Psychiatric Disorders in Dementia

9

Yannick Vermeiren, Debby Van Dam, Maartje de Vries, and Peter Paul De Deyn

Contents

Y. Vermeiren · D. Van Dam
Department of Biomedical Sciences, Neurochemistry and Behavior, Institute Born-Bunge, University of Antwerp, Wilrijk, Belgium

Department of Neurology, Alzheimer Center Groningen, University of Groningen and University Medical Center Groningen (UMCG), Groningen, The Netherlands
e-mail: yannick.vermeiren@uantwerpen.be; debby.vandam@uantwerpen.be

M. de Vries
Department of Neurology, Alzheimer Center Groningen, University of Groningen and University Medical Center Groningen (UMCG), Groningen, The Netherlands
e-mail: m.de.vries@umcg.nl

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

Department of Neurology, Alzheimer Center Groningen, University of Groningen and University Medical Center Groningen (UMCG), Groningen, The Netherlands

Department of Neurology and Memory Clinic, Hospital Network Antwerp (ZNA) Middelheim and Hoge Beuken, Antwerp, Belgium
e-mail: dedeyn@skynet.be

R. A. J. O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
https://doi.org/10.1007/978-3-030-57231-0_9

Abstract

Alzheimer's disease (AD) is the most common form of dementia, a neurodegenerative disorder which is characterized not only by cognitive deterioration but also by a diversity of *behavioral and psychological signs and symptoms of dementia* (BPSD). BPSD in AD or other dementia subtypes such as frontotemporal dementia (FTD) or dementia with Lewy bodies (DLB) consist of delusions, hallucinations, activity disturbances, aggression/agitation, diurnal rhythm disturbances, mood disorders, apathy, and anxieties/phobias. Neuroimaging modalities such as *positron emission tomography* (PET) and *single-photon emission computed tomography* (SPECT) are very essential and useful imaging tools to differentially diagnose between AD and non-AD or healthy control subjects or between different dementia subtypes, such as AD and DLB or FTD. Besides their diagnostic utility, PET and SPECT are useful tools to investigate the cerebral pathophysiology of BPSD in dementia.

Below, PET and SPECT neuroimaging research in dementia spanning the last three decades has been systematically reviewed. The most commonly used PET and SPECT radioligands, as well as new developments in the field, all targeting different and unique aspects of neurodegeneration, are described. Furthermore, PET and SPECT research in BPSD with a main focus on depression, apathy, and psychosis in AD, DLB, and FTD are discussed in detail. On the whole, both PET and SPECT have demonstrated that depending on the behavioral phenomenon and dementia subtype, BPSD are the fundamental expression of very regional cerebral pathological events rather than a diffuse brain illness.

Abbreviations

^{11}C-DASB	^{11}C-3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile
^{11}C-PMP	^{11}C-methylpiperidin-4-yl propionate
^{11}C-RAC	^{11}C-raclopride
^{123}I-β-CIT	^{123}I-2beta-carbomethoxy-3beta-(4-iodophenyl)tropane
^{123}I-IBVM	^{123}I-iodobenzovesamicol
^{123}I-IDEX	^{123}I-iododexetimide
^{123}I-FP	^{123}I-fluoropropyl
^{123}I-IMP	N-isopropyl-p-^{123}I-iodoamphetamine
^{18}F-FDG	^{18}F-fluorodeoxyglucose
^{99m}Tc-ECD	^{99m}Technetium-ethyl-cysteinate dimer
^{99m}Tc-HMPAO	^{99m}Technetium-hexamethylpropyleneamine oxime
3DSRT	3-D stereotactic region of interest template
5-HT	Serotonin (5-hydroxytryptamine)
Aβ	Beta-amyloid
ABS-score	Abe's BPSD score
AD	Alzheimer's disease
ADAS-(non)cog	Alzheimer's Disease Assessment Scale, (non)cognitive portion
AD+CVD	Alzheimer's disease with cerebrovascular disease
ADRDA	Alzheimer's Disease and Related Disorders (see NINCDS)
ALS	Amyotrophic lateral sclerosis
ANCOG	Antwerp cognition
APOE	Apolipoprotein E
APP	Amyloid precursor protein
BA	Brodmann area
BADL	Basic activities of daily living
Behave-AD	Behavioral pathology in Alzheimer's disease rating scale
BPSD	Behavioral and psychological signs and symptoms of dementia
BPSD-DS	Behavioral and psychological signs and symptoms of dementia in Down syndrome
bvFTD	Behavioral variant frontotemporal dementia
CBD	Corticobasal degeneration
CC	Cingulate cortex
CIS	Cingulate island score
COX	Cyclooxygenase
CMAI	Cohen-Mansfield agitation inventory
CSDD	Cornell Scale for Depression in Dementia
CSF	Cerebrospinal fluid
CVD	Cerebrovascular disease
DA	Dopamine
DAT	Dopamine transporter
DLB	Dementia with Lewy bodies
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

EPS	Extrapyramidal symptoms
ERDA	Epidemiology research on dementia in Antwerp
eZIS	Easy Z-score imaging system
FDDNP	^{18}F-2-(1-(2-(N-(2-fluoroethyl)-N-methylamino)naphthalene-6-yl) ethylidene)malononitrile
FDG	Fluorodeoxyglucose
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
GDS	Geriatric depression scale
HDS	Hamilton Depression Rating Scale
IAD	Instrumental activities of daily living
IDO	Indoleamine 2,3-dioxygenase
IMPY	6-Iodo-2-(4′-dimethylamino-)phenyl-imidazo[1,2]pyridine
LC	locus coeruleus
LOAD	Late-onset Alzheimer's disease
MAPT	Microtubule-associated protein tau
MCI	Mild cognitive impairment
MFS	Middelheim Frontality Score
MMSE	Mini-Mental State Examination
MRB	Methylreboxetine
MXD	Mixed dementia
NE	Norepinephrine
NET	Norepinephrine transporter
NFT	Neurofibrillary tangles
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke (see ADRDA)
NPI	Neuropsychiatric Inventory
NPI-C	Neuropsychiatric Inventory-Clinician
NPI-NH	Neuropsychiatric Inventory-Nursing Home version
NPI-Q	Neuropsychiatric Inventory Questionnaire
NPS	Neuropsychiatric symptoms
NSAID	Nonsteroidal anti-inflammatory drugs
PBR-TSPO	Peripheral benzodiazepine receptor-translocator protein
PD	Parkinson's disease
PD-1	Programmed death-1
PDD	Parkinson's disease dementia
PET	Positron emission tomography
PGRN	Progranulin
PiB	Pittsburgh compound-B
PSEN	Presenilin
PSP	Progressive supranuclear palsy
Py	Person years
RBD	REM sleep behavioral disorder
rCBF	Regional cerebral blood flow
ROI	Regions of interest

SB-13	4-N-methylamino-4'-hydroxystilbene
SD	Semantic dementia
SNCA	α-Synuclein
SPECT	Single-photon emission computed tomography
SPM	Statistical parametric mapping
TDP-43	TAR DNA-binding protein 43
U	Ubiquitin
VAD	Vascular dementia

9.1 Dementia: Definition and Epidemiology

9.1.1 Definition

According to the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5*, dementia is referred to as a "major or mild neurocognitive disorder (NCD)." Major or mild NCD include NCD due to Alzheimer's disease (AD), vascular NCD, NCD with Lewy bodies, NCD due to Parkinson's disease (PD), frontotemporal NCD, and NCD due to Huntington's disease. It is noted, however, that the term "dementia" is not precluded from use in etiological subtypes in which this term is standard and can be used in settings where physicians and patients are accustomed with this term. Overall, dementia is a clinical syndrome characterized by a gradual loss of function in multiple cognitive domains leading to a significant impairment in social and occupational functioning (American Psychiatric Association 2013). The diagnostic criteria for major NCD are summarized in Table 9.1.

Besides cognitive aspects, dementia is also characterized by numerous behavioral symptoms entitled *behavioral and psychological signs and symptoms of dementia* (BPSD) (Reisberg et al. 1987)—also referred to as *neuropsychiatric symptoms* (NPS) (Lyketsos et al. 2011). BPSD/NPS consist of delusional ideation, hallucinations, activity disturbances, agitation/aggression, circadian rhythm disturbances, affective disturbances, and anxiety disorders and is considered a major component of the dementia syndrome. Lastly, basic and instrumental activities of daily living (BADL and IADL, respectively) complete the definition of dementia. BADL refer to daily self-care activities such as personal hygiene, getting dressed, eating, and general mobility, whereas IADL require more complex abilities such as driving a car, utilizing a phone, taking medication, doing groceries, and managing finances (Lawton and Brody 1969). During the course of dementia, IADL are affected first, followed by BADL (Gauthier et al. 1997). Several studies also showed a direct association between cognitive decline and worsening of BADL and IADL in dementia patients and non-demented elderly (Mitnitski et al. 1999).

The difference between a major and mild NCD primarily lies in the fact that in mild NCD, the cognitive decline is rather modest and there is no interference with BADL or IADL.

Table 9.1 Diagnostic criteria for major NCD according to DSM-5

A.	Evidence of *significant cognitive decline from a previous level of performance in one or more cognitive domains* (complex attention, executive function, learning and memory (amnesia), language (aphasia), perceptual motor (apraxia), or social cognition (agnosia)) based on: 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function 2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment
B.	The cognitive deficits *interfere with independence in everyday activities* (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living (IADL) such as paying bills or managing medications)
C.	The cognitive deficits *do not occur exclusively in the context of a delirium*
D.	The cognitive deficits *are not better explained* by another mental disorder (e.g., major depressive disorder, schizophrenia)
Specification of	1. The etiological subtype (e.g., due to AD, frontotemporal lobar degeneration, or Huntington's disease) 2. Presence/absence of behavioral disturbance 3. Current severity (mild, moderate, severe)

Abbreviations: *AD* Alzheimer's disease; *DSM-5* Diagnostic and Statistical Manual of Mental Disorders, 5th edition, *NCD* Neurocognitive disorder. Based upon the American Psychiatric Association (2013)

The definition above emphasizes that the term "dementia/major NCD" is a syndrome (i.e., association of several clinically recognizable features, signs, and symptoms) rather than only a cognitive disorder and is completed by important behavioral and functional shortcomings (Fig. 9.1).

As a matter of convenience, the term "BPSD" rather than "NPS" will be used throughout this chapter.

9.1.2 Prevalence and Incidence

Although dementia strikes irrespective of age, the prevalence of dementia generally rises with it. Women seem to be more frequently affected by dementia than men (Breteler et al. 1992) although this observation might be attributed to a slower progression rate of the disease in women combined with a proportionally longer life expectancy (Bachman et al. 1993). Prevalence estimates of dementia in the aged population show distinct variation due to differences in population selection, case ascertainment procedures, and diagnostic criteria, which often results in overestimation or underestimation of dementia occurrence (De Deyn et al. 2011). In general, however, the prevalence of moderate-to-severe dementia approximately doubles every 5 years starting at a rate of 2% between the age of 65 and 69, augmenting to 4% in people aged between 70 and 74 up to 16% in octogenarians (Henderson 1990; Morris 1994). These numbers correspond to a prevalence of 5 up

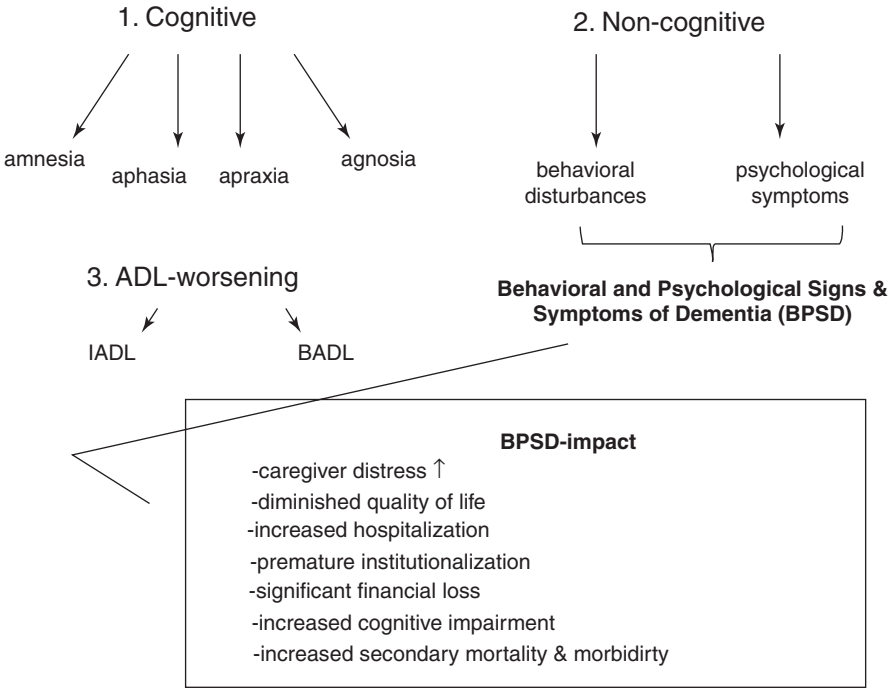


Fig. 9.1 Dementia symptomatology. The dementia syndrome consists of cognitive and noncognitive symptomatology. Worsening of BADL and IADL completes the definition. BPSD examples are delusional ideation and hallucinations, activity disturbances, aggression and agitation, sleep disturbances, mood disorders, and anxiety. Abbreviations: basic activities of daily living (BADL); behavioral and psychological signs and symptoms of dementia (BPSD); instrumental activities of daily living (IADL)

to 10% in the elderly aged 65 and older. In Europe, the prevalence of dementia varies between 1% at the age of 60 and 64 rising up to 34.7% in elderly aged 95 and 99 (Hofman et al. 1991). A recent study by Niu and colleagues (2017) confirms these figures for the European continent, with an overall prevalence rate for AD of 5.05%. Interestingly, the prevalence in women is twice as high as in men (7.13% versus 3.31%).

In the Netherlands, prevalence of dementia in people aged 75–79 was estimated to be 5.2% in 1992 (in a rural area near Zwolle) (Boersma et al. 1998) and 6.1% in 1993 (in the Rotterdam suburb of Ommoord) (Ott et al. 1995; Breteler et al. 1998), while in Belgium, it was estimated to be 7.6% in 1993 (in the semirural area of Heist-op-den-Berg) (Roelands et al. 1994). More recent figures of Belgian dementia prevalence estimates came from the *Antwerp Cognition* (ANCOG) study. This longitudinal cohort study of 825 community-dwelling elderly aged between 75 and 80, living in six different districts of Antwerp, with a 3-year follow-up period ($n = 363$) resulted in an overall prevalence rate of 8.7% (De Deyn et al. 2011).

To give exact numbers, Wimo et al. (2003) assessed the worldwide occurrence of dementia from 1950 until 2000 and also estimated its progression until 2050. The worldwide number of persons with dementia in 2000 was estimated at about 25 million persons. Almost half of the demented individuals lived in Asia (46%), 30% in Europe, and 12% in North America. Fifty-two percent lived in developing regions. About 6.1% of the population aged 65 years and older suffered from dementia (about 0.5% of the worldwide population), and 59% were female. The number of new cases of dementia in 2000 was calculated to be approximately 4.6 million. The forecast indicated a considerable increase in the number of demented elderly from 25 million in the year 2000 to 63 million in 2030 (41 million in less developed regions) and to 114 million in 2050 (84 million in developing regions). In the meantime, the 2015 World Alzheimer Report has updated these numbers, with an expected count of 131 million people worldwide suffering from dementia by 2050 (67 million in Asia, 19 million in Europe, 30 million in the Americas, and 16 million in Africa) (Alzheimer's Disease International 2015).

It thus becomes clear that due to progressive aging of the general population, a further increase of dementia prevalence during the next decades is expected, with an astonishing proportionate worldwide increase of 181% for the period 2015–2050. Moreover, the majority of demented elderly will live in low- and middle-income countries, with an approximate 68% in 2050 (Alzheimer's Disease International 2015).

Less data is available regarding dementia incidence estimates (i.e., a measure of the risk to develop dementia within a specific period of time). Versporten et al. (2005) reported an overall incidence rate of dementia of 41 per 1000 person years (Py) for men and 33 per 1000 Py for women (i.e., 41 or 33 persons out of 1000 that were observed for 1 year). This *Epidemiology Research on Dementia in Antwerp* (ERDA) study started in 1990 and consisted of 937 non-demented elderly aged 65 and older. Moreover, individuals with less than 7 years of education in this study population were—independent of gender—at higher risk of developing dementia compared with those receiving higher education (Versporten et al. 2005). In agreement with the ERDA study, the ANCOG study resulted in a cumulative incidence rate of 36.60 per 1000 Py with annual incidence rates ranging from 34.39 over 35.16 to 49.09 per 1000 Py. In America, the average incidence rate varies between 3 per 1000 Py in people aged 65 up to 69 years old and a maximum of 56 per 1000 Py in 90 year olds (Kukull et al. 2002). These age-dependent figures are consistent with a previously executed large-scale European study (Launer et al. 1999). More recently, Niu et al. (2017) conducted a meta-analysis and concluded that incidence rates of AD in Europe were 3.43, 13.78, and 35.74 cases per 1000 Py for patients aged 65–74 years, 75–84 years, and 85 and older, respectively.

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

Dementia syndromes are commonly subdivided according to their reversible or irreversible nature (Katzman et al. 1988).

Primary dementia syndromes are irreversible neurodegenerative disorders such as Alzheimer's disease (AD), frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD), Huntington's disease, and Creutzfeldt-Jakob disease.

On the contrary, secondary dementia syndromes are "potentially" reversible and originate from a specific acquired central nervous system disorder which led to "dementia-like deficits" (i.e., cognitive dysfunction, behavioral phenomenology). Some examples are brain tumors, cerebrovascular accidents (vascular dementia (VAD)), infections (meningitis, AIDS dementia complex), head traumas (subdural hematoma), alcohol abuse (Korsakoff syndrome), or normal pressure hydrocephalus.

Lastly, pseudodementias are "completely" reversible dementia subtypes that very much resemble primary dementia syndromes although the aspect of abundant neurodegeneration itself is absent. Examples are psychiatric disturbances (depression, schizophrenia), endocrine/metabolic disorders (hypothyroidism), malnutrition/vitamin deficiency (vitamin B12 or folic acid deficiency), or toxicological/pharmacological/substance-related conditions (certain sleep medication, anxiolytica, or sedatives) (Katzman et al. 1988).

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

9.1.3.1 Alzheimer's Disease (AD)

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and is named after Dr. Alois Alzheimer, who first described this syndrome in 1906 in a 51-year-old female patient, named Auguste Deter, who suffered from a progressive cognitive impairment associated with significant behavioral changes. A probable major NCD due to AD (code 331.0 (G30.9)) applies with the DSM-5 criteria for the dementia syndrome described above (Table 9.1) (American Psychiatric Association 2013) and is manifested by (1) evidence of a causative genetic mutation from either family history or genetic testing and (2) all three of the following: (a) multiple cognitive deficits such as memory impairment but also aphasia, apraxia, agnosia, and/or executive dysfunctioning; (b) steadily progressive, gradual decline in cognition, without extended plateaus; and (c) no evidence of mixed etiology (e.g., cerebrovascular disease (CVD)). If not all of the preceding criteria are met, possible NCD due to AD should be diagnosed. Additionally, a major NCD due to AD is encoded based on the presence (294.11 (F02.81)) or absence (294.10 (F02.80)) of an associated clinically significant behavioral disturbance. The same categorization can be applied for a probable or possible mild NCD due to AD (American Psychiatric Association 2013).

Diagnosis

The *National Institute on Aging-Alzheimer's Association* (NIA-AA) workgroups (McKhann et al. 2011) updated the *National Institute of Neurological and Communicative Disorders and Stroke* (NINCDS) and the *Alzheimer's Disease and*

Related Disorders (ADRDA) criteria of 1984 (McKhann et al. 1984), which ought to be used by both general healthcare providers without access to neuropsychological testing, advanced imaging, and cerebrospinal fluid (CSF) measures and specialized investigators involved in research or in clinical trial studies who would have these tools available. The NIA-AA criteria have subdivided AD into probable, possible, and definite. Probable AD is characterized by cognitive deficits in at least two cognitive domains with an insidious onset and a progressive worsening over time, a clear-cut history of cognitive worsening by report or observation, and the most prominent cognitive deficits are evident on history or clinical examination in an amnestic (e.g., impairment in learning recall and at least one other cognitive domain) or nonamnestic (aphasia/apraxia/agnosia/executive dysfunctioning) manner (core criteria) (McKhann et al. 2011). Supportive criteria are among others a family history of AD, associated BPSD, disturbed ADL, and a CT scan not displaying central nervous system pathology, which may underlie the dementia syndrome. A new subcategory of probable AD compared to the 1984 criteria is the *probable AD with evidence of the AD pathophysiological process* category. In this category, biomarker evidence of CSF amyloid-beta (Aβ), total- (T-tau) and phosphorylated tau (P-tau$_{181P}$) levels, positive PET amyloid imaging, or a decreased ^{18}fluorodeoxyglucose (FDG) uptake on PET in temporoparietal cortex may increase the certainty of an active AD pathophysiological process in persons who meet the core clinical criteria for probable AD. Possible AD differs from probable AD as it is manifested by a somewhat atypical course and heterogeneity of symptoms with an either sudden onset of cognitive impairment or etiologically mixed presentation, such as concomitant CVD. The core criteria of AD, however, remain present (McKhann et al. 2011).

Finally, definite AD (McKhann et al. 1984) or *pathophysiologically proved AD dementia* (McKhann et al. 2011) is applicable if the core criteria for probable AD were met and in addition a (postmortem) neuropathological examination demonstrated the presence of AD pathology.

In order to better define the various clinical phenotypes and integrate biomarkers into the diagnostic process, covering the full staging of the disease, the International Workgroup (IWG-2) proposed research diagnostic criteria for AD in 2014 (Dubois et al. 2014). Particularly the inclusion and combination of volumetric MRI, amyloid PET, and biomarker panel of CSF A$\beta_{1–42}$, T-tau, and P-tau$_{181P}$ levels have redefined the clinical states of AD into presymptomatic, asymptomatic, typical, atypical, and mixed (with CVD or DLB) (Dubois et al. 2014). Finally, in 2016, the A/T/N classification scheme was introduced by Jack Jr and colleagues (2016) to further highlight the importance of AD biomarkers. The A/T/N system includes the new modality tau PET. Following this classification system, seven major AD biomarkers are divided into three binary categories based on the nature of the pathophysiology that each measures. “A” refers to the value of an Aβ biomarker (amyloid PET or CSF A$\beta_{1–42}$), “T” the value of a tau biomarker (CSF P-tau$_{181P}$ or tau PET), and “N” biomarkers of neurodegeneration or neuronal injury (FDG-PET, structural MRI, or CSF T-tau). Each biomarker category is rated as positive or negative. An individual score might appear as A+/T+/N−, A+/T-/N−, etc.

With reference to the A/T/N classification system, Jack et al. introduced the NIA-AA research framework in 2018 (Jack Jr et al. 2018). Its intended use is for observational and interventional research only, not routine clinical care. Unlike the 2011 NIA-AA guidelines, AD is defined as a continuous process in both cognitive and biomarker domains rather than as three separate clinical entities (i.e., cognitively unimpaired, mild cognitive impairment (MCI), dementia). The use of biomarkers is also harmonized across the disease continuum in this research framework, which was not the case in 2011. Furthermore, the research framework outlines two different systems for staging of severity of cognitive symptoms, i.e., a *syndromal categorical scheme*, which defines different A/T/N biomarker combinations over the three previously mentioned cognitive stages in function of the Alzheimer's continuum profile, and, a *numerical clinical staging scheme* (stages 1–6), which describes the gradual disease progression for individuals of the Alzheimer's continuum, mainly based on clinical, neuropsychological, and neurobehavioral observations and tests.

Pathophysiological Mechanisms

AD and other dementia subtypes are all proteinopathies. The histopathological hallmarks of the AD brain are extracellular deposits of Aβ plaques and intracellular neurofibrillary tangles (NFT), which lead to a widespread synaptic loss and neurodegeneration with a consequent neurotransmission failure, especially of the cholinergic neurotransmitter system (Van Dam and De Deyn 2006). Familial AD is an autosomal dominant disorder with onset before the age of 65 (Blennow et al. 2006). Mutations in the amyloid precursor protein (APP) gene on chromosome 21 or in the presenilin 1 (PSEN1) or presenilin 2 (PSEN2) genes account for familial early-onset cases, which cause fully penetrant monogenic forms of AD. However, these rare familial forms, often explained by rare variants with a strong effect, only have a prevalence of approximately 1% (Harvey et al. 2003). In most sporadic AD cases (>95%) with an age of onset above 65, the etiology is not entirely known. These late-onset AD (LOAD) cases are influenced by multiple common variants with low effect sizes. In January 2019, a new genome-wide association study of more than 600,000 individuals identified nine novel AD risk genes, raising the total count of independent risk loci to 29 (Bertram and Tanzi 2019; Jansen et al. 2019). The apolipoprotein E (APOE) is the strongest genetic risk locus for LOAD. The APOE ε4 allele may increase the risk of the disease by 3 times in heterozygotes and 15 times in homozygotes (Jansen et al. 2019; Farrer et al. 1997). Other examples are PICALM, TREM2, ADAMTS4, ALPK2, ABCA7, HESX1, CLNK, and, KAT8 (Jansen et al. 2019).

The *amyloid cascade hypothesis* is the most dominant etiological AD hypothesis and states that Aβ accumulation results from an imbalance between Aβ production and clearance (Blennow et al. 2006). Physiologically, APP is a cell membrane expressed protein not only in neurons but also in many other tissues and is likely to be involved in maintenance and modulation of neuronal networks (Loo et al. 1993). Posttranslational cleavage of APP by consecutive α- and ɣ-secretases releases a p3-fragment (non-amyloidogenic pathway), whereas the combined effect of β- and

ɣ-secretases releases non-soluble Aβ peptides of various lengths, i.e., $Aβ_{1–40}$ or $Aβ_{1–42}$ (amyloidogenic pathway). In normal situations, the non-amyloidogenic pathway is mostly active. In familial AD, however, a mutation in PSEN1/PSEN2 (which form the catalytic subunits of the secretases) or around the cleavage site of APP causes an overproduction of the hydrophobic $Aβ_{1–42}$ and consequently leads to a shifted $Aβ_{1–40}/Aβ_{1–42}$ balance. This is mainly due to a destabilization of the ɣ-secretase/$Aβ_n$ complexes, which further enhances amyloidogenic $Aβ_{1–42}$ production (Szaruga et al. 2017). As a result, enormous amounts of $Aβ_{1–42}$ fragments aggregate and form extracellular "senile plaques" (Hardy and Selkoe 2002). Whereas in familial AD there is an overproduction of $Aβ_{1–42}$ due to certain mutations, sporadic AD cases seem to fail sufficient Aβ clearance which leads to gradually increasing and accumulating Aβ levels in the brain. As mentioned above, genetic risk factors such as APOE ε4 but also aging and certain environmental risk factors were proven to be strongly associated with sporadic AD (Blennow et al. 2006).

