

Cerebral correlates of psychotic syndromes in neurodegenerative diseases

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Abstract

Psychosis has been recognized as a common feature in neurodegenerative diseases and a core feature of dementia that worsens most clinical courses. It includes hallucinations, delusions including paranoia, aggressive behaviour, apathy and other psychotic phenomena that occur in a wide range of degenerative disorders including Alzheimer's disease, synucleinopathies (Parkinson's disease, dementia with Lewy bodies), Huntington's disease, frontotemporal degenerations, motoneuron and prion diseases. Many of these psychiatric manifestations may be early expressions of cognitive impairment, but often there is a dissociation between psychotic/behavioural symptoms and the rather linear decline in cognitive function, suggesting independent pathophysiological mechanisms. Strictly neuropathological explanations are likely to be insufficient to explain them, and a large group of heterogeneous factors (environmental, neurochemical changes, genetic factors, etc.) may influence their pathogenesis. Clinico-pathological evaluation of behavioural and psychotic symptoms (PS) in the setting of neurodegenerative and dementing disorders presents a significant challenge for modern neurosciences. Recognition and understanding of these manifestations may lead to the development of more effective preventive and therapeutic options that can serve to delay long-term progression of these devastating disorders and improve the patients' quality of life. A better understanding of the pathophysiology and distinctive pathological features underlying the development of PS in neurodegenerative diseases may provide important insights into psychotic processes in general.

Keywords: neurodegenerative disorders • dementia • psychotic and behavioural symptoms • Alzheimer's disease • Lewy body disease • frontotemporal dementia • neuroimaging • neuropathology

Introduction

Dementia is an acquired disorder characterized by progressive loss of memory and other cognitive functions that are severe enough to compromise an individual's daily activities [1]. Until recently clinico-pathological correlation studies focused on cognitive functions and neglected psychiatric symptoms [2]. In Alzheimer's disease (AD), the progression of cognitive impairment relates to a defined topographical pattern of neurodegenerative changes that first affect the medial aspect of the temporal

lobes, *i.e.* entorhinal cortex and hippocampus, with a gradual extension to isocortical association areas [3, 4]. This hierarchical pathology translates into a chronology of symptoms which first give rise to memory loss then followed by other cognitive dysfunction [5, 6]. It is now recognized that psychotic symptoms (PS) in neurodegenerative diseases arise from specific dysfunctions of brain systems that may or may not be associated with cognitive impairment [7–9].

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Psychiatric symptoms in dementing disorders include hallucinations, delusions, restlessness, aggressive behaviour, an argumentative nature and personality changes such as apathy. They show expression profiles that vary according to the underlying condition and thus represent a heterogeneous array of manifestations that punctuate individual differences among affected patients. Their presence in some types of dementia is so pervasive that they are part of consensus criteria for clinical diagnosis, *e.g.* visual hallucinations (VHs) and sleep disturbances as common features for dementia with Lewy bodies (DLB) [10, 11], behavioural, impulsive and activity disturbances being frequent in frontotemporal dementia (FTD) [12, 13], anxieties and phobias in AD [14] and affective disturbances in vascular dementia [15]. In the absence of severe behavioural symptoms, executive impairment is more characteristic of AD than FTD [16]. Neurobiological studies have reinforced the diagnostic validity of psychosis in AD [5, 7, 8, 14]. The occurrence of VHs predicts postmortem Lewy pathology with 93% accuracy, indicating their high specificity for Lewy body (LB) disorders [17]. Thus, psychiatric symptoms may offer worthwhile clues for the diagnosis of these disorders [18].

In 1996 the term 'behavioural and psychological symptoms in dementia' (BPSD) was introduced [19], and panels of experts have developed specific diagnostic instruments for various types of BPSD in AD and other disorders [20, 21], which will increase our knowledge by correlating them with neuroimaging, neurochemical and neuropathological changes. Recent studies have provided models for BPSD clusters which include psychotic, affective and behavioural elements [22]. The significance of these studies is demonstrated by the fact that some of these symptoms may respond to the same drugs [23]. Although AD patients display a high variability in the evolutionary course of BPSD, groups of patients with similar frequency and severity of these symptoms may be identified [22]. Untreated psychiatric manifestations in patients with dementia have a tremendous impact on the patient, family and caregiver. They lead to greater rates of institutionalization, worse outcome and increased mortality [24–28]. Therefore, psychotic conditions are an important source of comorbidity in patients with dementia.

The goal of this article is to review the current state of neuroimaging and neuropathological correlates to BPSD, in particular PSs in the most frequent neurodegenerative diseases. The cerebral correlates of effective and behavioural disorders in dementia will be reviewed elsewhere [29]. The multiplicity of causes, influence of premorbid personality, the overlap of various lesions and sparse literature limits this review to clinico-pathological correlates for PSs. One should bear in mind that clinico-pathological studies often suffer from limitations and conclusions should therefore be considered with caution.

Old age and Alzheimer's disease

Prevalence estimates (Table 1)

Psychiatric symptoms in old age are frequent and have been observed in 43% of non-demented and 58% of demented persons

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

	%	Author
Dementia—prevalence		
Delusions	60	[30]
Agitation	42	
Aggression	33	
Hallucination	20	
AD—prevalence		
Initial presentation	64	[31]
Total	88–90	[32, 33]
Average	28–38	[34]
Total	50–80	[35]
Delusions	36	[27]
Hallucinations	18	
Delusions + hallucinations	13	
— " —, persistent	40–50	[36]
PD—prevalence		
Hallucinations	42	[37]
Delusions	21	
Minor symptoms	45	
VHs lifetime prevalence	~50	[38]
PD—overall incidence	30.8 (range 22–65)	[39]
PD—VHs prevalence	15.8–50	[40]
PDD—overall incidence		
Hallucinations	45–79	[43]
Delusions	25–30	[41, 42, 44]
DLB—prevalence		
Hallucinations	13–92	[45, 46]
Hallucinations mean	63–78	
Misidentification	56	
Paranoid delusions	25–28.6	[47, 48]
Paranoid delusions	49	[49]

PD: Parkinson disease; PDD: Parkinson disease dementia; DLB: dementia with Lewy bodies; VHs: visual hallucinations.

