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REVIEW

Clinicopathological correlates of behavioral and psychological symptoms of dementia

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Abstract Behavioral and psychological symptoms are commonly observed in a majority of demented patients at some time during the course of their illness. Many of these psychiatric manifestations, especially those related to mood, may be early expressions of dementia and/or mild cognitive impairment. The literature suggests that behavioral and psychological symptoms of dementia (BPSD) are an integral part of the disease process. The dissociation, in many cases, between BPSD and the rather linear decline in cognitive functions suggests that independent pathophysiological mechanisms give rise to these symptoms. A review of the neuroimaging and neuropathology literature indicates that BPSD are the expression of regional rather than diffuse brain pathology. Psychotic symptoms in demented patients usually demonstrate preferential involvement of the frontal lobe and/or limbic regions. Visual hallucinations differentiate themselves from other psychotic symptoms by their tendency to involve the occipital lobes. There is a significant association between apathy and structural changes of the anterior cingulate gyrus. White matter hyperintensities occur in a significant number of depressed patients; otherwise, there is lack of association between depression and either specific brain changes or affected regions. Strictly neuropathological explanations are likely to be insufficient to explain BPSD. Environmental changes, neurochemical abnormalities, past psychiatric history (including premorbid personality), social history (e.g., intellectual achievement and life-long learning), family history, and genetic susceptibility are factors, among others, that influence BPSD.

Keywords Dementia · Alzheimer disease · Lewy body disease · Frontotemporal dementia · Psychotic disorders · Depression

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Introduction

It is now recognized that psychiatric manifestations of dementia arise from specific dysfunction of brain systems that are, in some cases, independent of cognitive impairment [150, 154]. Clinicians now accept that, if left untreated, these manifestations appear to be the most troublesome problems handled by caregivers of demented patients as they: pose the most significant risks to patients, provide the greatest deterioration in quality of life (for patients, relatives and caregivers), and portend both a faster cognitive decline as well as decreased survival for patients [2, 40, 190].

Ever since the term was introduced some 15 years ago there has been an ongoing debate as to whether "behavioral and psychological symptoms of dementia" (BPSD) are non-specific aspects of dementia or distinct phenotypes. BPSD may precede cognitive impairment by several years [82] and can rightfully be considered as prodromal symptoms to dementia [10]. This is most prominent in dementia with Lewy bodies (DLB) wherein characteristic visual

hallucinations may be marked in the presence of little or no cognitive impairment [89]. Similarly, in Alzheimer disease (AD), depression often occurs prior to or concurrent to the clinical onset of the condition [119].

Grouping studies have provided models of BPSD clusters which generally include psychotic, affective, and behavioral elements [54]. In this article, we follow the traditional model of psychiatry in grouping BPSD into components and examine neuropathological correlates to both psychotic (i.e., hallucinations and delusions) and affective (i.e., depression, apathy) symptoms. The resultant subdivisions are in agreement with the behavioral subtypes proposed by both DSM-IV and ICD-10. Wherever the literature is abundant, primarily in the case of psychosis, symptoms will be further described according to the type of dementia.

Besides psychotic and affective symptoms, numerous other psychiatric manifestations have been reported in dementia. However, abnormal behaviors such as agitation and aggression are often meant to describe a variety of manifestations. The multiplicity of inciting causes, heavy influence on personal characteristics, and sparse literature prompts us to avoid establishing clinicopathological correlates for behaviors other than psychotic and affective. Furthermore, within the BPSD components of psychotic and affective symptoms, we have opted to explore for clinicopathological correlates to individual psychiatric symptoms.

Psychotic symptoms

Alzheimer's disease

Psychosis, defined by hallucinations and delusions, occurs in a subset of AD patients (AD + P) during progression of the disease [26, 27]. Hallucinations can occur in any modality, but are typical visual [79, 162, 187]. They are usually associated with greater cognitive impairment [30, 201, 203] and a more severe cognitive decline [40, 160, 167, 186]. Common delusions are of persecution, infidelity, abandonment, or belief that deceased individuals are still alive [187]. Delusions become more fragmented as the disease progresses. Several authors have indicated that a certain threshold of cognitive integrity is required for delusions to occur [106, 158]. Forstl et al. [52] concluded that although some level of pathology is necessary to give rise to psychoses, patients need to be moderately intellectually preserved in order to elaborate the context of their delusions. In effect, delusions as well as other BPSD are rarely observed at terminal stages of dementia [113].

A review of 55 AD studies with 9,749 patients showed a median prevalence of psychotic symptoms in 41%, delusions in 36%, hallucinations in 18%, and both hallucinations and delusions in 13% [158]. Other estimates of psychosis in AD patients range from 10 to 73%, being more frequent in nursing home patients. Two-thirds of patients in nursing homes have persistent symptoms over 12 weeks. More specifically, among outpatients, hallucinations and delusions may persist in 40–50% over periods of 3 months up to 1 year [168]. AD + P is often associated with other psychiatric and behavioral disturbances, the most frequent and troublesome of which are agitation [56] and aggression [37, 57]. For epidemiology of psychotic symptoms see Table 1.

Neuroimaging (Tables 2, 3)

Single photon emission tomography (SPECT) studies in AD + P patients showed a pattern of cerebral blood flow (CBF) deficits significantly different from that in non-psychotic patients. Those with hallucinations had hypoperfusion in the parietal lobe while non-psychotic patients had similar deficits in the left frontal lobe [90]. Others have reported significant correlations between psychosis and metabolism in the frontal lobe, and between agitation/inhibition scores and metabolism in the frontal and temporal lobes [182]. AD + P patients revealed significant lower regional perfusion in bilateral dorsolateral frontal, left anterior cingulate gyrus, and left ventral striatal regions along with the left pulvinar and dorsolateral parietal cortex in comparison to a non-psychotic group [121].

Perfusion positron emission tomography (PET) studies in female AD + P showed lower perfusion in right inferior-lateral frontal cortex and inferior temporal regions compared to females without such symptoms, whereas in male AD + P patients, perfusion was higher in the right striatum, indicating gender differences in regional perfusion in AD + P [133]. An AD group with delusions had significant flow reductions in the prefrontal, anterior cingulate, inferior and middle temporal, and parietal cortices of the right hemisphere [139], while an AD group with autobiographic delusions had significant hypoperfusion in the right frontal lobe including BA 9 and 10, suggesting that a focal functional damage was liable for the content-specific delusions [176, 184].

