique imaging possibilities. The studies that are performed with radionuclides in patients with CFS/ME focus mainly on these possible neurological impairments. This chapter will now describe all SPECT and PET studies that are performed in CFS/ME patients.

33.2 SPECT Studies in Patients with CFS/ME

33.2.1 ^{99m}Tc-HMPAO

^{99m}Tc-labelled hexamethylpropyleneamine oxime (HMPAO), also called exametazime, is traditionally the most used tracer to image the regional perfusion of the brain. Already in 1992, the first study with ^{99m}Tc-HMPAO in patients with CFS/ME was published. In this study, regional cerebral blood flow (rCBF) was assessed in 60 clinically defined (according to the Canadian consensus criteria) CFS/ME patients and 14 normal control subjects using ^{99m}Tc-HMPAO SPECT. The CFS/ME group showed significantly lower cortical/cerebellar rCBF ratios, throughout multiple brain regions. Forty-eight patients with CFS/ME (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 CFS/ME patients. These findings may not be diagnostic of CFS/ME but ^{99m}Tc-HMPAO SPECT may play an important role in clarifying the pathophysiological development of CFS/ME (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 CFS/ME 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 CFS/ME 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 CFS/ME 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 CFS/ME. Three patients had a follow-up SPECT scan after clinical improvement and showed remission of the defects in 60 %. 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 CFS/ME and that SPECT may also prove to be useful in following the clinical progress of patients with this syndrome (Schwartz et al. 1994a).

The same authors also compared the results of ^{99m}Tc-HMPAO SPECT scans of 45 patients with CFS/ME to 27 patients with AIDS dementia complex (ADC), 14 with major unipolar depression (MUD) and 38 controls. The cause for ADC is viral encephalitis, and the aim of the study was to explore the specificity of SPECT to distinguish patients with CFS/ME from patients with viral encephalitis/ADC and from patients with MUD. The number of defects was evaluated by three independent radiologists in eight different regions of the brain. A defect was defined according to stringent criteria as a region of less than 60 % of the maximum activity, greater than 1 cm in diameter, and spanning the full thickness of the cortex. Furthermore, the midcerebral uptake index (MCUI), an objective measurement reflecting tracer uptake in the brain, was calculated. Patients with ADC were found to have the largest number of abnormalities (9.15 per patient) and healthy patients had the fewest abnormalities (1.66 per patient). Patients with CFS/ME and MUD had similar numbers of abnormalities per patient (6.53 and 6.43, respectively). In all groups, defects were located predominantly in the frontal and temporal lobes. The MCUI was found to be significantly lower in patients with CFS/ME and patients with ADC than in patients with MUD or healthy controls. Also, a significant negative correlation was found between the number of abnormalities and MCUI in patients with CFS/ME and ADC. So, the MCUI findings were nearly similar between the group with CFS/ME and the group with viral encephalitis/ADC and were consistent with the hypothesis that CFS/ME may be due to chronic (viral) encephalitis. The similar findings between the number of abnormalities in patients with CFS/ME and patients with MUD could be the reason for clinical similarities and symptoms (Schwartz et al. 1994b).

The largest study found in literature was initiated by Costa et al. in 1995. ^{99m}Tc-HMPAO SPECT was performed in 146 subjects, of which 67 patients were diagnosed with CFS/ME, 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 CFS/ME 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 CFS/ME was correlated to the brainstem perfusion in the other patient groups and the healthy volunteers. The brainstem perfusion ratios of the CFS/ME 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 CFS/ME 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 CFS/ME, 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).

All the above-mentioned studies have clear corresponding results: Patients with CFS/ME have a decreased perfusion, either generalised reduction of all cerebral regions or a hypoperfusion of the brainstem. Unfortunately, others reported no significant differences between perfusion rates in patients with CFS/ME and healthy volunteers or patients with depression (Fischler et al. 1996). Peterson also was not able to find differences between patients with CFS/ME and healthy control subjects in rest, but also scanned patients after exercise. The scan findings postexercise were accentuated in the CFS/ME patients, with more abnormalities found compared to the scans in rest. These findings however were not significantly different from those in the control group (Peterson et al. 1994).

Even in contrast with the results of the above-mentioned studies is the study of Machale et al. They studied the cerebral perfusion with ^{99m}Tc-HMPAO SPECT in 30 patients with CFS/ME (without depression), 12 patients with depression and 15 healthy volunteers. On SPM analysis they did not find a generalised cerebral hypoperfusion or hypoperfusion of the brain stem, but an increased perfusion in the right thalamus, pallidum and putamen in patients with CFS/ME and in patients with depressive illness. CFS/ME patients also had increased perfusion in the left thalamus. Depressed patients however differed from those with CFS/ME in having relatively less perfusion of the left prefrontal cortex. So, the authors could not find significant differences between CFS/ME and depressive patients. The thalamic overactivity, compared to the uptake in the healthy volunteer group, may be a correlate of increased attention to activity in CFS/ME and depression; the reduced prefrontal perfusion in depression may be associated with the greater neuropsychological deficits in that disorder (Machale et al. 2000).

Environmental and genetic factors could also play a role in the development of CFS/ME. All previous investigations have limitations: sometimes they lack healthy control subjects; sometimes they failed to account for coexistent psychiatric morbidities, age and sex; and sometimes they did not make adjustments for the subjects' emotional state or medication state at the time of injection. This was the reason for Lewis et al. to emphasise the need to better characterise the sociodemographic background, psychiatric status and physical fitness of patients with CFS/ME and control subjects in SPECT studies. They applied a co-twin control method, which is a matched-pair analysis that includes substantial adjustments for many genetic

and environmental factors that generally are not considered in typical case-control studies. They mailed an intake questionnaire to a total of 600 twins and found 22 monozygotic twins in which one twin met criteria for CFS and the other was healthy. The twins underwent a structured psychiatric interview and a resting ^{99m}Tc-HMPAO SPECT of the brain. The twins with and those without CFS/ME were similar in mean number of visually detected abnormalities and in mean differences quantified. These results were unaltered with adjustments for fitness level, depression and mood before imaging. So, these study results did not provide evidence of a distinctive pattern of resting brain perfusion abnormalities associated with CFS/ME (Lewis et al. 2001).

Schmaling et al. mentioned the importance of the use of activated scanning conditions. Activated scanning conditions may provide more useful data than scans under resting conditions and reflect patient subjective reports of impairments which increases in mental activity. Activation tasks must be controllable and replicable; performance must be monitored and must generate a detectable and reproducible change in regional cerebral blood flow. In this study, 15 patients with CFS/ME and 15 healthy control subjects were scanned with ^{99m}Tc-HMPAO SPECT in rest and during a demanding cognitive task, the Paced Auditory Serial Addition Test (PASAT). The PASAT is an information-processing task that places high demands on working memory and attention. The authors focused especially on blood flow changes in the left anterior cingulate region because of the association of this region with effortful information procession. The results, however, were disappointing. No group differences were found for performance on the PASAT despite CFS/ME subjects' perceptions of exerting more mental effort to perform the task than healthy subjects. Inspection of the aggregate scans by group and task suggested a pattern of diffuse regional cerebral blood flow among subjects with CFS/ME in comparison with a more focal pattern of cerebral blood flow seen among healthy subjects. The change in blood flow of the left anterior cingulate region in subjects with CFS/ME during the PASAT was greater than that observed for healthy subjects. The differences were not attributable to lesser effort by the subjects with CFS/ME, confounding effects of mood perturbation, or to poorer performance on the experimental task (Schmaling et al. 2003).

33.2.2 ^{123}I-IMP

N-isopropyl-4-[^{123}I]iodoamphetamine (^{123}I-IMP) has also been used for cerebral perfusion imaging with SPECT (Kanai et al. 2007), although much less than ^{99m}Tc-HMPAO. One study was found in the literature which used ^{123}I-IMP in children with CFS/ME. Chronic fatigue occurring in previously healthy children and adolescents is rare and one of the most vexing problems encountered in clinical practice. Usually the symptoms in these cases significantly interfere with normal school functioning. Three cases – 11-, 12- and 13-year-old children – with CFS/ME were reported by Kanai et al. The three children initially developed a low-grade fever and generalised fatigue, followed by sleep disturbances and psychosomatic symptoms, and their performance ability deteriorated. Eventually, they fulfilled the criteria for having CFS/ME. SPECT images were obtained and the regional cerebral

blood flow examined 30 min after intravenous injection of ^{123}I-IMP in the awake state. Blood flow, expressed as the corticocerebellar ratio (CCR), in the left temporal and occipital lobes was markedly lower in cases 2 and 3 than in healthy subjects reported by other investigators. In case 1, however, blood flow in the left basal ganglia and thalamus was markedly higher than in healthy subjects. So, all three SPECT scans were abnormal but with variable patterns. According to the authors, these findings suggest that the various clinical symptoms in CFS/ME patients may be closely related to an abnormal brain function (Tomoda et al. 2000).

33.2.3 ^{201}Thallium

One of the most characteristic features of CFS/ME is fluctuation in symptoms which can be induced by physical and/or mental stress. Other conditions in which fluctuating fatigue occurs are caused by abnormal ion channels in the cell membrane. These include genetically determined chanellopathies, e.g. hypokalaemic periodic paralysis, episodic ataxia type 2 and acquired conditions such as neuromyotonia, myasthenic syndromes, multiple sclerosis and inflammatory demyelinating polyneuropathies. All these diseases have symptoms that could also fit with CFS/ ME.

Another common symptom in CFS/ME patients is angina-like chest pain. Syndrome X is a term that is frequently used as a diagnostic label for patients who have exertional angina, a positive response to exercise testing and angiographically normal coronary arteries and is also a disorder of ion channels. Syndrome X and CFS/ME may share many similarities including identical clinical course, abnormal oxidative metabolism in skeletal muscle and increased lactate production. Recently, it has been shown that abnormal cardiac perfusion SPECT scans with ^{201}Thallium, which are found in a significant proportion of patients with syndrome X, are also common in patients with CFS/ME. All these results lead to the hypothesis that CFS/ ME may begin after exposure to specific toxins which are known to produce abnormal sodium ion channels (Chaudhuri et al. 2000).

Till now, no studies have been performed that provide answers to this hypothesis. Maybe it could be useful to study the relationship between abnormal myocardial perfusion scans and CFS/ME. SPECT tracers could be used for this reason; however, better quantification is possible with PET tracers. In patients with suspected syndrome X, a reduced coronary flow reserve was found with use of the PET tracer [^{13}N]ammonia (De Vries et al. 2006).

