Disorders of Visual Perception in Parkinson’s Disease and Other Lewy Body Disorders

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Abstract

Visual disturbances are common in Parkinson’s disease, Parkinson’s disease dementia, and other Lewy body disorders. Patients may report a wide range of symptoms from double and blurred vision to complex visual hallucinations and illusions. Investigations have shown impairments in virtually all aspects of vision from contrast sensitivity to object recognition and spatial orientation. Increasing visual disturbance, particularly the presence of hallucinations, is associated with poorer quality of life and increased risk of institutionalization and death. Increasing cognitive impairment, the use of medication with anticholinergic effects, sleep disturbance and poor eyesight are potential risk factors. Reduction and rationalization of medication may be as important as starting additional pharmacological therapies, which are currently limited in efficacy, and offset by negative effects on motor symptoms. Imaging and neuropathological studies suggest that multiple abnormalities in the distributed visual system, both in the dorsal and ventral visual streams, as well as in their associated frontal projections and regulatory systems play a role in the pathogenesis of visual disturbances in Lewy body disorders. The varied nature of visual symptoms and wide distribution of pathology through brain visual systems argues against a simple one-to-one correlation between specific visual symptoms and discrete cortical areas.

In this chapter, we aim to review the phenomenology, the course, the pathophysiology and the treatment of the most common visual symptoms in Parkinson’s disease (PD) and other Lewy body disorders; in particular the overlapping syndromes of PD dementia (PDD) and dementia with Lewy bodies (DLB). Given the overlap between the latter two, we will refer to them as a single symptom complex (PDD/DLB), unless there are specific reasons for distinguishing between them (see chapter 11).

In his original description of the disease which now bears his name, Charles Parkinson emphasised that ‘the senses and intellect are uninjured’; a statement which biased perceptions of the non-motor symptoms of PD until relatively recently. Even
though early descriptions of clinical parkinsonism [1] reported visual hallucinations (VH), they were generally ascribed to comorbid disorders or to the side effects of treatments given – opium, ergot derivatives and anticholinergic drugs (atropine, scopolamine and belladonna) were all popular – rather than being recognised as a core feature of the disease. Similarly, the high rate of psychiatric symptoms in encephalitis lethargica after the 1918 influenza epidemic led to the conclusion that this was a disorder different from PD, rather than broadening the view of what constituted PD. In line with this purely motor view of PD, the frequently reported visual symptoms were initially attributed to medication use when research intensified in the 1970s following the introduction of first levodopa and then direct dopamine agonists [for a discussion see 2].

Several factors have brought visual symptoms to the focus of attention in Lewy body disorders. Patients have been living longer. This lead to an increase in the prevalence of poor cognition and eyesight, two of the major risk factors for hallucinations and other disturbances. Increased clinical interest and consequent better ascertainment has overcome the understandable reluctance of patients to report seeing things not seen by other people. Patients often do not disclose VH, fearing the response of doctors or worrying about being diagnosed ‘insane’ [3]. As a result of greater ascertainment, there has been increasing recognition of the substantial burden of disability and distress that these symptoms cause for patients and families [4]. Particularly since DLB was identified as a common disorder in the 1990s, research has emphasised on the overlapping pathology between classical motor symptom PD and the multisymptom complexes of distributed Lewy body pathology.

Clinical Disorders of Vision in Parkinson’s Disease

In patient surveys, large proportions of PD and virtually all PDD/DLB patients report some disturbance of vision. Symptoms include complaints about dry eyes, photophobia, diplopia, difficulties with reading, difficulties estimating spatial relations, or freezing when passing narrow spaces. Although, as a group, PDD/DLB patients perform worse on just about every measure of visual function – visual acuity, contrast sensitivity, motion and colour perception are all impaired in PD [for review see 5, 6] – there is substantial individual variation [7].

The causes of such symptoms and signs can rarely be established with confidence. Potential explanations include reduced blink rate, oculomotor abnormalities or reduced retinal contrast sensitivity. Alternatively, they may be an expression of cortical dysfunction manifesting as visuoperceptual, visuospatial and attentional impairment, or general perceptual slowing. As these factors usually co-exist, it can be difficult to disentangle the purely ‘perceptual’ from ‘lower level’ disturbances of visual and motor function.