Volumetric magnetic resonance imaging (MRI) studies showed an association between visual hallucinations (VHs) and decreased occipital-to-whole brain ratio [71]. Voxel-based morphometry (VBM) from T1-weighted MRI revealed association of delusions with decreased gray matter (GM) density in the left frontal lobe, right fronto-parietal cortex, and left claustrum; apathy with GM density loss in the anterior cingulate and frontal lobe bilaterally, the head of left caudate nucleus and bilateral putamen, while agitation was associated with decreased GM values

Table 1 Epidemiology of psychotic symptoms in Alzheimer and Lewy body diseases

	%	Authors
AD: prevalence		
Initial presentation	64	Devanand et al. [38]
Total	88–90	Brodaty et al. [22], Mega et al. [120]
Delusions	36	Ropacki and Jeste [158]
Hallucinations	18	
Delusions + hallucinations	13	
PD: overall incidence	30.8 (range 22–65)	Molho and Factor [132]
PDD: overall incidence	45–68	Aarsland et al. [3, 4]
PD: prevalence		
Hallucinations	42	Ravina et al. [153]
Delusions	21	
Minor symptoms	45	
VHs lifetime prevalence	~50	Fénelon and Alves [48]
DLB: prevalence		
Hallucinations	13–92	Apostolova [8], Byrne et al. [28]
Hallucinations mean	63–78	
Misidentification	56	
Paranoid delusions	25–28.6	Nagahama [136], Perneczky et al. [148]
	49	Simard et al. [174]

Table 2 Resting brain metabolism and perfusion in Alzheimer disease + psychosis (AD + P)

Main symptom	Location of reduced CBF	Method	Authors
Hallucinations	Parietal lobe	SPECT	Kotrla et al. [90]
Psychosis	Frontal lobe	SPECT	Sultzer et al. [182]
Agitation	Frontal + temporal lobe	SPECT	Sultzer et al. [182]
AD + P vs. non-P	Dorsal frontal, bilateral, left anterior cingulate, left ventral striatum, pulvinar, dorsolateral parietal cortex	SPECT	Mega et al. [121]
AD + P female	Right frontal, inferior temporal cortex	PET	Moran et al. [133]
Delusions	Prefrontal, anterior cingulate, right temporal + parietal cortex	PET	Staff et al. [176], Sultzer et al. [184]

CBF cerebral blood flow, *SPECT* single photon emission computer tomography, *PET* positron emission tomography

Table 3 MRI findings in Alzheimer disease + psychosis

Major symptom	Major changes	Method	Authors
Visual hallucinations	Occipital/whole brain volume ↓	MRI	Holroyd et al. [71]
Delusions	GM density ↓, left frontal, right frontoparietal cortex, left claustrum	VMRI	Bruen et al. [25]
	GM volume ↓, right hippocampus	VMRI	Serra et al. [171]
Delusional misinterpretation	WMLs bilateral frontal, parietal-occipital, left basal ganglia	MRI	Lee et al. [97]
Apathy	GM density ↓, anterior cingulate bilateral frontal	VMRI	Bruen et al. [25]
Agitation	GM ↓ left insula, bilateral anterior cingulate	VMRI	Bruen et al. [25]

GM gray matter, *WML* white matter lesions, *VMRI* volumetric magnetic resonance imaging

in the left insula and anterior cingulate bilaterally. These data indicated that psychiatric symptoms in AD seem to associate with neurodegeneration affecting specific neural networks [25]. The interplay of neuropathologic and neurochemical factors in the pathogenesis of AD and its neuropsychiatric disorders is depicted in Fig. 1.

In amnestic mild cognitive impairment (MCI) patients, VBM showed only limited areas of GM atrophy, with

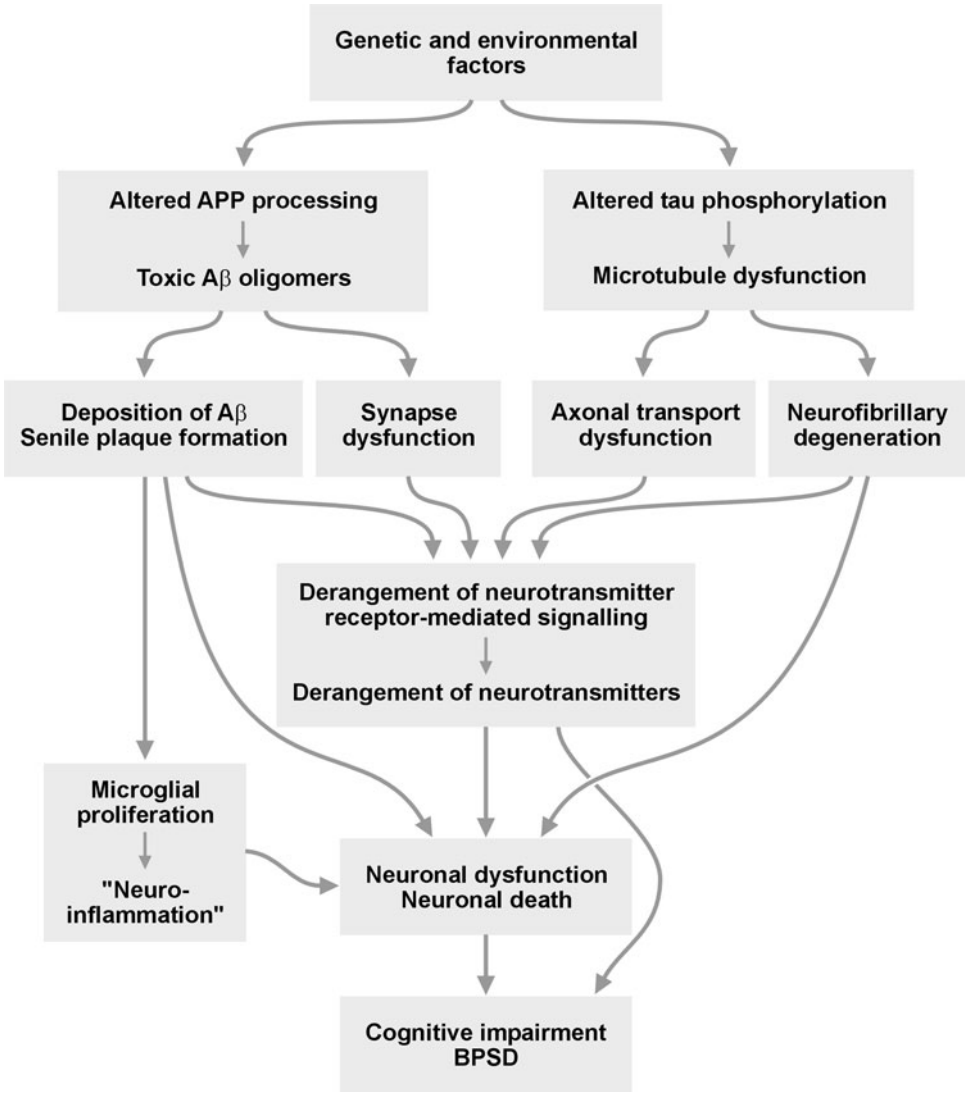

Fig. 1 Scheme of the interplay of neurochemical and neuropathological factors in the pathogenesis of AD and its neuropsychiatric disorders

progressive extensions in AD + P patients. Delusion was associated with GM volume reduction in the right hippocampus; disinhibition was strongly associated with GM volume in bilateral cingulate and right middle frontal gyrus [171]. MRI showed white matter lesions (WMLs) in bilateral frontal or parieto-occipital regions and left basal ganglia significantly correlating with the score of Psychotic Symptoms Subscale of Behavioral Rating Scale for Dementia (BRSD). WMLs were only associated with delusional misinterpretation but not with hallucinations and paranoid delusions. These findings suggested that white matter changes in AD patients, especially located in frontal and parieto-occipital regions, may contribute to the development of a specific type of psychotic symptoms, namely delusional misidentification, while other neuropsychiatric symptoms seemed not to be related with WMLs [97]. A small MRI study of five AD patients each with and without VHs showed a higher occipital periventricular hyperintensity score (PHV) in those with VHs, while the occipital deep white matter hyperintensity (DWH) score was zero in both groups, implying that structural lesions in the geniculocalcarine region and preserved subcortical connections with visual association areas are involved in the genesis of VHs in AD [100]. Older magnetic resonance spectroscopy (MRS) studies showed significant elevation of glycerophosphoethanolamine and reduction of *N*-acetyl-L-aspartate in postmortem brains, indicating impairment of neocortical neuronal and synaptic integrity as the structural substrate of AD + P [185].