[50]. Others reported a higher prevalence of PSs in elderly people with dementia than in those without, suggesting that dementia with psychosis is not a reflection of cognitive impairment associated

with aging but rather a distinct syndrome that warrants specific treatment [51]. In fact, psychosis was the presenting symptom followed by rapid memory loss in the original case described by Alzheimer [52]. A study of psychiatric symptoms in AD found a prevalence rate of 64% at initial evaluation [31], which may precede diagnosis by up to 3 years [53]. The prevalence of psychosis in AD patients increases from the earliest stages of cognitive impairment to reach a maximum value by the middle stages of illness [24]. Sleep disorders and hallucinations, on the other hand, tend to occur in later stages [54]. Among 226 demented patients (174 with postmortem examination), 27% had transient agitation and delirant confusion, 18.9% predominant confusion and 9.2% paranoid symptoms [55]. Conservative estimates of the prevalence of psychosis in AD have ranged from 10% to 73%, with an average range of 28% to 38% [34], an overall mean of 24% in clinic populations and 7–20% in community and clinical trial populations, depending on definition. Others have claimed 88% to over 90% [32, 56]. In longitudinal studies, PSs have been reported to emerge in approximately half of the patients with clinically diagnosed or histologically confirmed AD, with frequencies of hallucinations between 15% and 30% [57] and delusional misidentifications between 20% and 30% [27, 58].

In nursing home patients two thirds have persistent symptoms over 12 weeks. Among AD outpatients hallucinations and delusions may persist in 40–50% over periods of 3 months up to 1 year [36]. Analysis of frontal lobe features in AD showed associations not only with more pronounced cognitive deficits but also with increased severity of PSs [59]. Others reported frequencies of delusions in AD (range 16–70%, median 36.5%), hallucinations (range 4–76%, median 23%) [60] and of VHs, ranging from 25% to 83% [58, 61, 62]. A review evaluating 55 studies with 9749 patients showed a median prevalence of AD + psychosis (AD + P) of 41% (range 12.2–74.1%), of delusions of 36% (range 9.3–63%) and other PSs, *e.g.* misidentification delusions of 25% (range 3.6–38.9%), hallucinations (median 18%, range 4–41%), with VHs (median 18.7%) being more frequent than auditory hallucinations (median 9.2%), both hallucinations and delusions (median 13%, range 7.8–20%) [27]. In a population-based sample of 85-year-old demented individuals, the prevalence of PSs was 36% among AD patients compared to 54% in vascular dementia cases ($P < 0.04$); the proportion with PSs increased with increasing dementia severity in AD [63]. In a sample of 95 year olds in Goteborg, Sweden, 1 year prevalence of any PS in AD was 7.4% [64]. In a study of 56 autopsy-confirmed AD cases, 23% had hallucinations (18% visual, 13% auditory), 16% paranoid delusions and 24% delusional misidentifications, but there was no relationship between the presence of psychosis and differences of cognitive performance or the state of illness [65]. However, recent studies supported the relationship between greater cognitive impairment and AD + P [66, 67].

According to the International Psychogeriatric Association [30], the most common psychiatric manifestations in dementia, without specifying the underlying aetiology, appear to be delusions (60%), affective symptoms (40%), anxiety (35%), verbal outbursts (33%) and hallucinations (20%). Apathy and agitation

(41% and 42%) were most common in severe dementia; others reported apathy was the most common psychiatric symptom with almost 65% in AD [25, 68]. Variability within prevalence estimates for any given neuropsychiatric symptom depends on the type of populations (outpatients *versus* nursing home patients, cross-sectional *versus* longitudinal), the diagnostic criteria used and the severity/stage of dementia.

Clinical manifestations

Psychosis occurs in a subset of AD patients (AD + P) during progression of the disease in whom it is associated with a more aggressive cognitive deterioration and worse outcome [24, 57, 58, 69, 70]. It is defined by hallucinations and delusions. Contrary to schizophrenia, where delusions are often bizarre and/or complex, delusions in AD are typically paranoid and non-bizarre, of persecution, infidelity, abandonment or belief that deceased individuals are still alive [71]. Individuals with AD + P have frequent misidentification delusions [72]. Delusions and VHs have a distinct cognitive profile as do delusional misinterpretations, although there may be an overlap between both forms [73]. Persecutory delusions in demented elderly are common (2.9%) and have a higher prevalence than other delusions, hallucinations and physically aggressive behaviours [74]. In AD + P patients, the misidentification group was significantly more impaired than the non-psychotic group on tests of verbal fluency and visuospatial function, whereas the paranoid group did not differ from the others in any tests, suggesting that the misidentification and paranoid forms are distinct subgroups of AD + P [75]. Hallucinations can occur in any modality, but are typical visual [14, 71, 72]. They are usually associated with greater cognitive impairment [66, 67, 76], a more severe cognitive decline and a more rapidly deteriorating course [24, 57, 77–79]. Some studies reported a decreasing prevalence of PSs in the late course of AD [24, 80–82], probably as a consequence of the deteriorated capacity of the brain with difficulties to express the contents of their delusions/hallucinations. AD + P is often associated with other psychiatric and behavioural disturbances, the most frequent and troublesome of which is agitation [83] and aggression [84–86].

Clinical studies have identified AD + P as a distinct subtype of AD [14, 79]. There is growing evidence that AD + P aggregates within families and may result, in part, from effects of genetic variations and risk factors [21, 35, 87, 88], and studies revealed that the heritability of psychosis in late-onset AD doubled from 30% to 60% by including only patients with multiple and/or recurrent PSs [89].

Although no definite association with the apo-lipoprotein E (ApoE) 4 allele has been found [79, 90], some studies have suggested relations to putative schizophrenia risk genes, *e.g.* neuroregulin-1 [91], but in recent times no association between neuroregulin-1, involved in neurodevelopment and in schizophrenia risk [91], and PSs in AD has been found [92]. Several studies showed linkage of chromosomes 2p, 15 and 7, and 8p, respectively, with AD + P [88, 89, 91], whereas one linkage analysis implicated the region of

chromosome 14 near the locus of presenilin-1 in AD patients without hallucinations [93]. Previous findings indicating relations to serotonin receptors/transporters and dopamine-3 receptor were not reproduced [68, 94–96], whereas serotonin system genes [97], dopaminergic receptors [98, 99], genetic variations of catechol-O-methyltransferase [100] and of neurotrophins, such as brain-derived neurotrophic factor [35] may increase the risk of psychosis in AD. Recent studies found no association of AD + P with neurodegenerative pathway genes (β -secretase 1, microtubule-associated protein τ , amyloid precursor protein, sortilin-related receptor, etc.) [101]. Although it is evident that AD + P is a distinct subtype with a frequent genetic base, the inconsistent findings of genetic association studies indicate that many challenges still face elucidation of genetics behind this syndrome [102].