The second hallmark of AD pathology is the presence of intracellular NFT, which results from the hyperphosphorylation and aggregation of the axonal tau proteins, a group of microtubule-associated proteins that contribute to the assembly and stabilization of microtubules in neurons among others (Grundke-Iqbal et al. 1986). Tau phosphorylation is regulated by the balance between multiple kinases (e.g., GSK-3β and CDK5) and phosphatases (e.g., PP-1 and PP-2A) (Iqbal et al. 2005). An imbalance between the protein kinases and phosphatases causes tau to be hyperphosphorylated into insoluble fibrils, also called "paired helical filaments." Tau hyperphosphorylation starts intracellularly and leads to sequestration of normal tau and other microtubule-associated proteins, which causes disassembly of microtubules and thus impaired axonal transport, compromising neuronal and synaptic function (Iqbal et al. 2005). Tau pathology starts early in the disease process in neurons of the transentorhinal region, from where it further spreads to the hippocampus and amygdala and finally to other cortical and neocortical association areas (Braak et al. 1999; Smith 2002).

Figure 9.2 depicts the pathological spread of Aβ and tau in AD brain. Interestingly, tau aggregates have been theorized to spread in a bottom-to-top-like fashion, starting from the locus coeruleus (LC) in the brainstem and moving upward toward the entorhinal cortex and neocortex.

Besides Aβ deposits and NFT, oxidative stress and inflammation are two key factors in the etiological hypotheses of AD as well.

Oxidative damage to different classes of biological molecules such as sugars, lipids, proteins, and DNA is a common aspect of both normal aging and most neurodegenerative disorders (Moreira et al. 2005). In early AD, oxidative stress might have an important pathogenic role as neurons themselves use different antioxidant defense systems in case of increased oxidative stress. Evidence demonstrates that Aβ depositions and hyperphosphorylation of tau form two primary defense lines against oxidative stress. With disease progression, both Aβ and tau transform into prooxidants due to a profound redox imbalance (Smith et al. 2002).

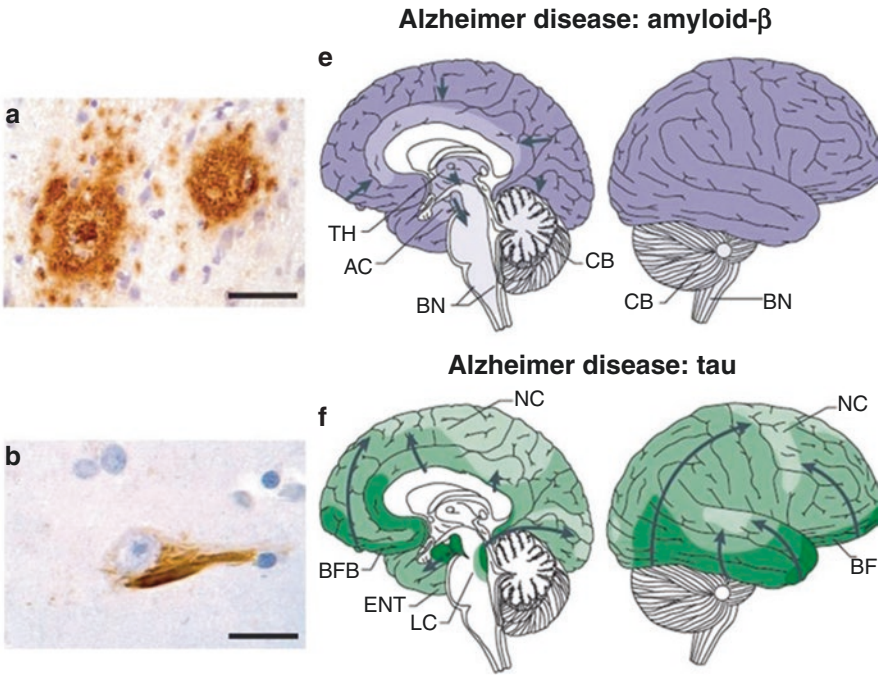


Fig. 9.2 Progressive expansion of amyloid-beta (Aβ) and tau pathology in Alzheimer's disease (AD) brain. (**a**) Aβ plaques in the cortex of an AD patient (50 μm scale bar); (**b**) tau neurofibrillary tangle in a neuron of an AD patient (20 μm scale bar); (**e**) Aβ deposits are first observed in the neocortex and are then detected in all cortical, diencephalic, and basal ganglia structures (in a caudal direction) and in the brainstem, and occasionally in the cerebellum; (**f**) tau aggregates develop in the locus coeruleus, then in the transentorhinal and entorhinal regions, and, subsequently, in the hippocampal formation and in broad areas of the neocortex. Abbreviations: *AC* Allocortex; *BFB* Basal forebrain, *BN* Brainstem nuclei, *CB* Cerebellum, *ENT* Entorhinal cortex, *LC* Locus coeruleus, *NC* Neocortex, *TH* Thalamus. Adapted with permission from Carbonell F et al. (2018) Front Neurol 9:37 under the CC-BY license 4.0 (http://creativecommons.org/licenses/by/4.0). Copyright © 2018 Carbonell, Iturria-Medina and Evans

With regard to inflammation, it has been proven that many neuroinflammatory mediators are upregulated in affected areas of the AD brain, including prostaglandins, complement components, anaphylatoxins, cytokines, chemokines, proteases, protease inhibitors, adhesion molecules, and free radicals (Akiyama et al. 2000). Côté et al. (2012) established a direct association between the prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs), which target cyclooxygenase (COX), and a decreased risk of subsequently developing AD even though several other clinical studies using NSAIDs in AD patients yielded a negative outcome (ADAPT Research Group et al. 2008; Breitner et al. 2011). Initially, the effect of NSAIDs in AD was thought to be attributed to a reduction of inflammation. In 2001, however, it was reported that a subset of NSAIDs reduced $A\beta_{1-42}$ production in cultured cells and mouse brain through a mode of action different from COX inhibition

(Weggen 2001). On the other hand, recent studies have observed that immune checkpoint blockade directed against the programmed death-1 (PD-1) pathway evokes an interferon-γ-dependent systemic immune response, which is followed by the recruitment of monocyte-derived macrophages to the brain. In mice with established AD pathology, this leads to clearance of plaques and improved cognitive performance (Baruch et al. 2016). As a consequence, anti-PD-1 ligand antibodies (immunotherapy) hold promise as a new therapeutic avenue for AD.

Interestingly, the induced neuroinflammation in AD might also lie at the basis of some BPSD, such as depression. For example, the enzyme indoleamine 2,3-dioxygenase (IDO) metabolizes tryptophan, the precursor of serotonin (5-hydroxytryptamine (5-HT)), into kynurenine. Due to neuroinflammation, the IDO activity becomes upregulated, and eventually the kynurenine catabolization further leads to an overproduction of quinolinic acid, the neurotoxic end product of the tryptophan pathway which also contributes to the excitotoxic effects in an AD brain. The altered tryptophan levels consequently affect 5-HT synthesis, which is a neurochemical hallmark in the etiology of depression. Neuroinflammation by upregulating IDO and consequently lowering tryptophan levels has thus been linked with major depressive disorder in AD patients (Dobos et al. 2010). Additionally, CSF levels of the anti-inflammatory cytokine interleukine-10 have also been inversely associated with BPSD in AD patients, of which agitation, depression, and nighttime behavior in particular (Holmgren et al. 2014).

AD is conventionally regarded as a central nervous system disorder, even though various studies implicated that the impact of the disease extends far beyond the brain. For instance, the gut microbiome has a profound impact on the formation of the blood-brain barrier, myelination, neurogenesis, and microglia maturation. The gut-brain axis, therefore, could be an important modifiable pathway in dementia as well (for review, see (Du et al. 2018)).

9.1.3.2 Other Dementia Subtypes

Apart from AD which is the most prevalent dementia syndrome (65% approximately), AD with cerebrovascular disease (AD+CVD), vascular dementia (VAD), dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD), and frontotemporal dementia (FTD) together roughly account for the other 35% (Fig. 9.3) (Small et al. 1997; Mikkelsen et al. 2016).

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

Dementia with Lewy Bodies (DLB)

Dementia with Lewy bodies (DLB) is the third most prevalent primary dementia subtype and is diagnosed according to McKeith et al. (McKeith et al. 2005, 2017). Similar with AD, several core and supportive criteria need to be present in order to establish a clinically acceptable DLB diagnosis. A fourth consensus report of the DLB consortium was established in 2017 (McKeith et al. 2017). The four core criteria are (i) a fluctuating cognition, (ii) recurrent and well-described visual

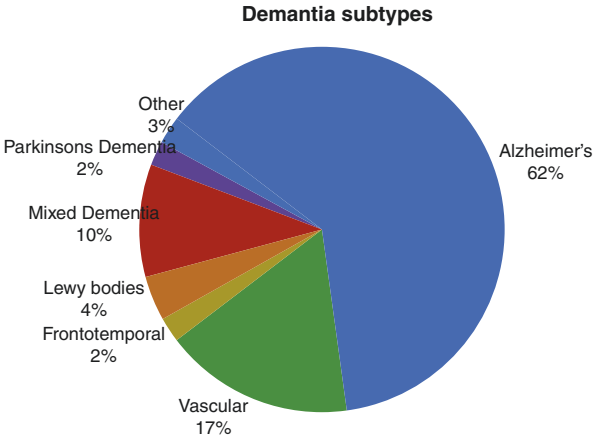


Fig. 9.3 Different etiological diagnoses of dementia. Alzheimer's disease is the most prevalent dementia subtype (±62%), followed by vascular dementia (±17%), Alzheimer's disease + cerebrovascular disease (mixed dementia; ±10%), dementia with Lewy bodies/Parkinson's disease dementia (±6% in total), frontotemporal dementia (±2%), and other dementias (±3%). Reprinted from Mikkelsen et al. (2016) Maturitas 93:108-113, with permission from Elsevier. Copyright © 2016 Elsevier Inc

hallucinations, (iii) REM sleep behavioral disorders (RBD), and (iv) clinical signs of overt parkinsonism (extrapyramidal symptoms (EPS), tremor, rigidity, and hypokinesia). The presence of only two core criteria or one core criterion but with one or more indicative biomarkers is sufficient to diagnose "probable" DLB. "Possible" DLB can be diagnosed if only one core criterion is present or no core criteria but only one or more indicative biomarkers. Some other supportive criteria are autonomic dysfunction, depression, apathy, anxiety, delusional ideation, repeated falls, and severe sensitivity to antipsychotic agents. New in comparison with the 2005 criteria is the inclusion of indicative biomarkers, such as reduced dopamine (DA) transporter (DAT) uptake in basal ganglia demonstrated by SPECT or PET, abnormal (low uptake) of ^{123}iodine-metaiodobenzylguanidine (MIBG) following myocardial scintigraphy, or, polysomnographic confirmation of REM sleep without atonia (McKeith et al. 2017). In addition, supportive biomarkers have been enlisted, such as the relative preservation of medial temporal lobe structures on CT/MRI scan, the generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity, and the cingulate island sign on FDG-PET imaging.

As in the 2005 criteria, the difference between DLB and PDD is solely based upon the temporal sequence of appearance of the extrapyramidal symptoms: DLB should be diagnosed when dementia occurs before (at least 1 year in research studies) or concurrently with parkinsonism. The term PDD should be used to describe dementia that occurs in the context of well-established PD (McKeith et al. 2005, 2017; Geser et al. 2005).

The main pathological characteristic of DLB is the presence of cytoplasmic aggregated inclusions of α-synuclein, generally known as "Lewy bodies" (Vladimir

2007). Synucleinopathies form a group of neurodegenerative disorders that share common pathologic proteinaceous lesions containing aggregated α-synuclein molecules which are deposited in neurons, nerve fibers, or glial cells (Goedert 1999, 2001), often in combination with AD plaques and NFT (McKeith et al. 2017), which frequently hampers differential diagnosis among these dementia syndromes. Specifically in DLB, Lewy bodies precipitate not only in the substantia nigra (pars compacta) of the basal ganglia and LC but also in the neocortex and hippocampus (McKeith et al. 2005). Only when a loss of dopaminergic neurons of 80% or more in the substantia nigra is reached, EPS will set off. Several case studies demonstrated the occurrence of familial DLB cases (Gwinn-Hardy and Singleton 2002) and that Lewy bodies are commonly seen in familial cases of AD as well (Trembath et al. 2003). There are reports of triplications of the α-synuclein (SNCA) gene in DLB, PD, and PDD patients, whereas SNCA gene duplications only seem to be associated with motor PD, suggesting a possible gene dose effect (Singleton and Gwinn-Hardy 2004). However, SNCA gene multiplications were not found in most sporadic DLB cases (Johnson et al. 2004). A study by Guerreiro and colleagues (2016) showed that DLB shares approximately the same amount of genetic determinants with PD as it does with AD, hereby excluding the strong association at the APOE locus.

Frontotemporal Dementia (FTD)

A less frequent and very heterogeneous neurodegenerative disorder is frontotemporal dementia (FTD). Neary et al. (1998) established the diagnostic criteria of among others *behavioral variant* FTD—simply referred to as FTD—which forms one of the three diagnostic entities of "frontotemporal lobar degeneration" (FTLD), together with primary progressive aphasia and semantic dementia (SD). Latter two syndromes have been recategorized into semantic variant primary progressive aphasia and nonfluent/agrammatic aphasia variant. Typical for FTD patients is the very early disease onset compared to AD or DLB, namely, between the age of 45 and 70. At onset of the syndrome, there may typically be a neglect of personal hygiene, disinhibition, loss of insight and judgment, social neglect, and emotional disturbance (i.e., emotional bluntness, impaired control of emotions) in contrast to a comparatively spared memory and spatial abilities (core criteria). A subsequent cognitive impairment is inevitable although in the beginning amnesia remains surprisingly absent. FTD thus initially manifests itself by subtle changes in behavior and character (Neary et al. 1998; De Deyn et al. 2005). Some other typical behavioral characteristics are the expression of stereotypes and changes in sexual behavior, dietary hyperactivity, speech disturbances (echolalia, mutism, logorrhea), and restlessness. From a clinical point of view, FTD is likely to be recognized and distinguished from AD solely due to this distinctive behavioral pattern (De Deyn et al. 2005).

Genetics have a major role in FTLD, with up to 43% of patients having a positive family history. On the neuropathological level, a distinction must be made between tauopathies and non-tauopathies. Tauopathies are caused by a mutation in the *microtubule-associated protein tau* (MAPT) gene (Bancher et al. 1987; Sieben et al. 2012), whereas non-tauopathies can be etiologically defined by mutations in the

progranulin (GRN) (Cruts et al. 2006) and *TAR DNA-binding protein 43* (TDP-43) gene among others (Arai et al. 2006; Neumann et al. 2006). Mutations in the MAPT gene cause cytoplasmic tau to aggregate which leads to the formation of tangles and eventually to neuronal death, especially in frontotemporal cortical areas. This phenomenon is known as Pick's disease, but also progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are classified as tauopathies (FTLD-tau; (Keith 2008)). In addition to GRN and TDP-43, mutations in C9Orf72, TBK1, and VCP genes all cause TDP-43 aggregates (non-tauopathies, FTLD-TDP), leading to a consequent neuronal degradation and dementia syndrome (for review, see (Sieben et al. 2012; Van Mossevelde et al. 2018)). Histopathologically, these aggregates are visible as tau-negative but ubiquitin (U)-positive inclusions so that non-tauopathies are generally categorized as FTLD-U. Approximately 60% of patients with FTLD have protein inclusions that stain positive for U and contain TDP-43 as the major constituent. Four distinct subtypes of FTLD-TDP pathology can be differentiated (A/B/C/D), and TDP-43 inclusions are also present in patients with motor neuron disease. Remarkably, an estimated 15% of all patients with FTD develop amyotrophic lateral sclerosis (ALS), indicating the presence of a disease continuum between FTLD and ALS (Gijselinck et al. 2012).

In addition to FTLD-TDP and FTLD-tau, three more subtypes are identified on the basis of the major protein inclusion constituent: FTLD-FET (a collective term for FTLD with inclusions of the RNA-binding proteins FUS or EWS (also known as EWSR1) or TATA-binding protein-associated factor 2N (TAF15)), FTLD-UPS (featuring inclusions of proteins of the ubiquitin-proteasome system, for instance, in the case of CHMP2B gene mutations), and FTLD-ni (no inclusions) (for review, see (Van Mossevelde et al. 2018)).

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

Besides cognitive disturbances, dementia is characterized by numerous behavioral disturbances too, categorized as *behavioral and psychological signs and symptoms of dementi*a (BPSD) (Reisberg et al. 1987; Finkel et al. 1996) and also referred to as *neuropsychiatric symptoms* (NPS) (Geda et al. 2013). BPSD are a heterogeneous group of behavioral, psychological, and psychiatric disturbances occurring in 50–80% of dementia patients of any etiology (Finkel et al. 1996) and affect almost all individuals with dementia (97%) over the course of the disease (Lanctôt et al. 2017). These behavioral and psychological symptoms are generally classified into seven main subtypes: paranoid and delusional ideation, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbances, and anxieties/phobias (Reisberg et al. 1987). BPSD often lead to a greater amount of caregiver distress, diminished quality of life for both patient and caregiver, greater cognitive impairment (Weamer et al. 2009), premature institutionalization, frequent (re)hospitalizations, and increased secondary morbidity and mortality (Finkel

2000). Last but not least, BPSD also have a significant and increasing socioeconomic impact (Beeri et al. 2002) (Fig. 9.1).

Distinct BPSD syndromes have different neurobiological underpinnings, so understanding the dysfunction or dysregulation of subcortical forebrain and diencephalic and brainstem nuclei that generate or mediate visceral, emotional, motivational, and other psychiatric symptoms will be required. The involvement of, for example, NFT and amyloid plaques in critical brain regions in AD regulating these behaviors, is, therefore, important and needs to be recognized. Understanding of neuropathology is also fundamental for future drug development, where currently approved treatments for mood and psychotic symptoms, such as antidepressants and antipsychotics, may not work because of the lack of target engagement in a degenerating brain (Lanctôt et al. 2017).

From a neurochemical point of view, alterations in central noradrenergic (Engelborghs et al. 2008; Herrmann et al. 2004; Lanari et al. 2006; Matthews et al. 2002), serotonergic (Engelborghs et al. 2008; Garcia-Alloza et al. 2005; Lanctôt et al. 2001; Vermeiren et al. 2014, 2015), and dopaminergic (Engelborghs et al. 2008; Lanari et al. 2006; Vermeiren et al. 2016) neurotransmitter systems and associated receptors proved to play a critical role in BPSD manifestation, irrespective of the dementia subtype (Vermeiren et al. 2016, 2013). Particularly the balance between those different neurotransmitter systems seems to be of importance as it is conceivable, due to the neurochemical complexity and diversity of BPSD, that more than one neurotransmitter system contributes to a particular behavioral syndrome (Lanari et al. 2006). Studying neurotransmitter systems in isolation cannot fully explain changes in behavior, given that many neurotransmitter systems work in conjunction with each other. In spite of this difficulty, the neurochemical mechanisms underlying BPSD are proven to be both BPSD- and dementia-specific (Engelborghs et al. 2008; Vermeiren et al. 2013), so that dementia-specific neurochemical alterations might be found. There is also supportive evidence for amino acids playing a functional role in the neurochemical pathophysiology of BPSD (Engelborghs et al. 2003; Fekkes et al. 1998; Francis 2009; Garcia-Alloza et al. 2006), with, for example, significantly high correlations between CSF taurine levels and depression in AD and CSF glutamate levels and agitation in FTD (Vermeiren et al. 2013).

Engelborghs et al. (2005) showed that different behavioral patterns can be observed depending on the dementia subtype, thereby further stressing that the behavioral assessment itself may help in differentiating between different forms of dementia (Fig. 9.4).

In 1996, Jost and Grossberg (Jost and Grossberg 1996) examined the frequency of BPSD in temporal relationship with the diagnostic progression of AD patients. The authors showed that, for example, depression occurs already 25 months before a proper clinical diagnosis was made in over 50% of patients. Agitation is mostly present some 10 months following the clinical AD diagnosis in over 80% of patients. In contrast to the cognitive symptoms in AD which progressively worsen during its course, BPSD seem different, as some behavioral symptoms are severely present during the early disease stages (e.g., depression, paranoia, diurnal rhythm disturbances) although later on these symptoms might gradually diminish or even

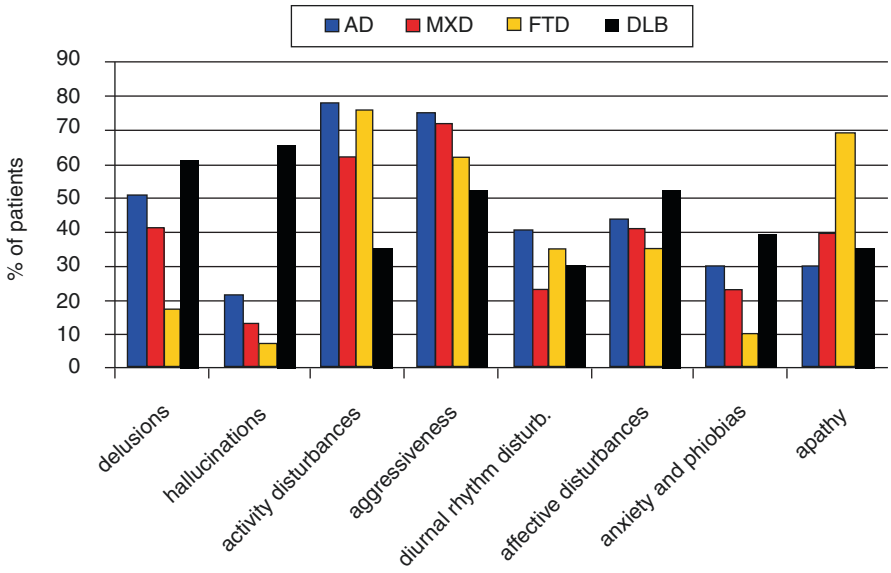


Fig. 9.4 Frequency of dementia-specific BPSD items. This figure shows that, for example, apathy is much more frequent in FTD as compared to AD/MXD/DLB, whereas delusions, hallucinations, and anxieties are less frequently present in FTD compared to DLB. Abbreviations: *AD* Alzheimer's disease, *BPSD* Behavioral and psychological signs and symptoms of dementia, *DLB* Dementia with Lewy bodies, *FTD* Frontotemporal dementia, *MXD* Mixed dementia. Based upon Engelborghs et al. (2005) *Int J Geriatr Psychiatry* 20:1028–1037

completely disappear, to be eventually replaced by other BPSD items (e.g., aggression, hallucinations, wandering). Another investigation regarding the prevalence of specific BPSD in AD was performed by Fernández et al. (2010). The authors concluded that out of a total of 1014 patients, almost all (90%) had BPSD at inclusion, 17% of which reported psychotic outbreaks. The most prevalent symptoms were lack of concentration (56%), tremors (56%), depression (44%), lack of cooperation (36%), and delusions (32%). They also showed that cognitive impairment and BPSD were correlated.

9.2.1 Delusional Ideation and Hallucinations: The Psychotic Syndrome

Approximately more than 40% of dementia patients of any etiology and up to 73% of AD patients suffer from delusional ideation during the disease course (Finkel 2001). The most prominent delusion according to Reisberg et al. (1987) is suspiciousness/paranoia, i.e., the conviction that people are stealing things from the patient. Other frequently occurring delusions are the "one's house is not one's home delusion" or the accusation of infidelity toward their spouse or caregiver. Delusions are frequently associated with verbal and physical aggression which in most cases

leads to an untenable situation at home and premature institutionalization (Deutsch et al. 1991). Deutsch et al. (1991) suggest delusions to be risk factors in patients with probable AD who have moderate-to-severe cognitive impairment.

In patients with AD, psychosis occurs more frequently in women than in men. Some other predisposing factors besides gender for psychotic symptoms are age, severity of illness, and cognitive deterioration (Hirono et al. 1998). Weamer et al. (2009) found that the severity of cognitive impairment was a strong predictor of psychosis in AD patients up to 2 years prior to psychosis onset.

Hallucinations in dementia patients are less frequent than delusions, with a prevalence rate of 12 up to 49% (Swearer 1994). Hallucinations and delusions are characteristic for specifically DLB patients, as shown in Fig. 9.4 (based upon Engelborghs et al. (2005)). A hallucination is the patient's strict conviction of a sensory perception in the absence of sensorial stimulation. Reisberg et al. (1987) made a distinction between visual, auditory, olfactory (smell), and haptic (touch) hallucinations. It is noticeable that hallucinations are more likely to occur in patients with more severe cognitive deterioration compared to patients with mild forms of dementia (Devenand et al. 1997). Moreover, hallucinations are less stressful for dementia patients than delusions so that pharmacological treatment is less mandatory (De Deyn 2004).

AD patients with psychosis have been reported to deteriorate twice as fast as patients without psychotic symptoms (Rosen and Zubenko 1991). Similarly, Scarmeas et al. (2005) studied whether the presence of delusions and hallucinations has predictive value for important outcomes in AD patients, such as cognitive and functional decline. Their results confirmed that the presence of delusions and hallucinations was associated with an increased risk for cognitive and functional decline, institutionalization, and even death.

It is noteworthy that psychosis of AD is a distinct syndrome that is markedly different from, for example, schizophrenia in elderly patients. Numerous research groups have reported potentially relevant clinical, neuropsychological, neurochemical, neurobiological, and neuropathological differences between AD patients with and without psychosis (Jeste and Finkel 2000). In the past, there have been no specific criteria for diagnosing psychosis in AD as a distinct entity. Therefore, Jeste and Finkel have proposed several core criteria in 2000 in order to correctly diagnose the psychotic syndrome in AD (Jeste and Finkel 2000). Characteristic symptoms are the presence of one (or more) visual/auditory hallucination(s) and/or delusion(s). Also, there has to be evidence from the patient's history that these symptoms have not been continuously present prior to dementia onset. The symptoms also must have been present for at least 1 month or longer and have to cause some disruption in the patient's functioning. Moreover, schizophrenia and related psychotic disorders as well as a delirium or other causes (e.g., substance-related) that might have initiated the psychosis need to be excluded. Finally, associated behavioral features such as agitation, negative symptoms, and/or depression might be present as well.