Neuropathology (Table 4)

Early studies on neuropathological and neurochemical correlates of psychosis in 13 of 27 (48%) autopsy-confirmed cases of AD showed significantly increased densities of neuritic plaques (NP) and neurofibrillary tangles (NFT) in the presubiculum and middle frontal cortex, respectively, with trends toward increased densities of

Table 4 Neuropathology findings in Alzheimer disease + psychosis

Major symptom	Major neuropathologic findings	Authors
Hallucinations + paranoid delusions	Severe neuron loss in parahippocampal gyrus	Forstl et al. [52]
Delusional misinterpretation	Neuron loss in CA-1 hippocampus	
Aggressivity	Increased tangle load in hippocampus	Lai et al. [93]

these lesions in other cortical areas (entorhinal and superior temporal cortex). This finding was consistent with the increased rate of cognitive decline that accompanies behavioral and psychotic disorders [213].

In a prospective clinicopathologic study of 56 patients with autopsy-confirmed AD (23% with hallucinations, 16% with paranoid delusions and 25% delusional misidentification), the subgroup with auditory hallucinations and paranoid delusions showed less severe neuron loss in the parahippocampal gyrus and non-significant lower neuron numbers in the serotonergic dorsal raphe nucleus than patients without those symptoms, but no differences in the locus coeruleus (these were associated with depression), whereas delusional misidentifications were seen in patients with lower neuron counts in the CA1 hippocampal subfield. Apart from a higher parahippocampal tangle count in AD patients with delusions, no significant differences in plaque and tangle counts between patients with and without psychotic phenomena, and no significant differences in substantia nigra, frontal and parietal lobes were found [52]. The reduction of pyramidal cell neurons in hippocampal area CA1 of AD patients with delusional misidentifications appeared in good agreement with the previously suggested association of a lesion in the mediobasal temporal lobe [180]. A recent semiquantitative study of neuropathological changes in postmortem hippocampus revealed that an increased tangle load, but no other hippocampal morphologic variables, was associated with increased severity of aggressive behaviors and presence of chronic aggression, suggesting a pathogenic link between tangle load in the hippocampus and aggressive behavior [93].

Lewy body diseases

Psychotic symptoms are frequent and disabling in patients with LB diseases—DLB and Parkinson's disease (PD) [4] (see Table 1). They include complex hallucinations (i.e. false sensory perception) and delusions (i.e., fixed false beliefs) of a paranoid type [47]. Hallucinations occurring in the course of PD either accompany the final phase of the disease (disease duration) or may reflect comorbidities [15, 46, 209]. The average overall incidence of psychotic symptoms is 30.8%, ranging from 22 to 65% [132]. They affect 50 to 65% of PD patients undergoing long-term treatment [15]. Their prevalence is higher in demented than non-demented PD patients [23, 91], ranging from 45 to 68% [3, 4]. Assessment of 116 PD patients using the new criteria for psychosis associated with Parkinson's disease (PDP) [153] revealed hallucinations in 42% (visual 16%, non-visual 35%), delusions in 21% and minor symptoms in 45%. The prevalence of PDP was 43% when the usual definitions were applied, and 60% when the new NINDS-NIMH criteria were used [49]. Most frequent are VHs that occur in about 25–44% of PD patients, auditory hallucinations in up to 20% [48, 72], whereas tactile [45], gustatory [72], and olfactory [58, 193] hallucinations are less frequent. VHs in PD are facilitated by impaired color and contrast discrimination [39]. Impaired visual processing precedes image recognition in PD patients with VHs [127]. Other phenomena, e.g., sense of presence and visual hallucinations affect 17–72% while delusions affect about 5% of patients. Delusions are less common as hallucinations, and typically co-occur with hallucinations [202]. Psychotic symptoms are often related to autonomic impairment and mechanisms underlying motor fluctuations [200]. Lifetime prevalence of VHs approximates 50%. They persist and worsen, their prevalence increases with time [48]. In a recent study of autopsy-confirmed PD cases the percentage of VHs, often associated with dementia, increased between age 70 and 84 years from 42 to 67% [85]. Longitudinal studies show a prevalence of hallucinations of 16–17% in population-based surveys and 30–40% in hospital-based series [204].

Dementia is the most robust risk factor for the onset of hallucinations in PD, and hallucinations are a possible risk factor for dementia [132, 164]. In a 12-year population-based study of 230 PD patients, 60% developed hallucinations or delusions. Their incidence rate was 79.7/1,000 patient/years, increasing with higher age at disease onset [51]. In a longitudinal study of PD patients, 95% had hallucinations and 60% had paranoia; psychosis was persistent in 69%, and dementia was diagnosed in 68%. Persistent psychosis was associated with younger age at onset of PD and longer disease duration; paranoia with more frequent nursing home placement. Within 2 years 28% of nursing home patients died; paranoia being associated with a poorer prognosis [44].

In DLB, both "common" and "mixed" forms (DLB + AD, LB variant of DLB/LBV/AD), psychotic symptoms are extremely common, including, predominantly

Table 5 Brain metabolism and perfusion in Lewy body disease + psychosis

Disease	Main symptom	Changes	Location	Method	Authors
PD	PD: VHs	CBF ↓	Occipito-temporo-parietal	PET	Boecker et al. [20]
		CBF ↓	Left temporal cortex	PET	Okada et al. [144]
		GU ↑	Left frontal lobe	PET	Nagano-Saito et al. [138]
		CBF ↓	Right fusiform gyrus	PET	Oishi et al. [143]
		CBF ↑	Right temporal gyrus	PET	
DLB	Hallucinations	CBF ↓	Posterior cingulate	SPECT	O'Brien et al. [141]
		GU ↓	Right posterio-temporal + parietal	SPECT	Imamura et al. [75]
		GU ↓	Right occipito-temporal + middle frontal gyri	PET	Perneczky et al. [148]
	Delusions	CBF ↓	Right prefrontal cortex	PET	
	Capgras syndrome	CBF ↓	Left hippocampus, insula, bilateral inferior frontal gyri	PET	Nagano-Saito et al. [138]
	VHs	CBF ↓	Left ventral occipital, bilateral parietal	PET	
	Delusions	CBF ↓	Right rostral medial frontal, left medial superior frontal, bilateral dorsolateral frontal cortex	PET	

