The psychosis spectrum in Parkinson disease

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Abstract

In 2007, the clinical and research profile of illusions, hallucinations, delusions and related symptoms in Parkinson disease (PD) was raised with the publication of a consensus definition of PD psychosis. Symptoms that were previously deemed benign and clinically insignificant were incorporated into a continuum of severity, leading to the rapid expansion of literature focusing on clinical aspects, mechanisms and treatment. Here, we review this literature and the evolving view of PD psychosis. Key topics include the prospective risk of dementia in individuals with PD psychosis, and the causal and modifying effects of PD medication. We discuss recent

developments, including recognition of an increase in the prevalence of psychosis with disease duration, addition of new visual symptoms to the psychosis continuum, and identification of frontal executive, visual perceptual and memory dysfunction at different disease stages. In addition, we highlight novel risk factors — for example, autonomic dysfunction — that have emerged from prospective studies, structural MRI evidence of frontal, parietal, occipital and hippocampal involvement, and approval of pimavanserin for the treatment of PD psychosis. The accumulating evidence raises novel questions and directions for future research to explore the clinical management and biomarker potential of PD psychosis.

In 2007, consensus recommendations from an international work group redefined the landscape of psychosis in Parkinson disease (PD)[1]. Symptoms of psychosis, such as illusions, hallucinations and delusions, are collectively referred to as 'positive', carrying the implication of an excess of function or brain activity, in contrast with 'negative' symptoms of deficit. Though all long recognized as nonmotor manifestations of PD, positive symptoms such as illusions, hallucinations and delusions were traditionally considered to be distinct from one another, with different clinical implications. In particular, hallucinations of a person, animal or indefinite object passing through the peripheral visual field (passage hallucinations), misperception of actual stimuli (illusions) and a distinct class of perceptual experiences without visual content but a 'feeling' of someone present (presence hallucinations) were not thought to carry the same clinical significance as formed visual hallucinations of animals, objects or figures. This distinction was reflected in the terminology, whereby illusions and passage and presence hallucinations were described as 'benign' or 'minor' hallucinations.

After reviewing the available evidence, the combined National Institute of Neurological Disorders and Stroke (NINDS) and National Institute of Mental Health (NIMH) work group concluded that instead of representing distinct symptom classes, the various phenomena formed a continuum progressing over the course of PD. The typical clinical scenario was of minor phenomena evolving to formed visual hallucinations, with insight initially preserved but lost in later stages, and with delusions and non-visual — for example, auditory, tactile and olfactory — hallucinations also developing (BOX 1). This spectrum of positive symptoms was termed 'PD psychosis', and the proposed diagnostic criteria included the chronology of symptoms (occurrence after the onset of PD) and symptom duration (recurrent or continuous for 1 month). The NINDS–NIMH recommendations led to a paradigmatic shift in focus from individual positive symptoms to a symptom continuum, which was further characterized in a series of landmark reviews published in the years that followed[2–8]. These reviews benchmarked knowledge of PD psychosis in terms of its phenomenology, prevalence, clinical implications, mechanisms, treatment and future research directions, and led to a rapidly expanding literature. In this Review, we reflect on the advances that have been made in the 10 years since the publication of the consensus work group criteria, highlighting key research findings and directions in PD psychosis, and their implications for clinical practice and the neuroscience of PD.

Box 1

The psychosis spectrum in Parkinson disease

Positive symptoms in Parkinson disease (PD) vary across its course. Early in the disease, symptoms experienced include passage hallucinations (where a person, animal or indefinite object is seen briefly passing in the peripheral visual field), illusions (for example, seeing the branch of a tree as a cat), and presence hallucinations (a feeling that someone is nearby). Pareidolia refers to a specific class of illusion where faces and objects are seen in formless visual stimuli, such as clouds, flames or tree bark, or in geometric visual patterns, such as carpets or wallpaper. This type of illusion can occur as a normal perceptual experience, but is increased in frequency in PD[159] and related disorders such as dementia with Lewy bodies.

Later in PD, formed visual hallucinations, typically of animals or people, occur. Insight — that is, recognition that the experiences are hallucinations — is preserved at this stage, but becomes lost as PD progresses, with the onset of false beliefs (delusions) and hallucinations in other sensory modalities (multimodality hallucinations). Cognitive decline and loss of insight parallel symptom progression, as illustrated by the transition in the arrow on the left from dark shading (cognition/insight intact) to light shading (cognition/insight impaired).

Approximate ratings of the Movement Disorder Society United PD Rating Scale (MDS-UPDRS) hallucination/psychosis item are shown on the right of the figure, marking progression through different categories of experience on the continuum. The terms pseudohallucination and hallucinosis are used as synonyms for hallucinations with insight in some psychiatric and neurological traditions, but also have other meanings and were not adopted by the NINDS–NIMH work group[1].
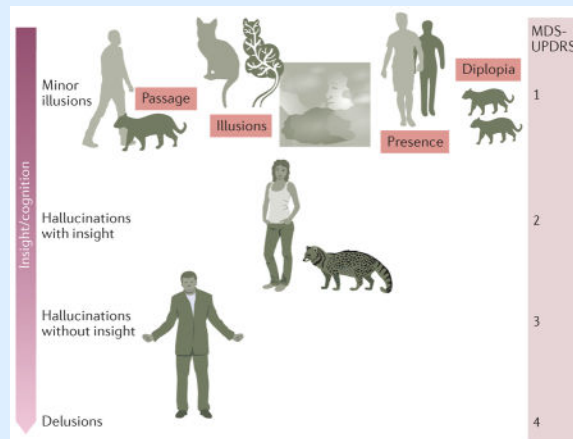
Phenomenology and diagnosis

As described by the NINDS–NIMH consensus work group[1], symptoms of the psychosis spectrum in early stages of PD include minor experiences, such as passage and presence hallucinations, illusions, and formed hallucinations — most commonly, recurring visual

hallucinations of people, animals or inanimate objects — with insight preserved (BOX 1). In later PD stages, delusions and hallucinations occur in other modalities, for example, auditory hallucinations consisting of a voice that may not be comprehensible[9], or non-verbal sounds, such as steps or music[10]. The hallucinations tend to occur in conditions of low ambient stimulation, typically when the individual is alone in a quiet environment, are experienced several times a day, and last for seconds to minutes in the early stages of PD psychosis. Evidence that has emerged since the publication of the consensus work group recommendations has helped to further characterize the phenomenology of different PD psychosis stages, and their relationship with the progression of Lewy body pathology (BOX 2).

Box 2

Psychosis spectrum progression and Braak stage

The fact that illusions, passage and presence hallucinations progress to formed visual hallucinations in Parkinson disease (PD) need not imply that they all have the same underlying mechanism. Evidence has emerged that minor hallucinations and formed visual hallucinations are associated with different sets of risk factors. For example, presence hallucinations have been linked to sleep regulation and somnolence scores, illusions are related to somnolence and motor severity scores[160], and neurobiological explanations of passage hallucinations implicate dysfunctional brainstem eye movement control mechanisms and subcortical and cortical motion pathways, including dorsal stream areas in the visual parietal lobe[105,161]. Previous studies of visual hallucinations have linked visual parietal areas to hallucinations in the peripheral visual field[162] (as described for passage hallucinations) and palinopsia (helping to account for palinparousia — recently decribed palinopsia-like presence hallucinations[11]), and subregions of the intraparietal sulcus are linked to eye movement control[163]. By contrast, formed visual hallucinations are associated with changes in cognition, visual function and affect[160], probably reflecting cortical involvement in ventral occipitotemporal lobe regions[162]. The onset of minor hallucinations might even precede the development of motor symptoms[28].