All criteria may also apply to a similar psychotic syndrome associated with other dementias such as DLB, VAD, and MXD.

9.2.2 Agitation and Aggression

Agitation includes inappropriate verbal, vocal, or motor behaviors that, in the opinion of an observer, do not result directly from the needs or confusion of the agitated individual (Cohen-Mansfield and Deutsch 1996). Approximately 80% of dementia patients will suffer from agitation during the disease course. Agitation therefore is one of the most frequently (re)occurring BPSD (Allen and Burns 1995). In 2000, Lyketsos et al. (2000) reported the prevalence of agitation and other BPSD in 329 participants with dementia (the Cache County Study on Memory in Aging, Utah), of which 65% had AD, and concluded that agitation and aggression were present in approximately 24% of dementia patients. Given that the estimates were only considered over 1 month before behavioral assessments and due to the episodic course of this behavioral symptom, Lyketsos et al. (2000) mentioned that these prevalence numbers were an underestimation of the cumulative prevalence which may approach 70–80%. Subsequently, the Cache County Study was resumed in 2003 (Steinberg et al. 2008) in which an incident sample of 408 dementia participants was behaviorally assessed during a 5-year follow-up period. At the end, 42% of dementia participants developed agitation.

In general, agitation mostly occurs in the moderate stages of dementia and less in mild or severe dementia stages (Lyketsos et al. 2000; Cohen-Mansfield et al. 1989). Cohen-Mansfield et al. (1989) make a distinction between physically nonagitated behavior (e.g., restlessness, pacing, cognitive abulia, wandering, inappropriate (dis)robing) and verbally agitated behavior (e.g., negativism, complaining, repetitive sentences or questions, strange noises, unwarranted request for attention).

Aggression has a frequency between 20 and 30% (Allen and Burns 1995) and can be divided into physically aggressive behavior (e.g., hitting, kicking, pushing, scratching, biting) and verbally aggressive behavior (e.g., screaming, cursing) (De Deyn 2004). In general, physically aggressive behavior is more common in male dementia patients compared to females (Cohen-Mansfield and Deutsch 1996). Furthermore, aggression in dementia patients is associated with depression according to Lyketsos et al. (1999).

9.2.3 Diurnal Rhythm Disturbances

Sleep disturbances can be subdivided into difficulties falling asleep, multiple awakenings during sleep, early morning awakenings, or a completely inversed sleep-wake pattern (Prinz et al. 1982). Insomnia in dementia also seems to be the most prominent reason for an eventual institutionalization according to Harper et al. (2001). One specific diurnal rhythm disturbance is *sundowning*, a situation in which patients are relatively calm during the day but as evening falls show an exacerbation of behavioral symptoms, such as pacing, wandering, and repetitive, purposeless activities (cognitive abulia) (Little et al. 1995).

9.2.4 Depression

In AD, depression has a prevalence of 20 (Castilla-Puentes and Habeych 2010) up to 50% (Starkstein et al. 2005). Depression is mostly present in mild-to-moderate AD or even 2 years before the established AD diagnosis (Jost and Grossberg 1996; Alexopoulos et al. 1988). A major depressive episode in dementia is characterized by mood-related signs (anxiety, lack of reactivity to pleasant events, irritability), behavioral symptoms (agitation, retardation (slow movements and speech), loss of interest, physical complaints), physical signs (appetite and weight loss, lack of energy), sleep rhythm disturbances, and ideational disturbances (pessimism, suicidal wishes, poor self-esteem) (Alexopoulos et al. 1988). Besides the behavioral aspects, depression is also characterized by deficits in verbal and visual memory, concentration, and executive functioning (Sierksma et al. 2010). Several research groups have even suggested that depression in general might be a prodrome (i.e., a premonitory symptom indicating the onset of a disease, risk factor) of developing AD (Caraci et al. 2010; Korczyn and Halperin 2009), given the fact that the pathophysiological properties of depression and some etiological hallmarks of AD are related (e.g., increased neuroinflammation, monoaminergic deficiency, increased synaptic neurodegeneration, and altered neurotrophic factors) (Sierksma et al. 2010). Depressed dementia patients also have a higher mortality rate compared to their nondepressed counterparts (Rovner et al. 1991).

9.2.5 Activity Disturbances

According to Reisberg et al. (1987), activity disturbances form a separate entity in the behavioral phenomenology of AD patients among others. Approximately 80% of AD patients suffer from activity disturbances (Engelborghs et al. 2005), which can be best described as a form of physical agitation. Some examples are wandering, purposeless activities (e.g., cognitive abulia, such as repetitive (dis)robing, pacing), and inappropriate activities (inappropriate physical sexual advances, hiding objects, hoarding) (Reisberg et al. 1987). In some cases, activity disturbances are severe enough to require restraint or even result in abrasions (e.g., pacing) or physical harm. Besides AD, FTD patients characteristically suffer from certain types of activity disturbances as well, mainly stereotype movements (e.g., tapping, hand clapping, patting, hand rubbing, wandering a fixed route) and general restlessness (aimless wandering, pacing, fidgeting, inability to sit still) (De Deyn et al. 2005).

9.2.6 Anxieties and Phobias

Although less frequent, anxiety is a psychological symptom in dementia patients which is present in different variants (De Deyn 2004). Anxiety or fear of being left alone and the "Godot syndrome" are two frequent types of anxiety in AD patients (Reisberg et al. 1987). In case of "Godot syndrome," patients repeatedly and

constantly ask questions concerning a completely normal but approaching event such as meeting with the family doctor (Reisberg et al. 1986). This term was firstly described in the late 1980s by Reisberg et al. (1986) and is an extreme form of anxiety in dementia patients and sometimes requires the patient to be accompanied at all times. On the other hand, pacing, stereotype behavior, and restlessness might be physical reflections of a rooted anxiety residing within the patient. A phobia is an anxiety disorder which is disproportional to the actual danger, often being irrational. Examples are fear of traveling, bathing, darkness, and overcrowded places (De Deyn 2004).

9.2.7 Apathy

In the context of dementia, apathy has been defined as a disorder of diminished motivation that persists over time for at least 4 weeks with an additional reduced goal-directed behavior, cognitive activity, and emotions (Robert et al. 2009). These relatively new criteria have been established due to the overlap between apathy and depression among others. Apathy is a common behavioral disorder not only in AD but also in PD, FTD, and stroke (Levy et al. 1998). Results from the *European Alzheimer's Disease Consortium* study in 2007 showed that apathy is the most prominent and persistent neuropsychiatric syndrome in dementia as it occurred in 65% of 2354 AD patients (Aalten et al. 2007). Additionally, it is also present during all stages of the disease (Lyketsos et al. 2011; Robert et al. 2009), and there is a growing body of evidence that it might be indicative of a pre-dementia state (Robert et al. 2009; Ready et al. 2003). More recently, van der Linde et al. (2016) performed a systematic literature review and analyzed the baseline prevalence, persistence, and incidence of 11 BPSD symptoms. In total, 59 studies were included in these analyses. In the end, the authors confirmed that despite heterogeneity across studies in terms of setting, focus, and length of follow-up, apathy was the only symptom with high baseline prevalence, persistence, and incidence during the course of dementia.

9.3 Behavioral Assessment Scales

In order to evaluate this large group of behavioral and neuropsychiatric symptoms in dementia patients, different behavioral assessment scales have been developed throughout the years. The most common are described below, i.e., *Middelheim Frontality Score* (MFS), *Behavioral Pathology in Alzheimer's Disease Rating Scale* (Behave-AD), *Cohen-Mansfield Agitation Inventory* (CMAI), *Geriatric Depression Scale* (GDS), *Cornell Scale for Depression in Dementia* (CSDD), and *Neuropsychiatric Inventory* (NPI). All these scales are very useful assessment tools to identify the behavioral profile of dementia patients or even to distinguish between different types of dementia (De Deyn et al. 2005). The efficacy of novel psychotropic medication in the treatment of BPSD can also be demonstrated by the use of these well-validated and drug-sensitive behavioral scales mentioned above, such as

Behave-AD, CMAI, and NPI (De Deyn and Wirshing 2001). Moreover, these behavioral assessment scales are widely used to study the neuroanatomical and pathophysiological etiology of different behavioral phenotypes in dementia in combination with neuroimaging data.

9.3.1 Middelheim Frontality Score (MFS)

The *Middelheim Frontality Score* (MFS) is a clinical and behavioral assessment tool which measures frontal lobe features and, in contrast to classical behavioral scales, reliably discriminates FTD from AD patients (De Deyn et al. 2005). The MFS is rated by a clinician and is obtained by summating the scores in a standardized fashion on ten different items. Each item is scored either zero (absent) or one (present) yielding a total maximal score of 10. Information is obtained through an interview of the patient and her/his professional and/or main caregiver, clinical files, and behavioral observation. The ten items are (item 1) initially comparatively spared memory and spatial abilities that reflect the neurobehavioral onset of the disease; frequently occurring personality and behavioral changes like (item 2) loss of insight and judgment; (item 3) disinhibition; (item 4) dietary hyperactivity (referring to overeating); (item 5) changes in sexual behavior (hypersexuality as well as the more frequently occurring hyposexuality); (item 6) stereotyped behavior (encompasses all kinds of stereotyped behavior, both simple repetitive behaviors (can also be oral) as complex behavioral routines as wandering); (item 7) impaired control of emotions, euphoria, or emotional bluntness; (item 8) aspontaneity; (item 9) speech disturbances such as stereotyped phrases, logorrhoea, echolalia, and mutism; and, finally, (item 10) restlessness. Although the NPI is able to correctly classify 77% of AD and FTD patients (Levy et al. 1996), the frequently used Behave-AD and CMAI lack sensitivity for FTD as they have been specifically developed for AD patients. The Behave-AD even underestimates BPSD in FTD patients as was shown by Engelborghs et al. (2004): 28 FTD patients had significantly lower Behave-AD total scores compared to 152 AD patients, whereas the Behave-AD global scores (reflecting caregiver burden) were not different between both patient groups. Moreover, Pickut et al. (1997) previously showed that the total MFS scores correlated with severity of bifrontal hyperperfusion on SPECT in FTD.

The discriminatory cut-off score of the MFS is set at a total score of 5 as, respectively, 85.9% and 76.6% of clinically diagnosed FTD and AD patients were correctly classified (De Deyn et al. 2005).

9.3.2 Behavioral Pathology in Alzheimer's Disease Rating Scale (Behave-AD)

In 1987, the *Behavioral Pathology in Alzheimer's Disease Rating Scale* (Behave-AD) was developed to correctly assess and categorize frequently occurring behavioral symptoms of AD patients (Reisberg et al. 1987). The first part of the Behave-AD

comprises 25 items of which each item can be rated from zero (absent) to three (severely present, with emotional and physical component, possibly requiring restricting) with a total maximum score of 75. The second part is the Behave-AD global score which assesses caregiver burden: 0 (not at all troubling to the caregiver or dangerous to the patient), 1 (mildly troubling to the caregiver or dangerous to the patient), 2 (moderately troubling to the caregiver or dangerous to the patient), and 3 (severely troubling to the caregiver or dangerous to the patient). The first 25 items are categorized into 7 behavioral clusters: cluster A (paranoid and delusional ideation: items 1–7), cluster B (hallucinations: items 8–12), cluster C (activity disturbances: items 13–15), cluster D (agitation and aggression: items 16–18), cluster E (diurnal rhythm disturbances: item 19), cluster F (affective disturbances: items 20, 21), and cluster G (anxieties and phobias: items 22–25).

The Behave-AD is a very detailed and relatively simple scale which allows an assessment within a short amount of time (De Deyn 2004). Several studies (Sclan et al. 1996; Patterson et al. 1990) showed that the reliability of the Behave-AD is comparable with those of several widely used cognitive assessment scales, such as the *Mini-Mental State Examination* (MMSE) *(*Folstein et al. 1975*)*. However, one disadvantage of the Behave-AD is its specificity for and usage in exclusively AD patients. Furthermore, only the intensity of the 25 BPSD items is rated (scores 0–3) and not frequency (De Deyn 2004).

9.3.3 Cohen-Mansfield Agitation Inventory (CMAI)

The *Cohen-Mansfield Agitation Inventory* (CMAI) was originally designed for the staff of nursing homes to rate the frequency of agitation and related behaviors in the elderly with cognitive deterioration. This scale assesses 29 types of agitated behavior which are subdivided into three main categories: items 1–10 comprise "aggressive behavior," items 11–21 consist of "physically nonaggressive behavior," and finally items 22–29 are clustered into the category "verbally agitated behavior." Each item is scored depending on its frequency, i.e., from 1 (never) to 7 (several times an hour) (Cohen-Mansfield et al. 1989).

9.3.4 Geriatric Depression Scale (GDS)

The *Geriatric Depression Scale* (GDS) is the eldest scale so far and was designed to estimate depression in non-demented elderly (Yesavage et al. 1983). It takes little or no experience for the investigator to use this scale which consists of 30 questions that are related to depression in the elderly. Each question should be answered with a simple "yes" or "no." A score of 12 or more is indicative of a "light" depression, whereas 18 or more point to moderate depression. Debruyne et al. (2009), using the CSDD as the golden standard, concluded that the GDS-30 is not a reliable screening tool when assessing depressive symptoms in dementia patients but only in patients with MCI and non-demented elderly.

9.3.5 Cornell Scale for Depression in Dementia (CSDD)

The *Cornell Scale for Depression in Dementia* (CSDD) dates from 1988 and is a very useful assessment tool to diagnose depression in dementia (Alexopoulos et al. 1988). The scale is a 19-item clinician-administered instrument that uses information from interviews with both the patient and nursing staff members, a method suitable for dementia patients. Each item is scored based on a three-point scale, i.e., 0 (absent), 1 (mild or intermittent), and 2 (severely present). If it is impossible to rate one of the items, a score remains absent (A: unable to evaluate). All 19 items are subdivided into five main categories:

A. Mood-related signs (anxiety, sadness, lack of reactivity to pleasant events, irritability)
B. Behavioral disturbances (agitation, retardation (slow movements and speech), multiple physical complaints, loss of interest)
C. Physical signs (appetite loss, weight loss, lack of energy)
D. Cyclic functions (diurnal variation of mood, diurnal rhythm disturbances)
E. Ideational disturbances (suicidal ideation, poor self-esteem, pessimism, mood-congruent delusions).

A score of 8 or more is suggestive for the presence of depression (Burns et al. 2004).

9.3.6 Neuropsychiatric Inventory (NPI)

The *Neuropsychiatric Inventory* (NPI) evaluates 12 types of behavioral disturbances that are dementia-specific, i.e., delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria, apathy/indifference, disinhibition, irritability/lability, repetitive purposeless behavior, insomnia/diurnal rhythm disturbances, appetite, or a change in dietary activity (Cummings et al. 1994). The severity and the frequency of these symptoms are rated by a series of questions which are intended for the main caregiver of the patient. The severity score is based on a three-point scale ranging from 1 (mild) to 3 (severe), and the frequency score can vary between 1 (occasionally, less than once a week) and 4 (very frequent, multiple times a day). The scores of each of these 12 behavioral symptoms need to be summed up to obtain a total NPI score. Besides the severity and frequency scores, the level of caregiver distress (emotional burden) of each of the 12 behavioral symptoms requires rating as well. In this case, a scale ranging from 0 (no distress) to 5 (severe and extreme distress) is provided (Kaufer et al. 1998). The total score of "caregiver distress" is yielded by summing up the 12 individual distress subscores.

Because the NPI consists of a gross variety of behavioral symptoms, it is a useful instrument to discriminate between different types of dementia as well as to evaluate the behavioral outcome due to pharmacological interventions (De Deyn 2004; De Deyn and Wirshing 2001). In 2001, a shortened version of the NPI, namely,

NPI-Q (questionnaire), was developed by Kaufer et al. (2000) which facilitates its daily use in a clinical setting. Several other forms of the NPI have also been proposed depending on the informant, such as clinicians (NPI-C) (de Medeiros et al. 2010), or the institutional setting, such as nursing homes (NPI-NH) (Wood et al. 2000). Finally, in 2018, a diary version of the NPI (NPI-Diary) was designed to overcome several shortcomings that are experienced while using the NPI-NH version, such as the tight work schedule of raters in a nursing home setting, resulting in rather arbitrary evaluations, or staff which is undertrained in the domain of neuropsychiatry (Morganti et al. 2018). Another problem is that the NPI is a retrospective caregiver-informant rating (up to 1 month) and that there frequently is insufficient monitoring. For these reasons, the NPI-Diary was created and showed appropriate validity and reliability compared to the NPI-NH, when administered in a highly variable sample, which generally is the case in a healthcare setting (Morganti et al. 2018).

9.3.7 Other Behavioral Assessment Scales

The *Alzheimer's Disease Assessment Scale* (ADAS) is widely used in clinical trials of potential treatments for AD. The cognitive portion of the ADAS (ADAS-Cog) consists of 11 items designed to assess the severity of memory, language, praxis, and orientation impairments. The noncognitive portion of the ADAS (ADAS-Noncog) consists of ten clinician-rated items assessing the severity of depressive symptoms, tearfulness, increased motor activity, hallucinations, delusions, pacing, increased/decreased appetite, agitation, concentration/distractibility, and tremors. Each item is rated on a 1–5 point severity scale, ranging from very mild to severe. The time period for evaluation includes the entire week before the interview (Rosen et al. 1984). An example in which the ADAS-Noncog has been applied to assess the prevalence of BPSD-specific items in AD comes from Fernández et al. (2010).

The *Hamilton Depression Rating Scale* (HDS) is one of the most commonly used depression rating scales. It requires 20–30 min of questions in a semi-structured interview by a trained interviewer and is, therefore, less suitable for usage in people with dementia. It is commonly used in antidepressant drug trials and has a preponderance of psychological rather than physical items (Hamilton 1960).

In 2017, a rating instrument to comprehensively assess the psychopathology in Down syndrome (DS) with or without AD, or with questionable dementia, was developed. In this European multidisciplinary study, the *Behavioral and Psychological Symptoms of Dementia in Down Syndrome* (BPSD-DS) scale identified frequency and severity of behavioral changes taking account of lifelong characteristic behavior in DS individuals. In total, 83 behavioral items in 12 clinically defined sections were evaluated. First exploratory data suggest promising interrater, test–retest, and internal consistency reliability measures. However, further study regarding applicability, reliability, and validity is necessary. Future application of the scale in daily care may aid caregivers to understand changes and contribute to timely interventions and adaptation of caregiving (Dekker et al. 2018).

Another example of a novel scale is the *Abe's BPSD score* (ABS). This swift and simple scoring instrument provides a new simple and quick test for BPSD assessment in mild-to-moderate dementia patients, with a good correlation to NPI but a shorter interview time and with high interrater reliability. A total of ten items are inquired (from wandering, eating or toilet problems, agitation, psychosis, apathy, day-night disturbances, irritability, depression to violent force), with item-specific weighted scores (taking temporal occurrences into account: seldom, occasionally, sometimes, often), varying from 0 to 9, and with a maximum ABS total score of 44 (Abe et al. 2015).

9.4 PET in the Differential Diagnosis of Dementia

Neuroimaging has played an important role in the study and differential diagnosis of dementia over the last 40 years. Positron emission tomography (PET) studies of cerebral metabolism with fluorine-18 (^{18}F)-labeled fluorodeoxyglucose (FDG) and amyloid tracers such as the carbon-11 (^{11}C)-labeled *Pittsburgh Compound-B* (PiB), and, since 2012, ^{18}F-labeled florbetapir, florbetaben, and flutemetamol, have provided invaluable information regarding specific AD-like brain changes ((Johnson et al. 2012); for review, see (Iaccarino et al. 2017)). Even in prodromal and presymptomatic states, PET imaging has emerged as a robust biomarker of neurodegeneration in individuals who were later found to progress to AD (de Leon et al. 2001; Bateman et al. 2012). Bateman et al. (2012), for instance, detected early Aβ deposition in the precuneus of 128 autosomal dominant AD patients measured by PET-PiB nearly 15 years before expected symptom onset, indicating PET imaging to be an essential and reliable imaging tool not only in the differential diagnosis between AD and non-AD dementias but even for asymptomatic disease states. One of the most recent advances of in vivo PET imaging from 2012 onward is the evaluation of tau burden in AD and non-AD. To date, four broad groups of tau PET radioligands are evaluated, i.e., ^{18}F-THK5351, ^{18}F-THK5117/5105, ^{18}F-AV1451/^{18}F-T807 (better known as ^{18}F-flortaucipir), and ^{11}C-PBB3.

Table 9.2 comprises a non-exhaustive list of the most frequently studied radiotracers for both PET- and SPECT-based analysis of AD pathophysiology and AD differential diagnostics (apart from ^{18}F-FDG for PET and ^{99m}Tc-HMPAO for SPECT).

9.4.1 Radioligands and Compounds

Brain FDG-PET primarily indicates synaptic activity. Because the brain relies almost exclusively on glucose as its main energy resource, the glucose analog FDG is suitable as indicator of brain metabolism and, when labeled with ^{18}F (half-life 110 min.), is detected with PET. Studies support the notion that astrocytes play a central role in neuronal glucose consumption. Decrease of ^{18}F-FDG-PET uptake is considered to be a direct index of synaptic dysfunction, which can result from a variety of neuropathological events, including but not limited to altered intracellular

Table 9.2 Most frequently used radiotracers designed for PET- and SPECT-based analysis of AD pathophysiology

Radiotracer	Half-life	Common name	Modality	Target	Category/ condition
^{11}C-PiB	20 min	Pittsburgh Compound-B	PET	Aβ	AD
^{11}C-AZD2184	20 min		PET	Aβ	AD
^{18}F-FDDNP	110 min		PET	Aβ and tau	AD
^{18}F-AV-45	110 min	Florbetapir	PET	Aβ	AD
^{18}F-BAY94-9172	110 min	Florbetaben	PET	Aβ	AD
^{18}F-GE067	110 min	Flutemetamol	PET	Aβ	AD
^{18}F-AZD4694	110 min		PET	Aβ	AD
^{11}C-BF-227	20 min		PET	Aβ	AD
^{11}C-SB-13	20 min		PET	Aβ	AD
^{123}I-SB-13	13.2 h		SPECT	Aβ	AD
^{123}I-IMPY	13.2 h		SPECT	Aβ	AD
^{18}FTHK5105	110 min		PET	Tau	AD/tauopathies
^{18}F-THK5107	110 min		PET	Tau	AD/tauopathies
^{18}F-T807/^{18}F-AV1451	110 min	Flortaucipir	PET	Tau	AD/tauopathies
^{18}F-T808	110 min		PET	Tau	AD/tauopathies
^{11}C-PBB3	20 min		PET	Tau	AD/tauopathies
^{11}C-THK5351	20 min		PET	Tau	AD/tauopathies
^{18}F-THK5351	110 min		PET	Tau	AD/tauopathies
^{11}C-PK11195	20 min		PET	PBR-TSPO	Neuroinflammation
^{123}I-PK11195	13.2 h		SPECT	PBR-TSPO	Neuroinflammation
^{18}F-DPA714	110 min		PET	PBR-TSPO	Neuroinflammation
^{11}C-PMP	20 min	Methylpiperidin	PET	AChE	Neurochemistry
^{18}F-FDOPA	110 min	Fluorodopa	PET	DA	Neurochemistry (dd. PD)
^{11}C-MRB	20 min	Methylreboxetine	PET	NET	Neurochemistry
^{123}I-FP-CIT	13.2 h	Ioflupane—DaTscan	SPECT	DAT	Neurochemistry (dd. PD)
^{123}I-β-CIT	13.2 h		SPECT	DAT	Neurochemistry (dd. PD)
^{123}I-IBVM	13.2 h	Iodobenzovesamicol	SPECT	VAChT	Neurochemistry
^{123}I-IDEX	13.2 h	Iododexetimide	SPECT	mAChR	Neurochemistry
^{123}I-5-I-R91150	13.2 h		SPECT	5-HT$_{2A}$	Neurochemistry

Abbreviations: *5-HT$_{2A}$* Serotonin (5-hydroxytryptamine) 2A receptor, *Aβ* Amyloid-beta, *ACh* Acetylcholine, *AChE* ACh Esterase, *AD* Alzheimer's disease, *DA* Dopamine, *DAT* DA transporter, *dd* Differential diagnosis, *mAChR* Muscarinic ACh receptor, *NET* Norepinephrine transporter, *PBR-TSPO* Peripheral benzodiazepine receptor-translocator protein, *PD* Parkinson's disease, *VAChT* Vesicular ACh transporter. Partly adapted with permission from Arora A and Bhagat N (2016) *Int J Biomed Imaging* 2016:7462014 under the CC-BY license 4.0 (http://creativecommons.org/licenses/by/4.0). Copyright © 2016 Arora A and Bhagat N

signaling cascades and mitochondria bioenergetics, impaired neurotransmitter release, and accumulation of neurotoxic protein species (for review, see (Iaccarino et al. 2017)). Especially the glutamatergic synaptic signaling is responsible for the maintenance of intrinsic, resting (task-independent) activity of the cerebral cortex, which, most of the time, is the brain's main task (Johnson et al. 2012; Sibson et al. 1997). Therefore, ^{18}F-FDG-PET is widely accepted to be a valid biomarker of the overall brain metabolism to which ionic gradient maintenance for synaptic activity is the most principal contributor (Schwartz et al. 1979; Magistretti 2006). The characteristic pattern found in AD generally is a hypometabolism of the temporoparietal cortex (Herholz et al. 2002; Ferreira and Busatto 2011) and specific limbic and association areas, such as the precuneus, posterior cingulate gyri, inferior parietal lobes, posterolateral portions of the temporal lobe, as well as the hippocampus and medial temporal cortices (Foster et al. 1983; Minoshima et al. 1997; Reiman et al. 2005). An asymmetry between both hemispheres is commonly seen in early stages of AD, whereas in a more advanced stage of the disease, usually the prefrontal association areas become affected (Johnson et al. 2012).