Neuroimaging

PS are produced by distributed neuronal dysfunction. Neuroimaging investigations found interesting changes in AD + P patients. Single photon emission tomography (SPECT) studies showed a pattern of cerebral blood flow (CBF) deficits significantly different from that in non-psychotic patients. The latter had hypoperfusion of the left frontal lobe, those with hallucinations in the parietal lobe [103]. Others reported significant correlation between psychotic factor and metabolism in the frontal lobe, and between agitation/inhibition score and metabolism in the frontal and temporal lobes [104]. AD patients with visuospatial deficits revealed severe glucose deficits in parietal and occipital visual cortical areas [105], AD + P cases significantly lower regional perfusion in bilateral dorsolateral frontal, left anterior cingulate and left ventral striatal regions along with the left pulvinar and dorsolateral parietal cortex in comparison to a non-psychotic group [106].

Perfusion positron emission tomography (PET) studies in female AD + P subjects showed lower perfusion in right inferolateral 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 compared to those without such symptoms, indicating gender differences in regional perfusion [107]. Aggressive AD patients compared with non-aggressive ones displayed significantly more severe hypoperfusion of the right middle temporal region, suggesting it as an important neuronal correlate of aggression [108]. Comparison of an AD group with delusions with a non-delusional one in the first group found significant flow reductions in the prefrontal, anterior cingulate, inferior and middle temporal, and parietal cortices of the right hemisphere [109], whereas an AD group with autobiographic delusions had significant hypoperfusion in the right frontal lobe including Brodman area 9 and 10, suggesting that a focal functional damage was liable for the content-specific delusions [110, 111].

Structural imaging revealed increase in frontal and temporal asymmetry in AD + P [112]. Volumetric magnetic resonance imaging (MRI) studies showed an association between VHs and decreased occipital-to-whole brain ratio [113]. Voxel-based morphometry from T(1) weighted MRI revealed association of delu-

sions with decreased grey matter (GM) density in the left frontal lobe, in the right frontoparietal 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, whereas agitation was associated with decreased GM values 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 [114].

In amnesic mild cognitive impairment patients, delusions were associated with GM volume reduction in the right hippocampus; disinhibition was strongly associated with GM volume in bilateral cingulate and right middle frontal gyrus [115]. The authors suggested that PSs represent clinical features of neurodegenerative changes in AD. MRI showed white matter lesions (WML) in the bilateral frontal or parieto-occipital region and left basal ganglia significantly correlating with the score of Psychotic Symptoms Subscale of Behavioural Rating Scale for Dementia. However, 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 PSs, namely delusional misidentification, whereas other neuropsychiatric symptoms seemed not to be related with WMLs [116]. The ratio of MRI measured occipital volumes to whole brain volumes in AD patients with VHs was significantly smaller than in those without them, suggesting that VHs in AD may be associated with atrophy of the occipital lobe [113]. A small MRI study of five AD patients each with and without VHs showed a higher occipital periventricular hyperintensity score in those with VHs, whereas the occipital deep white matter hyperintensity 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 [117]. Older magnetic resonance spectroscopy studies showed significant elevation of glycerophosphoethanolamine and reduction of N-acetyl-L-aspartate in prefrontal, superior temporal and inferior parietal cortex of postmortem brains of AD + P patients, indicating impairment of neocortical neuronal and synaptic integrity as the structural substrate of AD + P [118].

Neuropathology

Early studies on neuropathological and neurochemical correlates of psychosis in 48% of autopsy-confirmed cases of AD showed significantly increased densities of senile plaques and neurofibrillary tangles in the prosubiculum and middle frontal cortex, respectively, with trends towards increased densities of these lesions in other cortical areas (entorhinal and superior temporal cortex). These findings were consistent with the increased rate of cognitive decline that accompanies behavioural and psychotic disorders. Psychosis was also associated with relative preservation of norepinephrine (NE) in substantia nigra, with trends in this direction for several other subcortical regions (thalamus, amygdala

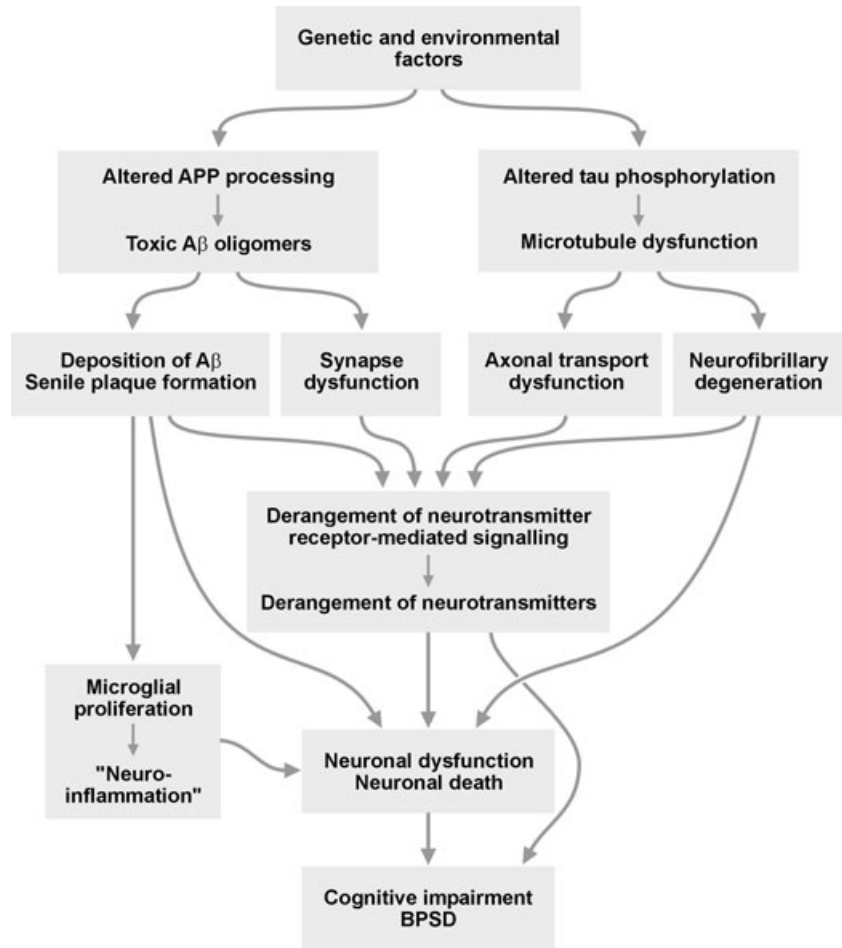


Fig. 1 scheme of the interplay of neurochemical and neuropathological factors in the pathogenesis of AD and its neuropsychiatric disorders.