The difference in timing of and risk factors for minor hallucinations and formed visual hallucinations mirrors the Braak progression of Lewy body pathology from brainstem to forebrain systems systems[164]. This observation suggests that symptom progression along the PD psychosis continuum begins with isolated minor experiences, indicating brainstem pathology (pink shading in figure) and its wider impact on subcortical and cortical motion and eye movement control networks, including the visual parietal lobe (arrows — note that dysfunction within these cortical networks does not necessarily imply cortical Lewy body pathology (BOX 4)). Subsequent emergence of visual hallucinations with insight indicates basal forebrain involvement (orange shading) and its wider impact on cortical cholinergic projections (arrows), in particular, projections to the ventral occipitotemporal cortex. Finally, multimodality hallucinations, delusions and loss of insight indicate widespread cortical Lewy body pathology.
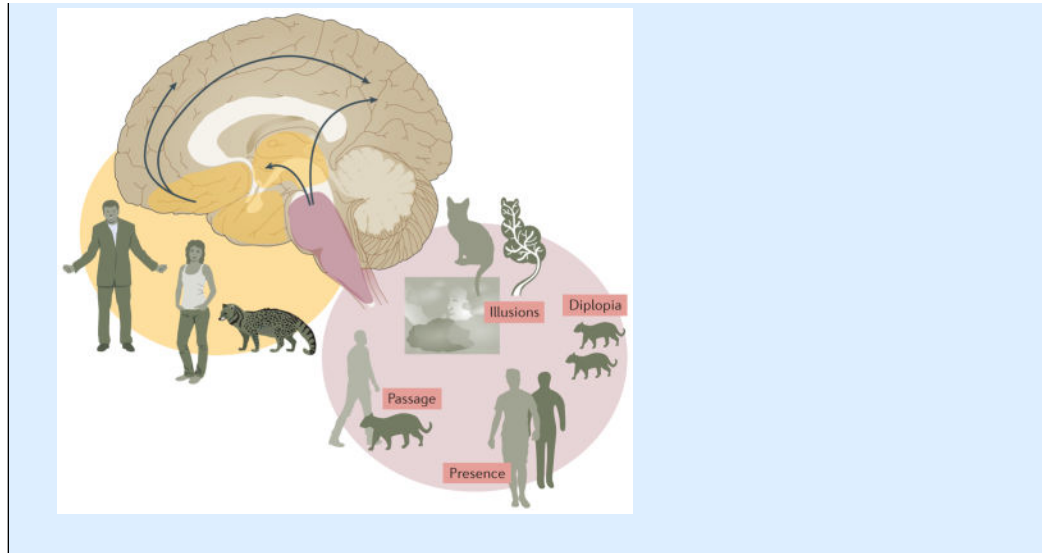
Box 4

Relationship between brain structure, function and neuropathology in PD psychosis

The relationship between different imaging biomarkers of Parkinson disease (PD) psychosis remains unclear. Areas of reduced posterior cortical metabolism[40] overlap with areas of reduced activation in functional MRI (fMRI) studies[125], so might reflect similar underlying functional alterations or a causal link (for example, an area of reduced metabolism might result in a reduced blood oxygen level-dependent (BOLD) signal). Likewise, regions of increased metabolic activity in the frontal cortex[118], as identified in some studies, may relate to regions of increased frontal fMRI activation[125].

One question that arises is why specific subregions of frontal, parietal, limbic and occipital lobes are altered in PD psychosis. Some regions with atrophic or metabolic change have shown increased Lewy body and/or amyloid and tau pathology in postmortem studies[55–57]. However, other regions, in particular the occipital cortex, have limited neuropathological load even in end-stage disease[58], contrasting with atrophy and possible hypometabolism in imaging studies. Therefore, in vivo imaging changes may not simply reflect localized neuropathology, but have other causes, for example, loss of cholinergic or serotonergic cortical projections, leading to a specific distribution of receptor upregulation, functional alterations and, in the longer term, atrophy.

Early PD psychosis symptoms

According to a report on the largest series of PD patients with presence hallucinations to date, the 'presence' is seen as an unformed visual shadow or mist in up to one-third of cases, may or may not be recognizable, and can be a persistent or recurrent experience of someone who has just left the room (palinparousia)[11]. An online questionnaire administered to individuals with PD suggested an overall prevalence of 50% for presence and passage hallucinations ('extracampine hallucinations' was used as a collective term for both

experiences, although this differs from its classic usage), with individual prevalences of 25% for presence hallucinations and 46% for passage hallucinations[12]. Studies of formed hallucinations in PD have found an association between the cognitive profile and the type of hallucination experienced[13]: patients with PD whose typical hallucinations are of unfamiliar content (for example, unidentified figures) have more-profound deficits of inhibitory executive function than do patients with hallucinations that are recognized (for example, family members). Additional visual symptoms that are observed in the early stages of PD and might be considered to belong to the psychosis spectrum are listed in TABLE 1.

Later PD psychosis symptoms

As PD progresses, hallucinations in non-visual (auditory, tactile and olfactory) modalities occur alongside visual hallucinations. In one cohort of PD patients without hallucinations at baseline, 60% were experiencing hallucinations in multiple sensory modalities by 10 years of follow-up[14,15]. These non-visual hallucinations are not confined to end-stage PD dementia; they are also found in patients whose cognition is relatively intact (Mini-Mental State Examination (MMSE) score 24 or 25)[16,17].

One study has estimated the prevalence of delusions in a PD clinical setting at 16%[18], rising to 47% in the subset of patients with PD psychosis[18]. Of note, an earlier study of patients with PD psychosis taking part in a clinical trial indicated an even higher prevalence of delusions (76%)[16]. The delusional themes that are identified depend on the assessment instruments used, but they typically encompass sin or guilt, grandiosity, reference, religion, persecution, jealousy, and theft, without prominence of any specific theme[16]. Delusional mis-identification syndromes, a specific subset of delusions characterized by pathological familiarity, include the Capgras delusion (the belief that someone familiar has been replaced by an imposter), reduplicative paramnesia (the belief that a room or place has been duplicated and is present at two locations simultaneously) and the mirror sign (failure to recognize oneself in the mirror)[19,20]. In patients who have dementia with Lewy bodies (DLB), the prevalence of misidentification syndromes was found to increase with greater cognitive decline (40% for MMSE score >20 compared with 60% for MMSE score <10)[21]. A similar trend was observed in individuals with AD, although the prevalence was lower overall (18% for MMSE score >20 and 28% for MMSE score <10). A smaller-scale study of patients with PD dementia found a 16.7% prevalence of misidentification symptoms, and also noted an association between these symptoms and a specific profile of memory and language deficits[20].

Assessment scales

Several scales to measure positive symptoms were available in 2007 (REF. 22), but none were specifically designed for use in PD. As a result, many of the studies reviewed here used a definition of psychosis spectrum status that was based on a single question item within the Movement Disorder Society United PD Rating Scale (MDS-UPDRS), with a range of 0–4 (BOX 1). New scales have emerged to better capture the diversity of symptoms and for use in clinical trials, including the North-East Visual Hallucinations Interview (NEVH-I)[23] and a shortened version of the Scale for Assessment of Positive Symptoms adapted for PD (SAPS-

PD)[24]. A test to measure susceptibility to pareidolia has been developed for DLB[25], and might also have a role in the assessment of early symptoms of PD psychosis.