A meta-analysis showed that hypometabolism of the inferior parietal lobes and precuneus is the most striking neurological finding on FDG-PET imaging in AD patients compared to non-demented elderly (Schroeter et al. 2009). Moreover, longitudinal neurofunctional imaging studies have demonstrated hypometabolism in the parietal lobe of MCI converters in comparison with those who did not convert to AD (Schroeter et al. 2009). In conclusion, FDG-PET can be useful in cases of diagnostic uncertainty and has even shown to be valuable in distinguishing AD from FTD (Foster et al. 2007). However, it is advisable to always combine FDG-PET findings with imaging data of other neuroimaging or biomarker techniques, as FDG-PET alone does not allow an adequate evaluation of the brain structure (Waldemar et al. 2007). For instance, complementary ^{18}F-FDG- and ^{11}C-PiB-PET scanning improves diagnostic accuracy of AD vs. non-AD from 76 to 94%, as shown by Hellwig et al. (2019). Moreover, the combination of FDG-PET with CSF biomarker analyses of $A\beta_{1–42}$, T-tau, and P-tau_{181P} levels highly improves clinical diagnostic accuracy, of which in particular T-tau deposition in brain is related to temporal, parietal, and frontal hypometabolism in AD (Perani et al. 2016; Chiaravalloti et al. 2018).

The pathological hallmark in the AD brain is the extracellular deposition of senile plaques and Aβ aggregates. Consequently, a second strategy to visualize AD pathology is not based on glucose metabolism, but on a synthesized derivate which in vivo binds Aβ, such as the N-methyl[^{11}C]2-(4′methylaminophenyl)-6-hydroxybenzothiazole, also known as "Pittsburgh Compound-B" (PiB) (Mathis et al. 2002). Amyloid imaging tracer compounds have binding properties for Aβ in the nanomolar range and are derivatives of histological dyes, such as Congo Red, thioflavin S and T, acridine orange, and chrysamine-G, or based on other molecules such as styrylbenzene ((Suhara et al. 2008); for review, see (Adlard et al. 2014)). PET studies using PiB labeled with ^{11}C showed that amyloid deposition already occurs years before the clinical diagnosis of dementia (Chetelat et al. 2010); is related to cortical atrophy rate, as well as cognitive decline (Braskie et al. 2010); and is more present

in MCI converters compared to non-converters (Forsberg et al. 2008). Peretti and colleagues even concluded that regional cerebral blood flow (rCBF) estimates from pharmacokinetic analysis of PiB scans might be a good alternative to an additional FDG-PET scan, thus bypassing the limitations of a dual examination (Peretti et al. 2019). One concern, however, is the short half-life of PiB labeled with ^{11}C (20 min.), which renders its use in some diagnostic clinical settings more difficult. Consequently, attempts were made to develop an amyloid-sensitive, radioactive-labeled Aβ tracer with longer half-life, such as ^{18}F-florbetapir (^{18}F-AV-45) (Choi et al. 2009; Wong et al. 2010), which has been approved by the US Food and Drug Association (FDA) on April 6, 2012, for the clinical evaluation of patients suspected with AD and other related syndromes. Various studies have compared the diagnostic utility of ^{18}F-florbetapir-PET compared to ^{11}C-PiB-PET (Wolk et al. 2012) and the commonly used ^{18}F-FDG-PET (Newberg et al. 2012), concluding that ^{18}F-florbetapir-PET produced comparable results in discriminating AD patients from cognitively normal adults. Next, Doraiswamy et al. (2012) proved that ^{18}F-florbetapir-PET may help in identifying individuals who are at increased risk of progressive cognitive decline. On the contrary, a recent study from Khosravi et al. (2019) concluded that ^{18}F-FDG-PET global quantification is a superior indicator of cognitive performance in AD and MCI patients compared to ^{18}F-florbetapir-PET. Accordingly, the authors still recommend ^{18}F-FDG-PET over amyloid imaging in the evaluation of AD and MCI. A tracer similar to florbetapir is florbetaben (BAY 94-9172). This ^{18}F-PET marker for Aβ imaging proved to have a sensitivity and specificity of 80 and 91% in an AD versus control comparison (Barthel and Sabri 2011). More importantly, ^{18}F-florbetaben could play a substantial role in the differential diagnosis of AD vs. PD(D)/DLB or AD vs. FTD. As an example, the radiotracer demonstrated a lower overall retention in DLB patients in spite of similar involvement of Aβ compared to AD subjects (Villemagne et al. 2011). Last in the series of most commonly used ^{18}F-labeled amyloid PET imaging tracers is ^{18}F-flutemetamol (^{18}F-GE067). Earlier work demonstrated similar findings of ^{18}F-flutemetamol in probable AD and MCI patients relatively to healthy controls with a similar performance as ^{11}C-PiB within the same subjects (Vandenberghe et al. 2010). Additionally, Wolk et al. (2011) demonstrated a high correspondence between immunohistochemical estimates of Aβ levels in brain tissue of seven AD patients who underwent previous biopsy and in vivo quantitative measures of ^{18}F-flutemetamol uptake at the location contralateral to the biopsy site (i.e., right frontal), supporting its sensitivity to detect Aβ and its use in the study and early detection of AD. Taken together, ^{11}C-PiB and ^{18}F-flutemetamol show similar topographical gray matter uptake in AD and cognitively normal participants, and the tracers show comparable group discrimination. The key disadvantage of such a class of ^{18}F-labeled amyloid radiotracers, however, is that they generate greater levels of nonspecific background noise and higher nonspecific uptake in white matter (also visible in elderly controls) in comparison with ^{11}C-PiB (Lowe et al. 2017).

Amyloid in vivo imaging is a very promising approach, with, currently, all three radiotracers (florbetapir, florbetaben, flutemetamol) approved by the FDA for their diagnostic utilities. At the same time, one should keep in mind that amyloid PET

imaging is restricted to specialized centers around the world, even though it seems that it is becoming more and more implemented in the routine diagnostic workup and differential diagnosis of AD patients (Witte et al. 2015).

Besides amyloid deposits, intracellular NFT consisting of tau protein are a pathological feature of AD as well. The development of PET probes for in vivo imaging of NFT has become an active research field from 2012 onward (Ono and Saji 2012). The first ^{18}F-labeled compound that was synthesized in order to bind NFT was ^{18}F-2-(1-(2-(*N*-(2-fluoroethyl)-*N*-methylamino)naphthalene-6-yl)ethylidene)malononitrile (FDDNP) (Agdeppa et al. 2001; Barrio et al. 1999). Interestingly, FDDNP does exclusively bind not only NFT but also senile Aβ plaques. A more recent tau imaging probe is 2-((1*E*,3*E*)-4-(6-((^{11}C-methylamino)pyridine-3-yl)buta-1,3-dienyl) benzo[d]thiazol-6-ol, better known as ^{11}C-PBB3 (Maruyama et al. 2013). Chiotis et al. (2018) have observed that if compared with ^{11}C-labeled THK5351, ^{11}C-PBB3 appeared to preferentially bind to tau deposits with a close spatial relationship to Aβ, whereas the binding pattern of ^{11}C-THK5351 fitted the expected distribution of tau pathology in AD better and was more closely related to downstream disease markers. The latest tau PET tracer is ^{18}F-AV1451/^{18}F-T807, better known as ^{18}F-flortaucipir. This tracer showed high specific binding in AD, moderate binding in Pick's disease and FTD with parkinsonism-17, and low but displaceable binding in CBD, PSP, and non-tau proteinopathies (Sander et al. 2016). Evidence for a non-tau binding site and lack of correlation between tracer binding and antibody staining suggest that reliable quantification of tau load with this tracer is still somewhat problematic.

These first generations of tau tracers often suffer from off-target binding in the basal ganglia, midbrain, thalamus, choroid plexus, and venous sinus, and ^{11}C-THK5351 may even bind monoamine oxidase B in disease-associated brain regions linked to neurodegeneration (Okamura et al. 2018).

Another approach to visualize AD pathology using PET as an imaging tool is the in vivo mapping of altered neurochemical processes which are typical in the AD brain, such as cholinergic denervation (Van Dam and De Deyn 2006). One example is N-^{11}C-methylpiperidin-4-yl propionate, known as ^{11}C-PMP (Kuhl et al. 1999). This radiopharmaceutical is used in PET imaging to determine the activity of the cholinergic neurotransmitter system by acting as a substrate for acetylcholinesterase. Besides the cholinergic neurotransmission, PET imaging with radioligands that are involved with several other neurotransmitter systems or receptors such as substrates for DA or serotonin (5-HT) signaling has provided important insights into several neurodegenerative disorders (Bohnen and Frey 2007) and has even helped in distinguishing AD from DLB and PD (Tatsch 2008). A frequently used radiotracer in this regard is ^{18}F-fluorodopa. As a fluorinated form of levodopa (i.e., the precursor of DA), ^{18}F-fluorodopa-PET is a valid method for assessing the functional state of the nigrostriatal dopaminergic pathway. It is particularly useful for studies requiring repeated measures such as examinations of the course of a disease and the effect of treatment. Studies using ^{18}F-fluorodopa-PET have also distinguished DLB from AD with a sensitivity of 86% and a specificity of 100% (Hu et al. 2000). Another brain region of particular neurochemical interest in AD, PD/DLB, and DS with(out)

AD—also in the study of BPSD—is the LC, which is the brain's main source of norepinephrine (NE) (Herrmann et al. 2004; Vermeiren and De Deyn 2017). Using PET, the NE transporter (NET) can be studied in vivo. In this regard, the most suitable radiotracer is ^{11}C-methylreboxetine (^{11}C-MRB). This compound is derived from reboxetine, primarily used as an antidepressant. Reboxetine is an NE reuptake inhibitor, binds to NET, and thus allows for accurate localization and quantification. So far, ^{11}C-MRB-PET has been used successfully in previous studies investigating the NE system, such as in healthy volunteers (Smith et al. 2014), patients with posttraumatic stress disorder (Pietrzak et al. 2013), PD patients (Sommerauer et al. 2018), and subjects suffering from depression (Yatham et al. 2018). Collectively, results show that ^{11}C-MRB-PET allows for differential characterization of NET concentration in examined NET-rich brain regions, including the LC, and correlates well with the clinical profile (e.g., Hoehn and Yahr staging in PD) (Sommerauer et al. 2018). The first pioneering study that will apply ^{11}C-MRB-PET in AD compared to PD, DS (with)out AD, and healthy controls to examine its potential diagnostic usage is on its way (see Acknowledgments section, JPND-HEROES).

Noteworthy, ^{11}C-PK11195 is the most successful radiotracer for PET-based neuroinflammation studies, since it specifically binds to the 18 kDa translocator protein (TSPO), also known as the peripheral benzodiazepine receptor (PBR). In normal physiological conditions, TSPO has only a basal expression in the microglial cells. However, when the microglia undergo inflammatory activation, PBR-TSPO expression is upregulated, thereby functioning as a putative biomarker for neuroinflammation. In 2001, it was investigated that there was a high localization of the radiotracer in the cingulate cortex (CC), amygdala, fusiform gyrus, and temporoparietal cortex of AD patients compared to aged healthy controls, triggering further investigation ((Cagnin et al. 2001); for review, see (Arora and Bhagat 2016)). The modified version of ^{11}C-PK11195 is ^{123}I-PK11195, with a significant longer half-life (Table 9.2) and is applied in SPECT to study neuroinflammation in dementia (cfr. Sect. 9.6.4).

Similar PET tracers related to all kinds of pathophysiological aspects of AD are enlisted in Table 9.2.

Please visit http://www.clinicaltrials.gov/ to look for ongoing clinical trials that concern the development of novel PET probes related to amyloid and tau imaging, or other neurodegenerative disease markers of interest, for the differential diagnosis of dementia.

9.5 PET Imaging in Neuropsychiatric Disturbances of Dementia

9.5.1 Alzheimer's Disease and Mild Cognitive Impairment

9.5.1.1 Depression

Loss of neurons in the serotonergic raphe nuclei and dysfunction of its nerve terminals in the neocortex have been reported in AD (Mann and Yates 1983; Palmer et al.

1987). Many lines of evidence suggest this serotonin (5-HT) deficiency to be strongly related with mood disorders in dementia patients and non-demented elderly (Sierksma et al. 2010). In vivo imaging studies that used PET have so far focused on 5-HT-receptors in the limbic brain regions associated with cognitive impairment in AD (Kepe et al. 2006; Meltzer et al. 1998). Ouchi et al. (2009) used a set of two different biomarkers in mild-to-moderate stage AD patients with and without depression to investigate the levels of presynaptic serotonergic function and cortical neuronal activity using PET with ^{11}C-DASB (^{11}C-3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile), a specific 5-HT transporter marker, and the more common ^{18}F-FDG-PET. Because the 5-HT transporter is located on presynaptic 5-HT terminals and regulates 5-HT signaling, levels of ^{11}C-DASB binding in these regions thus reflect the activity of presynaptic 5-HT neurons in the dorsal raphe nuclei. Thomas et al. (2006) previously found a marked reduction in the binding of 5-HT transporter levels in the prefrontal cortex of AD patients ($n = 14$) compared to control subjects ($n = 10$) and non-demented depressed subjects ($n = 8$), but not between depressed ($n = 9$) and nondepressed ($n = 5$) AD patients. Contrastingly, Ouchi et al. (2009) observed a negative correlation between ^{11}C-DASB binding potential levels in the subcortical serotonergic projection region (striatum) and GDS scores ($n = 15$) (Spearman rank-order correlation, $P < 0.01$), as well as significantly lower ^{11}C-DASB binding potential levels in AD patients, irrespective of depression, compared to healthy controls ($n = 10$) in the putamen, thalamus, and midbrain ($P < 0.05$). Consequently, Ouchi et al. (2009) suggested that a certain degree of presynaptic 5-HT function in the subcortical 5-HT projection region is compromised in AD patients even before the development of depression. Also, statistical parametric mapping (SPM) correlation analysis showed that glucose metabolism in the right dorsolateral prefrontal cortex was positively associated with the levels of striatal ^{11}C-DASB binding, suggesting that right dorsolateral prefrontal dysfunction in parallel with 5-HT inactivation is also implicated in the progression of emotional and cognitive deterioration in AD.

Holthoff et al. (2005) performed cerebral glucose metabolism measurements applying ^{18}F-FDG-PET in 53 AD patients. Neuropsychiatric symptoms were assessed using the NPI (Cummings et al. 1994), of which depression and apathy were the most frequently encountered of all symptoms. The group of depressed AD patients ($n = 10$) showed hypometabolism in left and right dorsolateral prefrontal regions (Brodmann area (BA) 6 and 45) in comparison with nondepressed AD patients ($n = 10$) ($P < 0.02$) (Fig. 9.5) (Holthoff et al. 2005).

The combination of ^{18}F-florbetapir-PET imaging, to assess brain amyloid load, with ^{18}F-FDG-PET has been attempted by Brendel et al. (2015). The researchers examined depressive symptoms by applying NPI-Q in 371 MCI subjects from the *Alzheimer's Disease Neuroimaging Initiative* (ADNI) study, dividing groups into Aβ-positive (Aβ+, 206 patients) or Aβ-negative (Aβ−, 165 patients) according to the ^{18}F-florbetapir-PET scanning, with a mean follow-up time of 21.5 months. The authors revealed that Aβ+ MCI subjects with depressive symptoms showed higher amyloid load in the left superior temporal gyrus, left uncus, left gyrus parahippocampalis, left insula, and left CC ($P < 0.001$), as well as in the left medial frontal

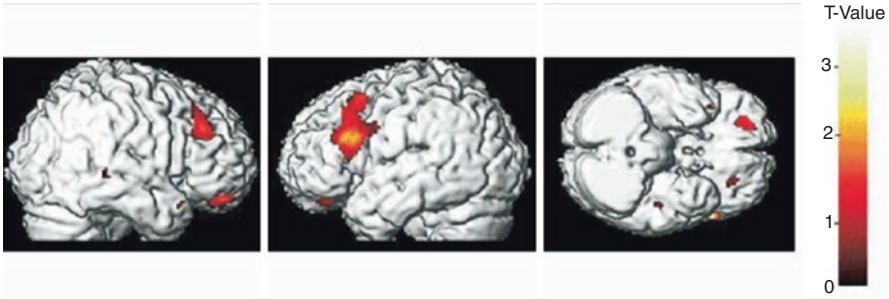


Fig. 9.5 Overlay images of the significant decreases in regional cerebral glucose metabolism in depressed AD patients ($n = 10$) compared to nondepressed AD patients ($n = 10$). Overlay of significant decreases in glucose metabolism by ^{18}F-FDG-PET in left and right dorsolateral prefrontal regions (BA6 and 45) of AD patients with clinically significant depression compared with AD patients free of depression on an MRI template (SPM analysis, $P < 0.05$, corrected). The left image displays the right hemisphere; in the middle, the left hemisphere is displayed; and, finally, the right image visualizes the caudal view of the brain. Abbreviations: *AD* Alzheimer's disease, *BA* Brodmann area, *^{18}F-FDG-PET* ^{18}F-fluorodeoxyglucose positron emission tomography, *MRI* Magnetic resonance imaging. Reprinted from Holthoff VA et al. (2005) Biol Psychiatry 57:412–421, with permission from Elsevier. Copyright © 2005 Elsevier Inc

and rectal gyrus ($P < 0.005$), compared to those without depression. Significantly lower levels of amyloid were found in a small cluster of the right cuneal cortex ($P < 0.001$). Corresponding FDG-PET data showed relative hypermetabolism in the bilateral frontal lobes, as well as in the left fusiform gyrus ($P < 0.001$). Hypometabolism was found in a small cluster of the left cuneal cortex (Fig. 9.6). Among Aβ− MCI subjects with depressive symptoms, small clusters with lower amyloid deposition in bilateral temporal, left precentral, and right inferior frontal gyri were seen compared to nondepressed MCI individuals. Both the depressed MCI subjects and the Aβ+ MCI subjects showed significantly faster progression to AD than their respective counterparts. The fastest progression rate was found in Aβ+ depressed MCI subjects.

In 2016, Ballarini et al. (2016) looked into the metabolic profile of depression in early-onset AD and generally assessed for BPSD using the NPI in 27 early-onset AD subjects (mean age of 58), subclustering the NPI into four subsyndromes (apathetic, hyperactive, affective, and psychotic subsyndromes). The authors further explored whether there was any association between ^{18}F-FDG-PET regional and connectivity-based brain metabolic dysfunctions and subsyndromes. Surprisingly, the affective subsyndrome was correlated with an increase of glucose metabolism in the left and right anterior CC and superior frontal gyrus, extending to the supplementary motor area.

Briefly, it seems that depression in MCI or prodromal/early-onset AD is manifested by a hypermetabolic (Brendel et al. 2015; Ballarini et al. 2016) or hypometabolic state (Holthoff et al. 2005) of frontal cortices and the anterior CC, a contradiction which, perhaps, necessitates further investigation. On the contrary, SPECT studies largely agree on the theory of hypoperfusion in depression in AD

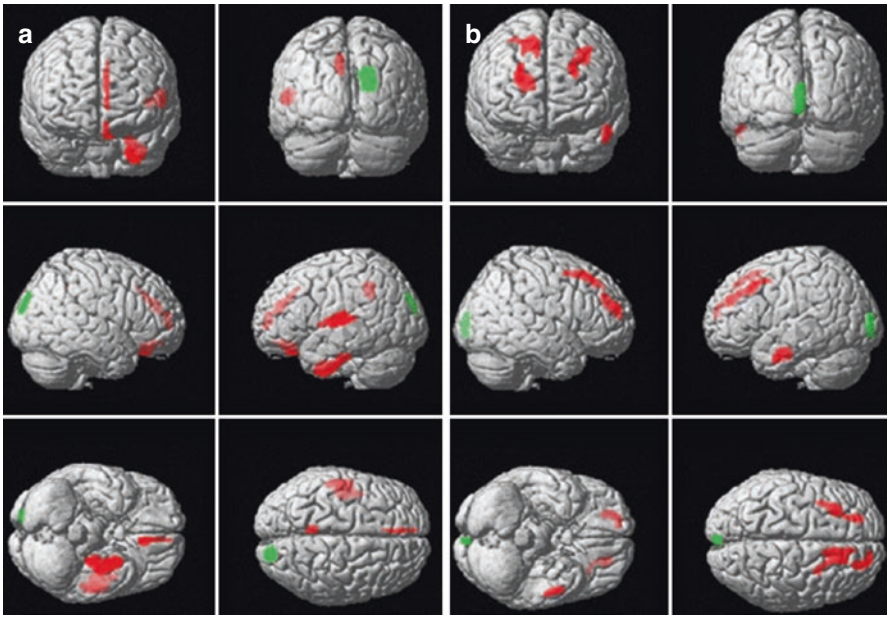


Fig. 9.6 Statistical parametric mapping (SPM) for ^{18}F-Florbetapir-PET (**a**) and ^{18}F-FDG-PET (**b**) in Aβ+ MCI subjects corrected for MMSE score, age, gender, APOE ε4 allelic status, and years of education. Subsyndromally depressed MCI subjects ($N = 65$) are contrasted with nondepressed MCI subjects ($N = 141$). Voxels exceeding a significance threshold of $P < 0.005$ (uncorrected for multiple comparisons, cluster size >100) for increased amyloid levels (**a**) or FDG hypermetabolism (**b**) in depressed MCI subjects are indicated in *red*, while voxels of decreased amyloid levels (**a**) or FDG hypometabolism (**b**) in depressed MCI subjects are indicated in *green*. Both contrasts are rendered on the surface of the standard SPM8 template. Abbreviations: *Aβ* Amyloid-beta, *APOE* Apolipoprotein E, *FDG* Fluorodeoxyglucose, *MCI* Mild cognitive impairment, *MMSE* Mini-Mental State Examination; *SPM* Statistical parametric mapping. Reprinted from Brendel et al. (2015) Eur J Nucl Med Mol Imaging 42:716–724, with permission from Springer. Copyright © 2015 Springer-Verlag Berlin Heidelberg 2015

(cfr. Sect. 9.7.1.1). In this regard, Ashraf et al. (2015) theorized that hypermetabolism in MCI might be indicative of a greater adaptive plasticity as a potential compensatory mechanism before Aβ has been sufficiently deposited.

9.5.1.2 Apathy

In the abovementioned study by Holthoff and colleagues (2005), apathy was rated too by means of the NPI, and it appeared to be one of the most frequent BPSD. The authors further evidenced that the apathetic AD group ($n = 17$) had significant hypometabolism in left orbitofrontal regions (BA10 and BA11) compared to non-apathetic AD patients ($n = 17$) ($P < 0.008$) (Fig. 9.7). In addition to the results of Ballarini et al. (2016) examining depression in early-onset AD (described in Sect. 9.5.1.1), they also found that apathetic subscores were inversely correlated with FDG uptake in the bilateral orbitofrontal and dorsolateral frontal cortex, known to

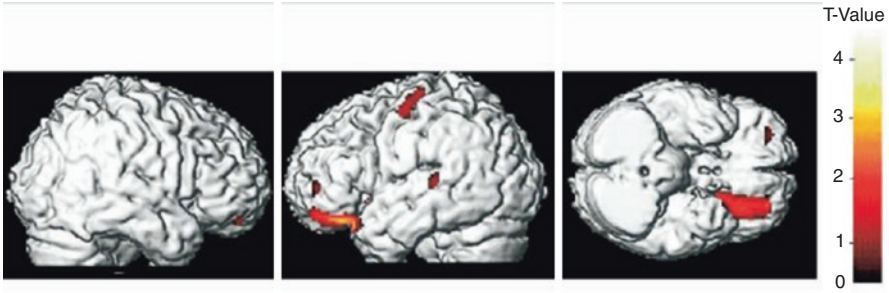


Fig. 9.7 Overlay images of the significant decreases in regional cerebral glucose metabolism in AD patients with clinically significant apathy (n = 17) compared to AD patients free of apathy (n = 17). Overlay of significant decreases in glucose metabolism by ^{18}F-FDG-PET in left orbitofrontal regions (BA10 and 11) of AD patients with clinically significant apathy compared with AD patients free of apathy on an MRI template (SPM-analysis; $P < 0.05$, corrected). The left image displays the right hemisphere; in the middle, the left hemisphere is displayed; and, finally, the right image visualizes the caudal part of the brain. Abbreviations: *AD* Alzheimer's disease, *BA* Brodmann area, *^{18}F-FDG-PET* ^{18}F-fluorodeoxyglucose positron emission tomography, *MRI* Magnetic resonance imaging. Reprinted from Holthoff VA et al. (2005) Biol Psychiatry 57:412–421, with permission from Elsevier. Copyright © 2005 Elsevier Inc

be involved in motivation and decision-making processes. Results are similar to those of Holthoff et al. (2005) and, again, point to the orbitofrontal cortex as an important key brain region that modulates apathetic behavior in AD.

Recently, similar neuroimaging research into apathy has been performed, albeit in MCI subjects. For instance, baseline data from 65 MCI participants (11 with apathy and 54 without) from the ADNI study were analyzed. All participants underwent a comprehensive cognitive and neuropsychiatric assessment, volumetric MRI, and measures of cerebral glucose metabolism applying ^{18}F-FDG-PET. The presence of apathy at baseline was determined by the NPI-Q. Compared with the apathy-free MCI patients, MCI patients with apathy had significantly decreased metabolism in the left and right posterior CC (BA31, $P < 0.001$). The authors further implied that apathy may belong to the spectrum of prodromal AD symptoms, since early metabolic reductions in the posterior cingulate are hypothesized to represent a more specific marker of AD than hippocampal atrophy and hypometabolism (Delrieu et al. 2015).

Similar to depression in AD/MCI, apathy seems to be characterized by a metabolic dysfunction in alike brain regions, i.e., the CC (Ballarini et al. 2016) or dorsolateral frontal/orbitofrontal cortices (Holthoff et al. 2005; Delrieu et al. 2015). The only difference is that, for apathy, a hypometabolic state has been measured thrice following FDG-PET (Holthoff et al. 2005; Ballarini et al. 2016; Delrieu et al. 2015), whereas in depression, both increases and decreases in FDG uptake have been found.

9.5.1.3 Psychosis

As described above, psychosis is a distinct AD syndrome and includes the presence of at least one (or more) hallucination(s) and/or delusion(s) (Jeste and Finkel 2000).

Hirono et al. (2000) studied the neuroanatomical basis of delusions in AD using ^{18}F-FDG-PET to measure cerebral glucose metabolism in 65 mild-to-moderate probable AD patients. The Behave-AD or NPI were used to assess for delusions, categorizing 26 patients as being delusional while 39 as not delusional. Surprisingly, a significant increase in glucose metabolism in the left inferior temporal gyrus and a significant decrease in the left medial occipital region in delusional AD patients were observed when compared to their non-delusional counterparts.