PD Parkinson disease, *DLB* dementia with Lewy bodies, *VHs* visual hallucinations, *CBF* cerebral blood flow, *GU* glucose utilization, *SPECT* single photon emission computer tomography, *PET* positron emission tomography

VHs, misidentifications, delusions, and other syndromes (Table 1). Hallucinations are the most frequent psychotic symptoms, with a prevalence range between 13% [28] and 92% [12] and means of 63–78%, followed by misidentifications (56%) and paranoid delusions (25.0–28.6%) [136, 148], while another group reported psychotic symptoms in 50% of the DLB patients, showing no association with the degree of motor disability [21]. VHs are generally present early in the course of illness [114]. They are significantly more frequent in "common" DLB than in LBV/AD [5, 36, 87]. VHs are the presenting feature in 33–65% of DLB versus 8–15% in AD [8]. Recurrent, complex VHs are one of the most useful signposts to a clinical diagnosis of DLB and, together with visuospatial/constructional dysfunctions are valid diagnostic criteria for DLB [115], and differentiate it in the earliest states from AD [5, 192]. The presence of VHs could be used to distinguish PD brains from atypical parkinsonism since they occur very rarely in progressive supranuclear palsy (PSP) and multiple system atrophy (MSA); their presence should be considered a red flag for understanding Lewy body parkinsonism [205, 206]. VHs tend to persist; they may remain over 20–52 weeks [13, 115]. They are similar to those in PD in that they are vivid, complex, colorful, three-dimensional, and generally mute images of animals, less frequently of other objects [3, 11, 115]. Patients with DLB have more frequent VHs than those with AD [181], showing more prominent visuospatial dysfunction compared to those without VHs [134].

In DLB, the most frequent psychotic manifestations are delusional misidentifications, followed by paranoid beliefs, Capgras syndrome (belief that an acquaintance has been replaced by an identical looking impostor), phantom syndrome, and reduplication of people and places [3, 87]. The persistence of delusions is similar in DLB and AD [13]. VHs and delusions are usually independent of each other, and the relationship between hallucinations/delusions and cognition is obscure [8]. In the population-based Vantaa 85+ study, among 109 patients with autopsy-proven LBD, 48% were reported to have VHs associated with dementia [142].

Neuroimaging (Tables 5, 6)

Neuroimaging in Parkinson disease with dementia (PDD) and DLB has been reviewed recently [173]. ^{18}F-FDG PET studies comparing PD patients with and without VHs revealed reduction in the regional cerebral glucose consumption in the occipitotemporoparietal regions, the ventral and dorsal visual streams ($P < 0.05$), sparing the occipital pole, indicating functional disorders of visual association areas in higher-order visual processing [20]. These data extended previous studies in PD and DLB reporting stronger functional involvement of posterior brain regions than in AD, including the primary visual cortex and the visual pathways [112].

HMPAO SPECT studies in DLB patients with hallucinations and fluctuations in consciousness showed a significant correlation between increased perfusion in midline posterior cingulate and decrease in hallucination severity, and between increased fluctuations of consciousness and increased thalamic and decreased inferior occipital perfusion [141]. There was reduced occipital uptake in areas identified as primary and secondary visual cortex [33, 67, 76, 103, 146]. Hallucinators showed lower right posterior temporal and parietal glucose uptake than non-hallucinators [75]. ^{18}F-FDG PET studies in DLB

Table 6 Volumetric studies in dementia with Lewy bodies and Parkinson disease with dementia with psychosis

Main symptom	Major changes	Method	Authors
DLB + VHs	GM loss in right inferior frontal gyrus	VMRI	Sánchez-Castañeda et al. [163]
PDD + VHs	GM loss in orbitofrontal lobe	VMRI	
PD + VHs	Hippocampal cell loss	VMRI	Ibarretxe-Bilbao et al. [73]
PDD + VHs	Atrophy limbic, paralimbic, neocortex	VMRI	Ibarretxe-Bilbao et al. [74]

DLB dementia with Lewy bodies, *PDD* Parkinson disease with dementia, *PD* Parkinson disease, *GM* gray matter, *VMRI* volumetric magnetic resonance imaging

patients with VHs revealed hypometabolic regions at the right occipito-temporal junction and in the right middle frontal gyrus, suggesting involvement of visual association areas rather than primary visual cortex; delusions were associated with hypometabolism of the right prefrontal cortex [148]. Recent SPECT studies revealed that factor 1 symptoms (Capgras syndrome, phantom boarder, etc.) were related to hypoperfusion in the left hippocampus, insula, ventral striatum and bilateral inferior frontal gyri; factor 3 symptoms (VHs of person and feeling of presence) to hypoperfusion in the left ventral occipital gyrus and bilateral parietal areas, while delusions were associated with hypoperfusion in the right rostral medial frontal cortex, left medial superior frontal gyrus and bilateral dorsolateral frontal cortices. These data suggest that VHs are related to dysfunction of the parietal and occipital association cortices, misidentifications to dysfunction of the limbic-paralimbic structures, and delusions to dysfunctions of the frontal cortex [137]. Recent studies imply that dysfunction of extrastriate downstream visual association areas, rather than the primary visual cortex, is involved in the occurrence of VHs in PD and DLB [137, 148] (Fig. 2).

Volumetric studies in DLB showed no occipital volume differences between hallucinators and non-hallucinators [130], while VBM in subjects with VHs showed greater GM loss than non-hallucinators, specifically in the right inferior frontal gyrus (BA 45) in DLB patients, and in the orbitofrontal lobe (BA 10) in PDD patients. Decreased volume in association with visual areas (left precuneus and inferior frontal lobe) correlated with VHs in DLB but not in PDD patients. In summary, DLB and PDD patients with VHs had more frontal GM atrophy than non-hallucinators, the impairment being greater in the DLB group [163]. Other MRI studies showed that PD + VH patients had significant hippocampal cell loss compared to controls; they frequently develop dementia and show widespread atrophy, involving limbic, paralimbic and neocortical structures [74].

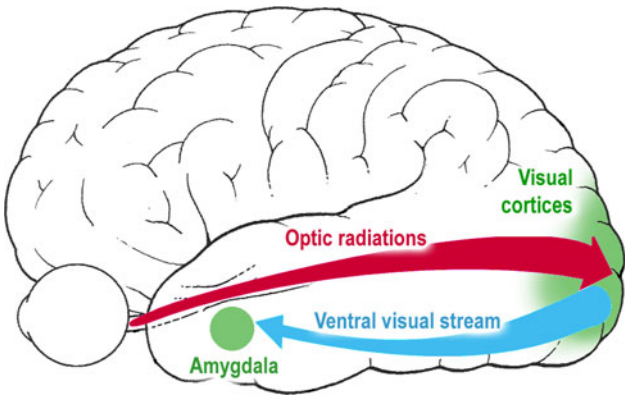

Fig. 2 Diagram of the major visual pathways implicated pathologically in visual hallucination in PD

Neuropathology (Table 7)

A few important associations between histopathology and psychotic symptoms have been described in PD and DLB. Psychopathology including VHs and dementia corresponds to LB distribution in the limbic system [59], the latter being significantly associated with α-synuclein (αSyn) deposition in anterior cingulate gyrus, entorhinal cortex, amygdaloid complex and nucleus basalis of Meynert as well as tau in the CA-2 sector of hippocampus, while αSyn burden in the amygdala is strongly related to the presence of VHs, but only in those PD cases with concomitant dementia [84].