Frequency and clinical consequences

As concluded by the NINDS–NIMH psychosis work group and related reviews, psychosis spectrum symptoms are common in PD and have important clinical consequences, in particular, an increased risk of dementia, nursing home placement and mortality. Quality of life is also impaired, both overall and in subdomains of emotional well-being, daily living, cognition and bodily discomfort[26]. Recent studies have provided revised prevalence estimates for PD psychosis based on longitudinal study data, and have better characterized the link to poor cognitive outcome.

Prevalence

In early cross-sectional studies, the prevalence of the psychosis spectrum varied depending on which symptoms were included, and which PD population was studied. For example, estimates of complex visual hallucinations ranged from 22–38%, compared with 0–22% for auditory hallucinations[3]. Prevalence estimates from older studies that excluded minor hallucinations required revision after the publication of the consensus guidelines[27]. According to the latest figures, minor phenomena are reported in 42% of patients with very early disease[28], although this high estimate could reflect recall bias[29]. In a large-scale study (n= 250) that excluded patients with MMSE scores   23, the prevalence of PD psychosis was 26%[30].

Longitudinal studies conducted in the wake of the consensus guidelines have established that the prevalence of the psychosis spectrum is time dependent, increasing with the duration of PD[3,31–33]. In a study that used detailed phenomenological interviews[31], 82.7% of patients experienced psychosis spectrum symptoms over a period of 36 months. In another study, which excluded minor hallucinations, 60% of patients had experienced psychosis spectrum symptoms by the end of a 12-year follow-up period[33]. The Parkinson's Progression Markers Initiative (PPMI) reported an increase in the prevalence of psychosis from 3% around the time of PD diagnosis to 10% at 2 years' follow-up[32].

Risk of cognitive decline

An association between visual hallucinations and the subsequent emergence of dementia was first reported in 2003 (REF. 34). Patients who reported previous visual hallucinations at study entry had an increased risk of dementia at 8 years (OR 3.1, 95% CI 1.6–6.2). This association has been replicated in several recent studies of shorter follow-up duration. One study[35] found that visual hallucinations and visual illusions at baseline had separate predictive effects for dementia at ~4 years, and another study[36] found that the longitudinal emergence of visual hallucinations — that is, emergence across the duration of the study — increased the risk of dementia at ~6 years. The PRIAMO study of early PD found a decline in cognitive function at 2 years in patients with psychosis spectrum symptoms[37]. The detailed profile of cognitive decline over 1–2 years has been reported in prospective cohorts defined at baseline by the presence or absence of visual hallucinations[38,39]. A significant

group × time interaction was found, with a steeper decline across a range of cognitive domains and an increased risk of dementia at follow-up in patients with visual hallucinations. A recent metabolic imaging study of PD-associated mild cognitive impairment (PD-MCI) has also found elevated rates of dementia at 30-month follow-up in patients with visual hallucinations[40].

Psychosis spectrum symptoms are not the sole predictors of future cognitive decline in PD: a range of factors have been identified, the interrelationship of which has yet to be clarified. According to multivariate analyses[34,36], visual hallucinations are independent of other factors, but their predicitive statistical significance is reduced when cognitive measures are included[36], suggesting that cognition and visual hallucinations are closely related.

Association with motor subtypes

Exploratory and confirmatory cluster analysis of a large PD data set revealed associations between non-tremor-dominant PD and psychopathology, including hallucinations and cognitive impairment[41]. The association between clinically defined non-tremor subtypes and dementia, but not the association with hallucinations, was replicated in a subsequent study[42]. This discrepancy between studies might be attributable to differences in methodology.

Mechanisms and risk factors

A range of possible mechanisms to explain the psychosis spectrum, including changes in visual function, sleep, medication effects and cognition, were identified by the NINDS–NIMH work group and in related reviews, with unifying models being presented to summarize the proposed interrelationship between these mechanisms[1–3].

The eye and low-level vision

The predominantly visual nature of PD psychosis spectrum symptoms points to dysfunction in the visual system, and early studies focused on low-level deficits in colour vision, contrast sensitivity and acuity (reviewed elsewhere[2]). More recently, evidence has emerged of retinal changes in PD, as measured by techniques such as ocular coherence tomography (OCT) and electroretinography[43]; however, to date, only one study using such techniques has investigated the retinal associations of the PD psychosis spectrum. In patients with visual hallucinations, OCT revealed thinning of the retinal ganglion cell layer in the dominant eye at both nasal and temporal retinal locations[44]. Such thinning could be the result of a primary process within the eye, or could be secondary to retrograde trans-synaptic degeneration caused by changes in the brain. Thinning was more pronounced in PD psychosis patients without dementia (as measured by MMSE score), pointing to a primary process within the eye.

Visual perception and cognition

Early studies of the psychosis spectrum focused on visual hallucinations, and included patients with a range of severity of what might now be termed PD-MCI. More-recent studies have concentrated on differences in cognitive profiles for specific symptom subtypes, and the cognitive profile of the psychosis spectrum at different stages of global cognitive

impairment. TABLE 2 shows a range of cognitive tests that have been repeated in different studies, although the same version of a given test is rarely used by different groups. Most studies investigating visual perception, irrespective of the selection criteria (for example, unselected PD-MCI cohorts versus participants selected for higher cognitive function) have shown deficits in the perception of objects, including faces. Similarly, most studies investigating executive function, as measured by the Stroop task, response inhibition and verbal fluency, have found deficits in patients with visual hallucinations.

Deficits in memory and related hippocampal function tests are found in PD patients with visual hallucinations, in both unselected PD-MCI and higher-function groups. These deficits withstand correction for MMSE score, depression and PD stage[45]. Some studies have reported deficits that are specific to visual — as opposed to verbal — memory[46]. Greater memory deficits have also been found for black-and-white visual stimuli than for coloured visual stimuli, perhaps reflecting more-limited encoding of visually impoverished stimuli in patients with visual hallucinations[47]. A transitive inference test thought to measure hippocampal function has uncovered impairments in patients with PD psychosis[48].

TABLE 2 helps to illustrate agreement between studies regarding cognitive functions that are deficient, but it does not reveal whether some cognitive functions show relative sparing. Tests purporting to measure visuospatial function, such as the Benton judgement of line orientation and the Rey complex figure test, are often included in test batteries for PD psychosis, but tend not to show significant differences[46,49] (although see Katzen *et al.*[50] for evidence of deficits on the Benton test). The lack of consistent findings could be a test sensitivity issue, as other measures of visuospatial function — for example, the Visual Object and Space Perception (VOSP) number location subtest[47,51] — have been shown to differ between patients with and without visual hallucinations. Tests examining motion, spatiotemporal aspects of visual perception, and eye movements in the PD psychosis spectrum have not been reported to date, but are of particular relevance given the hypothesized role of dysfunctional motion perception and eye movement control in passage and presence hallucinations.

Minor hallucinations—Only one study has focused on the cognitive profile associated with minor hallucinations in PD[52]. Compared with patients without psychosis spectrum symptoms, patients with minor hallucinations had no significant differences in verbal memory, verbal fluency or sustained attention. Progressive decreases in cognitive performance were seen across the spectrum from no hallucinations, through minor hallucinations and hallucinations with insight, to hallucinations without insight. The lack of cognitive deficits in patients with minor hallucinations raises the issue of whether the onset of psychosis spectrum symptoms predates measurable cognitive decline.