and caudate nucleus), and significant reduction of serotonin in prosubiculum, and trends towards reduced levels of serotonin and 5-hydroxyindole acetic acid in other regions. The NE metabolite 3-methoxy-4-hydroxyphenylglycol showed mild but insignificant increase in cerebral cortex and caudate nucleus. In contrast, psychosis was not associated with significant changes in dopamine, its metabolites homovanillic acid and 3,4-dihydroxy phenylacetic acid, or choline acetyltransferase activities in any of the brain regions studied. The profile of neuropathological and neurochemical changes in AD + P was distinct from that reported for major depression in primary dementia, and no effects of neuroleptic treatment on biogenic amine concentrations were detected [119] (Fig. 1).

Other studies suggested that imbalance of different neurotransmission systems and involvement of specific brain regions are responsible for BPSD (parahippocampal cortex, locus ceruleus and dorsal raphe [120]). Although cholinergic cell loss is an important attribute of the pathological process underlying BPSD, including psychosis, aggression and depression, an early feature in AD pathology is degeneration of the locus ceruleus which serves as the main source of NE supply of cortical and subcortical areas [121].

Other studies have described a relationship between prominent hallucinations and the presence of LBs in cortex and brainstem [122–124], or between delusions and basal ganglia mineralization [69, 70, 125].

In a prospective clinico-pathological study of 56 patients with autopsy-confirmed AD (23% with hallucinations, 16% with paranoid delusions and 25% with delusional misidentification), the subgroup with auditory hallucinations and paranoid delusions showed less severe neuron loss in the parahippocampal gyrus and non-significantly lower neuron numbers in the serotonergic dorsal raphe nucleus than patients without those symptoms, but no differences in the locus ceruleus (these were associated with depression). Delusional misidentifications were seen in patients with lower neuron counts in the hippocampal area cornu ammonis (CA)-1. Apart from a higher parahippocampal tangle count in AD patients with delusions, no significant differences of plaque and tangle counts between AD patients with and without psychotic phenomena, and no significant differences in substantia nigra, frontal and parietal lobes in AD + P patients were found [65]. These authors found no evidence for a relationship between LBs and PSs, whereas basal ganglia mineralization was observed in a

subset of five patients with a high rate of psychotic disturbances [7]. In a family with idiopathic basal ganglia calcifications, clinically presenting parkinsonism, cognitive deterioration and schizophrenia-like psychoses, (18)FDG uptake was significantly reduced in striatal or cortical areas, including the precuneus and posterior cingulate gyrus [126]. The reduction of pyramidal cell neurons in hippocampal area CA-1 of AD patients with delusional misidentifications appeared in good agreement with their previously suggested association with a lesion in the mediobasal temporal lobe [127]. A recent semi-quantitative study of neuropathological changes in postmortem hippocampus revealed that an increased tangle load, but no other hippocampal morphologic variables, were associated with increased severity of aggressive behaviours and presence of chronic aggression, suggesting a pathogenic link between tangle load and aggressive behaviour in the hippocampus of dementia patients [128]. Another recent study in AD patients with a history of major depression showed higher tangle and plaque counts in hippocampus and more rapid cognitive decline than in similar demented patients without depression [129]. Apathy in AD is related to disruption of transmission of decision value signals from orbitofrontal cortex to nucleus accumbens and midbrain dopaminergic ascending pathways and of frontostriatal circuits [130].

Lewy body diseases

Clinical features and prevalence (see Table 1)

Psychotic symptoms are frequent and disabling in patients with LB diseases-DLB and Parkinson's disease (PD) [41]. They share a similar profile in both disorders, including complex hallucinations (*i.e.* false sensory perception) and delusions (*i.e.* fixed false beliefs) of a paranoid type that are less frequent [131]. In PD, hallucinations were already observed in the prelevodopa era, and for early authors, such as Gowers and Charcot, hallucinations that occurred in the course of PD either accompanied the final phase of the disease or reflected comorbidities, and disease duration is one of the risk factors for their development [132–134]. International consensus criteria have been proposed [37], as well as a critical review of the available rating scales [134]. Psychiatric symptoms in early untreated PD included 17% apathy, whereas 30% had at least one such symptom [41]. The average overall incidence of PSs is 30.8%, ranging from 22% to 65% [39]. Reported prevalence of hallucinations and psychosis in PD is up to 48% and 80%, respectively. PSs generally develop 10 or more years after the onset of PD [37, 132]. Their prevalence in PD with dementia (PDD) is markedly higher than in non-demented PD patients [44, 135], ranging from 45% to 68% [41, 42], while chronic disorientation frequently occurs in PDD patients. Assessment of 116 PD patients for the presence of PSs using the recent new criteria for psychosis associated with PD [37] revealed hallucinations in 42% (visual 16%, non-visual 35%), delusions in 21% and minor symptoms in 45%. The prevalence of psychosis

associated with PD was 43% when the usual definitions were applied, and 60% when the new National Institute of Mental Health/National Institute of Neurological Disorders criteria were used [136]. Most frequent are VHs, that occur in about 25–44% of PD patients, auditory hallucinations in up to 20% [38, 137], whereas tactile [138], gustatory [137, 139], auditory [140] and olfactory [139, 141] hallucinations are less frequent. VHs are generally complex, well formed and kinematic [137, 142, 143]; preserved or disturbed insight on the nature of the hallucinations is a major prognostic factor, although eventually all hallucinations will present with reduced insight [144]. VHs in PD are facilitated by impaired colour and contrast discrimination, and may be associated with visual cognitive impairment attributable to PDD and DLB pathology [145]. Impaired visual processing precedes image recognition in PD patients with VHs [146]. Other phenomena, *e.g.* sense of presence and VHs affect 17–72% and delusions about 5%.