33.3 PET Studies in Patients with CFS/ME

33.3.1 ^{18}F-FDG

Despite the fact that the major breakthrough in nuclear medicine imaging of the brain – the development of the PET camera and consequently the possibility for absolute quantification and a better spatial resolution – already took place in the

mid nineties, there are still not many publications for PET tracers and CFS/ME. The most used tracer in these publications is [^{18}F]fluorodeoxyglucose (^{18}F-FDG).

In 1998, Tirelli et al. investigated the brain metabolism of 18 patients affected by CFS/ME with ^{18}F-FDG. Psychiatric diseases and anxiety/neurosis were excluded in all CFS/ME patients. The results of the CFS/ME patients were compared with a group of six patients affected by depression and 6 age-matched healthy controls. The patients with CFS/ME were not taking any medication at the time of the PET, and depressed patients were drug-free for at least 1 week before the PET examination. The PET images examined 22 cortical and subcortical areas. CFS/ME patients showed a significant hypometabolism in the right mediofrontal cortex and brainstem in comparison with the healthy controls. Moreover, comparing patients affected by CFS/ME and depression, the latter group showed a significant and severe hypometabolism of the medial and upper frontal regions bilaterally, whereas the metabolism of brain stem was normal. So, brain metabolism imaging with ^{18}F-FDG showed specific metabolism abnormalities in patients with CFS in comparison with healthy and depressed patients. The most relevant finding was the brain stem hypometabolism, which also was reported in a perfusion SPECT study. This brain stem hypoperfusion seems to be a marker for the in vivo diagnosis of CFS/ME (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 CFS/ME, 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 CFS/ME 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 CFS/ME patients. Brain ^{18}F-FDG PET was performed in 26 patients, with age 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 CFS/ME could be identified. The authors state, however, that PET may

provide valuable information in helping to separate CFS/ME patients into subpopulations with and without apparent alterations in the central nervous system (Siessmeier et al. 2003).

A last study that is worth discussing is not performed in a group of patients with CFS/ME, but in optimally treated HIV patients. The aim of the study was to determine the prevalence and severity of fatigue among these patients and to investigate the potential association with systemic inflammation and abnormalities of the distribution of cerebral glucose metabolism. This distribution was measured in a subgroup of patients suffering from severe fatigue ($n=9$) and a group with no fatigue ($n=7$) using ^{18}F-FDG. About 50 % of the patients showed minor abnormalities in the relative cerebral metabolic rate of glucose. These abnormalities were not associated with fatigue but with neurodegeneration as an aspect of HIV neuropathogenicity (Andersen et al. 2006). So, again no correlation was found between FDG-PET findings and existing fatigue.

33.3.2 Serotonin Tracers

At the moment, no effective somatic treatment for CFS/ME is available. Various drugs have been proposed and antidepressants are commonly described. Tricyclic antidepressants are tolerated poorly by patients with CFS/ME because side effects include sedation and exacerbation of fatigue symptoms. 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 CFS/ME 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). Other studies, however, mention no beneficial effects of fluoxetine therapy on any characteristic of CFS/ME (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 CFS/ME. 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 improve understanding of the pathogenesis of this disorder and also in the chronic fatigue syndrome (Bakheit et al. 1992). Another study showed a significant increase of variants in serotonin transporter gene promoter polymorphism, which emphasises the 'serotonergic system dysfunction hypothesis' when considering the aetiology of CFS/ME (Narita et al. 2003).

The hypothesis of a role of the serotonergic system in the pathophysiology of CFS/ME led to several studies that used serotonin PET tracers in patients with CFS/ME. [^{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 disorders (McCann et al. 1998; Simpsom et al. 2003). In ten

patients with CFS/ME, a significant reduction of the density of the 5-HT transporters was found in the rostral subdivision of the anterior cingulate as compared with ten normal volunteers (age matched). This division is different from that in the dorsal anterior cingulate in which binding potential values of individual patients showed a weak negative correlation with self-reported pain score of the patients. The authors concluded that an alteration of the serotonergic system in the rostral anterior cingulate plays a key role in the pathophysiology of CFS/ME (Yamamoto et al. 2004).

Another group used the selective 5-HT receptor ligand [^{11}C]WAY-100635 in 10 patients, who were completely medication-free and did not have current comorbid psychiatric illnesses, and in 10 healthy control subjects. They found a widespread reduction in 5-HT receptor binding potential in patients with CFS/ME 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 in CFS/ME, which may be a primary feature of CFS/ME, related to the underlying pathophysiology, or a finding secondary to other processes, such as previous depression, other biological changes or the behavioural consequences of CFS/ME (Cleare et al. 2005).

33.4 Discussion and Conclusions

The pathophysiology in the development of CFS/ME is still unclear. Neurological, infectious, immunologic, neuroendocrine and psychiatric mechanisms are extensively studied, but without clear results. CFS/ME is still seen as a heterogeneous disease in which probably several pathophysiological processes are involved.

An increasing amount of neurological imaging studies supports the hypothesis that CFS/ME patients have structural or functional abnormalities within the brain (Chen et al. 2008). However, until now no clear conclusion can be drawn from all these studies.

It is remarkable that objective impairment of quality of life and the severity of fatigue do not have a specific metabolic correlate. Abnormalities of perfusion or glucose metabolism in CFS/ME does not seem to be specific for the syndrome but is rather correlated with different neuropsychological symptoms shown during the course of the disease.

It seems that disease severity is determined not by the level of symptom expression but rather by the symptom mix and by the number of individual symptoms. The CFS/ME case definition does not define a single disease entity but rather identifies patients with different health problems but similar subjective complaints (Siessmeier et al. 2003).

The role of nuclear medicine to clarify the aetiology of CFS/ME remains controversial. Several SPECT studies have been performed with ^{99m}Tc-HMPAO. Unfortunately, no unequivocal observations were made. Studies in the early 1990s showed a global cerebral hypoperfusion. However, these studies made no

difference between CFS/ME patients with or without associated psychiatric diseases. Subsequent studies were performed in more homogeneous groups of patients with CFS/ME but found controversial results. One study showed hypoperfusion of the brainstem; another study hyperperfusion of the thalamus. Three studies did not found any difference between CFS/ME patients and healthy volunteers.

^{18}F-FDG PET studies also show various results. One study found hypometabolism of the brainstem; another study different regions of hypometabolism in approximately only half of the CFS/ME patients. Maybe it is possible with FDG to make a difference between CFS/ME patients with or without abnormalities of the central nervous system.

Corresponding results were found in the SPECT study with ^{99m}Tc-HMPAO of Costa et al. and the PET study with ^{18}F-FDG of Tirelli et al. The hypothesis of Costa et al., an abnormal physiology of the reticular formation, could be the right one. However, other studies did not find these results (see Table 33.1).

A recent development is the use of serotonin PET tracers. Two studies show involvement of the serotonergic system. The first study found abnormalities in the receptor binding in the rostral part of the anterior cingulate; the second study found a diffuse decrease of 5-HT receptor binding, most evident in the hippocampus bilaterally. However, since 2005, no studies are published with the use of this kind of tracers. This could be worthwhile to do; there is clinical and experimental evidence that indicate that a defect in serotonergic function is associated with CFS/ME.

33.5 Future Perspectives

On several areas, nuclear medicine may help to solve the problem of the unknown aetiology of CFS/ME. For the serotonergic system, the two published studies use tracers that are labelled with ^{11}C, which has a short half-life. Maybe future studies have to be performed with ^{18}F-labelled tracers, such as [^{18}F]methoxyphenyl-pyridinyl-fluoro-benzamide-methylpiperazine (MPPF), which is already successfully used for binding to the 5-HT receptor.

Several investigations reveal causes at the molecular level, and maybe in future nuclear medicine and molecular imaging may help to clarify the underlying pathogenesis.

For example, a study in Swedish patients with CSF mentioned reduced expression levels of the oestrogen receptor beta (Gräns et al. 2007). Others mention modifications in serotonin transporter genes (Narita et al. 2003; Falkenberg et al. 2011), glucocorticoid receptor genes (Rajeevan et al. 2007) and involvement of the human leukocyte antigen (HLA) class II (Carlo-Stella et al. 2009). Specific targeting of these molecules with radionuclides may reveal differences between patients with CFS/ME and healthy subjects.

A well-known PET tracer for neuroinflammation is [^{11}C]PK11195, which binds to the peripheral benzodiazepine receptors (PBRs). Expression of PBRs is linked to microglial activation and considered a hallmark of neuroinflammation (Doorduin et al. 2008). This tracer may be suitable for studies in CFS/ME patients.

Table 33.1 Nuclear medicine imaging findings in patients with chronic fatigue syndrome/myalgic encephalitis

Published year – First author	No. of patients	Tracer	Findings
1992 – Ichise	60	^{99m}Tc-HMPAO	Lower cortical/cerebellar regional cerebral blood ratios in comparison with healthy controls; regions involved – frontal, temporal, parietal, and occipital lobes and basal ganglia
1994 – Schwartz	16	^{99m}Tc-HMPAO	More defects throughout the cerebral cortex (lateral frontal cortex and lateral temporal cortex) and basal ganglia compared with healthy controls; more abnormalities found compared with MRI
1994 – Schwartz	45	^{99m}Tc-HMPAO	Similar number of defects in comparison with depressive patients; defects predominantly in frontal and temporal lobes; midcerebral uptake index lower than in patients with depression or healthy controls, but similar to patients with AIDS dementia complex
1994 – Peterson	10	^{99m}Tc-HMPAO	No differences in brain perfusion compared to healthy controls; more abnormalities found after exercise compared to rest scans
1995 – Costa	67	^{99m}Tc-HMPAO	Generalized lower brain perfusion ratios compared with healthy controls, lowest values in frontal cortex bilaterally and in brainstem; brainstem hypoperfusion also lower than patients with depression
1998 – Tirelli	18	^{18}F-FDG	Hypometabolism in the right mediofrontal cortex and brainstem
1998 – Abu-Judet	18	^{99m}Tc-HMPAO and ^{18}F-FDG	No correlation between the two modalities; no pattern in abnormalities found
2000 – Machale	30	^{99m}Tc-HMPAO	Increased perfusion of the right thalamus, pallidum and putamen in patients with CFS/ME and in depressive patients; also increased perfusion of the left thalamus in CFS/ME
2001 – Lewis	22	^{99m}Tc-HMPAO	Twins with and without CFS/ME showing no difference in abnormalities
2003 – Schmaling	15	^{99m}Tc-HMPAO	More diffuse regional cerebral blood flow in patients with CFS/ME in comparison with more focal pattern in healthy subjects; change in blood flow of the left anterior cingulate region in CFS/ME during PASAT greater than for healthy subjects
2003 – Siessmeier	26	^{18}F-FDG	Abnormalities detected in only half of the patients without specific patterns
2004 – Yamamoto	10	^{11}C-McN5652	Reduction of 5-HT density in the rostral subdivision of the anterior cingulate
2005 – Cleare	10	^{11}C-WAY-100635	Widespread reduction in 5-HT receptor binding potential; particularly bilateral in the hippocampus
2007 – Kanai	3	^{123}I-IMP	All three scans in children abnormal, but with variable patterns