Multimodal hallucinations—One might expect patients with non-visual hallucinations in the later stages of PD to exhibit greater cognitive deficits or a different cognitive profile compared with PD patients with visual hallucinations alone. However, one study that compared patients with visual only and visual plus non-visual hallucinations[50] found no evidence of significant additional decline in the latter group for any of the cognitive domains tested (including verbal memory and verbal fluency). The number of patients with

hallucinations in multiple modalities was small ($n = 12$), so the study might have been underpowered to detect such changes.

Delusions—Only one study has compared cognitive profiles between PD psychosis spectrum patients with hallucinations but not delusions and those with delusions but not hallucinations[18]. Cognitive profiles did not differ significantly between the two groups. Cognitive scores in a range of domains were found to correlate with the severity and number of hallucination modalities (for example, auditory, olfactory somatic and/or visual), but not with the severity and number of delusion modalities (for example, jealousy, grandiosity and/or religious delusions). These findings suggest that cognitive risk factors for hallucinations and delusions might differ. This view is supported by evidence from a study investigating risk factors for a specific delusion (delusional jealousy), where an association was found with dopamine agonist treatment but not dementia, in contrast to hallucinations, where an association was found with dementia but not dopamine agonist treatment[53].

Neuropathology

Neuropathological studies provide important insights into the distribution of Lewy body pathology at different stages of the PD psychosis spectrum (BOX 2). The first study to report on this issue found significantly higher Lewy body load in the amygdala and parahippocampal gyrus in patients with visual hallucinations, half of whom met the clinicopathological criteria for PD and half of whom met the criteria for DLB[54]. Subsequent studies have replicated the finding of limbic pathology associated with visual hallucinations[55,56], with increased pathology also found in other regions, including the superior and lateral frontal cortex (Brodmann area 8/9), inferior and lateral temporal cortex (Brodmann areas 20 and 21), inferior parietal cortex (Brodmann areas 39 and 40), and cingulate cortex (Brodmann area 24). Visual hallucinations are also linked to higher levels of amyloid and tau pathology in frontal, parietal and hippocampal areas[57]. Only one study has investigated the occipital lobe in patients with visual hallucinations: Lewy body and tau pathologies were found to be absent, and amyloid burden was rated as mild[58].

Unlike patients with PD psychosis who have dementia, those without dementia do not have cortical Lewy body involvement. An early study of PD patients with visual hallucinations and MMSE scores >25 found increased Lewy body load in the basolateral nucleus of the amygdala, but only sparse Lewy bodies in the cortex and hippocampus[59]. Consistent with the lack of cortical involvement, a recent study has found no association between Lewy body, tau or amyloid pathology in frontal, parietal and temporal regions and visual hallucinations after controlling for dementia, but found strong associations with dementia after controlling for visual hallucinations[58]. Such findings suggest that the neuropathological changes underlying visual hallucinations are distinct from those underlying dementia.

Involvement of the cholinergic system in visual hallucinations is suggested by brainstem atrophy in the pedunculopontine nucleus[60] and atrophy of the substantia innominata, which contains the nucleus basalis of Meynert[46]. The cause of the atrophy is unclear, as no association has been found between visual hallucinations and Lewy body, tau or amyloid load in the nucleus basalis of Meynert[58].

Non-cognitive risk factors

Patients with visual hallucinations exhibit abnormalities on a range of autonomic tests, including the tilt-table test, the Valsalva manouevre and cardiac ^{123}I-metaiodobenzylguanidine imaging, indicating sympathetic dysfunction[61]. In addition, autonomic dysfunction was found to be an independent risk factor for hallucinations (all modalities included) in PROPARK, a large-scale 5-year prospective study[62]. The same study also reported female sex as an independent risk factor[62]. REM sleep behaviour disorder (RBD) is also associated with visual hallucinations (recently reviewed elsewhere[63]), although the association is weak[64], and the proportions of patients with visual hallucinations who do and do not have RBD are similar. Vivid dreams are associated with visual hallucinations after controlling for factors including PD duration, depression, anxiety and UPDRS scores[65]. Depression has been associated with hallucinations in PD[2]. The urinary concentration of the oxidative stress marker 8-hydroxydeoxyguanosine was found to correlate with the hallucination score (modality unspecified) after controlling for MMSE score, age, duration and UPDRS part 3 score[66].

Dopamine agonists

The role of medication in PD psychosis was noted to be "the most controversial aspect of these criteria" in the 2007 consensus recommendations[1]. Clinical experience suggested that the onset of PD psychosis could be linked to medication onset and improved with dose reduction, but there was no evidence of a direct causal relationship between pharmacological treatments or medication dose and PD psychosis (for example, levodopa infusion did not induce hallucinations[67]), and PD psychosis was recognized to occur in unmedicated patients.

In the intervening years, the role of medication has received relatively little research attention. The lack of a direct causal role for medication is supported by a high prevalence of minor symptoms[28] or visual hallucinations[68] in drug-naive patients, and the finding that levodopa dose equivalence did not increase the risk of psychosis in some prospective studies[14,31], including the PPMI cohort[32]. However, though failing to reach statistical significance, a link to medication is implied in the threefold increase in psychosis onset for patients starting dopamine replacement therapy in the PPMI study. Similarly, a large-scale prospective study identified elevated baseline levodopa dose as a risk factor for PD psychosis, with an odds ratio of 1.26 per 100 mg of dose equivalence increase[33], and a prospective study of early PD (PRIAMO) found increased rates of dopamine agonist treatment in patients who went on to develop PD psychosis[37]. The PROPARK study also identified dyskinesia and levodopa equivalence measures as independent risk factors for PD psychosis[62].

The NINDS–NIMH work group[1] suggested "anti-parkinsons medication as a modifier rather than a necessary feature for the diagnosis of PD psychosis" to help reconcile the medication-related and medication-independent viewpoints. Evidence that has since emerged supports this 'modifier' account, but highlights the need for further work in this area to clarify the relationship between dopamine replacement therapy and PD psychosis.

Genetics

A recent review of the genetics of psychotic symptoms in PD identified 26 published articles on this topic[69]. The most commonly studied genetic factor is the apolipoprotein E ε4 (*APOE**ε4) allele, although dopaminergic pathway genes have been the focus of a number of studies.

With regard to *APOE**ε4, little evidence is available to suggest an association with psychotic symptoms in PD (only one of seven studies reported an association with visual hallucinations)[70–76], a finding that is mirrored in the AD literature[77]. The extended microtubule-associated protein tau (*MAPT*) haplotype is less well studied in PD psychosis: an initial study reporting an association between visual hallucinations and the H1 haplotype was not replicated by a second larger study[70,71]. By contrast, an increasing body of evidence suggests that glucosylceramidase (*GBA*) mutations are associated with psychosis in PD[78–80]. Of note, the influence of *GBA* is not limited to psychosis: *GBA*, like *APOE* and *MAPT*, has been associated with cognition in PD, as well as faster progression to dementia and more-severe motor stages[79,81]. Any associations between psychosis and these three genes are perhaps most likely to be driven by fundamental disease processes, such as tau or Lewy body accumulation. Therefore, considering any associations with a particular symptom in isolation would be too narrow an approach. Specifically, it will be important to establish whether any subtypes of PD have a pattern of cognitive impairment that is more similar to AD and carries a relatively low risk of psychosis (which might be predicted by *APOE*), compared with an early dysexecutive syndrome and greater risk of hallucinations (as indicated by the pattern of association with *GBA*).