Delusions are less common than hallucinations, and typically co-occur with hallucinations [43]. Most frequent forms are 'phantom boarder' phenomenon (the belief that a stranger is living in the patient's home), feeling of presence and delusions of infidelity. Imposter phenomenon is rare but can occur. Prevalence rates for delusions are reported to be 17% in PD patients overall and 25–30% in PDD patients [41, 42]. Studies investigating the prevalence of hallucinations and delusions in PD patients yielded a large difference range from 3% to 60% and for the incidence of hallucinations from 16% to 37% [147]. Prevalence rates for delusions were 17% in PD patients overall and 25–30% in PDD patients [42]. In a community based study that used the neuropsychiatric inventory (NPI) to identify neuropsychiatric symptoms in 100 PD patients with (43%) and without (57%) dementia, five NPI clusters were identified. The clusters with the highest representation of PDD patients were a group characterized primarily by hallucinations (79% PDD) and a group with high scores on several NPI items (57% PDD) [44].

Psychotic symptoms are frequent during night and associated with sleep disturbances, vivid dreams and sleep-related phenomena may lead to hallucinations [144]. They are often related to autonomic impairment or mechanisms underlying motor fluctuations [148] and other non-psychotic psychiatric disturbances, especially affective symptoms, are frequent comorbidities [149]. Olfactory impairment early in the disease course may be a useful marker for the risk of psychotic complications in PD. Lifetime prevalence of VHs ranges between 50 and 74% [17]. They persist and worsen, their prevalence increases with time [38]. A total of 30–40% of PD patients show fluctuating PSs [150], but, once present, they tend to persist and progress. Psychosis is a key feature to nursing home placement [151], and PSs are more common in patients living in nursing homes compared with home dwelling patients. They correlate with stage of the disease and cognitive impairment, but not with age or duration of disease [41, 152]. Longitudinal studies show a prevalence of hallucinations of 16–17% in population-based surveys and 30–40% in hospital-based series [153]. In a 10 year prospective longitudinal study of 89 patients, hallucination prevalence and severity increased significantly with time. They were highly associated with concurrent vivid dreams/nightmares [154].

Dementia is the most robust risk factor for the onset of hallucinations in PD, and hallucinations again are a possible risk factor for dementia [39, 155]. PD patients with hallucinations but without dementia have affection of executive functions [156].

In a 12 year population-based study of 230 PD patients, 60% developed hallucinations or delusions. Their incidence rate was 79.7/1000 patient/years, increasing with higher age at disease onset [157]. 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. A total of 28% of nursing home patients died within 2 years, paranoia being associated with a poorer prognosis [158]. A recent population-based long-term study demonstrated that, in addition to age at onset, chronological age, motor severity, dementia, PSs independently predict increased mortality in PD. Early prevention of motor progression and development of both dementia and psychosis may be the most prominent strategies to increase life expectancy in PD [159].

In DLB—both 'common' and 'mixed' forms (DLB + AD, LB variant of DLB/LBV/AD)—PSs are extremely common, predominantly VHs, misidentifications, delusions and other syndromes [160]. Although delusions and misinterpretation syndromes have a similar phenomenology in both DLB and PDD patients, they may be more prevalent in DLB, possibly due to morphological and neurochemical differences between both disorders [160]. Hallucinations are the most frequent PSs, with a prevalence range between 13% [46] and 92% [58] and means of 63–78%, followed by misidentifications [56%] and paranoid delusions (25–28.6%) [47, 48], whereas another group reported PS in 50% of the DLB patients, showing no association with the degree of motor disability [161]. VHs are generally present early in the course of illness with characteristics as described in the original report [10]. They are significantly more frequent in common DLB than in LBV/AD [162–164]. VHs are the presenting feature in 33–65% of DLB *versus* 8–15% in AD [45]. Unlike AD, 18% of common DLB and 14% of LBV/AD present with VHs prior to the dementia onset. Recurrent, complex VHs are one of most useful signposts to a clinical diagnosis of DLB and, together with visuospatial/constructional dysfunctions are a validated diagnostic criterion for DLB [165], and differentiate it in the earliest states from AD [164, 166]. VHs tend to persist; *e.g.* hallucinations were stable in a group over 20 weeks [165], and in a cohort over 52 weeks [167]. They are similar to those in PD in that they are vivid, complex, colourful, three dimensional and generally mute images of animals, less frequent of other objects [42, 165, 168]. Patients with DLB have more frequent VHs than those with AD [169], showing more prominent visuospatial dysfunction compared to those without VHs [170, 171].

In DLB, most frequent 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 [42, 162]. A meta-analysis calculated the mean prevalence of delusions in DLB at 49% compared to 31% in AD [49]. The persistence of

delusions is similar in DLB and AD [167]. VHs and delusions are usually independent of each other, and the relationship between hallucinations/delusions and cognition is obscure [45]. In the population-based Vantaa 85+ study, among 109 patients with autopsy-proven LBD, 48% were reported to have VHs associated with dementia [172].

Neuroimaging

(18)-F-FDG PET studies in PD patients with compared to those without VHs revealed reduction in the regional cerebral glucose consumption in the occipito-temporo-parietal regions, the ventral and dorsal visual streams ($P < 0.05$). Sparing the occipital pole indicated functional disorders of visual association areas in higher-order visual processing [173]. These data extended previous and partial contradictory SPECT and PET studies showing decreased rCBF in left temporal cortex in PD with VHs [173], greater relative glucose metabolism rates in the frontal areas, in particular the left superior frontal gyrus and in posterior cortical areas [175] or hypoperfusion in the right fusiform gyrus and hyperperfusion in the right superior and middle temporal gyri in non-psychotic PD patients with VHs [176]. Most other studies in PD and DLB reported stronger functional involvement of posterior brain regions than in AD, including the primary visual cortex and the visual pathways [34], whereas reductions in all cortical areas were reported in PDD [177].