A last area in which nuclear medicine may have added value is the role that cytokines play in the development of CFS/ME. It has been reported that patients with CFS/ME have experienced infections. In response to a peripheral infection, innate immune cells produce proinflammatory cytokines that act on the brain. When activation of the peripheral immune system continues unabated, the resultant immune signaling to the brain can lead to an exacerbation of feeling unwell. Cytokines produced in the brain exert various central actions, including activation of the sympathetic nervous system and impairment of learning memory. This opens the possibility that brain cytokines may play a role in the pathogenesis of CFS/ME (Chen et al. 2008). Levels of granulocyte-macrophage colony stimulating factor were lower in CFS/ME patients than in healthy controls; levels of interleukin (IL)-8 were higher in CFS/ME patients who experienced sudden, influenza-like onset compared with controls and patients who experienced gradual onset; IL-10 levels were higher in CFS/ME patients with abnormal spinal fluids than in those with normal spinal fluids or healthy controls (Natelson et al. 2005). Proinflammatory cytokines such as IL-1β, IL-6 and tumour necrosis factor (TNF)-α can elicit or aggravate fatigue and symptoms of anxiety and depression; IL-2 and interferon (INF)-α can promote depressive symptoms that are attenuated by antidepressant treatment (Anisman et al. 2005). Excessive sleepiness and night-time insomnia can be exacerbated by IL-6 and TNF-α (Vgontas and Chrousos 2002). Nuclear medicine is able to label most of these cytokines, in most cases with SPECT tracers, but developments are also ongoing in labelling cytokines with ^{18}F.

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PET and SPECT in Sleep Disorders

34

Thien Thanh Dang-Vu, Jordan O'Byrne, Gladys Mikolajczak, Oupam Malhi, Lindsay Reed, Audrée Arcelin, Nidhusha Vijayakumar, and Martin Desseilles

Contents

T.T. Dang-Vu, MD, PhD (✉)
Department of Exercise Science, Concordia University,
7141 Sherbrooke St W, Room SP 165.27, Montreal, QC H4B 1R6, Canada

Center for Studies in Behavioral Neurobiology,
Concordia University, Montreal, QC, Canada
e-mail: tt.dangvu@concordia.ca

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_34, © Springer-Verlag Berlin Heidelberg 2014

J. O'Byrne, BSc
Center for Studies in Behavioral Neurobiology,
Concordia University, Montreal, QC, Canada

Department of Exercise Science, Concordia University,
7141 Sherbrooke Street West, Montreal, QC H4B 1R6, Canada

G. Mikolajczak, MD
Department of Psychiatry, University of Liege,
Avenue de l'Hôpital 13, Sart Tilman (Bâtiment B35), Liege 4000, Belgium

O. Malhi • L. Reed • A. Arcelin • N. Vijayakumar, MD, PhD
Department of Exercise Science, Concordia University,
7141 Sherbrooke Street West, Montreal, QC H4B 1R6, Canada

M. Desseilles, MD, PhD
Department of Psychology, University of Namur Medical School,
Rue de Bruxelles 61, Namur 5000, Belgium

Clinique Psychiatrique des Frères Alexiens, Henri-Chapelle, Belgium

Abstract

Sleep disorders have been the subject of a number of positron emission tomography and single-photon emission computed tomography studies. Narcoleptic patients displayed decreased hypothalamic and thalamic perfusion during resting wakefulness, which may be related to hypocretinergic deficiency and altered vigilance. 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 Parkinson's disease. 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.

34.1 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; Maquet et al. 1990; Steriade and McCarley 1990). 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. Deactivations were present in the dorsolateral prefrontal cortex, posterior cingulate gyrus, precuneus, and inferior parietal cortex (Braun et al. 1997; Maquet 2000; Maquet et al. 1996, 2005; Nofzinger et al. 1997). 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 specificities of PET and SPECT measures in imaging 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. 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 (Dang-Vu et al. 2007, 2009; Desseilles et al. 2008).

34.2 Narcolepsy

Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness. Other frequent symptoms include transient loss of muscle tone triggered by emotions (cataplexy), sleep paralysis, and hypnagogic hallucinations. Individuals diagnosed with this disorder tend to have unstable sleep at night, with frequent 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 narcoleptics is the human leukocyte antigen (HLA) subtype DQB1*0602. More specific is the central deficiency in the hypothalamic peptide hypocretin-1, reflected by low levels in the cerebrospinal fluid, particularly in narcoleptic patients who present episodes of cataplexy. Hypocretinergic dysfunction is thought to underlie the unstable sleep–wake transitions and impaired vigilance in narcolepsy–cataplexy (Dauvilliers et al. 2007).

Neuroimaging techniques have been applied to narcolepsy 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 functional studies point to disturbed hypothalamic and limbic activity, consistent with reduced vigilance, hypocretinergic dysfunction, and abnormalities in emotional processing. A summary of these findings is provided in Table 34.1 and Fig. 34.1.

34.2.1 Acetylcholine, Serotonin, and Dopamine Functions in Narcolepsy

Sudo et al. (1998) focused on ACh neurotransmission in narcolepsy. 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 narcoleptics 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 narcolepsy–cataplexy. They used PET with 2′-methoxyphenyl-(*N*-2′-pyridinyl)-*p*-^{18}F-fluorobenzamidoethylpiperazine (^{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 using ^{123}I-(*N*)-(3-iodopropene-2-yl)-2b-carbomethoxy-3b-(4-chlorophenyl) tropane (^{123}I-IPT) SPECT (Eisensehr et al. 2003b) 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 narcoleptics and controls. When looking at postsynaptic D2 receptor binding, a study found a difference between narcoleptic 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 increased D2 binding in the striatum in seven narcoleptics. 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

Table 34.1 PET and SPECT studies in narcolepsy, 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

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. (2003b)	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. (2003b)	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
McFarlane 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
Yeon Joo et al. (2005)	SPECT ^{99m}Tc-ECD	rCBF	25/25	0/25	Reduced cerebral perfusion in hypothalami
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 brain stem. Decreased perfusion in prefrontal cortex and occipital lobe

(continued)

Table 34.1 (continued)

Study	Imaging technique employed	Target	Number of patients/ controls	Patients receiving treatment/ total number of patients	Results
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

dopamine and narcolepsy 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.

34.2.2 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 in particular assessed the CMRglu of 24 narcoleptic patients and 24 normal individuals using PET with ^{18}F-fluorodeoxyglucose (^{18}F-FDG). They found that narcoleptics had reduced CMRglu in the bilateral posterior hypothalami and mediodorsal thalamic nuclei (Joo et al. 2004). However, this study did not include EEG measurements, for vigilance monitoring. Another study used SPECT with ^{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 (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 mid-cingulate 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.

34.2.3 Neural Correlates of Cataplexy

Given the inherent difficulty in "catching" a narcoleptic patient in the scanner during a cataplectic episode, few studies have examined brain activity during cataplexy

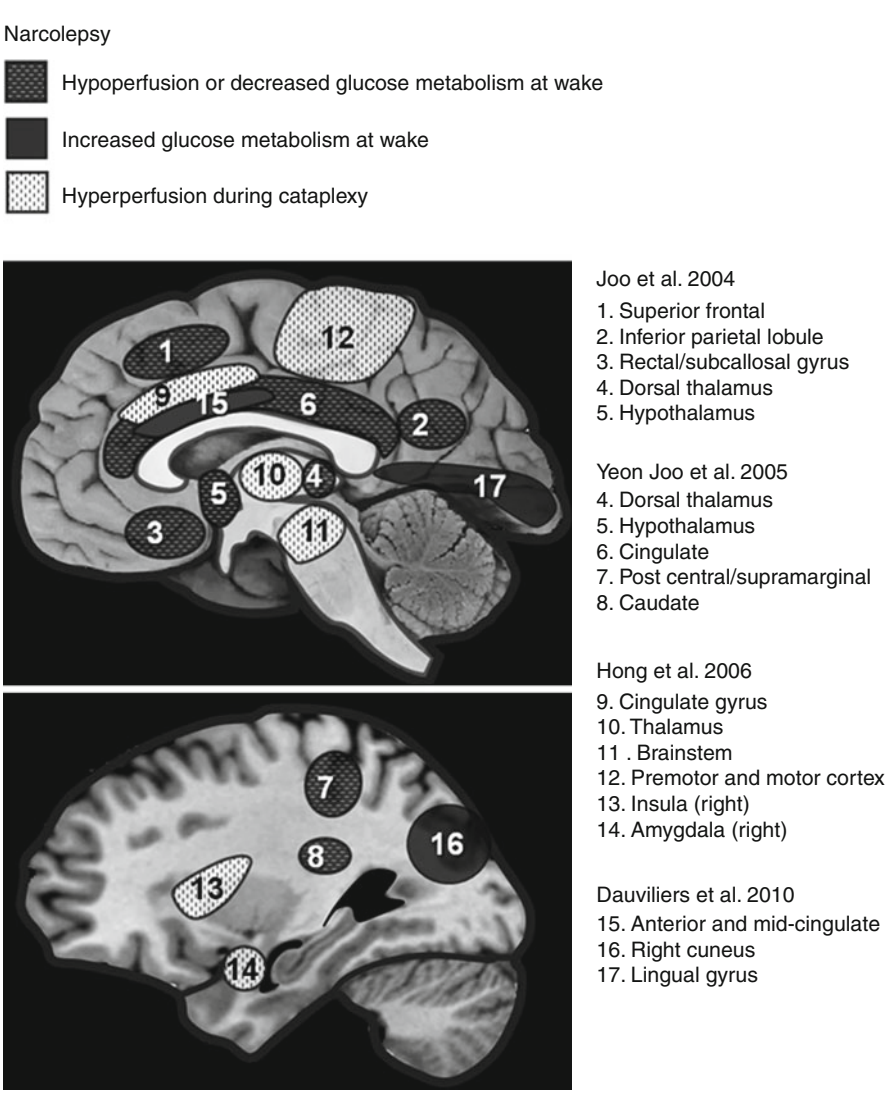

Fig. 34.1 Brain regions showing differences in CMRglu or rCBF during wakefulness in narcolepsy, as well as hyperperfusion (rCBF) during cataplectic attack (Adapted from Desseilles et al. (2008))

(loss of muscle tone). A study was conducted using technetium-99m ethylcysteinate dimer (^{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 narcoleptic patients using 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.