Clinicopathologic studies have consistently reported a higher frequency and earlier onset of VHs in subjects with Lewy pathology, i.e. subjects with DLB or PDD [13, 116] than in demented subjects with AD. Most prospective studies have reported VH frequencies greater than 50% in subjects with confirmed Lewy pathology [12, 197]. Some have suggested that concomitant AD pathology obscures the clinical presentations of VHs in subjects with Lewy-pathology [53, 65, 114], whereas others suggested that VH frequencies vary according to the location and severity of Lewy pathology, and that VH frequencies are especially associated with the density of LBs in the medial temporal lobe [196].

In a community-based clinicopathologic study of 148 demented subjects, subjects with VHs (18%) had significantly more frequent Lewy-related pathology than those without VHs (78 vs. 45%). In addition, a higher frequency of VHs was observed in subjects with neocortical LBs than

Table 7 Neuropathologic findings in Lewy body diseases with psychosis

Major symptom	Major neuropathologic findings	Authors
PD + VHs versus non-VHs	Higher cortical LB score	Kempster et al. [85]
PD + VHs	Neuron loss and αSyn deposition in intralaminar thalamic nuclei	Brooks and Halliday [24]
	Increased CAA in occipital cortex	Harrison et al. [68]
DLB + VHs	Higher LB density in amygdala and parahippocampus	Harding et al. [66, 67]
DLB + delusions	Less severe neocortical tangle pathology, higher neocortical tangle pathology	Ballard et al. [14]
DLB + VHs (aged 85 + years) versus non-VHs	Higher neuritic Braak stage (III–VI *vs.* 0–III)	Oinas et al. [142]

PD Parkinson disease, *DLB* dementia with Lewy bodies, *VHs* visual hallucinations, *LB* Lewy body, *CAA* cerebral amyloid angiopathy

in subjects with limbic-, amygdala- or brainstem-predominant LB pathology. Although AD with concomitant Lewy pathology was the most common neuropathological subtype in the VH-positive group (59%), the frequency of subjects with AD did not differ significantly between those with and without VHs (74 vs. 62%) [196].

VHs in DLB relate to LB density in amygdala and parahippocampi and, when present early in the course of disease to parahippocampal and inferior temporal cortical LB density [67]. Cases with DLB had higher LB densities in the inferior temporal cortex than cases with PDD. There was a striking association between the distribution of temporal lobe LBs and well-formed VHs. These data confirmed previous ones showing a strong correlation between cortical LBs with early onset VHs, their persistence and severity [118, 205], whereas others found no significant differences in LB density in any brain region among patients with and without VHs and delusions [60]. Among 129 cases of pathologically proven PD, patients with VHs had significantly higher LB scores (7.7) than those without VHs (6.6; $P = 0.02$) [85]. These data suggest that the distribution of LBs is more related to the presence and duration of VHs in LB diseases than to the presence and severity or duration of dementia [67]. Other studies showed an association between neuronal loss and the severity of αSyn deposition in the intralaminar nuclei of the thalamus and VHs, fluctuations in consciousness and other symptoms in PD [24]; these changes correlated with disease duration [64]. In autopsy-confirmed cases of DLB, the main neuropathological correlate of persistent VHs was the presence of less severe tangle pathology, but there was no significant association between tangle pathology and persistent delusions. LB staging was associated with the presence of persistent VHs and delusions. All baseline psychiatric features were significantly more frequent in DLB than in AD, as were persistent VHs, but DLB patients with severe tangle pathology (LBV/AD) had a clinical symptom profile more similar to that of AD and were less likely to have neocortical LBs. Thus, unlike AD, DLB cases showed a significant inverse association between tangle burden and psychosis [14]. A recent study of 162 autopsy-confirmed PD cases showed a relationship between cerebral amyloid angiopathy (CAA) in the occipital cortex and VHs during life that was not seen in non-PD cases, confirming the suggestion that pathology within the primary visual system may play a role in the pathogenesis of VHs [68].

In the population-based Vantaa 85+ study of DLB in individuals at least 85 years of age, VHs, reported in 48% of the patients, were associated with dementia and with neuritic Braak stage independently of the presence of dementia ($p = 0.041$), but no association was seen with the type of Lewy pathology (brainstem, limbic, or neocortical). The probability for VHs was more than three times higher in subjects with neuritic Braak stage III–VI compared to those with Braak stage 0–II [142]. These findings differ from others which reported that subjects with extensive NF pathology show fewer clinical features of DLB, like VHs [14, 128].

Huntington disease (HD)

Psychosis is more common in HD than in the general population, occurring in up to 15% of HD patients [29, 123, 195]. Paranoia rather than schizophrenia-like symptoms are the important and underestimated manifestations. PSs include paranoid delusions in up to 11%, while auditory and visual hallucinations are rare, occurring in about 2% [63, 147]. HD patients may have a familial predisposition to develop psychosis and it has been suggested that other genetic factors may influence susceptibility to a particular phenotype precipitated by CAG expansion in the *HTT* gene [195]. Gene carriers and non-carriers do not differ in terms of the lifetime frequency of psychiatric disorders, but gene-carriers had a significantly higher rate of depressive symptoms [83, 110], while symptomatic mutation carriers showed an increased prevalence of non-affective psychosis [198]. Specific psychiatric symptoms (e.g., paranoid ideation) differentiate non-mutation carriers from individuals in the early preclinical stage of HD who are either symptom

free or have minor non-specific motor anomalies [110]. Subclinical psychiatric symptoms are present in about one-third of preclinical HD patients, often occurring more than 10 years before HD diagnosis, thus probably being the earliest markers of the disease [41]. Psychiatric symptoms generally do not correlate with cognitive decline, abnormal movements, or CAG repeat length in HD [211].

Most psychotic symptoms in HD are believed to arise from subcortical neuropathological changes [161]. Although we are not aware of specific studies of neuropathology in HD cases with psychosis, these symptoms in early stages of the disease may be related to dysfunction of vulnerable striosomal spiny neurons in the neostriatum and central median nucleus of thalamus [17], involving the basal ganglia-thalamocortical circuit, but the models of striatal connectivity and pathology are insufficient to explain such features in early HD [80].

Frontotemporal dementia (FTD)

Although most patients with FTD present with neuropsychiatric symptoms, the frequency of psychotic symptoms is unclear. Among 86 patients who met consensus criteria for FTD, only two (2.3%) had delusions, one of whom had paranoid ideation, while no FTD patient had hallucinations; this was significantly less than in AD patients [126]. These and other case reports [95], and an evidence-based review of the psychopathology of FTD showed rare occurrence of delusions and hallucinations [125], possibly due to limited temporo-limbic pathology in this disorder. There are rare clinical reports about FTD patients presenting as acute later onset schizophrenia [86, 155]. Among 61 autopsy cases of FTD (43 with behavioral variant [bvFTD] and 18 with FTD + amyotrophic lateral sclerosis [FTD/ALS]), there was a significant association of the presence of delusions with FTD/ALS (50%), and their occurrence in bvFTD may clearly indicate combination with ALS features. The median survival from system onset was significantly shorter for the FTD/ALS group than for FTD cases (mean 2.4 vs. 6.6 years) [99].