Tc-Hexamethylpropyleneamine Oxime 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 [178]. There was reduced occipital uptake in areas identified as primary and secondary visual cortex [61, 179–183]. Hallucinators showed greater right posterior and parietal glucose uptake than non-hallucinators [184]. 18-F-FDG PET studies in DLB patients with VHs revealed hypometabolic regions at the right occipito-temporal junction and in the right middle frontal gyrus, suggesting hypometabolism in visual association areas rather than in the primary visual cortex [48], whereas delusions were associated with hypometabolism of the right prefrontal cortex. Although there was a significant correlation between the frequency and severity of delusions and other clinical variables such as VHs, the Mini Mental State Examination (MMSE) score and the regional glucose uptake of the right prefrontal cortex, only the regional metabolic alteration was a significant predictor of delusion symptomatology in this DLB group [48]. Functional MRI during visual stimulation showed hypometabolism in occipital and parietal cortex and hyperactivity in prefrontal regions [185]. SPECT studies in DLB patients revealed that factor 1 symptoms (Capgras syndrome, etc.) were significantly related to hypoperfusion in the left hippocampus, insula, ventral striatum and bilateral inferior gyri; factor 3 symptoms (VHs) were related to hypoperfusion in the left ventral occipital gyrus and bilateral parietal areas, whereas delusions were

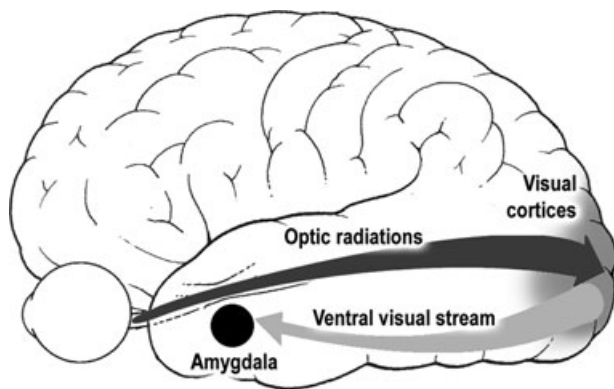


Fig. 2 Diagram of the major visual pathways implicated pathologically in VH in PD.

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 [186]. Despite the relative heterogeneity of previous reports [178, 184], which can partly be explained by differences in patient characteristics and imaging modalities, more recent studies imply that dysfunction of extrastriate downstream visual association areas, rather than the primary visual cortex, are involved in the occurrence of VHs [48, 186]. They consistently indicate an alteration of the ventral visual pathways along with disordered cortical inhibition (Fig. 2).

Volumetric studies in DLB showed no occipital volume differences between hallucinators and non-hallucinators [187], whereas voxel-based morphometry in subjects with VHs revealed 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 visual areas, namely left precuneus and inferior frontal lobe, correlated with VHs in DLB but not in PDD patients. In conclusion, DLB and PDD patients with VHs had more frontal GM atrophy than non-hallucinators, the impairment being greater in the DLB group [188]. Other MRI studies showed that PD + VH patients had significant hippocampal cell loss compared to controls [188]; they frequently develop dementia and show a widespread atrophy, involving limbic, paralimbic and neocortical structures [190].

Changes in DLB associated with psychosis include lowered choline acetyltransferase activity and increased muscarinic receptor binding (types 2 and 4) [191].

Neuropathology

Some important associations between histopathology and PSs have been described in PD and DLB. Psychopathology including VHs and dementia corresponds to LB distribution in the limbic

system [192, 193], the latter being significantly associated with α -synuclein (α Syn) deposition in anterior cingulate gyrus, entorhinal cortex, amygdaloid complex and nucleus basalis of Meynert as well as τ in the CA-2 sector of hippocampus. On the other hand, α Syn burden in the amygdala is strongly related to the presence of VHs, but only in those PD cases with concomitant dementia [194]. VHs in DLB relate to amygdala and parahippocampal LB density and, when present early in the course of disease, to parahippocampal and inferior temporal cortical LB density [61, 195]. Cases with DLB had higher LB densities in the inferior temporal cortex than cases with PDD. Patients with VHs had nearly double the density of LBs in the basolateral nucleus compared to non-hallucinators, however, without differences in neuronal loss, which suggests neuronal dysfunction rather than amygdala's ability to integrate coordinated behavioural responses between the two visual systems [61].

Alzheimer-related pathologies, including plaques and tangles, and ApoE status, do not appear related to psychosis in PD [196, 197]. Although there was no association across groups between any neuropathological variable and the presence or absence of fluctuating cognition, 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 [124, 198], whereas others found no significant differences in LB density in any brain region among patients with and without VHs and delusions [199]. A recent study of 129 cases of pathologically proven PD showed that patients with VHs had significantly higher cortical LB scores (7.7) than those without VHs (6.6; $P = 0.02$) [200]. Cases with well-formed VHs had high LB densities in amygdala and parahippocampus, with early hallucinations relating to higher densities in parahippocampal and inferior temporal cortices. 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 [61]. Other studies showed an association between neuronal loss and the severity of α Syn deposition in the intralaminar nuclei of the thalamus and VHs, fluctuations in consciousness and other symptoms in PD [201]; these changes correlated with disease duration [202]. In a series of 112 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, whereas LB staging was associated with 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 patients and were less likely to have neocortical LBs. Thus, unlike AD, DLB cases showed a significant inverse association between tangle burden and psychosis [11].

Several clinico-pathological studies have addressed the morphologic features underlying VHs in dementia. They have consistently reported a higher frequency and earlier onset of VHs in subjects with Lewy-related pathology, *i.e.* subjects with DLB or PDD [124, 167, 202], than in demented subjects with AD. Most

prospective studies have reported VH frequencies greater than 50% in subjects with confirmed Lewy-related pathology [58, 204]. Some have suggested that concomitant AD pathology obscures the clinical presentations of VHs in subjects with Lewy pathology [10, 205–207], whereas others suggested that VH frequencies are especially associated with the density of LBs in the medial temporal lobe [208].

In a community-based clinico-pathological study of 148 demented subjects, those with VHs (18%) had significantly more frequent Lewy pathology than those without VHs (78 versus 45%). A higher frequency of VHs was observed in subjects with neocortical LBs than 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⁺ group (59%), the frequency of subjects with AD did not differ significantly between those with and without VHs (74% versus 62%) [207].