34.2.4 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 narcoleptic patients.

34.2.4.1 Methylphenidate

Methylphenidate, an amphetamine derivative, is commonly used for treating narcolepsy. One SPECT study used ^{133}Xe inhalation to examine rCBF in narcoleptic individuals 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.

34.2.4.2 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 narcoleptic patients were in the awake state, both before and after a 4-week treatment with either modafinil or 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 narcoleptic patients (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). Seven

narcoleptics patients 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.

34.2.5 Summary

Generally, SPECT and PET studies did not demonstrate a consistent difference in ACh, DA, or 5-HT neurotransmission in narcolepsy. 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 post-treatment 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 narcoleptic patients.

34.3 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.

34.3.1 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 ^{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). The discrepancy in these findings may be attributable to particular pharmacokinetic properties of radioligands used in PET and SPECT. Earley and colleagues (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 and colleagues (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 and colleagues (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.

34.3.2 Periodic Limb Movements

Dopaminergic transmission has been studied in relation to PLM. At the presynaptic level, Happe and colleagues (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).

34.3.3 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.

34.4 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.

34.4.1 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) and culminate in walking around with an altered state of consciousness and impaired judgment" (AASM 2005). To date, there is only a single case studying sleepwalking with neuroimaging. 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 was thought to reflect persistent arousal patterns, which is in line with the hypothesis of a dissociated state. Further studies should confirm these findings using a larger sample size.

34.4.2 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. Parkinson's disease, dementia with Lewy bodies (DLB), and multiple system atrophy tend to develop in patients with RBD several years later (Postuma et al. 2009). SPECT and PET have played a significant role in highlighting the brain regions involved in RBD pathophysiology and clinical evolution (Fig. 34.2).

A study performed by Shirakawa et al. (2002) compared 20 male idiopathic RBD 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 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 they were experiencing.

Mazza et al. (2006) conducted a study using ^{99m}Tc-ECD SPECT, which included eight idiopathic RBD 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 Parkinson's disease (Imon et al. 1999). In addition, decreased perfusion was found in the frontal lobe, particularly in the motor cortices and in the temporo-parietal cortices. A larger study of 20 idiopathic RBD patients and 20 control subjects exhibited similar results (Vendette et al. 2011). Once again using ^{99m}Tc-ECD SPECT, hyperperfusion was displayed in pons, putamen, and bilaterally in 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 RBD patients, in the precuneus, cerebellum, and uncus, regions also identified by Vendette and colleagues (2011).

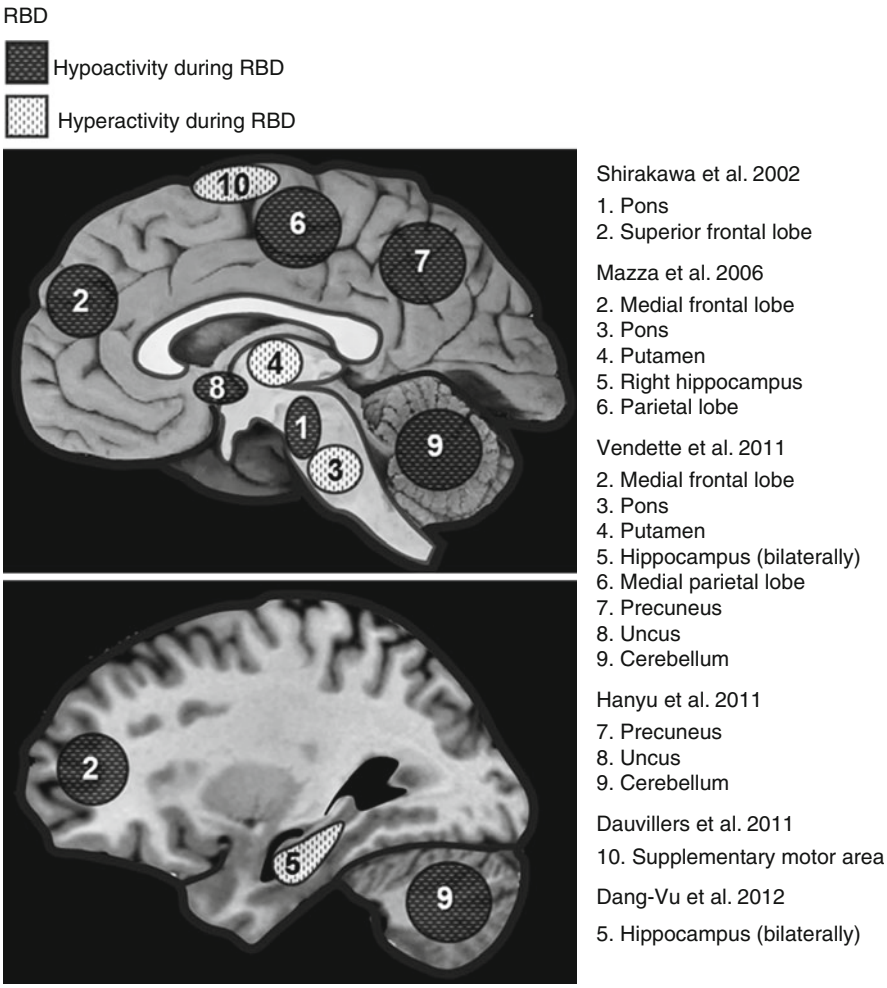

Fig. 34.2 Brain regions showing hyperperfusion or hypoperfusion in rCBF during wakefulness (except for Dauvilliers et al. (2011), which was conducted during a RBD episode in REM sleep) in RBD patients. Many of these changes in rCBF mirror those observed in the early stages of Parkinson's disease (Adapted from Desseilles et al. (2008))

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.

SPECT with ^{99m}Tc-ECD was recently used to predict the onset of PD and DLB in 20 idiopathic RBD 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, 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 RBD patients mainly during wakefulness, only one study reported brain activations associated with RBD behavioral manifestations. This study was conducted on a single patient, 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 versus wakefulness. No SPECT data was obtained during REM sleep outside the behavioral episode in RBD patients.

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. A group performed two SPECT studies with ^{123}I-IPT demonstrating a decrease in DAT at the presynaptic site of the striatum in idiopathic RBD 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 RBD 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).

The same conclusion was reached in a PET study using ^{11}C-dihydrotetrabenazine (^{11}C-DTBZ) in a study comparing 6 idiopathic RBD patients to 19 controls (Albin et al. 2000). In agreement with the studies conducted by Eisensehr and colleagues (2000, 2003a), the density of striatal DA was measured, and a decrease in presynaptic binding was found, most prominently in the posterior putamen.

Similarly, another PET study was performed using ^{11}C-DTBZ to measure presynaptic striatal binding. The 13 patients who had RBD and probable multiple system atrophy showed a decrease in binding, which was negatively correlated with the severity of REM atonia (Gilman et al. 2003). These results suggest that a presynaptic DA deficit might contribute to the frequent occurrence of RBD in patients with multiple system atrophy.

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, 6 of these 8 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 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.

34.4.3 Summary

Several SPECT and PET neuroimaging studies are available for RBD. However, to date, only one study has been devoted to sleepwalking. Sleepwalking demonstrates brain patterns reminiscent of both SWS and wakefulness states, therefore appearing as a dissociated state. Additional studies are needed to further qualify the role of SWS alterations in somnambulism.

In RBD patients, SPECT and PET have shown that there exists a presynaptic dysfunction of DA nigrostriatal pathways, further indicating that RBD represents the early stages of PD, DLB, and multiple system atrophy. Moreover, the risk of progression from RBD 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 examined to shed further light on the pathophysiology of RBD.

34.5 Insomnia

34.5.1 Idiopathic Insomnia

Insomnia is a common disorder in our society. Ten to twenty percent of the general population reports insomnia complaints and related problems of daytime functioning (Ohayon and Hong 2002). The AASM (2005) defines insomnia as a common symptom or syndrome including difficulty in initiating or maintaining sleep, or

"unrefreshing" sleep. This causes significant problems in several areas, including mood, motivation, attention, and vigilance. According to the ICSD (ICSD-2), idiopathic insomnia is a persistent failure to obtain adequate sleep that is probably due to an abnormal neurological control of the sleep–wake system (AASM 2005). Depression is often associated with insomnia (Tsuno et al. 2005).

Electroencephalography (EEG) and functional and structural imaging have contributed much to the current scientific knowledge of insomnia. In this section we will focus on the studies using PET and SPECT in idiopathic and fatal familial insomnia. Some other studies have been conducted using fMRI (e.g., (Altena et al. 2008)) and structural MRI, with various applications (e.g., voxel-based morphometry (VBM) and proton magnetic resonance spectroscopy (^{1}H-MRS)) (Desseilles et al. 2008).

Only a few studies have recorded brain activity during NREM sleep in order to assess the functional neuroanatomy of idiopathic insomnia disorder. 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 idiopathic insomnia 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, as illustrated in Fig. 34.3; 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, insomnia patients 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). If we consider these findings together, they indicate that insomnia might involve particularly elevated regional brain activity during the transition to sleep, with a localized decline in brain metabolism during wakefulness. The observed reduction in prefrontal cortex activity during wakefulness 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 insomniacs with four normal sleepers using SPECT, employing technetium-99 m-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 (Fig. 34.3). This result suggests that idiopathic 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 insomnia patients, but during wakefulness. It is necessary to consider methodological specificities in Smith's study. For instance, blood flow measurement was only sampled during the first NREM cycle. Therefore, the decreased metabolism in insomnia patients might reflect a cortical hypoarousal during the initial phases of NREM sleep following sleep onset.