In a small number of FTD cases presenting with schizophrenia-like psychosis years prior to the dementia diagnosis, neuropathology was consistent with TDP-3 and ubiquitin-positive FTD [104, 188, 199]. Recent studies identified a novel group of FTD patients with clinical features that overlap with DLB presenting, among others, with fluctuating cognition and hallucinations; SPECT showed frontal lobe hypoperfusion and pathology was consistent with frontotemporal lobe degeneration (FTLD) with ubiquitin-only immunoreactive changes (FTLD-U), type 1 [32], which represents a clinically heterogeneous subtype of FTLD. Another subtype, clinically characterized by early onset and progressive and behavioral and personality changes, morphologically being tau- and TDP-43-negative, with FUS pathology, has been classified as "atypical" FTLD [107, 140, 157].

Affective and behavioral disorders

According to the International Psychogeriatric Association [77] the most common psychiatric manifestations of dementia, without specifying an underlying etiology, appear to be delusions (60%), followed by affective symptoms (40%), anxiety (35%), verbal outbursts (33%), and hallucinations (20%). Prevalence depends on diagnostic criteria used, type of population sampled (e.g., outpatient vs. community-based samples), and the inclusion of patients in different stages/severity of dementia. In AD the most common neuropsychiatric symptom is apathy and the most uncommon is euphoria [10, 172]. Depression is seen in about 38% of AD patients and can be observed in AD in the absence of major depression [10]. Wandering and agitation may be the most enduring BPSD [38]. On the other hand, apathy seems to be the most severe as it typically worsens during the course of the illness and offers the most distressful behavior for caregivers [1, 111, 175]. Alzheimer disease patients who suffer from apathy also have a faster functional and cognitive decline [177].

Depression

Neuroimaging

In a population-based study of elderly individuals without dementia ($N = 503$), Geerlings and co-workers [55] reported no association between MRI-based volumes of the hippocampus or amygdala and depressive symptoms (as measured with the Center for Epidemiological Studies depression Scale [CES-D]) at the time of assessment. Also, there was no association between the above neuroradiological findings and an increased risk of developing AD. Using voxel-based morphometry in a series of 31 patients with mild AD and depression assessed with the Neuropsychiatric Interview (NPI), the authors were unable to find significant associations between depression and GM atrophy in any brain region [25].

White matter hyperintensities (WMH) are usually the expression of loss of axons and oligodendroglial cells, gliosis and thickening of small vessels supplying the white matter. In one of the first studies to examine the association between WMH and depression in dementia, no significant association between the severity of WMH and severity of depression (as assessed with Gottfries–Brane–Steen Scale) was found, but the study was limited by the inclusion of different types of dementia (AD, vascular or mixed

dementia), the use of a visual method to rate the scans, and a diagnosis of depression of unknown validity [101]. Assessment of depression and WMH using a semi-automated technique that consisted of the edition and segmentation of three-dimensional scans and the assignment of WMH to brain lobes showed a significant association between the severity of depression and larger WMH volumes in the right parietal lobe. On the other hand, there were no significant associations between apathy or depression and lobar gray or white matter atrophy [178]. Examination of lobar gray matter atrophy and WMH in 20 patients with AD and 11 patients with VaD showed a significant association between depression (diagnosis based on clinical assessment only) and increased load of WMH in the frontal lobe. On the other hand, there was no association between depression and gray matter atrophy [135]. More recent studies have challenged the possible role of vascular pathology in late-onset major depression (LOD). These studies have failed to find an association between LOD and lacunes or cortical microinfarcts [78, 165].

SPECT examination of FTD revealed that both dysthymia and anxiety (assessed with clinical examination only) were significantly associated with hypoperfusion in the right temporal lobe [124]. Lavretsky et al. [96] examined the association between depression (as assessed with the Geriatric Depression Scale), anxiety (as assessed with the State-Trait Anxiety Inventory [STAI]), and AD neuropathology in 23 patients with MCI and 20 healthy controls using 2-(1-{6-[(2-[^{18}F]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene) (FDDNP)-PET. In the MCI group depression correlated with increased lateral temporal FDDNP binding, whilst trait anxiety correlated with higher binding in the posterior cingulate gyrus. There was no association between state anxiety and FDDNP binding. The authors suggested that depression and anxiety may result in the overproduction of amyloid and NFTs. FDG-PET in a series of 53 patients with AD showed a significant correlation between the severity of depression (as assessed with the NPI) and lower metabolic activity in superior frontal gyri and left anterior cingulate gyrus [70].

Neuropathology

Depression is common in old age and is associated with the risk of dementia, but little is known about its neuropathologic correlates. Recent clinicopathologic studies in elderly non-demented subjects with late-life (late-onset) major depression (LOD) found no association between depression and cerebrovascular or Alzheimer pathology [165, 194], thus challenging the "vascular depression" hypothesis [6]. There was no association between LOD and WMLs, which (together with temporal lobe atrophy) have been related to long-term depression in the elderly [62, 145, 191], while others demonstrated the association between LOD and neuronal loss in hippocampus and some subcortical structures, together with subcortical Lewy bodies [194].

Rapp et al. [151] carried out a neuropathological study of 50 AD patients with and 52 patients without a lifetime history of depression (as determined by clinical consensus). Most patients in the AD-depression group had the onset of depression before the onset of AD. After adjusting for potential confounders, patients with depression had more NFT and NP in the hippocampus than patients without depression. Moreover, AD patients with depression at the baseline assessment had a larger proportion of AD neuropathology in the hippocampus than those with lifetime depression but no depression at baseline. The proportion of vascular lesions and Lewy bodies was similar for the depressed and non-depressed groups. The same researchers [152] carried out a larger neuropathological study of AD patients with ($N = 595$) or without ($N = 5{,}873$) depression at baseline. Depression was assessed based on a single question and rated as present or absent. Pathological analysis consisted of ratings of NP and Braak staging of NFT across the whole brain. After adjusting for age, gender, education, and cognitive status, AD patients with depression had more advanced stages of NFT than patients without depression, although the effect size was small. One limitation of the study was that the frequency of depression in the sample may have been underestimated given the low sensitivity of the method used to screen for depression.

Apathy

Neuroimaging

Assessment of the association between apathy, determined with the Stepwise Comparative Status Analysis, and WMH in a study that included 11 individuals with MCI, 84 patients with AD, and 50 patients with probable vascular dementia demonstrated a significant association between apathy and presence of WMH [81]. Starkstein et al. [179] examined the association between apathy and WMH in a series of 79 patients with AD. Apathy was assessed with the Apathy Scale. After correcting for MMSE scores, patients with apathy had significantly larger volumes of WMH in right and left frontal white matter.