Sultzer et al. (2003) similarly used FDG-PET and identified three specific regions in the right frontal cortex of 25 AD patients which were strongly associated with the *Neurobehavioral Rating Scale* delusion scores, i.e., the right superior dorsolateral frontal region (BA8) (hypometabolism), the right inferior frontal pole (BA10) (hypometabolism), and the right lateral orbitofrontal region (BA47) (hypometabolism), confirming a link between delusional ideation and right hemispheric pathology.

A similar study that examined the link between psychosis in AD and altered brain metabolism was performed by Koppel et al. (2014). In this study, 21 ADNI participants with AD who developed psychotic symptoms during the study but were not psychotic at baseline were matched with 21 participants with AD who never became psychotic during the study period, and mean brain ^{18}F-FDG-PET cerebral metabolic glucose rates by regions of interest (ROI) were compared. Additionally, 39 AD participants with active psychosis at the time of image acquisition were matched with 39 participants who were never psychotic during the study period, and mean brain FDG-PET cerebral metabolic glucose rates by ROI were, again, compared. The authors found no regional brain metabolic differences between those with AD destined to become psychotic and those who did not become psychotic. There was, however, a significant reduction in mean orbitofrontal brain metabolism in those with active psychosis.

Reeves et al. (2009) tested if delusions were associated with striatal DA D2/D3 receptor function in AD. The investigators used in vivo ^{11}C-raclopride-PET imaging (^{11}C-RAC-PET) in 23 patients with mild-to-moderate probable AD who underwent behavioral assessment by means of the NPI. They found that the mean ^{11}C-RAC-PET binding potential levels for striatal DA D2/D3 receptors were higher in AD patients with (n = 7 of which 5 were men) than without (n = 16 of which 6 were men) delusions. When women were excluded from the analysis, striatal ^{11}C-RAC-PET binding potential levels were still higher in delusional male AD patients compared to male AD subjects without delusions (P = 0.05). Furthermore, these results were comparable with the dopaminergic D2/D3 receptor availabilities of drug-naïve schizophrenia patients.

9.5.1.4 Agitation

Only one study so far has looked into the neurobiological correlates of agitation in AD using PET, in which a total of 85 outpatients with mild-to-moderate AD were recruited from the *VA Greater Los Angeles Healthcare System Geropsychiatry Outpatient Program (*Weissberger et al. 2017*)*. A cross-sectional investigation was conducted of the relationship between cerebral glucose metabolism measured via

^{18}F-FDG-PET and agitated symptoms from the NPI. Two empirically derived clusters of agitation symptoms were investigated: an *agitation factor*, comprising agitation/aggression and irritability/lability items of the NPI, and a *behavioral dyscontrol factor*, comprising elation/euphoria, disinhibition, aberrant motor behavior, sleep, and appetite items of the NPI. Mean cerebral metabolism for patients who scored positively on each of the two factors was compared with mean cerebral metabolism for those who did not. Patients with AD who scored positively on the *agitation factor* showed reduced glucose metabolism of the right temporal, right frontal, and bilateral CC. In contrast, the *behavioral dyscontrol factor* did not show specific neurobiologic correlates. These results warrant further study and confirmation.

9.5.1.5 Other Behavioral Disturbances

It becomes clear from the collective PET neuroimaging evidence that psychiatric and behavioral symptoms in dementia are not random consequences of diffuse brain illness, but are fundamental expressions of regional cerebral pathological events (Sultzer 1996). Tanaka et al. (2003) showed that a dysfunction of the striatal dopaminergic D2 receptor metabolism, characterized by significantly lowered ^{11}C-RAC-PET binding potential levels, is manifested in AD patients with more severe Behave-AD *Frequency Weighted Severity Scale* scores (Monteiro et al. 2001) compared to AD patients without BPSD. This study, however, comprised no more than ten AD patients and only reported Behave-AD total scores.

Ng et al. (2017) performed a longitudinal observation of 115 cognitively normal individuals stratified by hallmark AD biomarkers to identify individuals with preclinical AD with the highest risk of progression to clinical AD and tested the hypothesis that BPSD are associated with metabolic abnormalities in limbic regions and predict conversion. Both ^{18}F-florbetapir-PET and phosphorylated CSF tau biomarkers were used for stratification. Furthermore, regression and voxel-based regression models evaluated the relationships between baseline BPSD measured by the NPI and baseline and 2-year change in metabolism measured by ^{18}F-FDG-PET. Collectively, the researchers found that the magnitude of BPSD is linked to a transient metabolic dysfunction in limbic networks that are vulnerable to early AD pathophysiology in individuals with preclinical AD. Initially, individuals with preclinical AD with higher NPI scores had higher FDG uptake in the posterior CC, ventromedial prefrontal cortex, and right anterior insula at baseline, but high NPI scores predicted subsequent hypometabolism in the posterior CC over 2 years only in the individuals with preclinical AD. Moreover, this metabolic shift was driven by the sleep/nighttime behavioral disorders and irritability components of the NPI.

Apart from depression and apathy subsyndromes (cfr. Sects. 9.5.1.1 and 9.5.1.2, respectively), Ballarini et al. (2016) also rated the hyperactivity subsyndrome cluster of the NPI in 27 early-onset AD patients and, subsequently, performed interregional correlation analysis to explore metabolic connectivity following FDG-PET. These hyperactivity subsyndrome scores were associated with increases in glucose metabolism in the superior frontal gyrus and anterior CC with a left hemispheric predominance.

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

9.5.2 Other Dementia Subtypes

Rackza et al. (2010) examined behavioral deficits in 17 FTLD patients (diagnoses consisted of FTD ($n = 10$) and SD ($n = 7$)) using ^{18}F-FDG-PET imaging. Behavioral deficits were assessed using the NPI. Total NPI scores were significantly correlated with hypometabolism in various frontomedial regions, the left anterior middle frontal gyrus, the left anterior and superior insula, and the left inferior temporal gyrus. Imaging results were based mainly on apathy, disinhibition, and appetite changes because these behavioral disorders occurred most frequently in this cohort. Moreover, Peters et al. (2006) indicated that the known cerebral metabolic impairment in FTLD patients specifically affects areas specialized in emotional evaluation. This Belgian study obtained PET imaging and NPI behavioral data from 41 FTLD patients from specialized European PET centers around the world. The investigators primarily found decreased posterior orbitofrontal cortical activity to be related with both apathy and disinhibition, which neuroanatomically also corresponds to the hypometabolic pattern of apathy in AD or MCI (cfr. Sect. 9.5.1.2).

Results of a more recent PET imaging study investigating the neuroanatomy and pathophysiology of BPSD in FTD patients were reported by Schroeter et al. (2011). In total, 13 FTLD patients underwent ^{18}F-FDG-PET imaging after being behaviorally scored applying the NPI. The researchers performed a conjunction analysis across the common neural correlates of the three most relevant behavioral disorders as identified in the single regression analysis. All three behavioral disorders, i.e., apathy, disinhibition, and eating disorders, were related to mainly frontomedian hypometabolism. Afterward, a disjunction analysis aimed to specifically identify the neural correlates of these three relevant behavioral disorders individually: disinhibition was correlated with hypometabolism in both anterior temporal lobes, anterior hippocampi, left amygdala, left anterior and superior posterior insula, caudate head, and bilaterally lateral and posterior orbital gyri. Smaller clusters were detected additionally for disinhibition in the right superior middle insula, postcentral gyrus, left superior frontal gyrus, and posterior thalamus ($P < 0.001$); apathy was related to hypometabolism in, most remarkably, the ventral tegmental area and left inferior and middle temporal gyrus, whereas eating disorders were finally associated with the right inferior, middle, and superior frontal gyri with a same statistical threshold (Schroeter et al. 2011).

Lastly, PET imaging studies in DLB patients with BPSD, although sparse, have been performed as well. The first study investigated visual hallucinations in 14 DLB patients compared to 7 DLB patients without such visual hallucinations by means of ^{18}F-FDG-PET imaging (Perneczky et al. 2008). The imaging results revealed hypometabolic regions at the right occipitotemporal junction and in the right middle frontal gyrus only in the DLB group with visual hallucinations, suggesting that

hypometabolism in visual association areas rather than in the primary visual cortex might be involved in psychosis in DLB (Perneczky et al. 2008). Also, ^{18}F-FDG-PET data in ten DLB patients with delusions revealed a hypometabolism of the right middle frontal gyrus (BA9) and pars triangularis of the right inferior frontal gyrus (BA45) in comparison with non-delusional DLB patients (n = 11) (Perneczky et al. 2009). The delusion frequency and severity subscores of the NPI within the past 4 weeks prior to the examination were used to distinguish between delusional and non-delusional DLB patients. A hypometabolism of the right middle frontal gyrus (BA9) thus seems to be associated not only with visual hallucinations but also with delusions in DLB patients.

On the whole, psychosis seems more confined to right hemispheric pathologic disturbances in both DLB and AD, irrespective of PET or SPECT imaging (cfr. Sects. 9.5.1.3 and 9.7.1.3).

9.6 SPECT in the Differential Diagnosis of Dementia

The other commonly used nuclear gamma ray-emitting imaging modality besides PET which can provide functional information about the pathophysiological processes of neurodegenerative diseases is single-photon emission computed tomography (SPECT). It is well recognized that PET has a higher resolution, sensitivity, less artefact, and better quantitative capacity than SPECT; however, SPECT imaging is cheaper and more practical as a routine clinical diagnostic procedure, and SPECT scanners are widely installed in most hospitals (Kung et al. 2004). Limitations of a dual PET tracer approach, on the contrary, are the increased radiation exposure and costs. Another advantage of SPECT is the longer half-life of utilized radiotracers (^{123}I, 13.2 hours; or the technetium isotope ^{99m}Tc (^{99m}Tc), 6.06 h), so there is no requirement for an on-site cyclotron and a specialized radiochemistry facility. Such tracers are normally produced at a commercial scale (Arora and Bhagat 2016).

9.6.1 ^{99m}Tc-HMPAO-SPECT

For the differential diagnosis in dementia, the most commonly applied tracer is ^{99m}Tc-HMPAO (hexamethylpropyleneamine oxime, also known as exametazime). The technetium isotope ^{99m}Tc has a half-life of 6.06 h and is bound to HMPAO which allows ^{99m}Tc to be taken up by the brain tissue rapidly in a manner proportional to the brain's blood flow. Many research during the last decade has indicated that ^{99m}Tc-HMPAO-SPECT is very valuable not only in establishing an (early) AD diagnosis (Bonte et al. 2006; Nagao et al. 2006) but also in distinguishing between different types of dementia (Pickut et al. 1997; Charpentier et al. 2000; Rollin-Sillaire et al. 2012) or between very early AD/MCI and normal aging (Nagao et al. 2006).

Pickut et al. (1997) studied the discriminative use of ^{99m}Tc-HMPAO-SPECT in 21 FTLD versus 19 age- and severity-matched AD patients. The researchers found

significantly more bilateral hypoperfusion of parietal lobes in the AD patients as compared to more pronounced bifrontal hypoperfusion in FTLD patients. This bifrontal hypoperfusion was afterward identified by stepwise logistic regression as the most significant contributing parameter to correctly classify FTLD versus AD patients on SPECT. Comparable with Pickut et al. (1997), Charpentier et al. (2000) examined 20 probable AD and FTD patients by means of ^{99m}Tc-HMPAO-SPECT imaging and detected 5 specific variables after the bivariate and multivariate analyses with the highest predictive value rate for the differential diagnosis between both neurodegenerative disorders, i.e., right median frontal-, left lateral frontal-, left parietotemporal-, and left temporoparietal-occipital areas as well as MMSE scores. Rollin-Sillaire et al. (2012) evaluated the contribution of ^{99m}Tc-HMPAO-SPECT imaging to the differential diagnosis of dementia in 48 neuropathologically confirmed patients with a degenerative (AD or FTLD) or vascular dementia. SPECT-based diagnoses were then compared with clinical and neuropathological diagnoses. Compared with clinical diagnoses alone, SPECT imaging improved the specificity of the etiological diagnosis in degenerative dementia, although its sensitivity was not as good as that of the clinical diagnosis. Furthermore, for AD and FTLD patients, the agreement between the clinical and SPECT-based diagnoses was always confirmed by neuropathological assessment, again indicating that ^{99m}Tc-HMPAO-SPECT is very helpful in the differential diagnosis of dementia.

One last ^{99m}Tc-HMPAO-SPECT study quantified the heterogeneity of cerebral perfusion on SPECT images in elderly controls (n = 31) and very mild AD patients (n = 75) by using a three-dimensional fractal analysis (Nagao et al. 2006). Especially the posterior limbic fractal dimension significantly differed between very early AD and control persons so that authors concluded that ^{99m}Tc-HMPAO-SPECT imaging of the posterior limbic region (consisting of the hippocampal-amygdaloid complex, thalamus, a part of the anterior/posterior CC, and precuneus) combined with 3D fractal analysis may be useful in objectively distinguishing patients with very early AD and MCI from healthy elderly.

9.6.2 ^{123}I-IMP-SPECT

Another frequently administered SPECT imaging radionuclide to differentially diagnose dementia patients is the intravenous injection of N-isopropyl-p-^{123}I-iodoamphetamine (^{123}I-IMP). Combined with magnetic resonance imaging (MRI), Goto et al. (2010) were able to distinguish patients with mild DLB (n = 19) from those with AD (n = 19) with a high level of accuracy. More particularly, they found a significantly lower striatal volume on MRI plus a lower occipital SPECT ratio in the DLB group as opposed to AD patients. These results, therefore, point to a strong and added value of MRI combined with ^{123}I-IMP-SPECT imaging when distinguishing AD from DLB patients.

Hanyu et al. (2010) used the similar ^{123}I-IMP-SPECT imaging technique in 24 rapidly progressing and 24 slowly progressing AD patients based on annual MMSE score changes and assessed the possible relationship between the rate of cognitive

decline and the initial and follow-up rCBF patterns. At the initial evaluation, the rapidly progressing AD group had greater rCBF deficits mainly in the parietotemporal, frontal, and left posterior cingulate regions compared to the slowly progressing AD group. Moreover, follow-up SPECT data of the rapidly progressing AD group showed a significant rCBF reduction in widespread regions, including parietotemporal and frontal lobes, while in the slowly progressing AD group, rCBF patterns were reduced in rather small and more scattered regions of the parietal, temporal, and limbic lobes. Based on these results, Hanyu et al. (2010) suggested that rCBF deficits in specifically parietotemporal, posterior cingulate, and frontal brain regions are associated with subsequent rapid cognitive decline in AD.

9.6.3 SPECT Imaging with Cholinergic and Monoaminergic Radioligands

Altered neurochemical processes in AD have been described extensively throughout the years. One well-known example is the cholinergic denervation in cerebral AD pathology (Mash et al. 1985) which already occurs in very mild or even presymptomatic stages of the disease. Using a sensitive in vivo cholinergic neuron marker in combination with regular SPECT imaging might, therefore, be useful in establishing a very early AD diagnosis (Boundy et al. 1997) or in studying the involvement and alteration of cholinergic activity in AD brain (Boundy et al. 2005; Mazère et al. 2008).

Mazère et al. (2008) used a specific marker of the vesicular acetylcholine transporter, namely, ^{123}I-iodobenzovesamicol (^{123}I-IBVM), combined with SPECT imaging to image cholinergic activity in very early AD patients ($n = 8$ with MMSE scores of 23.8 ± 1.6). In comparison with eight age-matched control subjects (28.3 ± 1.3), the researchers found a significant decrease in ^{123}I-IBVM binding (47–62%) in the CC and parahippocampal-amygdaloïd complex of AD patients. These patterns, however, appeared to be independent of atrophied areas. These results suggest that a cholinergic degeneration already occurs in the very early stages of AD and that it could be associated with cognitive impairment. As a result, the imaging of cholinergic neurons by applying ^{123}I-IBVM-SPECT might also be an effective approach to identify potential cholinergic treatment responders. With regard to non-AD dementias, Mazère et al. (2017) recently evaluated the effectiveness of ^{123}I-IBVM-SPECT in the fundamental study of cholinergic pathways in DLB. The authors found that compared to healthy volunteers ($n = 12$), binding potential values for DLB patients ($n = 11$) were significantly lower in the Ch4 terminal regions of the anterior CC and the superior and inferior parietal cortices, in the Ch5 terminal region of the thalamus, and in the striatum. They concluded that alterations in cholinergic transmission in the anterior CC could be closely associated with the development of apathy in DLB.

Another cholinergic radioligand combined with SPECT to visualize cholinergic brain activity, is ^{123}I-iododexetimide (^{123}I-IDEX), which has shown to effectively bind muscarinic acetylcholine receptors (mACh) (Muller-Gartner et al. 1992).

Possible alterations in mACh levels were evaluated by Boundy et al. (2005) in early clinical AD patients (n = 11) compared to ten age- and gender-matched control subjects. In this study, ^{123}I-IDEX was combined with the previously described ^{99m}Tc-HMPAO-SPECT technique. Boundy et al. (2005) examined a deficit of ^{123}I-IDEX binding in the posterior CC of the mild AD group using a voxel-based approach with SPM99 software. In parallel with previous results of Mazère et al. (2008), this study provides further evidence for the involvement of altered cholinergic activity in the posterior cingulate region in early AD. Moreover, SPM99 found no deficits on ^{99m}Tc-HMPAO-SPECT scans, suggesting that neither atrophy nor hypoperfusion were involved in the reduced ^{123}I-IDEX-binding. Based on this evidence, Mazère et al. (2008) suggested that cholinergic changes in AD might proceed alterations in rCBF patterns. Already in 1997, Boundy et al. (1997) indicated that the use of ^{123}I-IDEX combined with ^{99m}Tc-HMPAO-SPECT might be discriminative enough to be used in the early diagnosis of AD.

The discriminative use of radio-iodinated monoaminergic SPECT ligands might be another efficient approach to distinguish between AD patients and cognitively healthy volunteers. Versijpt et al. (2003a) assessed this possibility by studying the binding potential of ^{123}I-5-I-R91150, a ^{123}I-labeled 5-HT$_{2A}$ receptor antagonist. ^{123}I-5-I-R91150-SPECT images of 9 AD patients revealed a generally decreased neocortical binding potential with a significant reduction in orbitofrontal, prefrontal, lateral frontal, cingulate, sensorimotor, parietal inferior, and occipital regions in comparison with SPECT images of 26 healthy control subjects. Furthermore, Versijpt and colleagues found an age-related decline in 5-HT$_{2A}$ receptor binding potentials, following which they stressed the necessity for inclusion of age-matched study samples (Versijpt et al. 2003a).

Finally, several other monoaminergic SPECT ligands have been developed to distinguish AD from DLB patients based on the fact that (i) severe nigrostriatal neurodegeneration in DLB occurs to greater extent than in AD and (ii) clinical symptoms show significant overlap, particularly in early stages of the disease (McKeith et al. 2017). As a consequence, the differential diagnosis between both conditions might be very challenging (Tatsch 2008). Multiple examples of monoaminergic SPECT ligands targeting the dopaminergic neurotransmitter system are given by Tatsch (2008), of which ^{123}I-β-CIT (^{123}I-2beta-carbomethoxy-3beta-(4-iodophenyl)tropane) and ^{123}I-ioflupane(FP)-CIT have shown to be most promising in correctly categorizing AD and DLB. Both ^{123}I-β-CIT and ^{123}I-FP-CIT-SPECT imaging modalities measure presynaptic striatal DA transporter (DAT) levels, which were always found to be significantly lower in DLB patients compared to AD patients. In contrast, corresponding monoaminergic SPECT ligands which targeted postsynaptic DA receptors showed to be much less efficient in differentiating DLB from AD patients. Kasanuki and colleagues (Kasanuki et al. 2017) investigated the clinical relevance of ^{123}I-FP-CIT-SPECT in prodromal DLB and concluded that mean striatal specific binding scores of both prodromal and clinical DLB patients were significantly lower than those of AD patients. Moreover, among the related nonmotor symptoms, duration of olfactory dysfunction and RBD demonstrated a negative correlation with striatal specific binding scores in prodromal DLB. Again,

this shows that the combination of SPECT with other disease-related biomarkers is preferred to increase the diagnostic specificity in (prodromal) DLB, in this case ^{123}I-FP-CIT-SPECT combined with measures of olfactory dysfunction/RBD.

Of note, ^{123}I-FP-CIT-SPECT is more familiar under the tradename of "DaTscan." The main advantage of ^{123}I-ioflupane is that a steady state allowing SPECT imaging is reached at 3 hours after a single bolus injection of the radioligand compared with 18–24 hours of ^{123}I-β-CIT. Evidence shows that ^{123}I-ioflupane uptake in the basal ganglia is markedly reduced in DLB compared to AD patients (Walker et al. 2002). Nowadays, ^{123}I-ioflupane-SPECT is widely used in clinical routine for the differential diagnosis between PD and essential/dystonic tremor or for clinical suspicion of psychogenic parkinsonism or parkinsonism secondary to drugs, although it might also be valuable to differentiate between DLB and AD patients. In general, DaTscan favors the diagnostic workup of PD-related disorders (Antonini 2007).

9.6.4 SPECT Imaging of Neuroinflammation

As mentioned before, inflammation in AD primarily contributes to neurodegeneration and is acknowledged to be a primary source of pathology. Consequently, SPECT imaging of neuroinflammation in AD brain might also be useful to differentially discriminate between AD patients and control subjects. One example comes from Versijpt et al. (2003b), who studied neuroinflammation in AD by using the radioligand ^{123}I-PK11195 with SPECT imaging. PK11195 is an isoquinoline carboxamide that selectively binds to PBR-TSPO which are expressed on microglia. Additionally, PK11195 becomes upregulated under inflammatory circumstances. The authors compared the SPECT images of ten AD and nine control subjects and showed that the mean ^{123}I-PK11195 uptake was increased in nearly all neocortical regions of AD patients; however, statistical significance was only achieved in the frontal and right mesotemporal regions.

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

9.6.5 SPECT Tracers Imaging Aβ Plaques

The development of PET as well as SPECT tracers for Aβ imaging represents an active area of radiopharmaceutical design. Finding a suitable radioligand is, however, very challenging as Aβ plaques are not homogenous and contain multiple binding sites for structurally different compounds (Valotassiou et al. 2010). One good example comes from Kung et al. (2004), who developed 6-iodo-2-(4′-dimethylamino-)phenyl-imidazo[1,2]pyridine (IMPY) and 4-N-methylamino-4′-hydroxystilbene (SB-13) as ligands for targeting amyloid plaques. The researchers firstly evaluated in vitro binding properties of these two potential Aβ-imaging agents in temporal, parietal, and cerebellar cortex of AD patients (n = 4) and control

persons (n = 4). When labeled with ^{125}I or H-3, ^{125}I-IMPY and ^{3}H-SB-13-SPECT, respectively, showed an abundant in vitro binding capacity with high binding affinities for Aβ plaques in all affected brain regions of AD patients compared to very low specific binding in cortical tissue of control brain homogenates. These properties suggest that both ligands are valuable in quantifying and localizing amyloid plaque burden in living AD patients if labeled with ^{11}C or ^{123}I, even though their use warrants further analysis (Chen et al. 2015).

Please visit http://www.clinicaltrials.gov/ to see ongoing clinical trials concerning the development of novel SPECT probes related to amyloid imaging or other neurodegenerative disease markers of interest for the differential diagnosis of dementia. As mentioned previously, Table 9.2 summarizes the most frequently used radiotracers for SPECT- and PET-based analysis of AD pathophysiology (apart from ^{18}F-FDG for PET and ^{99m}Tc-HMPAO for SPECT).

9.7 SPECT Imaging in Neuropsychiatric Disturbances of Dementia

During the last two to three decades, much SPECT-related research regarding neuropsychiatric disturbances in dementia has been performed. In general, literature comprises more SPECT- than PET-related BPSD studies for the period 1990–2010, whereas from 2010 onward, more PET studies have emerged. Of all BPSD, depression, apathy, and psychosis in AD have been examined the most. Besides, activity disturbances, agitation/aggression, and sleep disorders have also been the subject of SPECT research in AD, in addition to the study of psychosis and apathy in DLB and FTD patients.

9.7.1 Alzheimer's Disease

9.7.1.1 Depression

One of the first studies that dealt with mood disorders in AD was published by Galynker et al. (2000) who examined the relationship between rCBF patterns and negative symptoms in AD patients (n = 25). The AD group was subdivided in a high- (more negative symptoms) (n = 12) and low (less negative symptoms) severity group (n = 13). Each patient underwent ^{99m}Tc-HMPAO-SPECT. Categorization of negative symptoms was performed by means of the *Scale for the Assessment of Negative Symptoms*, the HDS, and the *Positive and Negative Symptom Scale*. Authors observed a significantly lower rCBF pattern in the dorsolateral prefrontal cortex bilaterally (right, P = 0.002, and left, P = 0.02), the main right frontal cortex (P = 0.02), and CC (P = 0.022) of the high-severity AD group compared to the low-severity group. Results point to a significant association between negative symptoms and hypofrontality in AD. Somewhat later in 2003, Liao et al. (2003) tested the hypothesis that depression in AD is the result of a specific cerebral pathogenesis rather than a diffuse event, as was previously shown by Galynker et al. (2000). In

total, 43 AD patients received a behavioral assessment with the HDS and underwent ^{99m}Tc-HMPAO-SPECT imaging. An inverse correlation was found between depression scores and cerebral perfusion in the bilateral anterior and posterior cingulate gyri and precuneus, which was in agreement with Galynker et al. Surprisingly, no hypoperfusion in (pre)frontal cortices of depressed AD patients was identified.