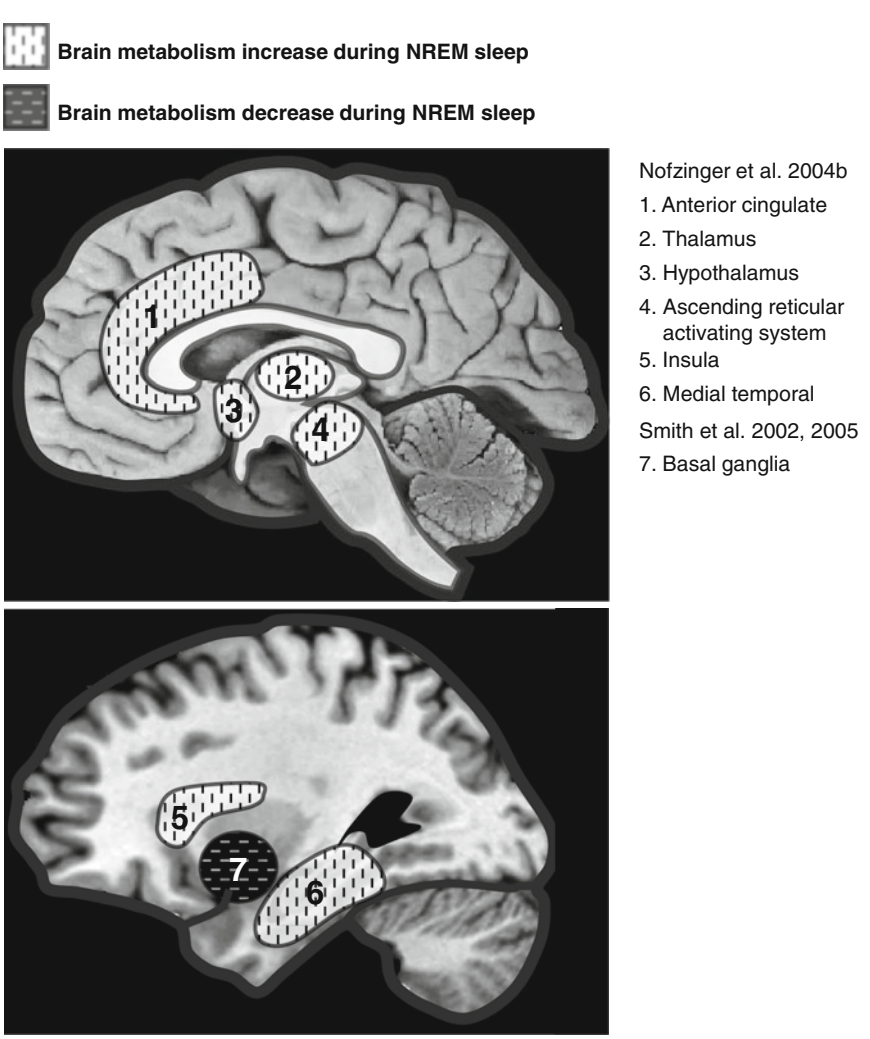

Fig. 34.3 Regional cerebral metabolism during NREM sleep in idiopathic insomnia. Nofzinger et al. (2004b) found increased regional metabolism (^{18}F-FDG PET) during NREM sleep in patients with idiopathic insomnia. Smith et al. found reduced regional cerebral blood flow (SPECT) in the basal ganglia in insomniacs (Smith et al. 2002, 2005) (Adapted from Desseilles et al. (2008))

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). Thus, these results cannot rule out the hyperarousal hypothesis of idiopathic insomnia. Cognitive behavioral therapy including sleep restriction and stimulus control was applied in Smith's study, and four of the insomnia 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.

34.5.2 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 ($n=4$) and 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), nine asymptomatic carriers of the D178N mutation, ten 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 cerebral metabolic rate of glucose (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 3 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.

34.5.3 Neuroimaging of Sleep in Depression

A pioneering study by Ho et al. (1996) examined the first NREM period in ten 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 nine 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. 34.4, 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, 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 as well as nonrestorative 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 pontogeniculo-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).

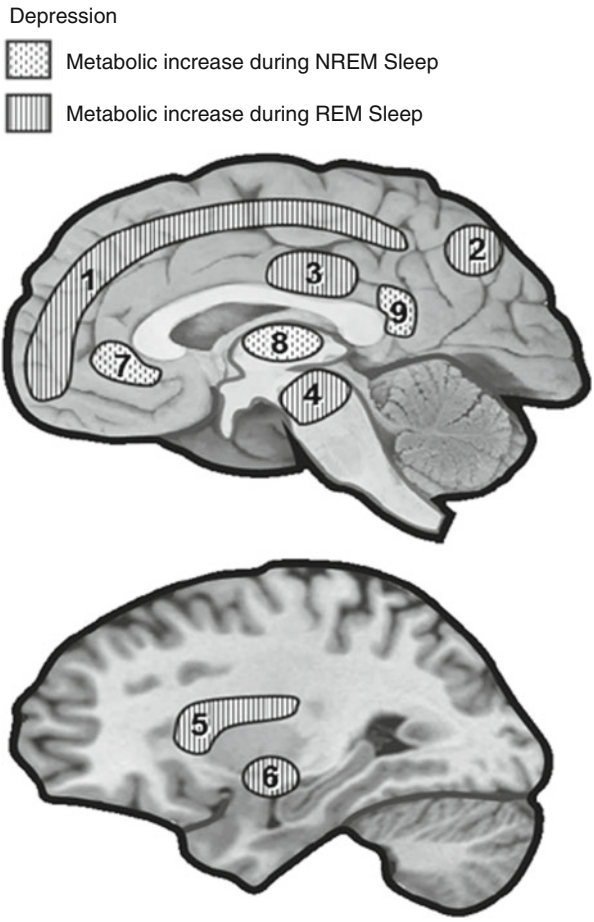

Fig. 34.4 Metabolic changes during REM and NREM sleep in depression. During NREM (Germain et al. 2004) and REM (Nofzinger et al. 2004a), depressed patients showed "elevated" activity measured by CMRglu across several cortical and subcortical regions in sleep compared to pre-sleep wakefulness. *1* frontoparietal, *2* posterior parietal, *3* supplementary motor area, *4* ascending reticular activating system, *5* insula, *6* ventral pallidum, *7* medial prefrontal, *8* thalamus, *9* posterior cingulate (Adapted from Desseilles et al. (2008))

34.5.4 Summary

Because currently available data are limited and not perfectly consistent, any conclusion about the cerebral correlates of insomnia during NREM sleep has to 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 idiopathic insomnia and depression, together with persistent alterations in

sleep architecture in remitted depression, corroborates common neurophysiological mechanisms underlying sleep and mood regulation.

34.6 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. 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 blood flow in the pons, frontal lobes, striatum, and hippocampus, linking this disorder to later onset of Parkinson's disease. 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

35

Andrej Doma

Contents

Abstract

In spite of development in pharmacotherapy of psychiatric disorders, nonresponders and non-remitters remain a major problem. The chapter gives 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

A. Doma
Department of Nuclear Medicine, University Medical Centre Ljubljana,
Zaloška 7, Ljubljana, Slovenia
e-mail: andrej.doma@gmail.com

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2_35, © Springer-Verlag Berlin Heidelberg 2014

Abbreviations

^{99m}Tc-ECD	Technetium [^{99m}Tc] bicisate
^{99m}Tc-HMPAO	Technetium [^{99m}Tc] exametazime
CBT	Cognitive behavior therapy
CMRGlu	Cerebral metabolic rate for glucose
DBS	Deep brain stimulation
ECT	Electroconvulsive therapy
FDG	^{18}F-$_2$-fluoro-$_2$-deoxy-D-glucose
MDD	Major depressive disorder
OCD	Obsessive–compulsive disorder
PET	Positron emission tomography
rCBF	Regional cerebral blood flow
SPECT	Single-photon emission computed tomography
TMS	Transcranial magnetic stimulation
VNS	Vagus nerve stimulation

35.1 Introduction

In spite of development 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 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.

35.2 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 ventrolateral prefrontal cortex and dorsolateral prefrontal cortex (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 ventrolateral prefrontal cortex (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).

Obsessive–compulsive disorder (OCD) is a chronically debilitating anxiety disorder, characterized by two sets of symptoms: obsessions, which are impulsive recurrent thoughts usually in concern of 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 increased cerebral activity of the orbitofrontal cortex and anterior cingulate cortex, angular gyrus in the parietal lobe, 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 2003; Rauch et al. 1994; 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.

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 cortex, as well as in the parietal and temporal associative cortex of drug-naïve OCD patients in comparison to healthy controls.

35.3 PET and SPECT in Electrical Neurostimulation

Seventy-five years after Celetti 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 brain activity at a molecular basis (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.

35.3.1 Deep Brain Stimulation

Deep brain stimulation (DBS) is a nondestructive, reversible, and highly adjustable method of electrical stimulation, first used in the early 1970s for the control of pain. In the 1990s, the use of DBS was introduced for the treatment of movement disorders, and it is now under investigation for treatment of OCD and treatment-resistant depression

(reviewed in Larson 2008). DBS is achieved through stereotactically implanted intracranial electrodes connected to an implanted pulse generator/battery pack in the chest wall. Side effects from stimulation vary widely depending on the stimulation targets. An additional drawback to DBS is the need to avoid certain situations and treatments that may damage the device or heat its components and cause injury to the patient, such as metal detectors, strong magnetic fields, and diathermy. Repeated operations are also needed over time (anywhere from 6 months to 5 years) to replace the pulse generator/battery pack (reviewed in Holtzheimer and Mayberg 2010).

Several stimulation targets can be used for DBS in OCD treatment: the early procedures targeted anterior internal capsule and ventral striatum on the basis of reports of success of lesion procedures in these areas in severe psychiatric disorders (reviewed in Larson 2008). Nucleus accumbens and subthalamic nucleus have been implicated as a potential target (Mallet et al. 2008).