Consistent evidence links *GBA*, but not *APOE*, with psychosis in PD; however, findings related to other genes have been equivocal. Polymorphisms in dopaminergic pathway genes have been examined in 15 studies (BOX 3). Although there is some evidence of a relationship between polymorphisms in dopamine transporter and cholecystokinin genes and psychosis, the overall number of studies examining these associations is small, making it difficult to draw reliable conclusions. Research in serotonin (5-hydroxytryptamine, or 5-HT) pathway genes is limited to two studies[82,83], but with the recent demonstration of efficacy of pimavanserin for the treatment of PD psychosis (see below), serotonergic genes or other genes in serotonergic signalling pathways may provide promising avenues for future research.

Box 3

Genetic risk factors for psychosis in Parkinson disease

GBA

Associated with an increased risk of psychosis in three studies[78–80]. One study including only two cases with hallucinations found no association[165].

MAPT

Mixed findings: one positive association and one negative[71,72].

APOE

No association (in six of seven studies). The *APOE*ε*4* allele was associated with hallucinations within 5 years of diagnosis in one study[70–76].

COMT

No association[74,166].

SLC6A3 (also known as DAT1)

Mixed findings: two of three studies reported an association, one with the variable number tandem repeat and one with the 839C>T polymorphism[167–169].

DRD2

Mixed findings: one of four studies reported an association[73,167,168,170].

DRD3

No association[73,167,168,170].

DRD4

No association[73,167].

CCK

Mixed findings: two of four studies show evidence of an association with *CCK* 45C>T, and one reported a combined effect with the *CCKAR* CC genotype[171–174].

HTR2A

No association[83].

SLC6A4

One study reported an increased risk associated with the LL genotype in a mixed Lewy body dementia sample[82].

ACE

Mixed findings: one study reported a significant association with levodopa-induced psychosis, whereas another reported no association[175,176].

HOMER1

Mixed findings: one study reported an association with the A allele, and a second reported an association with the G allele and a reduced risk of adverse effects of levodopa treatment[177,178].

The genetic aetiology of psychosis in PD will be complex, and is likely to involve many genes each with a small effect size. As such, the most promising genetic approaches will probably be those that leverage genome-wide data, which has the advantage of full genome coverage and is not constrained by biases resulting from a priori hypotheses. In the broader literature, recent advances in the analysis of genome-wide data sets have uncovered genetic pleiotropy between clinically distinct diseases[84,85]. Moreover, analyses whereby biological pathways (for example, molecular, cellular, organ/system or disease) are constructed on the

basis of genomic data and tested for enrichment of single nucleotide polymorphisms in cases versus controls have shown promise in late-life depression[86]. These types of emerging techniques have clear applications in heterogeneous conditions such as PD, where questions surrounding the overlapping aetiology between psychosis across neurodegenerative diseases and psychiatric disorders remain unanswered. The increasing availability of larger, better-characterized data sets will provide greater potential to conduct these more-sophisticated genetic analyses.

Explanatory models

Explanatory models of PD psychosis attempt to integrate risk factors into unifying accounts (reviewed elsewhere[87]). The Activation–Input–Modulation (AIM) model[88] takes a dimensional approach to PD psychosis, with contributions from an activation factor (the level of arousal), an input factor (the spectrum of externally and internally driven visual percepts), and a modulation factor (neurotransmitter and medication effects). The activation factor may help to explain why hallucinations typically occur with low ambient stimulation. The Perception and Attention Deficit (PAD) model[89] argues that the core mechanism of complex hallucinations is dysfunctional integration of perceptual and attentional processing, leading to the intrusion of generic representations (proto-objects) into perceptual consciousness. In the attentional control model[90], the core pathology of PD psychosis is dysfunctional integration between three networks (dorsal attention network, ventral attention network and default mode network), with a failure to engage the dorsal attention network in the context of ambiguous visual input and the intrusion of default mode contents into perceptual consciousness[90–92]. This account is supported by evidence from PD patients with visual hallucinations or illusions of elevated strength of mental imagery[93], attentional set-shifting deficits[94], altered resting state and task activation networks[95], and increased functional connectivity in the default mode network[96]. A dopamine-based model of PD psychosis[97] argues for abnormalities of biasing and gating access to a global workspace that is thought, according to some accounts, to underlie conscious experience.

These unifying models are informed by clinical associations — for example, the combination of visual perceptual and frontal executive deficits — that were recognized at the time that the models were formulated. As the range of risk factors increases, the question arises as to whether all risk factors are linked to the mechanisms underlying PD psychosis. Distinctions may need to be drawn between associations that are integral to the mechanisms of PD psychosis or its individual symptoms, and syndromic associations caused by the spread of PD pathology to neighbouring brain regions or to separate brain regions at a similar disease stage. Which associations and risk factors are integral to PD psychosis and which are syndromic associations is unclear at present, and such information will be pivotal to the development of novel treatment approaches.

Imaging and electrophysiology

The raised profile of PD psychosis, combined with developments in imaging methodology, has resulted in a rapidly advancing evidence base that helps to inform the risk factor and mechanistic accounts of the symptom spectrum.

Structural MRI

Despite methodological differences, structural imaging studies of visual hallucinations have yielded a number of consistent findings[98–100]. Several studies have reported atrophy in the visual cortex[101–103] — broadly defined as extending into lateral and ventral occipitotemporal regions including the fusiform gyrus and visual parietal cortex (corresponding to dorsal and ventral visual streams) — although this finding is not univeral[104]. One study of PD patients with and without visual hallucinations (some patients had hallucinations in both visual and other modalities), matched for cognitive status, only detected atrophy in posterior cortical regions[101], whereas another study of visual hallucinations, in which global cognition (MMSE score) was included as a covariate, found atrophy in frontal, hippocampal and thalamic regions[46]. A study focusing on minor hallucinations found atrophy in the midbrain, cerebellar vermis and visual parietal cortex, as well as areas of increased cortical volume in the limbic cortex and the posterior lobe of the cerebellum, which might be linked to compensatory mechanisms[105]. Studies that did not control specifically for cognition found atrophy of the hippocampal head[106], frontal regions (particularly the lateral frontal cortex)[103,107,108], cerebellum[103] and lateral parietal cortex[103] in patients with visual hallucinations.

The distribution of atrophy described in the various studies is consistent with the profile of cognitive deficits found in PD psychosis (FIG. 1). At 30-month follow-up, patients who report visual hallucinations at baseline have greater progression of cortical atrophy within limbic, frontal and thalamic regions, and are more likely to have developed dementia[38]. The greater rate of atrophy and hypothesized progression from hippocampal head involvement to diffuse hippocampal atrophy in patients with visual hallucinations[106] might account for the association between visual hallucinations and poor cognitive outcome.