Akiyama et al. (2008) scrutinized previous results and used the so-called easy Z-score imaging system (eZIS) combined with ^{99m}Tc-ethyl-cysteinate dimer (ECD)-SPECT imaging, another frequently used radioligand (ECD) which binds the technetium isotope ^{99m}Tc, to investigate if hypoperfusion in prefrontal cortex or CC is associated with depression in AD. Depression scores were based on the NPI depression items, so in total 44 AD patients were subdivided into 26 depressed and 19 nondepressed AD subjects. Data from eZIS-^{99m}Tc-ECD-SPECT scans revealed that mean Z-scores of the left prefrontal cortex in the depressed AD group were significantly higher ($P < 0.0125$) than those in the nondepressed group. Moreover, there were no significant differences in Z-scores of the right prefrontal cortex or in the bilateral anterior CC between the two groups, which is in contrast but also in agreement with previous studies who found hypoperfusion in either CC alone (Liao et al. 2003) or in the prefrontal cortex as well as in the CC (Galynker et al. 2000). Also in 2008, Levy-Cooperman and colleagues (Levy-Cooperman et al. 2008) used the CSDD with a cut-off score of 8 or more as being indicative for depression to dichotomize depressed ($n = 27$) from nondepressed ($n = 29$) AD patients with the same ^{99m}Tc-ECD-SPECT technique combined with MRI. Similarly, this study aimed to determine neural correlates of depressive symptoms in 56 AD patients who met the criteria for probable AD. Results showed a hypoperfusion in the right superior and bilateral middle frontal ($P < 0.005$), left superior frontal ($P < 0.05$), and anterior cingulate gyri ($P < 0.005$) of depressed AD patients compared to nondepressed patients. SPM analyses also revealed a significantly lower perfusion in bilateral dorsolateral and superior prefrontal cortex of depressed AD patients (right, $P < 0.005$, and left, $P < 0.05$), which is consistent with previous reports that suggested that the prefrontal cortex and CC are involved in affect and emotional regulation in AD.

Finally, in 2010, Kataoka et al. (2010) again used ^{99m}Tc-ECD-SPECT but afterward analyzed all SPECT images with *3D stereotactic region of interest template* (3DSRT) software to compare rCBF ratios of each brain segment between depressed ($n = 17$) and nondepressed AD patients ($n = 18$). Depression scores were based on the Japanese version of the NPI depression subscale, and AD patients had mild-to-moderate AD according to DSM-IV criteria. The authors found that perfusion ratios (rCBF patterns) on 3DSRT images of the left callosomarginal segment, i.e., left prefrontal cortex, were significantly lower ($P < 0.05$) in the depressed AD group than those of the nondepressed group. In comparison with their own previous study where they used eZIS-^{99m}Tc-ECD-SPECT instead of 3DSRT-^{99m}Tc-ECD-SPECT (Akiyama et al. 2008), current results remained consistent, thus suggesting that frontal dysfunction is associated with the expression of depressive symptoms in AD patients.

9.7.1.2 Apathy

Apathy is closely related to depression as it is one of the main components of the CSDD (lack of reactivity to pleasant events, loss of interest (Alexopoulos et al. 1988)) to decide whether or not AD patients might be depressed. Therefore, it is very likely that the same affected brain ROI in depressed AD patients (prefrontal cortex, CC) might be comparable with those of apathetic AD patients on SPECT.

The first study that agrees with this hypothesis comes from Benoit et al. (1999) who studied regional cerebral perfusion with ^{99m}Tc-ECD-SPECT in 20 apathetic AD patients rated by the apathy subscale of the NPI. Authors indeed revealed that the apathy NPI scores were correlated with a right cingulate deficit, whereas MMSE scores positively correlated with the left temporoparietal area. A comparable study in 2002 from Benoit et al. (2002) used ^{99m}Tc-ECD-SPECT imaging again, but this time in combination with SPM99 analysis. Brain perfusion patterns were compared between apathetic (n = 15) and non-apathetic AD patients (n = 15), as well as healthy control subjects (n = 11). SPECT data indicated that compared to healthy subjects, the apathy-free AD subgroup had significantly lower cerebral perfusion of the inferior temporal and occipital regions. In contrast, the apathy subgroup had significantly decreased perfusion of the left anterior cingulate, right inferior medial, and left orbitofrontal gyrus and right gyrus lingualis. When both AD groups were compared, a significantly lower perfusion in BA8, BA9, and BA10 (bilateral medial frontal gyri) was observed in the apathetic AD group but not in the group free of apathy. On the other hand, apathetic AD patients tended toward a decreased perfusion in the anterior CC, even though this finding did not reach statistical significance.

Benoit et al. (2004) further assessed apathy in AD by making a distinction between the separate behavioral, cognitive, and emotional aspects of apathy, using the *Apathy Inventory*. Thirty AD patients were included, and brain perfusion was once more measured with ^{99m}Tc-ECD-SPECT and SPM99 analysis. Lack of initiative scores was negatively associated with perfusion in the right anterior CC, whereas lack of interest scores was negatively associated with perfusion in the right middle orbitofrontal gyrus. Lastly, emotional blunting scores inversely correlated with perfusion in the left superior prefrontal dorsolateral cortex.

Similarly as with Benoit et al. (2004), Robert et al. (2006) also studied the two major dimensions of apathy, i.e., lack of initiative and lack of interest, by using the *Apathy Inventory* combined with ^{99m}Tc-ECD-SPECT and SPM99 analysis in 19 AD subjects presenting this type of behavioral phenomenology compared to 12 AD subjects who did not. On the whole, AD patients with lack of initiative and interest showed a significantly lower perfusion in the right anterior CC than AD patients without such specific behavior (P = 0.00012). These parallel results, however, are not surprising as they both resulted from the same research group and were derived from a rather small subgroup of patients. Nonetheless, this is yet another confirmation of the CC to be involved in the pathophysiological processes of apathy in AD brain.

One last study that relates to apathy, as well as depression, in AD, originates from Kang and colleagues (2011). A rather large number of patients, namely, 81,

were enrolled in this prospective study. ^{99m}Tc-HMPAO-SPECT was performed to evaluate rCBF patterns, and according to the NPI subscores for apathy and depression, unfortunately only nine were classified as clinically depressed and nine as clinically apathetic. In addition, 18 more nondepressed and non-apathetic AD patients were classified as an age- and MMSE score-matched disease control group. Kang and colleagues found that depressed AD patients had a significantly lower perfusion in the right orbitofrontal and inferior frontal gyri than nondepressed AD patients, while apathetic AD patients displayed a hypoperfusion in the right amygdala; temporal, posterior cingulate; and right superior frontal, postcentral, and left superior temporal gyri compared to non-apathetic AD patients. Also, when the rCBF patterns were correlated with NPI subscores in the total group of 81 AD patients, depression subscores negatively associated with perfusion in the left inferior frontal and right middle frontal gyri, whereas apathy subscores inversely correlated with perfusion in the right temporal and right medial frontal gyri.

In conclusion, much evidence resulting from not only SPECT but also PET imaging uniformly suggests that mainly (pre)frontal areas as well as the anterior/posterior CC are involved in the cerebral pathophysiology of depression and apathy in AD.

9.7.1.3 Psychosis

Already in 1994, Starkstein et al. investigated whether delusions in AD were associated with dysfunction in specific brain areas (Starkstein et al. 1994). In total, 45 probable AD patients received ^{99m}Tc-HMPAO-SPECT, and delusions were assessed by the *Present State Examination* so that patients were subdivided in delusional (n = 16) or non-delusional (n = 29). The most common delusion was "paranoia," which was present in 75% of AD patients besides hypochondriac-, grandiose-, and infidelity-type delusions. Four patients also suffered from *Capgras* (impostors) and two from *Cotard* syndrome (delusions of deformity of body parts). Imaging results only revealed that delusional AD patients had a bilateral hypoperfusion in inferior and temporal lobes compared to non-delusional subjects. However, the mixture of different types of delusions might have accounted for the lack of laterality and loss of frontal significance (Ismail et al. 2012).

Somewhat later, Ponton et al. (1995) included 15 initially non-delusional AD patients who underwent SPECT scanning and psychometric testing with the *Alzheimer's Disease Assessment Scale*. Procedures were repeated 1 year later, when 6 out of the original 15 AD patients had developed several types of delusions. When comparing the original baseline SPECT data between delusional (n = 6) and non-delusional (n = 9) subjects, the investigators found that delusional patients already had a significantly higher perfusion in the right hemisphere, particularly in the inferior and superior temporal gyrus, the temporoparietal area, the Broca's area, the prefrontal region, and the primary visual cortex. Afterward, when comparing SPECT data which were yielded at year one between both subgroups, a lower perfusion in the right temporal region was observed in the delusional group compared with those who did not develop any type of delusion. Ponton et al. (1995), subsequently, were the first to suggest that specifically right temporal lobe dysfunction

might predict the onset of delusions in AD. Staff et al. (1999) were also able to identify a relationship between right hemispheric hypoperfusion, namely, in right frontal and limbic regions, and delusions in 18 probable AD patients compared to 15 AD patients who were free of delusions using ^{99m}Tc-HMPAO-SPECT with SPM. The same goes for Fukuhara et al. (2001), who investigated a very specific type of delusions, i.e., delusion of theft, in only nine age- and cognitive-matched AD patients by means of ^{99m}Tc-HMPAO-SPECT imaging and SPM. AD patients with delusions of theft showed a significant hypoperfusion in right medial posterior parietal region compared to patients without such delusions, indicating that right parietal dysfunction may play a role in producing this type of delusions in AD.

Nakano et al. (2006a) obtained similar results, also using ^{99m}Tc-HMPAO-SPECT, when examining the relationship between delusions and rCBF in AD. This time, however, SPECT data of 64 probable AD patients were compared to a group of 76 age-matched controls. Delusions were assessed by the NPI delusion subscale following which AD patients were categorized into delusional (n = 25) and non-delusional (n = 39), without any significant difference between age and MMSE scores. Neuroimaging results showed that, when compared to healthy volunteers, AD patients had significantly decreased perfusion in the posterior cingulate gyri, precuneus, and parietal association cortices. In comparison with non-delusional AD subjects, the delusional one's displayed a significantly decreased perfusion in the prefrontal cortex, anterior cingulate gyri, inferior to middle temporal cortices, and parietal cortex with a right hemispheric predominance ($P < 0.01$).

In 2010, Matsuoka et al. studied the relationship between brain perfusion and associated delusion severity in individuals with AD, using SPECT and NPI (Matsuoka et al. 2010). In total, 35 patients entered this study of which 14 suffered from delusions, whereas 21 did not. The delusion subscale scores of the NPI were negatively correlated with rCBF patterns in the right anterior insula ($P < 0.01$) when the total AD group was taken into account (n = 35). However, rCBF patterns in the right anterior insula were not significantly decreased in delusional AD patients when compared to non-delusional patients. The authors suggest that although it may not be responsible for the onset of delusions, the right anterior insular dysfunction may be responsible for exacerbation of these symptoms.

SPECT imaging has also been used to investigate gender differences in regional perfusion in the brains of psychotic AD patients. For instance, Moran et al. (2008) assessed cerebral perfusion of 51 probable AD patients with psychosis (16 males, 35 females) compared to 52 nonpsychotic probable AD patients (19 males, 33 females). The researchers used the Behave-AD scale to rate the presence or absence of psychosis within 1–2 weeks of ^{99m}Tc-HMPAO-SPECT imaging. The authors concluded that perfusion was lower in female patients with psychotic symptoms in right infero-lateral prefrontal cortex and in inferior temporal regions compared to female patients without such symptoms. In contrast, perfusion was higher in male patients with psychotic symptoms in the right striatum compared to nonpsychotic male subjects. Comparison groups did not differ in age nor dementia severity, which was estimated by the MMSE. These results support the role of right hemispheric prefrontal and lateral temporal cortex in psychosis of AD in women, but not in men,

and raise the possibility that there might be a gender-related regional specificity in the pathophysiology of psychosis in AD.

As distinct from delusions, SPECT studies examining the neuropathophysiology of hallucinations are very limited. For instance, Mori et al. (2006) investigated rCBF changes in a case of AD with music hallucinations compared to a control AD group ($n = 747$). The patient was a 73-year-old right-handed woman who developed AD at the age of 69. ^{99m}Tc-HMPAO-SPECT imaging data revealed that rCBF of the case was significantly increased in the left superior temporal and left angular gyrus compared to control persons. This specific profile thus could be relevant to the neuroanatomical basis of music hallucinations.

In summary, delusions in AD seem to be primarily associated with right hemispheric pathology as was shown not only by SPECT but also by PET imaging data (cfr. Sect. 9.5.1.3). More neuroimaging research, however, is mandatory with regard to hallucinations in AD.

9.7.1.4 Activity Disturbances

Wandering is a common activity disturbance in AD and one of the most exhausting for the caregiver (Rolland et al. 2003). For the moment, only Rolland et al. (2005) tried to study the brain's possible underlying physiological processes of wandering behavior in AD patients. For this purpose, they used ^{99m}Tc-ECD-SPECT and NPI. SPECT scans were then compared between AD subjects with ($n = 13$) and without ($n = 13$) wandering behavior. Despite similar clinical dementia severity based on MMSE scores, wanderers exhibited a more severely reduced rCBF in the left parietotemporal lobe than AD patients without wandering behavior. SPM analysis further revealed a reduced rCBF in the left middle temporal gyrus (BA21) and left parahippocampal gyrus (BA37). Unfortunately, these results did not confirm the authors' hypothesis of the involvement of the supervisory role of the frontal lobes and neither seemed to be associated with a dysfunction of the spatial navigation located in the right parietal cortex nor with a disorder of perception or reality, which should have involved the right temporal lobe. In contrast, wandering in AD, as physical activity and aberrant motor behavior, might enhance an extensive cortico-subcortical network interaction.

9.7.1.5 Agitation and Aggression

Nakayama et al. (2017) analyzed the effect of galantamine on BPSD and caregiver burden and treated a total of 50 mild AD patients for 12 weeks, followed by NPI scoring at baseline and follow-up. ^{123}I-IMP-SPECT was performed at baseline. In the end, the authors could not find any significant improvement of NPI scores after treatment. Baseline comparison of rCBF SPECT between agitated vs. non-agitated AD patients based on the NPI subitems, however, demonstrated increased perfusion in the right prefrontal cortex in the agitated subgroup. In one patient of this subgroup who underwent multiple SPECT scannings at 20 and 56 months after commencement of galantamine treatment, the increase in the rCBF of the right prefrontal lobe disappeared at 20 months but, unfortunately, reappeared 36 months thereafter, suggesting that the magnitude of rCBF increase in this area may affect a patient's

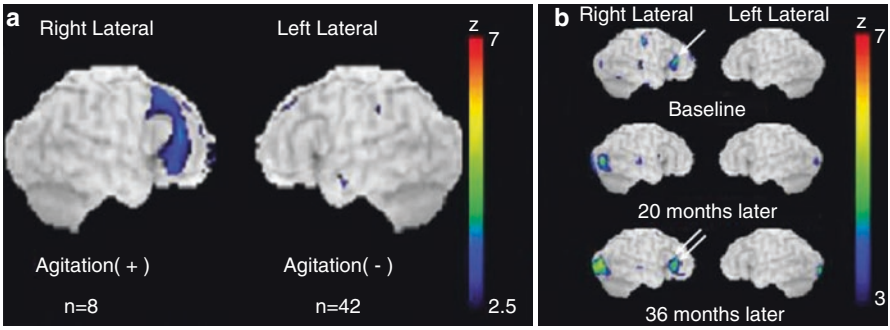


Fig. 9.8 Statistical parametric map on a surface standard anatomical image following ^{123}I-IMP-SPECT in agitated vs. non-agitated mild AD subjects. The map reflects regions with significantly higher blood flow in the group with agitation at baseline than without. The differences were found in the right lateral prefrontal cortex (**a**). The maps show the changes of rCBF in a 67-year-old female patient. The maps reflect regions with significantly high blood flow compared with normal controls. The increased region in the right lateral prefrontal cortex at baseline decreased 20 months after commencement of galantamine treatment but had reappeared in 36 months (**b**). Abbreviations: *AD* Alzheimer's disease, *rCBF* Regional cerebral blood flow. Reprinted from Nakayama S et al. (2017) J Alzheimer's Dis 57:267–273, with permission from IOS Press. Copyright © 2017 IOS Press

response to galantamine (Fig. 9.8). The agitated subgroup only consisted of 8 AD patients (compared to 42 non-agitated patients), so the observed results should be interpreted with caution.

Another very common behavioral disturbance in AD is aggression. So far, only two studies have investigated regional brain perfusion in dementia patients with this specific behavioral phenomenology.

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

The second study of Lanctôt and colleagues (Lanctôt et al. 2004) was slightly different, as they used 30 aggressive and 19 nonaggressive AD patients who were rated by the Behave-AD and underwent ^{99m}Tc-ECD-SPECT instead of ^{99m}Tc-HMPAO-SPECT. This time, diagnoses were made according to the NINCDS-ADRDA criteria for probable AD, thereby excluding vascular pathology. Unfortunately, SPECT scanning had to be performed only within 3 months of their behavioral assessments, which is a rather large interval. Compared with nonaggressive patients, the aggressive subjects displayed hypoperfusion in the right and left middle temporal ROI ($P = 0.02$ for both). Supplementary SPM analysis further revealed a right middle medial temporal hypoperfusion in the aggressive AD group ($P = 0.008$). This region includes the hippocampus, parahippocampus, and posterior amygdala and corresponds to BA28, BA35, and BA36. The authors, therefore,

suggested that the right middle medial temporal region is an important neural correlate of aggression in AD, which is somewhat comparable with Hirono et al. (2000), who also identified the temporal cortex as an important key factor in the onset of aggression, although in this case the hypoperfusion was located in the left hemispheric temporal region.

9.7.1.6 Sleep Disorders

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

In this study of Ismail et al. (2009), authors aimed to investigate the possible association of regional cerebral perfusion and sleep loss in AD. A group of 55 AD patients was characterized as having or not having nocturnal sleep loss based on standardized AD scales assessing sleep over the previous 4 weeks. Regular ^{99m}Tc-ECD-SPECT imaging scans were performed when patients were in a relaxed, wakeful state. Afterward, SPM5 analysis was performed to compare brain perfusion across both groups. In addition, the two AD groups were also compared with a healthy control group of the same age and gender. Results showed increased perfusion in the right middle frontal gyrus (BA9) ($P = 0.016$) in AD patients suffering from nocturnal sleep loss as opposed to patients who were free of sleep loss. Comparison with the normal control subjects indicated that the hyperperfusion in the right middle frontal gyrus among AD patients with sleep loss was not supreme, given the fact that the hyperperfusion of this region which was found in the healthy control group after AD patients with sleep loss versus control group comparison could not be exceeded. Authors thus concluded that in mild-to-moderate AD, relative hyperperfusion (rather than absolute hyperperfusion) of the right middle frontal gyrus might be associated with reports of sleeplessness in AD. Furthermore, this region might play an important role in the regulation of sleep.

9.7.1.7 Other Behavioral Disturbances

The cingulate island score (CIS) indicates the Z-score ratio of the posterior CC relative to the medial occipital area and has been evidenced to be useful for differentiating DLB from AD (Imamura et al. 1997). It reflects the preservation of glucose metabolism in the mid- or posterior cingulate. Only recently, Yasuno et al. (2019) looked into the potential association between BPSD and CIS by applying ^{99m}Tc-ECD-SPECT in 17 early-stage AD patients and 13 amnestic MCI subjects combined into one single group. ^{99m}Tc-ECD-SPECT images acquired from all patients were converted, and the CIS was determined by using the easy Z-score imaging system. A significant correlation between CIS and the NPI-Q was identified, with the increase in CIS reflecting the relative decrease in posterior CC perfusion. Afterward, based on a CIS of 0.39, patients with and without (i.e., NPI-Q score = 0) BPSD were correctly classified with a sensitivity and specificity of 72.2% and 75.0%, respectively. The authors concluded that CIS may not only be useful in

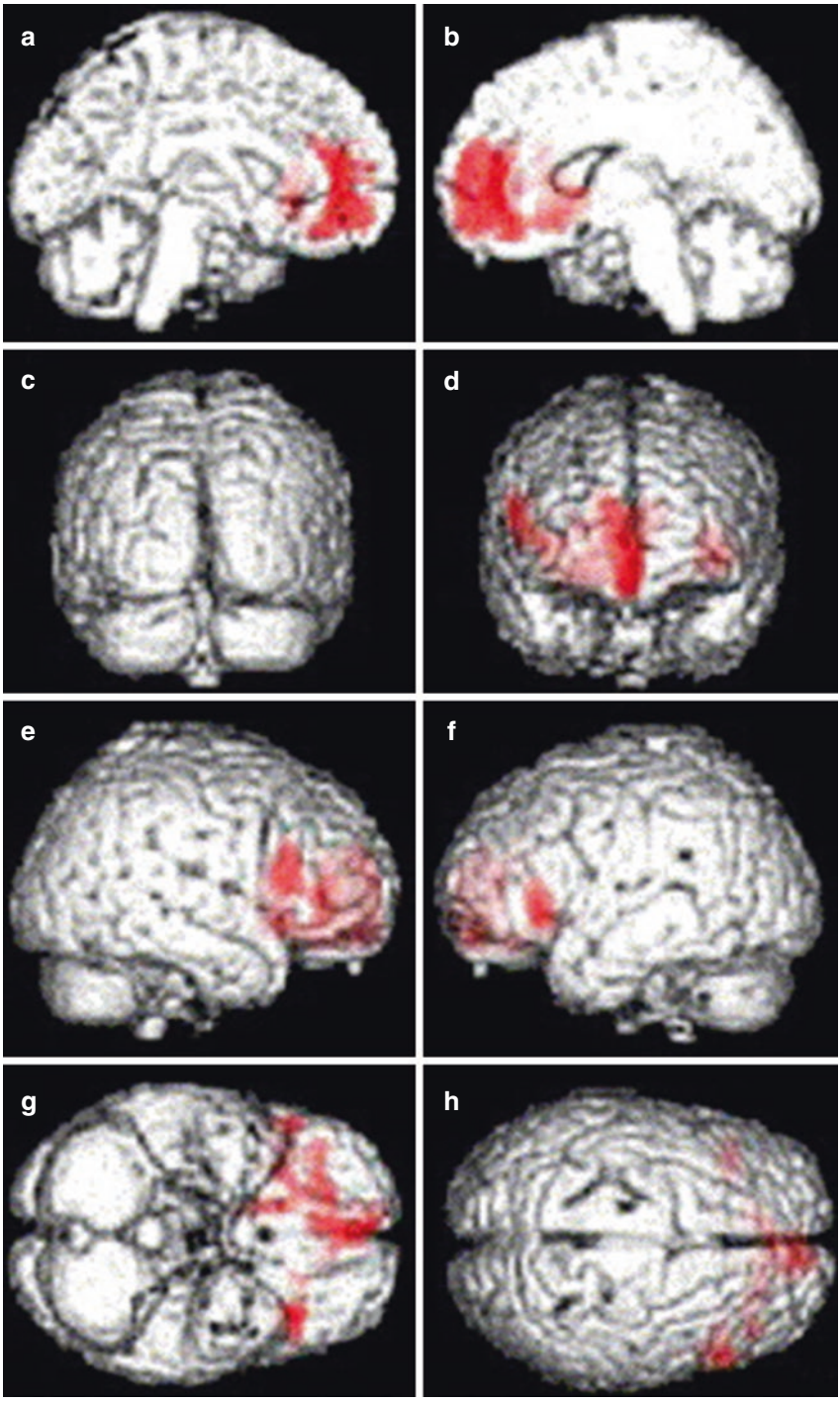
discriminating DLB from AD subjects, but that it can also be a valuable and clinically effective tool indicating vulnerability to BPSD at the prodromal to early stages of AD.

9.7.2 Other Dementia Subtypes

Personality changes such as antisocial behavior are a prominent part of the behavioral symptomatology in FTD patients. This topic was studied by Nakano et al. (2006b) who assessed 22 FTD patients with the NPI and categorized five types of antisocial behavior (stealing, traffic accident (e.g., hit and run), physical assault, sexual comments or advances, public urination). These antisocial behaviors were rated independently by three different geriatric psychiatrists who had not been given the information of the SPECT images. A control group of 76 healthy volunteers was included also, and both groups underwent ^{99m}Tc-ECD-SPECT and SPM99 analysis. Compared to controls, FTD patients showed a significant reduction of rCBF in the widespread frontal cortical areas (such as the superior, middle, and inferior frontal gyri), as well as in subcortical structures (particularly thalamus and caudate nuclei). A subsequent correlation analysis further revealed that antisocial behavioral symptoms were associated with reduction of the rCBF in the orbitofrontal cortex, BA47, BA32, the right caudate nucleus, and the left insula of FTD patients, suggesting that mainly a functional decline of the orbitofrontal cortex in FTD patients is related to antisocial behavior (Fig. 9.9). This conclusion is not surprising at all, given the fact that orbitofrontal cortex dysfunction is mostly associated with disinhibition, facetiousness, sexual and personal hedonism, and lack of concern for others (Nakano et al. 2006b).

The study of Roselli et al. in 2009 targeted BPSD symptoms in 18 well-characterized DLB patients and measured striatal DAT levels by ^{123}I-FP-CIT-SPECT imaging (DaTscan) after NPI assessment (Roselli et al. 2009). Imaging data showed a significant correlation between decreased DAT levels and visual hallucinations. Although no other correlations were observed, delusions, apathy, and depression were also inversely correlated to decreased caudate DAT levels when putamen and caudate nucleus were considered separately. Hence, these results provide important evidence on the involvement of mesocortical dopaminergic pathways in neuropsychiatric symptoms in DLB, such as delusions, apathy, and depression.

Fig. 9.9 Results of SPM analyses displaying rCBF patterns that correlated with antisocial behavioral scores in FTD patients ($n = 22$). Representation in stereotaxic space of cerebral regions that correlated with antisocial behavioral scores in FTD patients ($n = 22$) displayed on a 3D surface anatomical template ($P < 0.005$, not corrected for multiple comparisons). Images show that antisocial behavioral symptoms are, in particular, associated with reduction of rCBF in the orbitofrontal cortex. Views are medial right (**a**), medial left (**b**), posterior (**c**), anterior (**d**), right lateral (**e**), left lateral (**f**), inferior (**g**), and superior (**h**). Abbreviations: *FTD* frontotemporal dementia, *rCBF* Regional cerebral blood flow, *SPM* Statistical parametric mapping. Reprinted from Nakano et al. (2006a) Neuroimage 32:301–306, with permission from Elsevier. Copyright © 2006 Elsevier Inc


a
b
c
d
e
f
g
h

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

Finally, Nagahama et al. (2010) utilized ^{99m}Tc-HMPAO-SPECT imaging and found that visual hallucinations in DLB patients (n = 100) were related to hypoperfusion in the left ventral occipital gyrus and bilateral parietal areas, whereas delusions were rather associated with hypoperfusion in the right rostral medial frontal cortex, left medial superior frontal gyrus, and bilateral dorsolateral frontal cortices. Based on these results, the authors concluded that visual hallucinations in DLB may be related to a dysfunction of parietal and occipital association areas, while delusions may rather be associated with dysfunctions of the frontal cortex. The latter statement fully agrees with similar PET research of Perneczky et al. (2008) (cfr. Sect. 9.5.2).