The implantation of electrodes itself into the subthalamic nucleus can impart a microlesion effect on a regional brain function. This was seen as a decreased glucose utilization on off-stimulation postoperative ^{18}F-$_2$-fluoro-$_2$-deoxy-D-glucose (FDG) scans compared to preoperative scans in six Parkinson's disease (PD) patients (Pourfar et al. 2009). Nevertheless, the disruption of regional brain function in that study did not cross the threshold of network modulation needed to achieve clinical benefit.

Three studies evaluated changes in rCBF and cerebral metabolic rate for glucose (CMRGlu) after DBS treatment: 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), hypometabolism was seen preoperatively in the ventral prefrontal cortex and anterior cingulate in six refractory OCD patients. After chronic anterior capsular electrostimulation, a significant decrease of metabolism was seen in anterior cingulated gyrus, and changes in symptoms after treatment were inversely related to metabolic changes in the left ventral striatum, left amygdala, and left hippocampus.

Rauch et al. (2006) measured rCBF during high- and low-frequency stimulation and during off condition using inhalation of ^{15}O–CO_2 admixed with air, 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 high-frequency DBS, rCBF significantly increased in the orbitofrontal cortex, anterior cingulated cortex, putamen, and globus pallidus.

The results are somewhat inconsistent with previous studies, where response to neurosurgery, pharmacotherapy, and psychotherapy of OCD resulted in decrease of metabolism in bilateral caudate, the head of the right caudate, and in bilateral thalamus (Baxter et al. 1992; Biver et al. 1995; Sachdev et al. 2001; Saxena et al. 2002, 2009; Schwartz et al. 1996). Further research is needed to improve the understanding of pathophysiological processes involved in OCD and mechanisms of treatment techniques.

35.3.2 Vagus Nerve Stimulation

Efferent fibers of the vagus nerve (VN) provide parasympathetic innervation primarily to the gastrointestinal, cardiovascular, and respiratory system. The VN also consists of approximately 80 % afferent fibers projecting from the viscera to the nucleus tractus solitarius. Further on, 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) for refractory epilepsy has become a well-established, safe, and effective treatment method as an adjunct to medicamentous therapy, Elger 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 for a treatment-resistant depression in 2005 (Groves and Brown 2005).

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).

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, in 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 gamma-aminobutyric acid (GABA), as well as inhibition of aberrant cortical activity by reticular system activation (reviewed in Milby et al. 2008).

Several PET and SPECT studies assessed the effects of VNS in depressed patients. The results are discrepant, and differences among reports might originate from concomitant and previous medication or subjects' individual responses to stimulation.

Acute changes in rCBF in response to VNS in patients with treatment-resistant MDD were assessed in two studies by Conway and colleagues using $H_2{}^{15}O$ PET. Changes in rCBF were consistent with the known afferent pathway of the vagus nerve and models of brain network in depression. Significant rCBF decrease was found in response to acute VNS in a study of 13 subjects (Conway et al. 2012a) in the left and right lateral orbitofrontal cortex and left inferior temporal lobe. Significant increase in the right dorsal anterior cingulate, the left posterior limb of the internal capsule, the right superior temporal gyrus, and the left cerebellar body was also found. Moderate correlations between baseline acute change in rCBF and antidepressant response after 12 months of VNS existed. In contrast, the rCBF in the bilateral orbitofrontal cortex (OFC) was increased in a study of four patients

(Conway et al. 2006), probably due to use of significantly higher dosing of VNS and a small sample.

Three studies focused on long-term effects of VNS. Using technetium [^{99m}Tc] exametazime (^{99m}Tc-HMPAO), decrease of rCBF in the medial frontal and limbic regions was observed at 4 weeks of VNS in 12 major depressive patients (Zobel et al. 2005) and in insular and precuneus regions after 10 weeks of VNS stimulation in 15 depressive patients (Kosel et al. 2011). Increase of rCBF was seen in the left middle frontal gyrus in a study by Zobel and in the left dorsolateral/ventrolateral prefrontal cortex in the Kosel study. Pardo et al. (2008) found decreased CMRGlu in subgenual cingulate and ventromedial prefrontal regions and increase in ventromedial prefrontal cortex 1 year after VNS therapy in eight severely depressed patients. Overall results of these studies prove the relationship between VNS, the modulation of the posttreatment activity in the left DLPFC, and the antidepressant effect. The effects of the treatment are closely dose and time related.

The association between pretreatment brain activity and antidepressant response over time was examined by Conway et al. (2012b) in 15 treatment-resistant MDD patients. CMRGlu in selected regions (anterior insular, orbitofrontal, anterior cingulate, and dorsolateral prefrontal cortices) was assessed at baseline and compared to depression severity at baseline and after 12 months of VNS using Hamilton Depression Rating Scale (HDRS). Response to VNS 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 to nonresponders.

In conclusion, pronounced changes in the activity during and after VNS were observed that correspond to synaptic pathways, associated with depression. Further neuroimaging studies are needed to establish the pretreatment activity measurement as a useful tool for prediction of response to VNS in treatment-resistant MDD.

35.3.3 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 ($\leq$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).

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).

35.3.3.1 Dorsolateral Prefrontal Cortex as a Target of rTMS Stimulation in Depression

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 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 decrease of CMRglu in 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 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 eighteen depressed patients. Acute low-frequency rTMS over the left DLPCF did not cause any significant changes in the frontal region. When high-frequency rTMS was applied, an increase in rCBF was observed in the area of stimulation. Relative decrease of rCBF was observed in the left DLPFC after low-frequency rTMS and increase after fast 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 (Catafau et al. 2001; Feinsod et al. 1998; Fujita and Koga 2005; George et al. 1995; Kimbrell et al. 1999; Klein et al. 1999; Mottaghy et al. 2002; Nahas et al. 2001; 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 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 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 the 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.

35.3.3.2 Neuronavigated rTMS

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 dorsolateral prefrontal cortex (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 both left and right DLPFC rTMS 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. Study was done on 21 antidepressant-free treatment-resistant depression patients of the melancholic subtype.

35.3.3.3 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.

Reduced blood flow in orbitofrontal and anterior cingulate was associated with good response to high-frequency rTMS treatment in eight depressed patients (Nadeau et al. 2002). Responders also exhibited significantly lower pretreatment blood flow in the left amygdala compared to nonresponders.

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 (Kito et al. 2008; Mottaghy et al. 2002; Teneback et al. 1999), and the inferior frontal (Kito et al. 2008; Teneback et al. 1999), periinsular (Kito et al. 2008; Mottaghy et al. 2002), bilateral frontal, 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 (Baeken et al. 2009; Kito et al. 2008; Speer et al. 2000; 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 (Langguth et al. 2007).

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 similar protocol of high-frequency rTMS stimulation of the left DLPFC in depressed patients (Mottaghy et al. 2002; Richieri et al. 2011).

Using simultaneous dual isotope technique of FDG and 99mTc-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 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.

35.3.3.4 TMS and Imaging of Dopamine Activity

Several studies explored the effect of acute rTMS to 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 receptors 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 (Halldin et al. 1995). No significant changes were observed after the rTMS over the right DLPFC. The difference in uni- and bilateral release of dopamine between healthy subjects and patients could be influenced by the underlying neurochemical changes in disease. Hemispheric differences after stereotactic stimulation are also known from other studies (Knoch et al. 2006; Saijo et al. 2010b).

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 recent 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. Results of both studies suggest that chronic rTMS, in contrast to acute rTMS, has a limited effect on the dopamine system.

35.3.3.5 TMS in Schizophrenia

In a study by Horacek et al. (2007), the effect of rTMS to 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. The 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 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-controlled 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, 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.

35.3.4 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).

35.3.4.1 Glucose Metabolism Changes in ECT

Several studies evaluated changes in rCBF and cerebral glucose metabolism before and after a series of ECT in depressed patients (Table 35.1). The results are somewhat inconsistent, ranging from overall decrease to 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 (Henry et al. 2001; Nobler et al. 1994, 2001; Suwa et al. 2012; Volkow et al. 1988; Yatham et al. 2000). 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 increase in rCBF or glucose metabolism in these cortical regions (Awata et al. 2002; Blumenfeld et al. 2003; Mervaala et al. 2001; Milo et al. 2001; Ota et al. 2003; Suwa et al. 2012; Takano et al. 2006; Vangu 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 (Elizagarate et al. 2001; Henry et al. 2001; Nobler et al. 2001; Suwa et al. 2012; Takano et al. 2007; Yuuki et al. 2005). No statistical difference in glucose metabolism was reported by Yatham et al. (2000) and Reininghaus et al. (2012) on post-ECT scans in comparison to 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 antidepressant mechanism of action of ECT.

Table 35.1 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 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
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)	11C-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)	15O-H2O	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 thalamus, anterior cingulate, dorsolateral, medial frontal cortex comparing the pre-ECT baseline	During ECT. Basal ganglia, midbrain, pontine tegmentum, thalamus, amygdala, hypothalamus, vermis, inferior frontal, parietal, and temporal cortex (comparing to pre-ECT baseline)	–
Mervaala et al. (2001)	99mTc-ECD, 123I-iomazenil	20 (ECD), 5(iomazenil) MDD (20)	None	1 week	6–11, bilateral	None	ECD: right temporal, bilateral parietal cortices Lomazenil: bilateral frontal, parietal, occipital cortices, right prefrontal cortex	–
Segawa et al. (2006)	99mTc-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)	99mTc-ECD	15 MDD	None	After 45 min	Single, bilateral	Inferior anterior cingulate cortex	None	–

(continued)

Table 35.1 (continued)

Author	Radiotracer used	Number of patients, type of disorder (responders)	Healthy controls	Timing of 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
Awata et al. (2002)	99mTc-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)	99mTc-HMPAO	8 MDD (7)	25	1 week	9.9 ± 1.9, bilateral	Responders: parietotemporal, cerebellar cortices Nonresponders: none	None	–
Elizagarate et al. (2001)	99mTc-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)	99mTc-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	–

Bonne et al. (1996)	99mTc-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)	99mTc-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)	99mTc-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)	99mTc-HMPAO	8 MDD (8)	12	5 days (Post 1) and 1 month (Post 2)	5–10, bifrontotemporal	Decrease in right cuneus at Post 1	Post 1: right hippocampal gyrus Post 2: right medial frontal	–
Vangu et al. (2003)	99mTc-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)	99mTc-HMPAO	8 MDD, 3 schizoaffective disorder		Imaging during acute ECT		Parietal, occipital cortex	Frontal, temporal cortex, basal ganglia	–

Based on the initial table by Schmidt et al. (2008)
MDD major depressive disorder, *BD* bipolar disorder, *DDST* delusional disorder somatic type

35.3.4.2 Long-Term Effect of ECT

The safety and long-term effects of ECT were evaluated by several authors (Anghelescu et al. 2001; Navarro et al. 2004a, b; reviewed in Petrides et al. 2011). Navaro and colleagues found no differences in both studies 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 to 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 treatments 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.