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 Braak stage independent of the presence of dementia ($P = 0.041$), but no association was seen with the type of Lewy pathology ($P = 0.78$). The probability for VHs was more than three times higher in subjects with neuritic Braak stages III–VI compared to those with Braak stages 0–II [172]. These findings differ from others which reported that subjects with extensive neurofibrillary pathology show fewer clinical features of DLB, like VHs [11, 208].

Huntington's disease (HD)

Psychosis is more common in HD than in the general population, occurring in up to 15% of HD patients [210–212]. Paranoia rather than schizophrenia-like symptoms are the important and underestimated manifestations. PSs include paranoid delusions in up to 11%, although auditory hallucinations and VHs are rare, occurring in about 2% [212, 214]. 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 cytokine-adenine-guanine (CAG) expansion in the HD gene [212]. Gene carriers and non-carriers do not differ in terms of the lifetime frequency of psychiatric disorders or subclinical symptoms, but gene carriers had a significantly higher rate of depressive symptoms [215, 216], whereas symptomatic mutation carriers showed an increased prevalence of non-affective psychosis [216]. Specific psychiatric symptoms (*e.g.* paranoid ideation and psychoticisms) 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 [216]. 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 [218]. Psychiatric symptoms generally do not correlate with cognitive decline, abnormal movements, or CAG repeat length [219].

Most of PSs in HD are believed to arise from subcortical neuropathological changes [220]. Although we are not aware of

specific studies of neuropathology in HD cases with psychosis, PSs in early stages of the disease may be related to dysfunction of vulnerable striosomal spiny neurons in the neostriatum and centre median of thalamus [221], involving the basal ganglia-thalamocortical circuit, but the models of striatal connectivity and pathology are insufficient to explain such features in early HD [222].

Frontotemporal dementia (frontotemporal lobe degeneration [FTLD])

Although most patients with FTD present with neuropsychiatric symptoms, the frequency of PSs is unclear. Among 86 patients who met consensus criteria for FTD, only two (2.3%) had delusions, one of whom had paranoid ideation, whereas no FTD patient had hallucinations; this was significantly less than in AD patients [223]. These and other case reports [224, 225], and an evidence-based review of the psychopathology of FTD showed rare occurrence of delusions and hallucinations [226], possibly due to limited temporo-limbic pathology in this disorder. There are rare clinical reports about FTD patients presenting as acute later onset schizophrenia [227–229]. Among 61 autopsy cases of FTD (43 with behavioural [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 early indicate combination with ALS features. The median survival from symptom onset was significantly shorter for the FTD/ALS group than for bvFTD cases (mean 2.4 versus 6.6 years) [230]. Apathy and disinhibition in FTLD was associated with lesions in the anterior cingulate and dorsolateral prefrontal cortex [13].

In a small number of FTD cases presenting with schizophrenia-like psychosis years prior to the dementia diagnosis, neuropathology was consistent with TDP-43 and ubiquitin⁺ FTD [231–233]. 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. Pathology was consistent with FTLD with ubiquitin-only immunoreactive changes, type 1 [234], which represent a significant, clinically heterogeneous subtype of FTLD [235]. Another subtype clinically characterized by early onset and progressive and behavioural and personality changes, morphologically being τ - and TDP-43⁺, with fused in sarcoma pathology, has been classified as 'atypical' FTLD [236, 237].

PSs, occasionally mimicking schizophrenia, have been reported in rare clinical cases of ALS, but no neuropathological findings were available [238, 239].

Prion diseases

Sporadic Creutzfeldt–Jakob disease (sCJD) is characterized by prominent neurological symptoms and less common psychiatric disorders, whereas the variant form (vCJD) is described as primary psychiatric in presentation and course [240, 241]. A retrospective review of 126 sCJD patients at the Mayo Clinic revealed

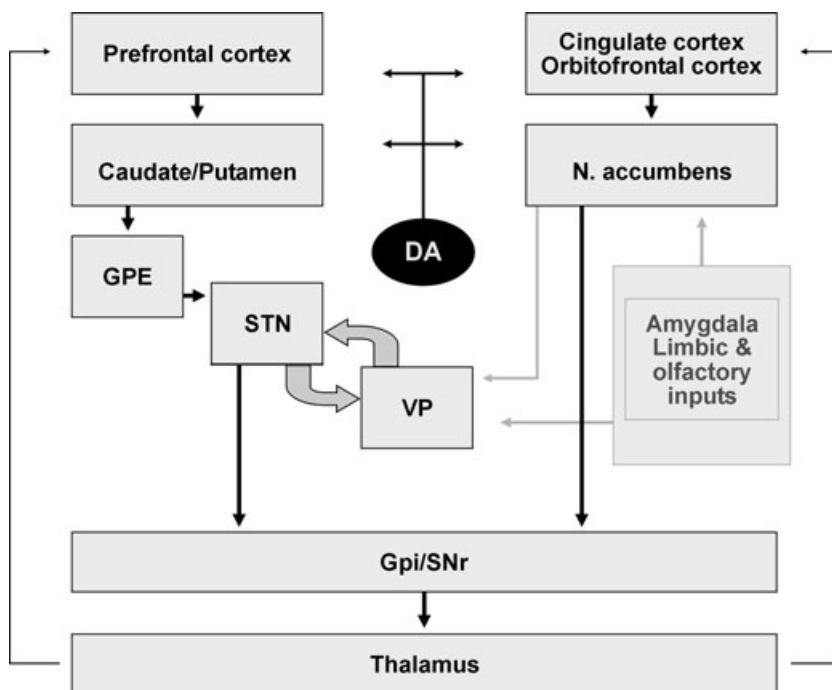


Fig. 3 Circuiting interconnections between psychotic and cognitive functions. GPE: external globus pallidus; STN: subthalamic nucleus; VP: ventral pallidum; Gpi-SNr: internal globus pallidus and substantia nigra pars reticulata; DA: dopamine. Modified from **Barone P, Santangelo G.** Interaction between affect and executive functions in Parkinson's disease. In: Emre M, editor. *Cognitive Impairment and Dementia in Parkinson's Disease*. Oxford, UK: Oxford University Press; 2010. pp. 65–73.

that 80% of the cases demonstrated psychiatric symptoms within the first 100 days of illness, with 26% occurring at presentation. The most common symptoms included sleep disturbances, PSs and depression. Psychiatric manifestations as an early and prominent feature of sCJD often occurred prior to formal diagnosis [241, 242]. In one patient, anxiety and irritability also occurred early, followed by transitory hallucinatory psychosis [243], whereas others presented as depressive disorder with psychotic features [244]. Psychiatric symptoms as a consistent early clinical feature in vCJD, in addition to depression, include transient delusions and auditory hallucinations or VHs [245], and are difficult to distinguish from common psychiatric disorders [246]. CJD affects multiple brain areas, which causes multifocal deficits involving movement, cognition and psychiatric status. Modern neuroimaging helps to track the progression of the disease course and provides insight into clinico-anatomical correlations [247], but relevant neuropathological data about PSs in prion diseases, to the best of our knowledge, are not available so far.