9.8 Concluding Remarks

PET and SPECT neuroimaging techniques have played an important role in the differential diagnosis of dementia over the past three decades. They have both provided invaluable information regarding characteristic pathophysiological changes during the course of AD. Presently, both imaging modalities have proven to be crucial to most efficiently facilitate dementia diagnosis, indicate disease staging, visualize plaque burden, as well as monitor the effects of disease-modifying therapies. However, recent developments evinced that it is best to combine both *state-of-the-art* imaging techniques with other biomarkers of disease to considerably enhance differential dementia diagnostics, such as CSF $A\beta_{1–42}$, T-tau, and P-tau_{181P} measurements. PET and SPECT also work very complementary. In the last 6 years, a lot of tau radiotracers have emerged, in addition to improved ligands for amyloid pathology. A future challenge will be to continue developing novel radioligands which target different and unique aspects of the etiology of dementia, so that patients might be even more adequately diagnosed, perhaps in an asymptomatic or prodromal phase

With regard to BPSD, PET and SPECT have repeatedly shown that depending on the behavioral phenomenon and dementia subtype, BPSD such as depression, apathy, or psychosis are the result of a very specific, cerebral pathophysiology rather than a diffuse brain event. Evidence resulting from not only SPECT but also PET imaging uniformly suggests that mainly (pre)frontal areas and anterior/posterior CC are involved in the cerebral pathophysiology of depression and apathy in AD and MCI, even though both hypermetabolic and hypometabolic states have been reported, potentially due to early compensatory mechanisms in MCI. Delusions in AD and both delusions and visual hallucinations in DLB seem to be primarily associated with right hemispheric pathology, as was shown by SPECT and PET research. For agitation in AD, only one SPECT and one PET study have been performed so far, with contradictory results—but with a consensus on brain regions—measuring

increased perfusion or reduced glucose metabolism, respectively, in prefrontal and temporal cortices. As for aggression, hypoperfusion in the temporal cortex has been indicated among others, following a handful of SPECT studies in AD, without confirmatory evidence of alike PET research. A general remark is that for PET-related BPSD research, studies were hitherto mostly confined to ^{18}F-FDG as the standard radiotracer, so combinations of various tracers are preferred in future studies, similar as in Ng et al. (2017).

By and large, this shows that more PET and SPECT neuroimaging research is mandatory with special attention to activity disturbances, anxieties, hallucinations, diurnal rhythm disturbances, and aggression/agitation to fully characterize the pathophysiology of each of these neuropsychiatric disturbances in not only AD but also other dementia subtypes, such as FTD and DLB.

Acknowledgments This work was supported by the Research Foundation-Flanders (FWO); the Belgian Alzheimer Research Foundation—Stichting Alzheimer Onderzoek (SAO-FRA grants #2017/0025 and #2018/0027); the Joint Programming Initiative Neurodegenerative Diseases (JPND) multinational research project HEROES (ZonMw project 733051072); the agreement between the Institute Born-Bunge and the University of Antwerp; the Medical Research Foundation Antwerp; the Thomas Riellaerts research fund; and Neurosearch Antwerp.

References

Aalten P, Verhey F, Boziki M et al (2007) Neuropsychiatric syndromes in dementia; results from the European Alzheimer disease consortium. Dement Geiatr Cogn Disord 24:457–463

Abe K, Yamashita T, Hishikawa N et al (2015) A new simple score (ABS) for assessing behavioral and psychological symptoms of dementia. J Neurol Sci 350:14–17

ADAPT Research Group, Martin BK, Szekely C et al (2008) Cognitive function over time in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT): results of a randomized, controlled trial of naproxen and celecoxib. Arch Neurol 65:896–905

Adlard PA, Tran BA, Finkelstein DI et al (2014) A review of β-amyloid neuroimaging in Alzheimer's disease. Front Neurosci 8:327

Agdeppa ED, Kepe V, Liu J et al (2001) Binding characteristics of radiofluorinated 6-dialkyla mino-2-naphthylethylidene derivatives as positron emission tomography imaging probes for β-amyloid plaques in Alzheimer's disease. J Neurosci 21:189

Akiyama H, Barger S, Barnum S et al (2000) Inflammation and Alzheimer's disease. Neurobiol Aging 21:383–421

Akiyama H, Hashimoto H, Kawabe J et al (2008) The relationship between depressive symptoms and prefrontal hypoperfusion demonstrated by eZIS in patients with DAT. Neurosci Lett 441:328–331

Alexopoulos GS, Abrams RC, Young RC et al (1988) Cornell scale for depression in dementia. Biol Psychiatry 23:271–284

Allen NHP, Burns A (1995) The noncognitive features of dementia. Rev Clin Gerontol 5:57–75

Alzheimer's Disease International (2015) World Alzheimer report: the global impact of dementia: an analysis of prevalence, incidence, costs and trends—executive summary. Alzheimer's Disease International (ADI), London

American Psychiatric Association (2013) Section II: diagnostic criteria and codes, neurocognitive disorders. In: Diagnostic and statistical manual of mental disorders, 5th edn; DSM-5. American Psychiatric Association, Washington, DC. doi: https://doi.org/10.1176/appi.books.9780890425596.dsm17

Antonini A (2007) The role of 123I-ioflupane SPECT dopamine transporter imaging in the diagnosis and treatment of patients with dementia with Lewy bodies. Neuropsychiatr Dis Treat 3:287–292

Arai T, Hasegawa M, Akiyama H et al (2006) TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Biochem Biophys Res Commun 351:602–611

Arora A, Bhagat N (2016) Insight into the molecular imaging of Alzheimer's disease. Int J Biomed Imaging 2016:7462014

Ashraf A, Fan Z, Brooks DJ et al (2015) Cortical hypermetabolism in MCI subjects: a compensatory mechanism? Eur J Nucl Med Mol Imaging 42:447–458

Bachman DL, Wolf PA, Linn RT et al (1993) Incidence of dementia and probable Alzheimer's disease in a general population: the Framingham Study. Neurology 43:515–519

Ballarini T, Iaccarino L, Magnani G et al (2016) Neuropsychiatric subsyndromes and brain metabolic network dysfunctions in early-onset Alzheimer's disease. Hum Brain Mapp 37:4234–4247

Bancher C, Lassmann H, Budka H et al (1987) Neurofibrillary tangles in Alzheimer's disease and progressive supranuclear palsy: antigenic similarities and differences. Microtubule-associated protein tau antigenicity is prominent in all types of tangles. Acta Neuropathol 74:39–46

Barrio J, Huang S, Cole G et al (1999) PET imaging of tangles and plaques in Alzheimer disease with a highly hydrophobic probe. J Labelled Comp Radiopharm 42:194–195

Barthel H, Sabri O (2011) Florbetaben to trace amyloid-β in the Alzheimer brain by means of PET. J Alzheimers Dis 26:117–121

Baruch K, Deczkowska A, Rosenzweig N et al (2016) PD-1 immune checkpoint blockade reduces pathology and improves memory in mouse models of Alzheimer's disease. Nat Med 22:135–137

Bateman RJ, Xiong C, Benzinger TL et al (2012) Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med 367:795–804

Beeri MS, Werner P, Davidson M et al (2002) The cost of behavioral and psychological symptoms of dementia (BPSD) in community dwelling Alzheimer's disease patients. Int J Geriatr Psychiatry 17:403–408

Benoit M, Dygai I, Migneco O et al (1999) Behavioral and psychological symptoms in Alzheimer's disease. Relation between apathy and regional cerebral perfusion. Dement Geriatr Cogn Disord 10:511–517

Benoit M, Koulibaly PM, Migneco O et al (2002) Brain perfusion in Alzheimer's disease with and without apathy: a SPECT study with statistical parametric mapping analysis. Psychiatr Res Neuroimaging 114:103–111

Benoit M, Clairet S, Koulibaly PM et al (2004) Brain perfusion correlates of the Apathy inventory dimensions of Alzheimer's disease. Int J Geriatr Psychiatry 19:864–869

Bertram L, Tanzi RE (2019) Alzheimer disease risk genes: 29 and counting. Nat Rev Neurol 15:191–192

Blennow K, de Leon MJ, Zetterberg H (2006) Alzheimer's disease. Lancet 368:387–403

Boersma F, Eefsting JA, van den Brink W et al (1998) Prevalence of dementia in a rural Netherlands population and the influence of DSM-III-R and CAMDEX criteria for the prevalence of mild and more severe forms. J Clin Epidemiol 51:189–197

Bohnen NI, Frey KA (2007) Imaging of cholinergic and monoaminergic neurochemical changes in neurodegenerative disorders. Mol Imaging Biol 9:243–257

Bonte FJ, Harris TS, Hynan LS et al (2006) Tc-99m HMPAO SPECT in the differential diagnosis of dementias with histopathological confirmation. Clin Nucl Med 31:376–378

Boundy KL, Rowe CC, Reid M, Kitchener M, Barnden L et al (1997) Comparison of cholinergic neuroreceptor SPECT with 123I-iododexemetide and 99mTc-HMPAO in the early diagnosis of Alzheimer's disease. In: De Deyn PP, Dierckx RA, Alavi A, Pickut BA (eds) A textbook of SPECT in neurology and psychiatry. John Libbey & Company Ltd, London

Boundy KL, Barnden LR, Katsifis AG et al (2005) Reduced posterior cingulated binding of I-123-iodo-dexetimide to muscarinic receptors in mild Alzheimer's disease. J Clin Neurosci 12:421–425

Braak E, Griffi K, Arai K et al (1999) Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? Eur Arch Psychiatry Clin Neurosci 249:14–22
Braskie MN, Klunder AD, Hayashi KM et al (2010) Plaque and tangle imaging and cognition in normal aging and Alzheimer's disease. Neurobiol Aging 31:1669–1678
Breitner JC, Baker LD, Montine TJ et al (2011) Extended results of the Alzheimer's disease anti-inflammatory prevention trial. Alzheimers Dement 7:402–411
Brendel M, Pogarell O, Xiong G et al (2015) Depressive symptoms accelerate cognitive decline in amyloid-positive MCI patients. Eur J Nucl Med Mol Imaging 42:716–724
Breteler MM, Claus JJ, van Duijn CM et al (1992) Epidemiology of Alzheimer's disease. Epidemiol Rev 14:59–82
Breteler MM, Ott A, Hofman A (1998) The new epidemic: frequency of dementia in the Rotterdam study. Haemostasis 28:117–123
Burns A, Lawlor B, Craig S (2004) Assessment scales in old age psychiatry, 2nd edn. Martin Dunetz, London
Cagnin A, Brooks DJ, Kennedy AM et al (2001) In-vivo measurement of activated microglia in dementia. Lancet 358:461–467
Caraci F, Copani A, Nicoletti F et al (2010) Depression and Alzheimer's disease: neurobiological links and common pharmacological targets. Eur J Pharmacol 626:64–71
Castilla-Puentes RC, Habeych ME (2010) Subtypes of depression among patients with Alzheimer's disease and other dementias. Alzheimers Dement 6:63–69
Charpentier P, Lavenu I, Defebvre L et al (2000) Alzheimer's disease and frontotemporal dementia are differentiated by discriminant analysis applied to 99mTc HMPAO SPECT data. J Neurol Neurosurg Psychiatry 69:661–663
Chen CJ, Bando K, Ashino H et al (2015) In vivo SPECT imaging of amyloid-β deposition with radioiodinated imidazo[1,2-a]pyridine derivative DRM106 in a mouse model of Alzheimer's disease. J Nucl Med 56:120–126
Chetelat G, Villemagne VL, Bourgeat P et al (2010) Relationship between atrophy and beta-amyloid deposition in Alzheimer disease. Ann Neurol 67:317–324
Chiaravalloti A, Barbagallo G, Ricci M et al (2018) Brain metabolic correlates of CSF Tau protein in a large cohort of Alzheimer's disease patients: a CSF and FDG PET study. Brain Res. 1678:116–122
Chiotis K, Stenkrona P, Almkvist O et al (2018) Dual tracer tau PET imaging reveals different molecular targets for 11C-THK5351 and 11C-PBB3 in the Alzheimer brain. Eur J Nucl Med Mol Imaging 45:1605–1617
Choi SR, Golding G, Zhuang ZP et al (2009) Preclinical properties of 18F-AV-45: a PET agent for Aβ plaques in the brain. J Nucl Med 50:1887–1894
Cohen-Mansfield J, Deutsch LH (1996) Agitation: subtypes and their mechanisms. Semin Clin Neuropsychiatry 1:325–339
Cohen-Mansfield J, Marx MS, Rosenthal AS (1989) A description of agitation in a nursing home. J Gerontol 44:77–84
Côté S, Carmichael PH, Verreault R et al (2012) Nonsteroidal anti-inflammatory drug use and the risk of cognitive impairment and Alzheimer's disease. Alzheimers Dement 8:219–226
Cruts M, Gijselinck I, van der Zee J et al (2006) Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature 442:920–924
Cummings JL, Mega MS, Gray K et al (1994) The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. Neurology 44:2308–2314
De Deyn PP (2004) Dementie—Medisch, psychosociaal, ethisch & preventief, 1st edn. Kluwer, Mechelen
De Deyn PP, Wirshing WC (2001) Scales to assess efficacy and safety of pharmacologic agents in treatment of behavioral and psychological symptoms of dementia. J Clin Psychiatry 62:19–22
De Deyn PP, Engelborghs S, Saerens J et al (2005) The Middelheim Frontality Score: a behavioural assessment scale that discriminates frontotemporal dementia from Alzheimer's disease. Int J Geriatr Psychiatry 20:70–79

De Deyn PP, Goeman J, Vervaet A et al (2011) Prevalence and incidence of dementia among 75-80-year-old community-dwelling elderly in different districts of Antwerp, Belgium: The Antwerp Cognition (ANCOG) Study. Clin Neurol Neurosurg 113:736–745

Debruyne H, Van Buggenhout M, Le Bastard N et al (2009) Is the geriatric depression scale a reliable screening tool for depressive symptoms in elderly patients with cognitive impairment ? Int J Geriatr Psychiatry 24:556–562

Dekker AD, Sacco S, Carfi A et al (2018) The behavioral and psychological symptoms of dementia in down syndrome (BPSD-DS) scale: comprehensive assessment of psychopathology in down syndrome. J Alzheimers Dis 63:797–820

Delrieu J, Desmidt T, Camus V et al (2015) Apathy as a feature of prodromal Alzheimer's disease: an FDG-PET ADNI study. Int J Geriatr Psychiatry 30:470–477

Deutsch LH, Bylsma FW, Rovner BW et al (1991) Psychosis and physical aggression in probable Alzheimer's disease. Am J Psychiatry 148:1159–1163

Devenand DP, Jacobs DM, Ming-Xin T et al (1997) The course of psychopathologic features in mild to moderate Alzheimer disease. Arch Gen Psychiatry 54:257–263

Dobos N, Korf J, Luiten PG et al (2010) Neuroinflammation in Alzheimer's disease and major depression. Biol Psychiatry 67:503–504

Doraiswamy PM, Sperling RA, Coleman RE et al (2012) Amyloid-β assessed by florbetapir F-18-PET and 18-month cognitive decline: a multicenter study. Neurology 79:1636–1644

Du X, Wang X, Geng M (2018) Alzheimer's disease hypothesis and related therapies. Transl Neurodegener 7:2

Dubois B, Feldman HH, Jacova C et al (2014) Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 13:614–629

Engelborghs S, Marescau B, De Deyn PP (2003) Amino acids and biogenic amines in cerebrospinal fluid of patients with Parkinson's disease. Neurochem Res 28:1145–1150

Engelborghs S, Vloeberghs E, Maertens K et al (2004) Correlations between cognitive, behavioural and psychological findings and levels of vitamin B12 and folate in patients with dementia: a prospective study. Int J Geriatr Psychiatry 19:365–370

Engelborghs S, Maertens K, Nagels G et al (2005) Neuropsychiatric symptoms of dementia: cross-sectional analysis from a prospective, longitudinal Belgian study. Int J Geriatr Psychiatry 20:1028–1037

Engelborghs S, Vloeberghs E, Le Bastard N et al (2008) The dopaminergic neurotransmitter system is associated with aggression and agitation in frontotemporal dementia. Neurochem Int 52:1052–1060

Farrer LA, Cupples LA, Haines JL et al (1997) Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: a meta-analysis. JAMA 278:1349–1356

Fekkes D, van der Cammen TJ, van Loon CP et al (1998) Abnormal amino acid metabolism in patients with early stage Alzheimer dementia. J Neural Transm 105:287–294

Fernández M, Gobartt AL, Balañá M, COOPERA Study Group (2010) Behavioural symptoms in patients with Alzheimer's disease and their association with cognitive impairment. BMC Neurol 10:87

Ferreira LK, Busatto GF (2011) Neuroimaging in Alzheimer's disease: current role in clinical practice and potential future applications. Clinics 66:19–24

Finkel SI (2000) Introduction to behavioural and psychological symptoms of dementia (BPSD). Int J Geriatr Psychiatry 15:2–4

Finkel SI (2001) Behavioral and psychological symptoms of dementia. A current focus for clinicians, researchers, and caregivers. J Clin Psychiatry 62:3–6

Finkel SI, Costa e Silva J, Cohen G et al (1996) Behavioral and psychological signs and symptoms of dementia: a consensus statement on current knowledge and implications for research and treatment. Int Psychogeriatr 8:497–500

Folstein MF, Folstein SE, McHugh PR (1975) Mini mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198

Forsberg A, Engler H, Almkvist O et al (2008) PET imaging of amyloid deposition in patients with mild cognitive impairment. Neurobiol Aging 29:1456–1465
Foster NL, Chase TN, Fedio P et al (1983) Alzheimer's disease: focal cortical changes shown by positron emission tomography. Neurology 33:961–965
Foster NL, Heidebrink JL, Clark CM et al (2007) FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. Brain 130:2616–2635
Francis PT (2009) Altered glutamate neurotransmission and behaviour in dementia: evidence from studies of memantine. Curr Mol Pharmacol 2:77–82
Fukuhara R, Ikeda M, Nebu A et al (2001) Alteration of rCBF in Alzheimer's disease patients with delusions of theft. Neuroreport 12:2473–2476
Galynker II, Dutta E, Vilkas N et al (2000) Hypofrontality and negative symptoms in patients with dementia of Alzheimer type. Neuropsychiatry Neuropsychol Behav Neurol 13:53–59
Garcia-Alloza M, Gil-Bea FJ, Diez-Ariza M et al (2005) Cholinergic-serotonergic imbalance contributes to cognitive and behavioral symptoms in Alzheimer's disease. Neuropsychologia 43:442–449
Garcia-Alloza M, Tsang SW, Gil-Bea FJ et al (2006) Involvement of the GABAergic system in depressive symptoms of Alzheimer's disease. Neurobiol Aging 27:1110–1117
Gauthier S, Gelinas I, Gauthier L (1997) Functional disability in Alzheimer's disease. Int Psychogeriatr 9:163–165
Geda YE, Schneider LS, Gitlin LN et al (2013) Neuropsychiatric symptoms in Alzheimer's disease: past progress and anticipation of the future. Alzheimers Dement 9:602–608
Geser F, Wenning GK, Poewe W et al (2005) How to diagnose dementia with Lewy bodies: state of the art. Mov Disord 20:11–20
Gijselinck I, Van Langenhove T, van der Zee J et al (2012) A C9orf72 promotor repeat expansion in a Flanders-Belgian cohort with disorders of the frontotemporal lobar degeneration-amyotrophic lateral sclerosis spectrum: a gene identification study. Lancet Neurol 11:54–65
Goedert M (1999) Filamentous nerve cell inclusions in neurodegenerative diseases: tauopathies and alpha-synucleinopathies. Philos Trans R Soc Lond B Biol Sci 354:1101–1118
Goedert M (2001) Alpha-synuclein and neurodegenerative diseases. Nat Rev Neurosci 2:492–501
Goto H, Ishii K, Uemura T et al (2010) Differential diagnosis of dementia with Lewy bodies and Alzheimer disease using combined MR imaging and brain perfusion single-photon emission tomography. Am J Neuroradiol 31:720–725
Grundke-Iqbal I, Iqbal K, Tung YC et al (1986) Abnormal phosphorylation of the microtubule-associated protein τ (tau) in Alzheimer cytoskeletal pathology. Proc Natl Acad Sci 83:4913–4917
Guerreiro R, Escott-Price V, Darwent L et al (2016) Genome-wide analysis of genetic correlation in dementia with Lewy bodies, Parkinson's and Alzheimer's diseases. Neurobiol Aging 38:214.e7–214.e10
Gwinn-Hardy K, Singleton AA (2002) Familial Lewy body diseases. J Geriatr Psychiatry Neurol 15:217–223
Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62
Hanyu H, Sato T, Hirao K et al (2010) The progression of cognitive deterioration and regional cerebral blood flow patterns in Alzheimer's disease: a longitudinal SPECT study. J Neurol Sci 290:96–101
Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 297:353–356
Harper DG, Stopa EG, McKee AC et al (2001) Differential circadian rhythm disturbances in men with Alzheimer's disease and frontotemporal degeneration. Arch Gen Psychiatry 58:353–360
Harvey RJ, Skelton-Robinson M, Rossor MN (2003) The prevalence and causes of dementia in people under the age of 65 years. J Neurol Neurosurg Psychiatry 74:1206–1209
Hellwig S, Frings L, Bormann T et al (2019) Amyloid imaging for differential diagnosis of dementia: incremental value compared to clinical diagnosis and [18F]FDG PET. Eur J Nucl Med Mol 46:312–323
Henderson AS (1990) Epidemiology in dementia disorders. Adv Neurol 51:15–25

Herholz K, Schopphoff H, Schmidt M et al (2002) Direct comparison of spatially normalized PET and SPECT scans in Alzheimer's disease. J Nucl Med 43:21–26
Herrmann N, Lanctôt KL, Khan LR (2004) The role of norepinephrine in the behavioral and psychological symptoms of dementia. J Neuropsychiatry Clin Neurosci 16:261–276
Hirono N, Mori E, Yasuda M, Ikejiri Y et al (1998) Factors associated with psychotic symptoms in Alzheimer's disease. J Neurol Neurosurg Psychiatry 64:648–652
Hirono N, Mega MS, Dinov ID et al (2000) Left frontotemporal hypoperfusion in associated with aggression in patients with dementia. Arch Neurol 57:861–866
Hofman A, Rocca WA, Brayne C et al (1991) The prevalence of dementia in Europe: a collaborative study of 1980-1990 findings. Int J Epidemiol 20:736–748
Holmgren S, Hjorth E, Schultzberg M et al (2014) Neuropsychiatric symptoms in dementia-a role for neuroinflammation? Brain Res Bull 108:88–93
Holthoff VA, Beuthien-Baumann B, Kalbe E et al (2005) Regional cerebral metabolism in early Alzheimer's disease with clinically significant apathy or depression. Biol Psychiatry 57:412–421
Hu XS, Okamura N, Arai H et al (2000) 18F-fluorodopa PET study of striatal dopamine uptake in the diagnosis of dementia with Lewy bodies. Neurology 55:1575–1577
Iaccarino L, Sala A, Caminiti SP et al (2017) The emerging role of PET imaging in dementia. F1000Res 6:1830
Imamura T, Ishii K, Sasaki M et al (1997) Regional cerebral glucose metabolism in dementia with Lewy bodies and Alzheimer's disease: a comparative study using positron emission tomography. Neurosci Lett 235:49–52
Iqbal K, Alonso Adel C, Chen S et al (2005) Tau pathology in Alzheimer disease and other tauopathies. Biochim Biophys Acta 1739:198–210
Ismail Z, Herrmann N, Francis PL et al (2009) A SPECT study of sleep disturbance and Alzheimer's disease. Dement Geriatr Cogn Disord 27:254–259
Ismail Z, Nguyen MQ, Fischer CE et al (2012) Neuroimaging of delusions in Alzheimer's disease. Psychiatry Res Neuroimaging 202:89–95
Jack CR Jr, Bennett DA, Blennow K et al (2016) A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology 87:539–547
Jack CR Jr, Bennett DA, Blennow K et al (2018) NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement 14:535–562
Jansen IE, Savage JE, Watanabe K et al (2019) Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. Nat Genet 51:404–413
Jeste DV, Finkel SI (2000) Psychosis of Alzheimer's disease and related dementias: diagnostic criteria for a distinct syndrome. Am J Geriatr Psychiatry 8:29–34
Johnson J, Hague SM, Hanson M et al (2004) SNCA multiplication is not a common cause of Parkinson disease or dementia with Lewy bodies. Neurology 63:554–556
Johnson KA, Fox NC, Sperling RA (2012) Brain imaging in Alzheimer's disease. Cold Spring Harb Perspect Med 2:a006213
Jost BC, Grossberg GT (1996) The evolution of psychiatric symptoms in Alzheimer's disease: a natural history study. J Am Geriatr Soc 44:1078–1081
Kang JY, Lee JS, Kang H et al (2011) Regional cerebral blood flow abnormalities associated with apathy and depression in Alzheimer's disease. Alzheimer Dis Assoc Disord 26:217–224
Kasanuki K, Iseki E, Ota K et al (2017) 123I-FP-CIT SPECT findings and its clinical relevance in prodromal dementia with Lewy bodies. Eur J Nucl Med Mol Imaging 44:358–365
Kataoka K, Hashimoto H, Kawabe J et al (2010) Frontal hypoperfusion in depressed patients with dementia of the Alzheimer type demonstrated on 3DSRT. Psychiatr Clin Neurosci 64:293–298
Katzman R, Lasker B, Bernstein N (1988) Advances in diagnosis of dementia: accuracy of diagnosis and consequences of misdiagnosis of disorders causing dementia. In: Terry RD (ed) Aging and the brain. Raven Press, New York, pp 17–62
Kaufer DI, Cummings JL, Christine D et al (1998) Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: the Neuropsychiatric inventory caregiver distress scale. J Am Geriatr Soc 46:210–215