Few studies have investigated white matter changes in PD psychosis. An early study found no differences with regard to a range of clinically defined white matter lesion indices in patients with and without visual hallucinations[109]. A more recent volumetric study described decreased white matter volume in occipital and parahippocampal regions[103]. Another study showed that the microstructural integrity of deep white matter, as measured by fractional anisotropy, was affected in PD psychosis (defined as the presence of perceptual errors, hallucinations in any modality, or delusions). When fractional anisotropy was compared across groups as an absolute measure or normalized to globus pallidus or substantia nigra values, reduced fractional anisotropy was detected within regions of interest in the occipital lobe, frontal lobe and cingulate gyrus, and deep to the left hippocampal head[110].

Neurotransmitter imaging

Reduced dopamine transporter binding in the striatum in early PD, as measured by the ^{123}I-β-CIT tracer, is associated with an increased prospective risk of PD psychosis at 5 years (assessed using the UPDRS thought disorder item)[111]. It is unclear whether this binding reduction represents the underlying mechanism of the psychosis spectrum or is an indirect association, for example, reflecting more-extensive neurodegenerative involvement in PD psychosis.

In a serotonergic imaging study that used the 5-HT$_{2A}$ receptor ligand ^{18}F-setoperone, increased binding in ventral occipitotemporal regions and bilateral frontal cortex was identified in patients with visual hallucinations[112]. By contrast, a 5-HT$_{1A}$ receptor binding study in postmortem tissue found no association with visual hallucinations, although 5-HT$_{1A}$ binding was elevated in sublayers of the orbitofrontal, ventral temporal and motor cortex in patients with PD, irrespective of visual hallucinations[113].

Metabolic and blood flow imaging

Occipital hypometabolism and reduced regional cerebral blood flow (rCBF) are characteristics of DLB[114,115], and have been linked to visual hallucination severity[116]. Whether the same regions exhibit reduced metabolism and rCBF in PD psychosis is less clear. Metabolic imaging studies of PD patients with and without visual hallucinations have identified reductions in posterior metabolism that spare the occipital pole[117] or primary visual cortex (data from table in Nagano-Saito *et al.*[118]). In addition to posterior metabolic deficits, one study found increased frontal metabolism in PD psychosis[118]. Another study found that posterior metabolic deficits were more pronounced in patients with visual hallucinations and cognitive impairment (defined by the K-MMSE cut-off score, the Korean version of the MMSE), but were also present in patients with K-MMSE scores above the threshold value[119].

In contrast to spared occipital metabolism in the studies described above, a recent study of PD-MCI has found evidence of occipital hypometabolism in PD patients with visual hallucinations[40]. The hypometabolism did not differ between patients who did and did not subsequently develop dementia[40]. Evidence also exists of decreased posterior perfusion in 'medication-induced' hallucinations (mostly visual) that would now be termed PD psychosis, with significant reductions of rCBF in the posterior temporo-occipital cortex but not in the occipital lobe[120]. Similarly, another study of visual hallucinations in PD found trend-level posterior perfusion deficits that spared occipital cortices[121]. A region of decreased perfusion outside the occipital lobe in the ventral temporal cortex (fusiform gyrus) became significant after controlling for confound covariates, as did a region of increased perfusion in the superior and middle temporal gyrus[121].

In summary, consistent evidence points towards posterior changes in metabolism and perfusion in PD patients with visual hallucinations, but the presence or absence of involvement of the occipital lobe remains unclear.

Functional MRI

There is a paucity of data on brain changes occurring in PD at the time of a hallucination (capture studies). One functional MRI (fMRI) case study found a decrease in activity in visual areas coincident with visual hallucinations[122]. This decrease in occipital activity contrasts with evidence from eye disease, schizophrenia and induced visual hallucinations, which indicates that activity in visual areas increases at the time of visual hallucinations[123]. The PD case study also reported increased activity in the frontal lobe during the hallucinations[122]. Frontal activations are not found in eye disease and schizophrenia during hallucinations; however, another PD case report, in which a different technique was used

(single-photon emission CT with technetium-99m ethyl cysteinate dimer), documented frontal and anterior temporal increases in rCBF during visual hallucinations[124]. Contrasting findings of occipital increases or decreases and the presence or absence of frontal activations across clinical contexts may suggest differences in the underlying mechanisms of hallucinations.

Studies in which visual stimulation was used to probe cerebral activity have reported decreased activation in the parietal lobe, lateral occipitotemporal cortex[125] and occipital cortex[126] in PD patients with a history of visual hallucinations. An early fMRI study reported decreased activity in the primary visual cortex but increased activation in the visual association cortex[127]. In the frontal lobe, both activation increases[125] and activation decreases[126,128] have been reported in response to visual stimulation. The contrasting findings might relate to differences in the stimuli and tasks used.

Reduced occipital low frequency fluctuations have been found in the resting state in PD patients with a history of visual hallucinations[129]. These fluctuations are thought to be an indirect measure of cerebral glucose metabolism and local field potentials, supporting the idea of occipital hypometabolism in patients with PD who are susceptible to visual hallucinations. Increased connectivity between occipital and frontal regions, the striatum and the thalamus[129] and greater co-activation of default mode network nodes in the posterior cingulate/precuneus and lateral frontal cortex are associated with susceptibility to visual hallucinations in PD[96].

Electrophysiology

In PD patients with a history of visual hallucinations, the P100 component of visual evoked potentials in response to reversing checkerboard stimulation was found to be delayed[130], as was the P300 component of a visual odd-ball task[131]. A delay in evoked potential latency has also been found in association with illusions and visual hallucinations in an immersive virtual reality environment following short-term PD medication deprivation[132]. The evoked potential delays might fall within the distribution of normal variation, however, as rates of retinal and cortical evoked measures categorized as normal or abnormal on the basis of normal population standard deviation cut-off values do not differ between patients with and without hallucinations[132,133]. Changes in cholinergic-related electrophysiological measures (short-latency afferent inhibition) associated with susceptibility to visual hallucinations in PD are consistent with a loss of cortical cholinergic input[134].

Treatment

As outlined in previous reviews, treatment of PD psychosis includes psychological therapies, dose reduction of PD medication, and medication to treat psychosis symptoms[1,2,135]. TABLE 3 summarizes double-blind, placebo controlled trials in patients with PD psychosis, including trials of pimavanserin (a 5-HT$_{2A}$ inverse agonist) and memantine that have been published since this topic was last reviewed. For patients without prominent cognitive impairment, clozapine and pimavanserin have the best evidence of efficacy in PD psychosis. In patients with cognitive impairment and visual hallucinations, rivastigmine was found to reduce the Neuropsychiatric Inventory score (predominantly the agitation component) in a

secondary analysis, and unpublished evidence suggests efficacy of pimavanserin in PD psychosis with cognitive impairment. The clozapine and pimavanserin trials have indicated a therapeutic effect specific to hallucinations as a whole but, to date, no studies have reported a specific effect on visual hallucinations. No treatment trials targeting minor symptoms have yet been reported.

Atypical antipsychotics

Evidence for the efficacy of clozapine in PD psychosis[136–138] sparked interest in the potential efficacy of quetiapine, a structurally related compound. Although early studies suggested a beneficial effect of quetiapine, several subsequent studies failed to replicate the findings in PD[139,140] and across the spectrum of dementia with parkinsonian symptoms[141]. Similarly, open-label studies suggested that olanzapine was efficacious for PD psychosis, but placebo-controlled[142] and comparative[143] trials found a worsening of motor symptoms without significant improvement of hallucinations. The 2011 Movement Disorder Society evidence-based medicine review of treatments for nonmotor symptoms concluded that there was insufficient evidence on the efficacy of quetiapine, and that olanzapine carried unacceptable risk[135].