MRI brain morphometry in a series of 35 patients with AD found significant correlations between apathy scores and GM atrophy bilaterally in the supracallosal cingulate and the left medial frontal cortex. After controlling for relevant demographic variables there were also significant correlations between increased apathy scores (as assessed with the NPI) and more severe atrophy in left and right cingulate regions [9]. Bruen and co-workers [25] assessed correlations between apathy and brain regional atrophy in

31 patients with AD. There was a significant correlation between more severe apathy and greater gray matter atrophy in the bilateral anterior cingulate, orbitofrontal cortex and dorsolateral prefrontal cortex, as well as significant bilateral findings of increased apathy with loss of putamen and head of the caudate volume.

Assessment of 21 patients with FTD (15 with and 6 without apathy as assessed with the NPI) using volumetric MRI showed no association between apathy and basal ganglia atrophy, suggesting that the mechanism of apathy in FTD may be different from the mechanism of apathy among patients with acute brain lesions [102]. In 40 patients with FTD, the main finding was a significant association between apathy and GM atrophy in frontomedial regions, middle orbitofrontal cortex, and bilateral inferior frontal, bilateral temporal and right dorsolateral prefrontal regions [111]. Rosen et al. [159] examined with MRI volumetry a heterogeneous group of patients with FTD, semantic dementia, non-fluent aphasia, cortico-basal degeneration, PSP, and AD. Apathy was assessed with the NPI. The main finding was a significant association between apathy and atrophy of the ventromedial superior frontal gyrus for patients with FTD or semantic dementia, but not for the other groups. The authors suggested that the ventromedial superior frontal gyrus may play a critical role in a "motivation brain network" [159]. Zamboni and co-workers [210] examined the association between apathy and MRI-based brain morphometry in a series of 62 patients with a clinical diagnosis of FTD. Apathy was assessed with the Frontal System Behavioral Scale. The main finding was that apathy was significantly associated with more severe atrophy in the right dorsolateral prefrontal cortex.

Craig and co-workers [34] assessed 31 AD patients with ^{99m}TC hexamethyl-propyleneamine-oxime (HMPAO) SPECT, and apathy was assessed with the NPI. They found a significant association between the presence of apathy and hypoperfusion in bilateral prefrontal and anterior temporal regions. ^{99m}TC-labeled bicisate (ECD) SPECT studies found a significant association between apathy and hypoperfusion in bilateral superior orbitofrontal regions [18]. AD patients with apathy ($N = 23$) showed significantly lower perfusion than patients without apathy ($N = 27$) in the right orbitofrontal cortex and left anterior cingulate [94]. Robert et al. [156] assessed 31 patients with ^{99m}TC-ECD and the Apathy Inventory. After controlling for depression they found a significant correlation between higher apathy scores and hypoperfusion in the right anterior cingulate gyrus.

^{18}FDG-PET studies in 14 AD patients with apathy and 27 AD patients without apathy (as diagnosed with the Scale for the Assessment of Negative Symptoms in AD), after controlling for global cognitive impairment, depressed mood, and education, showed reduced activity in bilateral anterior cingulate and medial orbitofrontal regions in patients with apathy [109].

David et al. [35] used ^{123}I-FP-CIT (DaTSCAN) SPECT to examine dopamine transporter uptake in 14 patients with AD and 8 patients with DLB. They found a significant association between increased apathy scores (as assessed with the NPI) and lower dopamine uptake in the right and left putamen, suggesting that apathy in different types of dementia may be associated with some degree of neuronal loss in the basal ganglia.

^{18}FDG-PET assessment of the metabolic pattern associated with galantamine therapy in 19 patients with mild to moderate AD showed that metabolic changes from baseline to end of treatment studies correlated with changes in apathy and depression (as assessed with the NPI). Increase in the metabolic activity in the right cingulate significantly correlated with improvements in depression, whilst increased metabolic activity in the right putamen correlated significantly with improvements on apathy [122].

McMurtray et al. [117] assessed 74 patients with FTD for the presence of apathy as assessed with the FTD Inventory. All patients received a SPECT scan at baseline and had a 2-year follow-up. The main finding was that apathy was significantly associated with bilateral lower frontal metabolism. Frontal hypoperfusion was a significant predictor of loss of insight and stereotyped behavior, but not apathy.

Neuropathology

Studies of the neuropathological correlates of apathy in 29 autopsied subjects with definite AD found that chronic apathy (as clinically diagnosed) was significantly associated with NFT (but not with neuritic plaques) in the anterior cingulate cortex [108]. In a study of 31 autopsy patients with a diagnosis of definite AD, quantifying NFT, NP and Lewy bodies in specific brain regions, a significant association between apathy (as assessed with the NPI) and the amount of NFT in the left anterior cingulate gyrus was reported [189].

Anxiety

There are few studies on the brain structural or metabolic correlates of anxiety in dementia. Hashimoto et al. [69] examined the severity of anxiety using the NPI in 41 patients with AD. After controlling for MMSE scores, they found a significant correlation between higher anxiety scores and lower metabolic activity (as assessed with ^{18}FDG-PET) in bilateral entorhinal cortex, anterior parahippocampal gyrus, left superior temporal gyrus and left insula.

In FTD, studies found a significant association between dysthymia and anxiety (as assessed with the NPI) and hypoperfusion in the right temporal lobe as assessed with SPECT [124]. Finally, in a series of 23 patients with MCI, a significant correlation between trait anxiety (as assessed with the STAI) and FDDNP binding in the posterior cingulate gyrus was found [96]. Future studies should further examine brain structural, metabolic, and neuropathological correlates among patients with dementia and comorbid anxiety without depression.

Discussion

The present article provides for a revision of the literature on possible clinicopathological correlates to BPSD. This approach may be simplistic as BPSD are a heterogenous group of psychiatric symptoms associated at variable intensities and time points with the various forms of dementia. It is therefore important to note that the preponderance of previous studies have not attempted to control for either evolution over time and/or symptom severity when correlating individual psychiatric symptoms to pathology or state-related parameters. The lack of data in regards to the aforementioned variables limits the scope of possible interpretations. Still, some conclusions appear warranted and will be discussed in subsequent paragraphs.

The classical nosological model of psychiatry emphasizes the value of differentiating symptom domains, such as psychotic and affective, in demented patients [169]. In this article, we have opted for analyzing individual symptoms (i.e., hallucinations, delusions, apathy, and depression) from each BPSD component or domain (i.e., psychosis and affective disorders). This follows a current trend in research indicating, for example, that hallucinations and delusions may be independent composites of the psychotic syndrome. According to Cassimjee [31] this dichotomy among psychotic symptoms warrants independent discussions of prevalence, risk factors, symptom co-morbidity, and etiology. Thus, in spite of co-concurrence, the majority of community population cross-sectional and longitudinal studies have shown a higher frequency of delusions as compared to hallucinations [31]. Studies showing a correlation between hallucinations/delusions and a more rapid cognitive decline in demented patients may, by themselves, not justify grouping these symptoms into a psychotic syndrome.