35.3.4.3 Serotonin and Dopamine Changes in ECT

The mechanisms underlying the therapeutic effect of ECT are not completely known (reviewed in Kupfer et al. 2012), and potential targets considered are brain serotonin-2 (5-HT_2) and serotonin-1A (5-HT1a) receptors, as well as dopamine D2 receptors. While various antidepressant medications cause 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_2receptors (Petit-Taboué et al. 1996). 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 nonresponsive individuals may explain its efficacy in patients with antidepressant refractory depression. Downregulation of brain 5-HT_2 receptors after ECT was also observed by 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 receptors regulation. Likewise, a widespread reduction of binding of a radioligand ^{11}C-WAY100635, a highly selective and potent c5-HT_{1A} antagonist to postsynaptic brain 5-HT_{1A} receptors (Ito et al. 1999), 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. (2010a) 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 to 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 human brain was studied by Saijo et al. (2010b), using dopamine D2/D3 agonist radioligand ^{11}C FLB457. The comparison was made between D2 receptor binding in pre- and post-ECT scans in seven 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.

35.4 Cognitive Behavior Therapy

The investigation of mechanisms of psychotherapy action has up to the last decade been only possible at the cognitive and behavioral level. The advance in neuroimaging has only recently enabled investigation of biological consequences of psychotherapy. These new findings will allow a selection of a proper psychotherapeutic treatment and follow its effects.

35.4.1 Imaging of Cognitive Behavior Therapy in Obsessive–Compulsive Disorder

Several studies identified changes of CMRGlu and rCBF after cognitive behavior therapy (CBT) in OCD patients. Elevated baseline rCBF and CMRGlu was observed in OCD patients in the orbitofrontal cortex, anterior cingulate cortex, basal ganglia, and thalami (Baxter et al. 1987; Perani et al. 1995; Nakatani et al. 2003; Nordahl et al. 1989; Yamanishi et al. 2009). The decrease of metabolism in connection to response to psychotherapy was observed in the prefrontal cortex (Brody et al. 2001; Kennedy et al. 2007; Yamanishi et al. 2009), the bilateral caudate (Schwartz et al. 1996), the head of the right caudate (Baxter et al. 1992; Nakatani et al. 2003), and the bilateral thalamus (Saxena et al. 2009), replicating the results of several studies of OCD treatment using neurosurgery (Biver et al. 1995; Sachdev et al. 2001) and pharmacotherapy (Baxter et al. 1992; Saxena et al. 2002). Good response to psychotherapy was associated with greater decrease in the right caudate metabolism compared to nonresponders (Schwartz et al. 1996; Nakatani et al. 2003). In contrast, Apostolova et al. (2010) reported increase in the right caudate nucleus in both CBT and paroxetine group of OCD patients. 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.

Posttreatment changes of activity in the dorsal anterior cingulate cortex are somewhat dubious: increase of the activity in this area was reported by Saxena et al. (2002), while decrease was observed by Brody et al. (2001) and some other pharmacotherapy studies (Perani et al. 1995; Baxter et al. 1992; Saxena et al. 2001). No changes after CBT were seen in the study by Baxter et al. (1992). Decrease in cingulate activity may not be a necessary mechanism of action for the improvement of

OCD symptoms, but may still be associated with treatment response. Increase was also reported in the temporal lobes (Brody et al. 2001; Kennedy et al. 2007).

Response to CBT and antidepressant pharmacotherapy in patients with panic disorder resulted in decrease of right frontal and temporal regions in both treatment groups (Prasko et al. 2004).

Pretreatment metabolic predictors of response to CBT and pharmacotherapy were studied and the results are dubious: positive correlation was found between treatment response in the CBT-treated group and pretreatment left orbitofrontal cortex metabolism (Brody et al. 1998), the left and right lateral orbitofrontal cortex, the left dorsomedial prefrontal cortex, and thalamus (Kennedy et al. 2007). A tendency to a negative correlation exists between the relative response to treatment and the pretreatment glucose metabolism in the left orbitofrontal cortex (Apostolova et al. 2010) and in the right inferior occipital cortex and left inferior temporal cortex (Kennedy et al. 2007). Yamanishi et al. reported significant correlation of the baseline rCBF in the bilateral orbitofrontal cortex and the change in the severity score among responders (Yamanishi et al. 2009). Schwartz et al. (1996) reported significant bilateral decrease in caudate glucose metabolic rates in the CBT responders group in comparison to nonresponders.

35.4.2 Imaging of Cognitive Behavior Therapy in Depression

Brody et al. (2001) compared DMM patients treated with either CBT or selective serotonin reuptake inhibitors (SSRI) and healthy controls. Regional brain metabolic abnormalities seen at baseline tended to normalize with both treatments. Decrease in prefrontal cortex and left anterior cingulated gyrus and increase in left temporal lobe were seen. Martin et al. (2001) compared changes in rCBF after venlafaxine, an antidepressant of the serotonin–norepinephrine reuptake inhibitor class and CBT. Increase in the right basal ganglia was seen in both types of therapy, and increase in the right posterior cingulate followed CBT. Goldapple et al. (2004) compared CMRGlu changes after CBT and SSRI therapy. Widespread decrease of activity in frontal regions was associated with both types of therapy, and increase in hippocampus, parahippocampus, and dorsal cingulate was seen in CBT group.

Several treatment-dependent differences in limbic and cortical activity may reflect treatment modalities' specific mechanisms, which are yet to be explained in future studies.

35.4.3 Dopamine and Serotonin Changes After Cognitive Behavior Therapy

Several authors explored the 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 midbrain serotonin transporter density, marked by 5-HT_{1a} receptor

binding of ^{11}CWAY-100635, significantly increased (Karlsson et al. 2010). Lehto et al. (2008) observed midbrain serotonin (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 decrease in density of serotonin receptors in depression (Drevets et al. 1999; Hirvonen et al. 2008). Antidepressive effect of enhanced serotonergic activity is widely used in therapy with SSRI. According to similar clinical improvement in both types of therapy, we can assume that CBT enhances serotonergic activity through increased levels of SERT.

Cervenka et al. (2012) showed a direct relationship between symptom change after CBT and extrastriatal binding of ^{11}C FLB457, a high-affinity dopaminergic D_2/D_3 antagonist in nine patients with social anxiety disorder (SAD). Negative correlation between change in D_2 receptor binding potential and the anxiety symptoms change was found for the medial prefrontal cortex and hippocampus.

35.5 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.

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 Watts. 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).

35.5.1 Anterior Cingulotomy

Anterior cingulotomy is currently the most common neurosurgical procedure for treatment-refractory psychiatric syndromes. In this procedure, 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 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 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 gives evidence to the functional connectivity of the hierarchical pain network.

35.5.2 Subcaudate Tractotomy

Subcaudate tractotomy is primarily used for the treatment of refractory depression. It targets a region of 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 to 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.

35.5.3 Limbic Leucotomy

Limbic leukotomy 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 leukotomy 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 leukotomy. 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 postsurgical, metabolism was still reduced in the anterior cingulate gyrus, caudate, and thalamus compared to baseline.

35.5.4 Anterior Capsulotomy

Anterior capsulotomy targets the fronto-limbic fibers that pass in the anterior limb of the internal capsule. Liu et al. (2008) reported that 57 % of treatment-refractory OCD patients treated with anterior capsulotomy became symptom-free with another 29 % experiencing significant improvement. Fourteen percent of patients experienced no meaningful improvement.

Mindus et al. (1986) reported statistically significant reduction of postoperative glucose metabolism in the orbitomedial frontal cortex after performing capsulotomy in five severe anxiety disorder patients. Four out of five patients improved after the operation.

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 preoperational FDG scan as well as 16 months later.

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.

There are major variations in results due to different methodologies in precise location of the treatment, the duration of treatment prior to scanning, different time points of scanning, small sample size in these comparisons, 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 might play an important role in the effect of treatment.

Pathophysiological processes of different psychiatric diseases, as well as 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. Results of several non-pharmacological therapies are promising, and future functional imaging studies are needed to gain better understanding.

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The Editors

Prof. Dr. Rudi AJO Dierckx
Board-certified in Neuropsychiatry and Nuclear Medicine

Affiliations:
Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen. Hanzeplein 1, 9713GZ Groningen, Netherlands. E-mail: r.a.dierckx@umcg.nl

Nuclear Medicine, University Hospital Gent, University of Gent, De Pintelaan 185, 9000 Gent, Belgium

Research fields:
Broad interest in nuclear medicine, focus on neuroscience and oncology
- SPECT/conventional nuclear medicine
- PET: research and clinical applications
- Development of novel radiotracers
- Rodent models of human disease
- Medical physics
- Quality, Ethics and Economics

Prof. Dr. med. Andreas Otte
Board-certified in Nuclear Medicine

Affiliation:
Biomedical Engineering, Faculty of Electrical Engineering and Information Technology, University of Applied Sciences Offenburg, Badstr. 24, D-77652 Offenburg, Germany, E-mail: andreas.otte@hs-offenburg.de

Research fields:
Focus on neurosciences and functional biomedical imaging
- Research in neurosciences includes functional neuroimaging of various indications (e.g., traumatic brain injury, whiplash syndrome, Alzheimer's disease). In addition, there is a special focus on deep-brain stimulation.
- Research in biomedical imaging ranges from opening new applications to optimizing image reconstruction. This comprises, e.g., sonography, statistical parametric mapping, nuclear medicine or radiological imaging instruments (SPET, PET; PET/CT, MR/PET; DSA, CT, MRT).