Kaufer DI, Cummings JL, Ketchel P et al (2000) Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neurosci 12:233–239
Keith AJ (2008) Frontotemporal dementia and related disorders: deciphering the enigma. Ann Neurol 64:4–14
Kepe V, Barrio JR, Huang SC et al (2006) Serotonin 1A receptors in the living brain of Alzheimer's disease patients. Proc Natl Acad Sci USA. 103:702–707
Khosravi M, Peter J, Wintering NA et al (2019) 18F-FDG is a superior indicator of cognitive performance compared to 18F-florbetapir in Alzheimer's disease and mild cognitive impairment evaluation: a global quantitative analysis. J Alzheimers Dis 70:1197–1207. https://doi.org/10.3233/JAD-190220
Koppel J, Sunday S, Goldberg TE et al (2014) Psychosis in Alzheimer's disease is associated with frontal metabolic impairment and accelerated decline in working memory: findings from the Alzheimer's disease neuroimaging initiative. Am J Geriatr Psychiatry 22:698–707
Korczyn AD, Halperin I (2009) Depression and dementia. J Neurol Sci 283:139–142
Kuhl DE, Koeppe RA, Minoshima S et al (1999) In vivo mapping of cerebral acetylcholinesterase activity in aging and Alzheimer's disease. Neurology 52:691–699
Kukull WA, Higdon R, Bowen JD et al (2002) Dementia and Alzheimer disease incidence—a prospective cohort study. Arch Neurol 59:1737–1746
Kung MP, Hou C, Zhuangn ZP et al (2004) Binding of two potential imaging agents targeting amyloid plaques in postmortem brain tissue of patients with Alzheimer's disease. Brain Res 1025:98–105
Lanari A, Amenta F, Silvestrelli G et al (2006) Neurotransmitter deficits in behavioural and psychological symptoms of Alzheimer's disease. Mech Ageing Dev 127:158–165
Lanctôt KL, Herrmann N, Mazzotta P (2001) Role of serotonin in the behavioral and psychological symptoms of dementia. J Neuropsychiatry Clin Neurosci 13:5–21
Lanctôt KL, Herrmann N, Nadkarni NH et al (2004) Medial temporal hypoperfusion and aggression in Alzheimer disease. Arch Neurol 61:1731–1737
Lanctôt KL, Amatniek J, Ancoli-Israel S et al (2017) Neuropsychiatric signs and symptoms of Alzheimer's disease: new treatment paradigms. Alzheimers Dement (NY) 3:440–449
Launer LJ, Andersen K, Dewey ME et al (1999) Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. EURODEM Incidence Research Group and Work Groups. European studies of dementia. Neurology 52:78–84
Lawton MP, Brody EM (1969) Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 9:179–186
de Leon MJ, Convit A, Wolf OT et al (2001) Prediction of cognitive decline in normal elderly subjects with 2-[(18)F]fluoro-2-deoxy-D-glucose/positron-emission tomography (FDG/PET). Proc Natl Acad Sci 98:10,966–10,971
Levy ML, Miller BL, Cummings JL et al (1996) Alzheimer disease and frontotemporal dementias. Behavioral distinctions. Arch Neurol 53:687–690
Levy ML, Cummings JL, Fairbanks LA et al (1998) Apathy is not depression. J Neuropsychiatry Clin Neurosci 10:314–319
Levy-Cooperman N, Burhan AM, Rafi-Tari S et al (2008) Frontal lobe hypoperfusion and depressive symptoms in Alzheimer's disease. J Psychiatry Neurosci 33:218–226
Liao YC, Liu RS, Lee YC et al (2003) Selective hypoperfusion of anterior CC in depressed AD patients: a brain SPECT finding by statistical parametric mapping. Dement Geriatr Cogn Disord 16:238–244
van der Linde RM, Dening T, Stephan BCM et al (2016) Longitudinal course of behavioural and psychological symptoms of dementia: systematic review. Br J Psychiatry 209: 366–377
Little JT, Satlin A, Sunderland T et al (1995) Sundown syndrome in severely demented patients with probable Alzheimer's disease. J Geriatr Psychiatry Neurol 8:103–106
Loo D, Copani A, Pike C et al (1993) Apoptosis is induced by B-amyloid in cultured central nervous. Proc Natl Acad Sci USA 90:7951–7955

Lowe VJ, Lundt E, Knopman D et al (2017) Comparison of [18F]Flutemetamol and [11C]Pittsburgh compound-B in cognitively normal young, cognitively normal elderly, and Alzheimer's disease dementia individuals. Neuroimage Clin 16:295–302
Lyketsos CG, Steele C, Galik E et al (1999) Physical aggression in dementia patients and its relationship to depression. Am J Psychiatry 156:66–71
Lyketsos CG, Steinberg M, Tschanz JT et al (2000) Mental and behavioral disturbances in dementia: findings from the Cache County Study on memory in aging. Am J Psychiatry 157:708–714
Lyketsos CG, Carrillo MC, Ryan MJ et al (2011) Neuropsychiatric symptoms in Alzheimer's disease. Alzheimers Dement 7:532–539
Magistretti PJ (2006) Neuron-glia metabolic coupling and plasticity. J Exp Biol 209:2304–2311
Mann DM, Yates PO (1983) Serotonin nerve cells in Alzheimer's disease [letter]. J Neurol Neurosurg Psychiatry 46:96
Maruyama M, Shimada H, Suhara T et al (2013) Imaging of tau pathology in a tauopathy mouse model and in Alzheimer patients compared to normal controls. Neuron 79:1094–1108
Mash DC, Flynn DD, Potter LT (1985) Loss of M2 muscarine receptors in the cerebral cortex in Alzheimer's disease and experimental cholinergic denervation. Science 228:1115–1117
Mathis CA, Bacskai BJ, Kajdasz ST et al (2002) A lipophilic thioflavin-T derivative for positron emission tomography (PET) imaging of amyloid in brain. Bioorganic Med Chem Lett 12:295–298
Matsuoka T, Narumoto J, Shibata K et al (2010) Insular hypoperfusion correlates with the severity of delusions in individuals with Alzheimer's disease. Dement Geriatr Cogn Disord 29:287–293
Matthews KL, Chen CP, Esiri MM et al (2002) Noradrenergic changes, aggressive behavior, and cognition in patients with dementia. Biol Psychiatry 51:407–416
Mazère J, Prunier C, Barret O et al (2008) In vivo SPECT imaging of vesicular acetylcholine transporter using [123I]-IBVM in early Alzheimer's disease. Neuroimage 40:280–288
Mazère J, Lamare F, Allard M et al (2017) 123I-iodobenzovesamicol SPECT imaging of cholinergic systems in dementia with Lewy bodies. J Nucl Med 58:123–128
McKeith IG, Dickson DW, Lowe J et al (2005) Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 65:1863–1872
McKeith IG, Boeve BF, Dickson DW et al (2017) Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. Neurology 89:88–100
McKhann G, Drachman D, Folstein M et al (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34:939–944
McKhann G, Knopman DS, Chertkow H et al (2011) The diagnosis of dementia due to Alzheimer's disease: Recommendation from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:263–269
de Medeiros K, Robert P, Gauthier S et al (2010) The Neuropsychiatric Inventory-Clinician rating scale (NPI-C): reliability and validity of a revised assessment of neuropsychiatric symptoms in dementia. Int Psychogeriatr 22:984–994
Meltzer CC, Smith G, DeKosky ST et al (1998) Serotonin in aging, late-life depression, and Alzheimer's disease: the emerging role of functional imaging. Neuropsychopharmacology 18:407–430
Mikkelsen K, Stojanovska L, Tangalakis K et al (2016) Cognitive decline: a vitamin B perspective. Maturitas 93:108–113
Minoshima S, Giordani B, Berent S et al (1997) Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. Ann Neurol 42:85–94
Mitnitski AB, Graham JE, Mogilner AJ et al (1999) The rate of decline in function in Alzheimer's disease and other dementias. J Gerontol A Biol Sci Med Sci 54:65–69
Monteiro IM, Boksay I, Auer SR et al (2001) Addition of a frequency-weighted score to the behavioral pathology in Alzheimer's disease rating scale: the BEHAVE-AD-FW: methodology and reliability. Eur Psychiatry 16:5–24
Moran EK, Becker JA, Satlin A et al (2008) Psychosis of Alzheimer's disease: gender differences in regional perfusion. Neurobiol Aging 29:1218–1225

Moreira PI, Smith MA, Zhu X et al (2005) Oxidative stress and neurodegeneration. Ann NY Acad Sci 1043:545–552
Morganti F, Soli A, Savoldelli P et al (2018) The Neuropsychiatric Inventory-Diary Rating Scale (NPI-Diary): a method for improving stability in assessing neuropsychiatric symptoms in dementia. Dement Geriatr Cogn Disord Extra 8:306–320
Mori T, Ikeda M, Fuhukara R et al (2006) Regional cerebral blood flow change in a case of Alzheimer's disease with musical hallucinations. Eur Arch Psychiatry Clin Neurosci 256:236–239
Morris JC (1994) Differential diagnosis of Alzheimer's disease. Clin Geriatr Med 10:257–276
Muller-Gartner HW, Wilson AA, Dannals RF et al (1992) Imaging muscarinic cholinergic receptors in the human brain in vivo with SPECT, 123I-4-iododexemitide. J Cereb Blood Flow Metab 12:562
Nagahama Y, Okina T, Suzuki N et al (2010) Neural correlates of psychotic symptoms in dementia with Lewy bodies. Brain 133:557–567
Nagao M, Sugawara Y, Ikeda M et al (2006) Heterogeneity of posterior limbic perfusion in very early Alzheimer's disease. Neurosci Res 55:285–291
Nakano S, Yamashita F, Matsuda H et al (2006a) Relationship between delusions and regional cerebral blood flow in Alzheimer's disease. Dement Geriatr Cogn Disord 21:16–21
Nakano S, Asada T, Yamashita F et al (2006b) Relationship between antisocial behavior and regional cerebral blood flow in frontotemporal dementia. Neuroimage 32:301–306
Nakayama S, Suda A, Nakanishi A et al (2017) Galantamine response associates with agitation and the prefrontal cortex in patients with Alzheimer's disease. J Alzheimers Dis 57:267–273
Neary D, Snowden JS, Gustafson L et al (1998) Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 51:1546–1554
Neumann M, Sampathu DM, Kwong LK et al (2006) Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science 314:130–133
Newberg AB, Arnold SE, Wintering N et al (2012) Initial clinical comparison of 18F-florbetapir and 18F-FDG-PET in patients with Alzheimer disease and controls. J Nucl Med 53:902–907
Ng KP, Pascoal TA, Mathotaarachchi S et al (2017) Neuropsychiatric symptoms predict hypometabolism in preclinical Alzheimer disease. Neurology 88:1814–1821
Niu H, Álvarez-Álvarez I, Guillén-Grima F et al (2017) Prevalence and incidence of Alzheimer's disease in Europe: a meta-analysis. Neurología 32:523–532
O'Brien JT, Firbank MJ, Mosimann UP et al (2005) Change in perfusion, hallucinations and fluctuations in consciousness in dementia with Lewy bodies. Psychiatry Res 139:79–88
Okamura N, Harada R, Ishiki A et al (2018) The development and validation of tau PET tracers: current status and future directions. Clin Transl Imaging 6:305–316
Ono M, Saji H (2012) Molecular approaches to the treatment, prophylaxis, and diagnosis of Alzheimer's disease: novel PET/SPECT imaging probes for diagnosis of Alzheimer's disease. J Pharmacol Sci 118:338–344
Ott A, Breteler MM, van Harskamp HF et al (1995) Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study. BMJ 310:970–973
Ouchi Y, Yoshikawa E, Futatsubashi M et al (2009) Altered brain serotonin transporter and associated glucose metabolism in Alzheimer disease. J Nucl Med 50:1260–1266
Palmer AM, Francis PT, Benton JS et al (1987) Presynaptic serotonergic dysfunction in patients with Alzheimer's disease. J Neurochem 48:8–15
Patterson MB, Schnell AH, Martin RJ et al (1990) Assessment of behavioral and affective symptoms in Alzheimer's disease. J Geriatr Psychiatry Neurol 3:21–30
Perani D, Cerami C, Caminiti SP et al (2016) Cross-validation of biomarkers for the early differential diagnosis and prognosis of dementia in a clinical setting. Eur J Nucl Med Mol Imaging 43:499–508
Peretti DE, Vállez García D, Reesink FE et al (2019) Relative cerebral flow from dynamic PIB scans as an alternative for FDG scans in Alzheimer's disease PET studies. PLoS One 14(1):e0211000
Perneczky R, Drzezga A, Boecker H et al (2008) Cerebral metabolic dysfunction in patients with dementia with Lewy bodies and visual hallucinations. Dement Geriatr Cogn Disord 25:531–538

Perneczky R, Drzezga A, Boecker H et al (2009) Right prefrontal hypometabolism predicts delusions in dementia with Lewy bodies. Neurobiol Aging 30:1420–1429
Peters F, Perani D, Herholz K et al (2006) Orbitofrontal dysfunction related to both apathy and disinhibition in frontotemporal dementia. Dement Geriatr Cogn Disord 21:373–379
Pickut BA, Saerens J, Mariën P et al (1997) Discriminative use of SPECT in frontal lobe-type dementia versus (senile) dementia of the Alzheimer's type. J Nucl Med 38:929–934
Pietrzak RH, Gallezot JD, Ding YS et al (2013) Association of posttraumatic stress disorder with reduced in vivo norepinephrine transporter availability in the locus coeruleus. JAMA Psychiatry 70:1199–1205
Ponton MO, Darcourt JL, Miller BL et al (1995) Psychometric and SPECT studies in Alzheimer's disease with and without delusions. Neuropsychiatry Neuropsychol Behav Neurol 8:264–270
Prinz PN, Peskind ET, Vitaliano PP et al (1982) Changes in the sleep and waking EEG's of nondemented and demented elderly subjects. J Am Geriatr Soc 30:86–93
Rackza KA, Becker G, Seese A et al (2010) Executive and behavioral deficits share common neural substrates in frontotemporal lobar degeneration—a pilot FDG-PET study. Psychiatry Res 182:274–280
Ready RE, Ott BR, Grace J et al (2003) Apathy and executive dysfunction in mild cognitive impairment and Alzheimer disease. Am J Geriatr Psychiatry 11:222–228
Reeves S, Brown R, Howard R et al (2009) Increased striatal dopamine (D2/D3) receptor availability and delusions in Alzheimer's disease. Neurology 72:528–534
Reiman EM, Chen K, Alexander GE et al (2005) Correlations between apolipoprotein E 14 gene dose and brain-imaging measurements of regional hypometabolism. Proc Natl Acad Sci 102:8299–8302
Reisberg B, Borenstein J, Franssen E et al (1986) Remediable behavioral symptomatology in Alzheimer's disease. Hosp Commun Psychiatry 37:1199–1201
Reisberg B, Borenstein J, Salob SP et al (1987) Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. J Clin Psychiatry 48:9–15
Robert PH, Darcourt G, Koulibaly MP et al (2006) Lack of initiative and interest in Alzheimer's disease: a SPECT study. Eur J Neurol 13:729–735
Robert PH, Onyike CU, Leentjens AFG et al (2009) Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. Eur Psychiatry 24:98–104
Roelands M, Wostyn P, Dom H et al (1994) The prevalence of dementia in Belgium: a population-based door-to-door survey in a rural community. Neuroepidemiology 13:155–161
Rolland Y, Gillette-Guyonnet S, Nourhashemi F et al (2003) Wandering and Alzheimer's type disease. Descriptive study. REAL.FR research program on Alzheimer's disease and management. Rev Med Interne 24:333–338
Rolland Y, Payoux P, Lauwers-Cances V et al (2005) A SPECT study of wandering behavior in Alzheimer's disease. Int J Geriatr Psychiatry 20:816–820
Rollin-Sillaire A, Bombois S, Deramecourt V et al (2012) Contribution of single photon emission computed tomography to the differential diagnosis of dementia in a memory clinic. J Alzheimers Dis 30:833–845
Roselli F, Pisciotta NM, Perneczky R et al (2009) Severity of neuropsychiatric symptoms and dopamine transporter levels in dementia with Lewy bodies: a 123I-FP-CIT SPECT study. Mov Disord 24:2097–2103
Rosen J, Zubenko GS (1991) Emergence of psychosis and depression in the longitudinal evaluation of Alzheimer's disease. Biol Psychiatry 29:224–232
Rosen WG, Mohs RC, Davis KL (1984) A new rating scale for Alzheimer's disease. Am J Psychiatry 141:1356–1364
Rovner BW, German PS, Brant LJ et al (1991) Depression and mortality in nursing homes. JAMA 265:993–996
Sander K, Lashley T, Gami P et al (2016) Characterization of tau positron emission tomography tracer [18F]AV-1451 binding to postmortem tissue in Alzheimer's disease, primary tauopathies, and other dementias. Alzheimers Dement 12:1116–1124

Scarmeas N, Brandt J, Albert M et al (2005) Delusions and hallucinations are associated with worse outcome in Alzheimer's disease. Arch Neurol 62:1601–1608
Schroeter ML, Stein T, Maslowski N et al (2009) Neural correlates of Alzheimer's disease and mild cognitive impairment: a systematic and quantitative meta-analysis involving 1351 patients. Neuroimage 47:1196–1206
Schroeter ML, Vogt B, Frisch S et al (2011) Dissociating behavioral disorders in early dementia—an FDG-PET study. Psychiatry Res 194:235–244
Schwartz WJ, Smith CB, Davidsen L et al (1979) Metabolic mapping of functional activity in the hypothalamo-neurohypophysial system of the rat. Science 205:723–725
Sclan SG, Saillon A, Franssen E et al (1996) The behavioral pathology in Alzheimer's disease rating scale (BEHAVE-AD): reliability and analysis of symptom category scores. Int J Geriatr Psychiatry 11:819–830
Sibson NR, Dhankhar A, Mason GF et al (1997) In vivo 13C NMR measurements of cerebral glutamine synthesis as evidence for glutamate-glutamine cycling. Proc Natl Acad Sci 94:2699–2704
Sieben A, Van Langenhove T, Engelborghs S et al (2012) The genetics and neuropathology of frontotemporal lobar degeneration. Acta Neuropathol 124:353–372
Sierksma AS, van den Hove DL, Steinbusch HW et al (2010) Major depression, cognitive dysfunction and Alzheimer's disease: is there a link? Eur J Pharmacol 626:72–82
Singleton A, Gwinn-Hardy K (2004) Parkinson's disease and dementia with Lewy bodies: a difference in dose? Lancet 364:1105–1107
Small GW, Rabins PV, Barry PP et al (1997) Diagnosis and treatment of Alzheimer disease and related disorders. Consensus statement of the American association for geriatric psychiatry, the Alzheimer's association, and the American geriatrics society. JAMA 278:1363–1371
Smith AD (2002) Imaging the progression of AD pathology through the brain. Proc Natl Acad Sci USA 99:4135–4137
Smith MA, Casadesus G, Joseph JA et al (2002) Amyloid-β and tau serve antioxidant functions in the aging and Alzheimer brain. Free Radic Biol Med. 33:1194–1199
Smith JA, Bourdet DL, Daniels OT et al (2014) Preclinical to clinical translation of CNS transporter occupancy of TD-9855, a novel norepinephrine and serotonin reuptake inhibitor. Int J Neuropsychopharmacol 18(2):pyu027
Sommerauer M, Hansen AK, Parbo P et al (2018) Decreased noradrenaline transporter density in the motor cortex of Parkinson's disease patients. Mov Disord. 33:1006–1010
Staff RT, Shanks MF, Macintosh L et al (1999) Delusions in Alzheimer's disease: spet evidence of right hemispheric dysfunction. Cortex 35:549–560
Starkstein SE, Vazquez S, Petracca G et al (1994) A SPECT study of delusions in Alzheimer's disease. Neurology 44:2055–2059
Starkstein SE, Jorge R, Mizrahi R et al (2005) The construct of minor and major depression in Alzheimer's disease. Am J Psychiatry 162:2086–2093
Steinberg M, Huibo S, Zandi P et al (2008) Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cach County Study. Int J Geriatri Psychiatry 23:170–177
Suhara T, Higuchi M, Miyoshi M (2008) Neuroimaging in dementia: in vivo amyloid imaging. Tohoku J Exp Med 215:119–124
Sultzer DL (1996) Behavioral syndrome in dementia: neuroimaging insights. Semin Clin Neuropsychiatry 1:261–271
Sultzer DL, Brown CV, Mandelkern MA et al (2003) Delusional thoughts and regional frontal/temporal cortex metabolism in Alzheimer's disease. Am J Psychiatry 160:341–349
Swearer JM (1994) Behavioral disturbances in dementia. In: Morris JC (ed) Handbook of dementing illnesses. Marcel Dekker, New York, pp 499–527
Szaruga M, Munteanu B, Lismont S et al (2017) Alzheimer's-causing mutations shift Ab length by destabilizing g-Secretase-Abn interactions. Cell 170:443–456
Tanaka T, Meguro K, Yamaguchi S et al (2003) Decreased striatal D2 receptor density associated with severe behavioral abnormality in Alzheimer's disease. Ann Nucl Med 17:567–573
Tatsch K (2008) Imaging of the dopaminergic system in differential diagnosis of dementia. Eur J Nucl Med Mol Imaging 35:51–57

Thomas AJ, Hendriksen M, Piggott M et al (2006) A study of the serotonin transporter in the prefrontal cortex in late-life depression and Alzheimer's disease with and without depression. Neuropathol Appl Neurobiol 32:296–303
Trembath Y, Rosenberg C, Ervin JF et al (2003) Lewy body pathology is a frequent co-pathology in familial Alzheimer's disease. Acta Neuropathol 105:484–488
Valotassiou V, Archimandritis S, Sifakis N et al (2010) Alzheimer's disease: SPECT and PET tracers for beta-amyloid imaging. Curr Alzheimer Res 7:477–486
Van Dam D, De Deyn PP (2006) Drug discovery in dementia: the role of rodent models. Nat Rev Drug Discov 5:956–970
Van Mossevelde S, Engelborghs S, van der Zee J et al (2018) Genotype-phenotype links in frontotemporal lobar degeneration. Nat Rev Neurol 14:363–378
Vandenberghe R, Van Laere K, Ivanoiu A et al (2010) 18F-flutemetamol amyloid imaging in Alzheimer's disease and mild cognitive impairment: a phase 2 trial. Ann Neurol 68:319–329
Vermeiren Y, De Deyn PP (2017) Targeting the norepinephrinergic system in Parkinson's disease and related disorders: the locus coeruleus story. Neurochem Int 102:22–32
Vermeiren Y, Le Bastard N, Van Hemelrijck A et al (2013) Behavioral correlates of cerebrospinal fluid amino acid and biogenic amine neurotransmitter alterations in dementia. Alzheimers Dement 9:488–498
Vermeiren Y, Van Dam D, Aerts T et al (2014) Monoaminergic neurotransmitter alterations in postmortem brain regions of depressed and aggressive patients with Alzheimer's disease. Neurobiol Aging 35:2691–2700
Vermeiren Y, Van Dam D, Aerts T et al (2015) The monoaminergic footprint of depression and psychosis in dementia with Lewy bodies compared to Alzheimer's disease. Alzheimers Res Ther 7(1):7. https://doi.org/10.1186/s13195-014-0090-1. eCollection 2015
Vermeiren Y, Janssens J, Aerts T et al (2016) Brain serotonergic and noradrenergic deficiencies in behavioral variant frontotemporal dementia compared to early-onset Alzheimer's disease. J Alzheimers Dis 53:1079–1096
Versijpt J, Van Laere KJ, Dumont F et al (2003a) Imaging the 5-HT2A system: age-, gender-, and Alzheimer's disease-related findings. Neurobiol Aging 24:553–561
Versijpt J, Dumont F, Van Laere KJ et al (2003b) Assessment of neuroinflammation and microglial activation in Alzheimer's disease with radiolabelled PK11195 and single photon emission computed tomography. A pilot study. Eur Neurol 50:39–47
Versporten A, Bossuyt N, Meulenberghs L et al (2005) The incidence of dementia: relationship with educational attainment. Arch Public Health 63:279–292
Villemagne VL, Ong K, Mulligan RS et al (2011) Amyloid imaging with (18)F-florbetaben in Alzheimer disease and other dementias. J Nucl Med 52:1210–1217
Vladimir NU (2007) Neuropathology, biochemistry, and biophysics of α-synuclein aggregation. J Neurochem 103:17–37
Waldemar G, Dubois B, Emre M et al (2007) Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. Eur J Neurol 14:1–26
Walker Z, Costa DC, Walker RWH et al (2002) Differentiation of dementia with Lewy bodies from Alzheimer's disease using a dopaminergic presynaptic ligand. J Neurol Neurosurg Psychiatry 73:134–140
Weamer EA, Emanuel JE, Varon D et al (2009) The relationship of excess cognitive impairment in MCI and early Alzheimer's disease to the subsequent emergence of psychosis. Int Psychogeriatr 21:78–85
Weggen SA (2001) Subset of NSAIDs lower amyloidogenic Aβ42 independently of cyclooxygenase activity. Nature 414:212–216
Weissberger GH, Melrose RJ, Narvaez TA et al (2017) 18F-fluorodeoxyglucose positron emission tomography cortical metabolic activity associated with distinct agitation behaviors in Alzheimer disease. Am J Geriatr Psychiatry 25:569–579
Wimo A, Winblad B, Aguero-Torres H et al (2003) The magnitude of dementia occurrence in the world. Alzheimer Dis Assoc Disord 17:63–67

Witte MM, Foster NL, Fleisher AS et al (2015) Clinical use of amyloid-positron emission tomography neuroimaging: practical and bioethical considerations. Alzheimers Dement (Amst) 1:358–367

Wolk DA, Grachev ID, Buckley C et al (2011) Association between in vivo fluorine 18-labeled flutemetamol amyloid positron emission tomography imaging and in vivo cerebral cortical histopathology. Arch Neurol 68:1398–1403

Wolk DA, Zhang Z, Boudhar S et al (2012) Amyloid imaging in Alzheimer's disease: comparison of florbetapir and Pittsburgh compound-B positron emission tomography. J Neurol Neurosurg Psychiatry 83:923–926

Wong DF, Rosenberg PB, Zhou Y et al (2010) In vivo imaging of amyloid deposition in Alzheimer disease using the radioligand 18F-AV-45 (florbetapir [corrected] F 18). J Nucl Med 51:913–920

Wood S, Cummings JL, Hsu MA et al (2000) The use of the neuropsychiatric inventory in nursing home residents. Characterization and measurement. Am J Geriatr Psychiatry 8:75–83

Yasuno F, Matsuoka K, Miyasaka T et al (2019) Decreased perfusion of the posterior cingulate gyri shown by a cingulate island score is a possible marker of vulnerability to behavioural and psychological symptoms of Alzheimer's disease: a pilot study. Psychogeriatrics 19:165–170

Yatham LN, Sossi V, Ding YS et al (2018) A positron emission tomography study of norepinephrine transporter occupancy and its correlation with symptom response in depressed patients treated with quetiapine XR. Int J Neuropsychopharmacol 21:108–113

Yesavage JA, Brink TL, Rose TL et al (1983) Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 17:37–49