The same arguments espoused for psychosis similarly apply to affective disorders. Thus, the symptoms of apathy and depression seem to be clinically and anatomically independent of each other [7, 92, 98]. Factor analyses have repeatedly shown a dissociation of these symptoms into separate dimensions [1, 214]. Apathy has been associated with extrapyramidal signs and psychological deficits which appear unrelated to depression [61]. Hence, despite the traditional model of psychiatry in grouping hallucinations with delusions and apathy with depression, current research attests to the diagnostic and prognostic significance of considering symptoms individually [50, 203]. Our revision of the current literature on pathological correlates to BPSD supports this partite model of study.

Clinicopathological correlations

In the absence of prominent behavioral symptoms executive impairment is more characteristic of AD than FTD [208]. Frontal lobe dysfunction may predispose demented patients to BPSD by exaggerating their response to environmental provocations [170] and/or diminishing their verbal fluency [88]. The findings suggest that frontal lobe dysfunction is closely associated with individual BPSD [149]. Psychotic symptoms, in particular, appear to be related to lesions in heteromodal association areas of the frontal and temporal cortices as well as limbic/paralimbic brain regions [183]. The data indicate that psychotic symptoms in dementia are the expression of regional rather than diffuse brain pathology affecting primarily the frontal lobe and limbic regions. The salient exception appears to be VHs where lesions of either idiotypic visual cortex or downstream visual association areas appear to be involved (Fig. 2).

The association between depression and structural brain changes in dementia remains unclear. Only two studies examined structural correlates of depression in AD, and the findings were negative [25, 55]. On the other hand, there is a significant association between depression and WMH, but the location of these changes has differed between studies. One study showed a significant association between depression in dementia and increased binding of pathological markers of apathy in the left temporal lobe. Two neuropathological studies showed an association between depression and a higher density of NP and NFT in the hippocampus [151, 152]. Taken together neuroradiological and neuropathological studies in dementia have failed to show a clear association between depression and specific brain changes.

On the other hand, there is convergent evidence from neuroradiological and neuropathological studies of a significant association between apathy in dementia and changes in the anterior cingulate gyrus. Brain volumetric studies showed a significant association between apathy and atrophy in the frontal lobe, although changes involved heterogeneous regions such as the fronto-medial, orbitofrontal, dorsolateral prefrontal, inferior frontal and superior

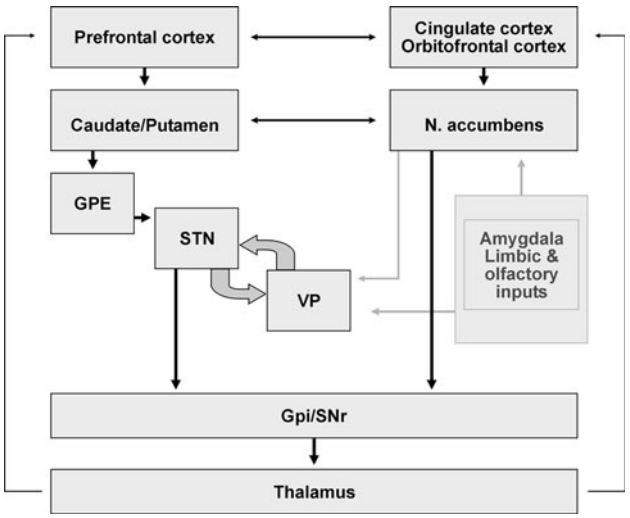

Fig. 3 Circuiting interconnections between affective and cognitive functions. *GPE* external globus pallidus, *STN* subthalamic nucleus, *VP* ventral pallidum, *GPi-SNpr* internal globus pallidus and substantia nigra pars reticulata, *DA* dopamine (modified from [16])

frontal regions [9, 25, 111, 159, 210]. Metabolic studies showed homogeneous involvement of the anterior cingulate and the orbito-frontal cortex [94, 109, 122, 156], whilst neuropathological studies showed increased pathology in the anterior cingulate gyrus [108, 189] (Fig. 3). Finally, few studies have examined the radiological or neuropathological correlates of anxiety in AD and no homogeneous pattern of brain changes has yet emerged.

Limitations to clinicopathological correlations

Equivocal results regarding neuropathological correlates of BPSD may be the result of undiagnosed comorbid conditions (e.g., vascular disease, DLB) or derive from the use of medications [31, 186]. In effect, comorbidity among dementing disorders may be the norm rather than the exception. According to some researchers the combination of AD and cerebrovascular pathology is the most common form of dementia [212]. Cerebrovascular abnormalities by themselves carry an increased risk for depression and apathy [88]. Seventy-five percent of patients with DLB have neuropathological features of AD [65].

Neuroleptic agents offer an unaccounted variable to many studies as they may increase the risk for cerebrovascular adverse events in demented patients [19], and accelerate cognitive decline in patients with AD. It has therefore been habitual for current clinical protocols to mix different types of dementia, e.g., FTD and DLB in AD series and vice versa [42], therefore avoiding reporting BPSD by dementia subtypes.

The rather heterogeneous results found on clincopathological correlations may also be explained by differences in assessment methodologies. In depression, the literature shows marked variability in symptom assessment, i.e., structured psychiatric interviews followed by standardized diagnostic criteria versus cut-off score on severity rating depression scales. This weakness is compounded by the fact that some screening instruments have difficulties in sorting out different psychiatric symptoms and were meant to be used in specific disorders, e.g., AD versus FTD [111]. Furthermore, screening techniques do not take into account that many of the psychiatric symptoms observed in dementia are inter-related, e.g., the presence of aggression is associated with depression [105], agitation [43], and psychosis [37].

Finally, temporal correlations are difficult to assess as both the disease process and its attendant psychiatric manifestations tend to have insidious onsets that preclude accurate staging. Furthermore, most studies on the temporal evolution of BPSD are based on cross-sectional rather than longitudinal analyses [131]. Longitudinal studies provide for more accurate observational changes over time but are limited by the high mortality/drop-out rate and lack of patient cooperation. Cross-sectional studies provide a suitable alternative but need larger population sizes to support any conclusions. Despite limitations, cross-sectional studies attest to the correlation of individual manifestations of BPSD with the chronology of the underlying dementing process. Irritability seems to be most characteristic at initial stages of dementia. Sleep disorders and hallucinations, on the other hand, tend to occur at later stages [129]. In a longitudinal cohort study during 6–7 years of observation, depressive symptoms were the most stable as the disease progressed to a moderate level of dementia [207]. The findings suggest that BPSD follow a complex course that needs to be examined in a longitudinal setting [166] and further underscore the importance of these symptoms for both their diagnostic and prognostic value.

In summary, it is difficult to envision how neuropathology alone accounts for the heterogeneity of BPSD manifestations. Individual manifestations of BPSD take place along with other specific psychological and behavioral symptoms suggesting a complex network of neuropathological, neurochemical, and psychological factors [31]. However, within this quagmire of possible interactions, different dementing conditions exhibit specificity and persistence of symptoms. Patients with BPSD differ clinically and neuropathologically from those without psychiatric symptoms. The validity and importance in making this distinction is that treatment of BPSD subtypes can improve cognitive symptoms, delay or prevent institutionalization, improve quality of life for patients and

caregivers, and diminish medical costs associated with the condition.

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