Despite the lack of an evidence base, atypical and typical antipsychotics continue to be used in clinical practice[144], but are associated with increased mortality in the context of clinical trials[145] and a retrospective database analysis, which ranked haloperidol as carrying the highest risk, followed by olanzapine, risperidone and quetiapine[144]. Such evidence cautions against the use of antipsychotics in PD, and highlights the need for further studies in this area, as well as the development of new therapeutic approaches for PD psychosis.

Pimavanserin

The therapeutic effect of clozapine in PD psychosis is thought to relate, in part, to blockade at the 5-HT$_{2A}$ receptor[146]. A large double-blind, placebo-controlled study of pimavanserin found a significant improvement on the SAPS-PD[147], with greater improvement in a subgroup with more-pronounced cognitive impairment (Ballard, C. *et al.*, unpublished work, see TABLE 3). In an earlier study, a global measure of hallucinations assessed as a secondary end point improved in patients treated with pimavanserin, but the reduction in visual hallucinations was not significant when considered separately[146]. The relative lack of efficacy of pimavanserin for visual hallucinations suggests that the wider improvement in psychotic symptoms is mediated by a different subset of 5-HT receptors than those stimulated by lysergic acid diethylamide (LSD), the use of which is associated with predominantly visual phenomena. Pimavanserin received FDA approval in April 2016 for the treatment of PD psychosis. Its adverse event profile to date suggests advantages over other anti-psychotics in terms of risk of stroke, falls, fatigue, blood dyscrasia, neuroleptic malignant syndrome, orthostatic hypotension, and worsening of motor symptoms.

Apomorphine

The chemical structure of apomorphine includes a piperidine moiety and, unlike other dopamine agonists, this drug exerts intrinsic antagonist effects at the 5-HT$_{2A}$ receptor as well as agonist affects at both D1-like and D2-like receptors[148]. This unique profile might

account for case report and open-label study evidence that apomorphine does not exacerbate psychosis symptoms and, in some studies, may ameliorate these symptoms[149] or improve visual contrast sensitivity[150]. The mode of apomorphine administration may influence its impact on psychotic symptoms[151]. The open-label EUROINF study found improvements in perceptual and hallucination symptoms in patients treated with either apomorphine or intrajejunal levodopa[152]. The effect size for apomorphine (0.32) was larger than for intrajejunal levodopa (0.29), although the difference was not significant[152]. Apomorphine might have a place in the treatment of PD psychosis; however, a better evidence base is needed to guide future recommendations[148,152,153].

Electroconvulsive therapy

No sham-controlled studies of electroconvulsive therapy (ECT) for PD psychosis have been undertaken, but two case series have reported improvements in PD psychosis spectrum symptoms. In one study ($n = 5$), Brief Psychiatric Rating Scale scores improved after five to 12 ECT sessions, and the effects persisted for 5–30 weeks[154]. In another study ($n = 8$), SAPS scores improved at 1 week (longer-term data not reported) after a mean of six ECT sessions[155].

Systemic illness

Psychosis is part of a range of acute events in PD, and is often seen in hospitalized patients with systemic infection, dopamine agonist withdrawal syndrome or parkinsonism–hyperpyrexia syndrome, as well as in postsurgical states[156]. Management of the underlying precipitant, along with rehydration, cautious use of antipsychotic agents and — in suitable cases — gentle introduction of low-dose dopamine agonists, may be required.

Conclusions

The paradigmatic shift in perspective that followed the 2007 consensus definition of PD psychosis revitalized research interest and led to a rapidly expanding literature. The impact of these studies is still evolving, but there have already been important clinical consequences, such as a change in our understanding of the prevalence of PD psychosis, given that it increases with PD duration; expansion of the range of symptoms considered part of the psychosis spectrum; and recognition of new prospective risk factors for PD psychosis. The largest expansion of literature has been in the mechanism domain, particularly in studies of cognitive profile, structural brain imaging and genetics.

Despite substantial progress over the past decade, our current state of knowledge leaves key questions unanswered (BOX 4). For example, the relationship between PD psychosis, PD-MCI and PD dementia is unclear. Most patients with PD dementia will have psychosis, but only a small proportion of those with PD-MCI have such symptoms. Does this observation imply a difference in PD-MCI cognitive profiles for patients with and without psychosis? If so, an understanding of these profile differences might help to explain the link between early PD psychosis symptoms and the subsequent development of dementia. Another unresolved issue is the relationship between individual symptoms in the PD psychosis spectrum in terms of underlying pathophysiological mechanisms. Evidence from studies of minor

hallucinations, formed hallucinations and delusions, for example, suggest that the mechanisms are not the same for all symptoms, with important implications for the assessment of PD psychosis in research studies. A continuum assessment scale might be helpful in epidemiological and risk factor studies, but may be less useful for studying specific symptoms and their underlying mechanism.

Other areas identified as requiring further research include the role of PD medication as a modifier or unmasker of psychosis symptoms, motion perception and eye movement control deficits associated with passage and presence hallucinations, and the transition from hallucinations with insight to those without insight and its impact on quality of life and the move to supervised care. These negative outcomes are arguably the most clinically relevant aspects of PD psychosis; however, the brain changes that underlie them are unclear.

Finally, visual hallucinations are not unique to synucleinopathies, and patients with eye disease, serotonergic dysfunction or AD also have visual symptoms that overlap with those of PD but are associated with different cognitive profiles[157,158]. The progressive improvement of visual hallucinations in eye disease contrasts with the progressive deterioration in PD and AD psychosis[157,158], and comparative studies of brain changes associated with visual hallucination susceptibility across clinical contexts might shed light on why these differences exist.

Overall, two major themes can be recognized in the literature that has emerged over the past decade. One theme highlights the clinical challenges of PD psychosis, with an urgent need for better characterization of its symptoms and their impact, and for evidence on how to assess and treat these symptoms. The second theme highlights what the psychosis spectrum reveals about PD in terms of disease stage and distribution, and its role as a clinical biomarker for PD outcomes. Further research in this area will have implications that extend beyond the symptoms themselves to the wider issues of cognitive decline in PD, patient and carer experience, and the development of novel treatments for positive symptoms in PD and other clinical contexts.

Acknowledgments

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Key points

- Parkinson disease (PD) psychosis refers to a spectrum of illusions, hallucinations and delusions that occur throughout the disease course

- Evolving literature highlights the importance of recognizing and treating PD psychosis, and understanding its role as a clinical biomarker of disease stage, distribution and future progression

- Current evidence points to PD psychosis as a set of symptoms with distinct pathophysiological mechanisms, as opposed to a single pathophysiological symptom with a spectrum of severity

- The relationship between neuropathology in PD psychosis and *in vivo* measures of reduced metabolism, functional MRI alterations and cortical volume loss remains unclear