Conclusions and future prospects

The aetiology of PSs in neurodegenerative disorders is complex and likely includes a variety of interactions between genetic and personality factors, medication exposure, morphological, neurochemical, hitherto unknown molecular changes and comorbid conditions, particularly cognitive impairment, visual disturbances and others. There has been an ongoing debate as to whether BPSD are non-specific aspects of neurodegeneration or distinct phenotypes. Because several of them may precede cognitive impairment by

several years and can be considered as prodromal symptoms to dementia [68], the question arises which neuropathological changes may be important as risk factors for PSs in neurodegenerative disorders. The separation of BPSD and cognition into relative distinct domains suggests that different neuroanatomical systems may be involved in the genesis of these symptoms [248], but recent imaging studies have suggested that behavioural symptoms in AD are directly associated with neurodegeneration [115]. Because the onset of psychiatric symptoms varies for each individual manifestation and may appear at any stage of illness, temporal correlation is difficult to assess as all these processes and their psychiatric manifestations tend to have insidious onsets that preclude accurate staging and a fluctuating course, causing difficulties in their relation to anatomical and molecular biological changes. PSs are frequently present in patients with executive deficits, suggesting an association with frontal lobe dysfunctions [2, 59], related to interruption of corticosubcortical circuits involving the basal ganglia and frontal lobes [249]. They are associated with lesions in meso/paralimbic, prefrontal and temporal cortical association areas [250], suggesting that regional rather than diffuse brain pathology may be a primary response (Fig. 3).

There is increasing information about the neurobiological substrate of VHs and other PSs in PD and DLB [251]. These symptoms have been commonly viewed as an adverse effect of anti-Parkinson treatment [252, 253]; but more recent studies indicated that VHs do not directly relate to medication doses, and factors intrinsic to the disease process may also cause PSs [254–256]. Other studies linked VHs to cholinergic deficits with up-regulation of post-synaptic muscarinic acetylcholine (ACh) receptors [122], delusions correlating with post-synaptic up-regulation of nicotinic

receptors [62], and hallucinations with decreased binding to nicotinic receptors (α_7 nAChR) in the temporal cortex [257]. Serotonergic/dopaminergic imbalance has also been implicated in the development of psychosis in PD [123, 253, 258]. Moreover, altered visual information processing in PD and DLB with predominant visual cognitive impairments and alterations of the extrastriatal visual pathways were discussed [259]. Increase of blood flow in the ventral occipital regions and improvement of VHs in DLB after donepezil administration suggested that hypofunction in the visual association areas caused by a lack of cholinergic inputs from the forebrain or brainstem may be a key for the genesis of VHs [260]. Others suggested alterations of brainstem sleep-wake and dream regulation, and impaired attentional focus [261]. Genetic variation analysis in PD patients with and without VHs showed they were neither associated with the genetic pattern seen in patients with AD nor with an ApoE genotype [262].

Dopamine has been linked to DLB + psychosis (Fig. 3). Neuronal loss in the substantia nigra, albeit not as severe as that in PD, occurs in DLB [123, 205]. Dopamine uptake in the basal ganglia is more uniformly but less decreased compared with PD; dopamin receptor D-2 binding is decreased in DLB and increased in PD [263]. Although in psychotic AD patients, receptor D-3 density is increased, in DLB cases D-1 are increased and D-2 and D-3 receptor densities are decreased [264]. These data suggest that dopaminergic compounds may indirectly influence VHs, increasing the dopaminergic/cholinergic imbalance [45]. NE may also contribute to DLB psychopathology, because NE is depleted in the putamen [265], and the neuronal loss in the locus ceruleus is more severe compared with AD [122, 123, 205].

Although previous studies showed that VHs in PD are not influenced by polymorphisms of serotonin 5-HT_{2A} receptor and transporter genes [266], recent pilot studies provided *in vivo* evidence suggesting a role for serotonin 2A receptors in mediating VHs via the ventral visual pathway [267]. DLB showed a significantly higher frontal 5-HT_{1A} receptor binding compared with PDD, suggesting distinct neurochemical features for the two disorders [252].

Some of the correlations between PSs and neuropathology may be the result of comorbid conditions, *e.g.* cerebrovascular

or Lewy pathology which, however, frequently are missed clinically and could not be identified without neuropathological examination [268–277]. Some authors have avoided reporting BPSD by dementia subtypes because of the high degree of mixed pathology [269, 278].

It would be difficult to evaluate how neuropathology alone counts for the heterogeneity of psychiatric manifestations in neurodegenerative disorders, because current opinion suggests a complex network of genetic, morphological, neurochemical, neuropsychological and hitherto poorly understood molecular factors to be responsive for PSs. The burden of different lesions, although frequently overlapping, is considered to be independent of each other, and is consistent with an additive or synergistic effect, but this effect could hardly be measured so far [15, 273, 275, 276]. It should be emphasized that patients with PSs differ clinically and neuropathologically from those without psychiatric symptoms. Despite the increased focus on psychiatric symptoms associated with neurodegenerative diseases and dementia in neurobiological research, many challenges remain. Clinical phenotypes are imperfect and at times overlap increasing the difficulty of finding significant biological correlates, particularly in small samples. Although functional imaging, genetic and clinico-pathological studies hold immense promise, many studies will require replication and validation in larger samples. Understanding of these manifestations may lead to the development of more effective preventive and therapeutic options that may delay long-term progression of these devastating disorders and improve the patients' quality of life [279]. It is important to recognize these subtypes and to better understand the pathophysiological cascade underlying the development of psychiatric syndromes in neurodegenerative and dementing diseases, which also may provide important insights into psychotic processes in general [280].

Conflict of interest

The author confirms that there are no conflicts of interest.

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