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2, © Springer-Verlag Berlin Heidelberg 2014

Dr. Erik F.J. de Vries
Radiochemist

Affiliation:
Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen. Hanzeplein 1, 9713GZ Groningen, Netherlands. E-mail: e.f.j.de.vries@umcg.nl

Research fields:
Focus on the development and application of radiopharmaceuticals for PET imaging of inflammation and hormone receptors
- Monitoring of immune cell activation and migration
- Inflammation and related events in psychiatric and neurodegenerative disorders
- Visualization of the gut-immune-brain interaction
- Treatment-induced immune response in tumors
- Steroid hormone receptor expression in tumors and the brain

Dr. Aren van Waarde
Biologist

Affiliation:
Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen. Hanzeplein 1, 9713GZ Groningen, Netherlands. E-mail: a.van.waarde@umcg.nl

Research fields:
Focus on small animal imaging
- Development of techniques for quantification of neuroreceptors in the living brain (adenosine A1 and A2A receptors, beta-adrenoceptors, serotonin-1A and 2A receptors, sigma-1 receptor)
- Development of targeted imaging probes for early in vivo diagnosis of cancer and evaluation of tumor response to therapy (ABC transporter substrates, matrix metalloproteinase inhibitors, sigma receptor ligands)

Guest Editor

Prof. Dr. Johan A. den Boer
Psychiatrist

Affiliation:
Division of Psychiatry, University Center for Psychiatry, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713 GZ Groningen, Netherlands, E-mail: j.a.den.boer@umcg.nl

Research fields:
- Neurobiology of anxiety disorders and depression
- Behavioral and molecular biological aspects of stress
- Psychopharmacology of anxiety and depression
- Neuroimaging

Reviewers

Aleman, André (Cognitive Neuropsychiatry, UMC Groningen, Groningen, Netherlands)
An, Young-Sil (Nuclear Medicine & Molecular Imaging, Ajou University, Suwon, S.Korea)
Baris, Ekici (Pediatric Neurology, Istanbul University, Istanbul, Turkey)
Bauer, Martin M (Psychiatry and Psychotherapy, Medical University, Vienna, Austria)
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Boer, Johan A. den (Psychiatry, University Medical Center Groningen, Netherlands)
Boileau, Isabelle (Center for Addiction and Mental Health, Toronto, ON, Canada)
Burroni, Luca (Nuclear Medicine, University of Siena, Siena, Italy)
Carré, Justin M (Psychology, Wayne State University, Detroit, MI, USA)
Casse, Rey (Nuclear Medicine, Queen Elisabeth Hospital, Woodville, SA, Australia)
Chou, Yuan-Hwa (Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan)
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Dierckx, Rudi A (Nuclear Medicine and Molecular Imaging, UMC Groningen, Netherlands)
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Eslinger, Paul (Neurology, Penn State Hershey Medical Center, Hershey, PA, USA)
Ettinger, Ulrich (Psychology, University of Bonn, Bonn, Germany)
Feng, Ling (Integrated Molecular Brain Imaging, Rigshospitalet, Copenhagen, Denmark)
Finnema, Sjoerd J (Psychiatry, Karolinska Institute, Stockholm, Sweden)
Geuze, Elbert (Neuroscience, University of Utrecht Medical Center, Utrecht, Netherlands)
Godani, Massimiliano (Neurology Unit, Andrea Hospital, La Spezia, Italy)
Gonul, Ali Saffet (Psychiatry, Ege University of Medicine, Bornova Izmir, Turkey)

Graff, Ariel (Center for Addiction and Mental Health, Toronto, Canada)
Haahr, Mette Ewers (Neurobiology Research Unit, Rigshospitalet, Copenhagen, Denmark)
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Horga, Guillermo (New York Psychiatric Institute, Columbia College of Physicians, USA)
Huntjens, Rafaele (Clinical Psychology, University of Groningen, Groningen, Netherlands)
Ichise, Masanori (Clinical Radiology, Columbia University, New York, NY, USA)
Irimajiri, Mami (Animal Science, Kitasato University, Towada-Shi, Japan)
Ito, Hiroshi (Molecular Imaging, National Institute of Radiological Sciences, Chiba, Japan)
Kalbitzer, Jan (Psychiatry and Psychotherapy, Charité-Universitätsmedizin, Berlin, Germany)
Kim, Sang Eun (Nuclear Medicine, Seoul National University, Seongnam, S.Korea)
Kimmel, Heather L (Neuropharmacology, Emory University Sch. Med., Atlanta, GA, USA)
Kobayashi, Katsuji (Nuclear Medicine, Yawata Med. Center Hospital, Ishikawa-Ken, Japan)
Kotagal, Vikas (Neurology, University of Michigan, Ann Arbor, MI, USA)
Kranz, Georg (Functional Neuroimaging, Medical University, Vienna, Austria)
Lee, I Hui (Psychiatry, College Medicine, National Cheng Kung University, Tainan, Taiwan)
Lin, Chien Ting (Psychiatry, Cheng Kung University Med. Center, Tainan, Taiwan)
Lothe, Amélie (Neuroscience Research Center, University of Lyon, Lyon, France)
Luiz Pedroso, Jose (Neurology, Ataxia Unit, Universidade Federal de São Paulo, Brazil)
Marsh, Abigail (Psychology, Georgetown University, Washington, DC, USA)
Mehta, Mitul (Institute of Psychiatry, King's College London, London, UK)
Michaelides, Michael (Pharmacology, Mount Sinai School of Medicine, New York, USA)
Miller, Jeffrey M (Molecular Imaging, Columbia University, New York, USA)
Molina, Mario E (PROBIOL, Universidad Nacional de Cuyo, Mendoza, Argentina)
Morris, Evan (Yale PET Center, Yale University, New Haven, CT, USA)
Nikolaus, Susanne (Nuclear Medicine, Heinrich-Heine University, Düsseldorf, Germany)
Otte, Andreas (Biomedical Engineering, University Applied Sciences Offenburg, Germany)
Paillère-Martinot, Marie-Laure, Maison de Solenn, Hôpital Cochin, Paris, France)
Pattij, Tommy (Mol. and Cellular Neurobiology, Free University, Amsterdam, Netherlands)
Politis, Marios (Neurology, Department of Medicine, Imperial College London, UK)

Reininghaus, Eva (Psychiatry, Medical University Graz, Graz, Austria)
Richieri, Raphaëlle-Marie (Psychiatrie, Université d'Aix-Marseille, Marseille, France)
Rónai, Zsolt (Mol. Biology & Pathobiochemistry, Semmelweis Univ., Budapest, Hungary)
Ryding, Erik (Clinical Neurophysiology, Karolinska Hospital, Huddinge, Sweden)
Sacher, Julia (Max Planck Institute for Cognitive and Brain Sciences, Leipzig, Germany)
Salavert, José (Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Spain),
Sar, Vedat (Psychiatry, Faculty of Medicine, Istanbul University, Istanbul, Turkey)
Schild, Sven (Trauma Research Institute, Alliant Internat. University, San Diego, CA, USA)
Schmahl, Christian (Zentralinstitut für Seelische Gesundheit, Mannheim, Germany)
Schmitt, Ulrich (Psychiatry, Johannes Gutenberg University, Mainz, Germany)
Shin, Lisa (Psychology, Tufts University, Medford, MA, USA)
Sjoerds, Zsuszika (Psychiatry, VU Medical Ctr, Free University, Amsterdam, Netherlands)
Takano, Harumasa (Molecular Imaging Center, Nat. Inst. Radiological Sciences, Chiba, Japan)
Varnäs, Katarina (Psychiatry, Karolinska Institute, Stockholm, Sweden)
Vérin, Marc (Clinique Neurologique, Université Rennes 1, Rennes, France)
Vries, Erik F. de (Nuclear Medicine and Molecular Imaging, UMC Groningen, Netherlands)
Waarde, Aren van (Nuclear Medicine and Molecular Imaging, UMC Groningen, Netherlands)
Warwick, James M (Nuclear Medicine, Stellenbosch University, Cape Town, South Africa)
Wilcox, Claire E (Psychiatry, University of California, San Francisco, CA, USA)
Yalachkov, Yavor (Medizinische Psychologie, Goethe-Universität, Frankfurt, Germany)
Yamaguchi, Shihei (Neurology, Shimane University School of Medicine, Shimane, Japan)
Yang, Yeng Kuang (Psychiatry, Cheng Kung University Med. Center, Tainan, Taiwan)
Zantvoord, Jasper (Brain Imaging, Academic Medical Center, Amsterdam, Netherlands)

Anthology of Apologies

While the authors' expert contributions lead to book chapters, it is the task of editors to determine the contents of a book and to orchestrate its realization. As all parties volunteer for the sake of science, timely publication according to schedule depends on the efforts of many human beings, intending to do their best but often delayed by daily realities.

Such realities may complicate the life of an editor. Clear deadlines can be neglected and even repeated reminders do not always lead to the expected results. In the (unlikely) case that one receives a speedy reply, the returning messages contain a plethora of apologies. We recognize these reflections of our daily struggles to comply and respect the authors for their efforts. Some responses made us smile; we hope this will also be the case with the reader. Examples from e-mail correspondence concerning the Psychiatry volume are listed below:

1. "We will contact you again about our time schedule for submission" (after the deadline had already been exceeded by several months).
2. "I used to fulfil virtually all my promises in the past, but after one has become a full professor, limits are rapidly reached and writing becomes virtually impossible – even during the Christmas break!" (This author decided to no longer contribute, after ten months…).
3. "None of my co-authors has put anything on paper, thus the chapter should wait until next year" (What about the man himself?).
4. "Hi, I am adding last references and hope to have it to you in two weeks. Sorry, I had too many deadlines!" (We received the chapter finally after three months).
5. "Hate to write this, but I will not manage to write the book chapter. I expected to write it during my pregnancy leave, but I returned to work last Monday; thus, I don't see any possibility for writing anymore". (During further negotiations, this author agreed to re-write an existing manuscript and submit it as the promised book chapter).
6. "I sincerely apologize for my constant delay in submitting the promised chapter. I recently got a new position at another university and moved there in the last weeks. As a consequence, I fell back with many obligations. The good news is that I was able to gain Dr. X as a co-author, who is an international expert in this field". (The chapter that we finally received was great).

7. “I apologize for the delay. This is a holiday weekend here in the US and I am on travel. I will get this to you by the end of the day”. (This reviewer really responded in a single day).
8. “I’m sending you my chapter. I must apologize for being late - my work at the hospital is very intense, and a toddler and baby-girl in our home let me work night shifts as well …”

Index

R.A.J.O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
DOI 10.1007/978-3-642-40384-2, © Springer-Verlag Berlin Heidelberg 2014

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