- Further studies are needed to explore the role of PD medication in unmasking psychosis symptoms, why psychosis symptoms predict worse cognitive outcome, comparisons of psychosis symptoms and mechanisms in different clinical conditions, and development of novel treatments
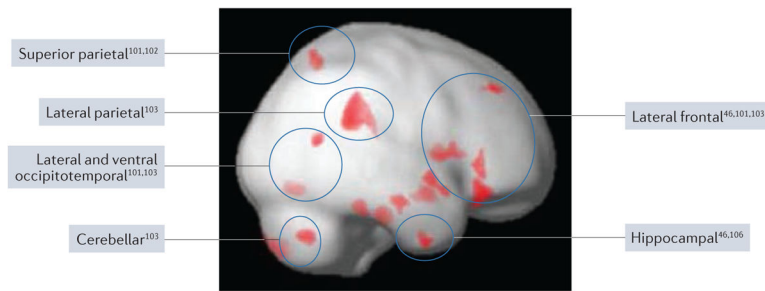
Figure 1. Regions of cortical atrophy in PD psychosis
The figure summarizes studies that have reported regions of increased atrophy in patients with Parkinson disease (PD) psychosis (defined by visual hallucinations in most studies) compared with PD controls. The results are superimposed on a lateral view of the right hemisphere. The approximate locations of regions of atrophy identified in previous work are indicated by circles annotated by the relevant references. The red regions indicate atrophy in our own study (ffytche, D. *et al.*, unpublished work), in which PD patients with visual hallucinations (*n* = 8; mean Mini-Mental State Examination (MMSE) score 27.3) were compared with PD controls (*n* = 9; mean MMSE score 29.6). A lenient statistical threshold (*P* < 0.01; 100 contiguous voxels) is used for illustrative purposes. Lighter red shading indicates regions deep to the rendered cortical surface. These summary findings indicate that visual hallucinations in PD are associated with widely distributed but specific regions of cortical atrophy.

Table 1

Symptoms related to the PD psychosis spectrum

Symptom	Phenomenology	Association with psychosis spectrum
Isolated diplopia[179]	Image doubling related to an isolated object or figure — as opposed to the whole scene — in the visual environment	May precede the onset of visual hallucinations by 2–3 years
Freezing[180]	Walking cessation when passing through narrow spaces	Associated with passage hallucinations in PD without cognitive impairment
Spatial misjudgement[180]	Difficulty estimating distance of objects when walking	Associated with presence and passage hallucinations

PD, Parkinson disease.

Table 2

Visual and cognitive deficits in the PD psychosis spectrum

Domain	Subdomain or task	Significant deficit associated with PD psychosis spectrum		Minor hallucinations
		Unselected PD-MCI	MMSE score >25	
Visual perception	Object	Yes[51,55,181]	Yes[47,55]	–
	Face	Yes[45]	–	–
	Spatial	Yes[47,51]	–	–
Executive function	Stroop	Yes[46,49,182,183]	Yes[13]	–
	Go–no-go	Yes[46,182]	Yes[13]	–
	Verbal fluency	Yes[45,49,182–184]; No[50]	Yes[13]	No[52]
Attention	–	Yes[51,181]	–	No[52]
Memory	Visual	Yes[45,46,49]	Yes[47]	–
	Verbal	Yes[45,49,184]; No[50]	–	No[52]

'Yes' and 'No' refer to presence and absence, respectively, of significant deficit reported in studies cited; '–' indicates test not performed. In most studies, PD psychosis spectrum was defined by the presence of visual hallucinations. Studies that pooled z-transformed scores from a range of tests into a single domain summary (for example, Goldman et al.[101]) are not included, as individual test scores were lost. Studies using evidence from items within global assessment scales such as MOCA (for example, Chung et al.[185]) or SCOPA-COG (for example, Gallagher et al.[55]) are also excluded. MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PD, Parkinson disease.

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Table 3

Double-blind studies of psychosis spectrum treatments

Reference	Drug	Number of participants		Mean MMSE score		Psychosis (improvement over placebo)	Effect size	Visual hallucinations (improvement over placebo)
Atypical antipsychotics								
Pollak et al. (2014)[136]	Clozapine (4 weeks)	•	Drug: 32	•	26.1	CGI – 1.2 * (P = 0.001)	0.90 *	PANNS – 4.8 (P<0.0001)
		•	Placebo: 28	•	24.1			
The Parkinson Study Group[137]	Clozapine (4 weeks)	•	Drug: 30	•	23.8	CGI – 1.1 * (P<0.001)	4.40 *	SAPS – 8 * (P = 0.01)
		•	Placebo: 30	•	21.7			
Kurlan et al. (2007)[141]	Quetiapine (10 weeks)	•	Drug: 20	•	19.2	BPRS – 2.2 (not significant)	–	–
		•	Placebo: 20	•	17.2			
Ondo et al. (2005)[139]	Quetiapine (12 weeks)	•	Drug: 21	•	26.1	No significant change on Baylor Hallucination Questionnaire or BPRS	–	–
		•	Placebo: 10	•	27.0			
Shotbolt et al. (2009)[140]	Quetiapine (12 weeks)	•	Drug: 11	•	24.6	Secondary outcome: no significant change on BPRS	–	No significant change on Baylor Hallucination Questionnaire or NPI
		•	Placebo: 13	•	20.8			
Breier et al. (2002)[186]	Olanzapine (4 weeks)	•	Drug: 41	•	24.0	No significant change on BPRS positive symptom cluster subscore	–	No significant change on NPI hallucinations score
		•	Placebo: 42	•	24.7			
Breier et al. (2002)[186]	Olanzapine (4 weeks)	•	Drug: 49	•	24.7	No significant change on BPRS positive symptom cluster subscore	–	No significant change on NPI hallucinations score
		•	Placebo: 28	•	25.0			
Ondo et al. (2002)[142]	Olanzapine (9 weeks)	•	Drug: 16	26.8‡		No significant change on UPDRS thought disorder item	–	–
		•	Placebo: 11					
Cholinesterase inhibitor								
Burn et al. (2006)[187]	Rivastigmine(24 weeks): visual hallucination subgroup	•	Drug: 118	•	18.9	Secondary outcome: NPI 10 – 4.19 (P= 0.01)	0.40 *	No significant change on NPI-10 visual hallucination subscore
		•	Placebo: 70	•	17.9			
NMDA receptor antagonist								

Reference	Drug	Number of participants		Mean MMSE score		Psychosis (improvement over placebo)	Effect size	Visual hallucinations (improvement over placebo)
Aarsland *et al.* (2009)[188]	Memantine (24 weeks)	• Drug: 34	• Placebo: 38	• 20.0	• 20.0	Secondary outcome: NPI – 0.1 (not significant)	–	–
Serotonin 2A receptor inverse agonist								
Cummings *et al.* (2014)[147]	Pimavanserin (6 weeks)	• Drug: 95	• Placebo: 95	• 26.0	• 26.6	SAPS PD – 3.06 (*P* = 0.001)	0.50	SAPS hallucinations domain score – 2.08 (*P* = 0.003)
Ballard, C *et al.*, unpublished work	Pimavanserin (6 weeks)	• Drug: 27	• Placebo: 19	• <25.0	• <25.0	SAPS PD – 6.64	3.50*	–
Meltzer *et al.* (2010)[146]	Pimavanserin (4 weeks)	• Drug: 29	• Placebo: 31	Individuals with dementia excluded		SAPS total domain score – 4.6 (trend: *P* = 0.09)	0.56	No significant change on SAPS visual hallucinations score

*
Calculated from tabulated data: drug versus placebo difference divided by mean standard deviation of drug versus placebo change.

‡
MMSE scores for drug and placebo groups combined. BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; PANNS, Positive and Negative Symptom Scale; SAPS, Scale for Assessment of Positive Symptoms; PD, Parkinson disease; UPDRS, Unified PD Rating Scale (thought disorder item relates to illusions, hallucinations and delusions).