Validated questionnaire and interview-based assessments of some visual symptoms, specifically hallucinations, are now available, but these are restricted in the range of
visual and other symptoms investigated [8]. Commonly used structured assessments,
for example the Neuropsychiatric Inventory or Unified Parkinson’s Disease Rating
Scale, provide minimal detail on the types of symptoms seen in PD. The North-East
Visual Hallucination Interview [9] assesses the VH phenomenology and associated
cognitions and emotions more specifically. It is validated for use in the elderly as well
as those with cognitive impairment. It has also been used in PD samples with studies
due to be published soon. Until a wider range of assessments are available, a careful
clinical assessment remains the most generally useful way of ascertaining symptoms.

Cortical visual processing depends upon two overlapping, but distinct, networks –
the dorsal (occipitoparietal, ‘vision for action’) and ventral (occipitotemporal, ‘vision
for perception’) streams. There is now considerable evidence that the disease process
in PD and DLB impacts on both of these streams, influencing the nature of the visual
symptoms reported by patients.

In terms of putative disturbances in the ventral stream, hallucinations, generally
formed, and of figures and animals, occur both in population- and hospital-based
studies of PD with a prevalence of 20–40%, rising to 60–80% in studies of patients
with PDD and DLB (see chapter 2). Once present, VH are often persistent and pro-
gressive, and cause increasing neuropsychiatric impact. They are strong predictors of
nursing home placement and even mortality [4].

There are many anomalous visual experiences [10] which are often loosely included
in the same category as VH in clinical studies of PD. They include a sensation of
movement in the visual periphery (passage hallucinations), a sense of presence in the
room (extra-campine hallucinations) and illusory misperceptions of a visual stimu-
lus. Illusory misperception, feelings of presence and passage often co-occur with VH,
but also exist in isolation, and may not have the same predictive value in terms of the

VH are not unique to PD and DLB and are seen in a variety of normal and other
neurological, psychiatric and ophthalmological conditions, especially psychosis,
delirium, and eye disease [for reviews see 12, 13]. In eye disease, a broad range of
hallucinatory experiences are reported by psychologically normal people, i.e. the
Charles Bonnet syndrome. In this condition, patients experience a variety of visual
phenomena from simple visual disturbances (flashes of light) through to well-formed
VH of people, animals and panoramic scenes. Suggesting that processes underlying
hallucinations in different disorders may not be entirely distinct, poor visual acuity
and contrast specificity are identified as risk factors for VH in PD and PDD/DLB [14,
15].

Vivid nocturnal hallucinatory experiences are also seen in some patients with
brainstem disorders, where they are referred to as ‘peduncular’ hallucinations, and
transient hallucinations are also seen in the hypnopompic (waking up) and hypna-
gogic (falling asleep) state in narcolepsy, and indeed in the general population, too.
Peduncular hallucinations share phenomenological features with the ‘presence’ hal-
lucinations seen in PD and PDD, and raise the possibility of links between sleep
disorders, brainstem dysfunction and the development of hallucinations in PD [for example 16].

Disturbances in spatial perception, for example depth perception, orienting, and motion perception [17] may be due to dysfunction in the dorsal visual stream, although the association between the extensive dorsal stream dysfunction described later and specific visual symptoms in PD remains relatively unexplored.

**Associations with Other Features of Parkinson's Disease**

**Cognition**
The increase in the frequency of VH between PD and PDD/DLB suggests a role for cognitive impairment as a risk factor for hallucinations. PDD/DLB patients suffering VH perform less well on visuoperceptual tasks than PDD or DLB patients without VH [7, 18]. Indeed, even in non-demented PD patients, differences in cognitive profiles can be demonstrated between hallucinators and non-hallucinators in terms of executive function, visuoperceptual abilities and sustained attention [11, 19–26].

**Medication**
Once assumed to be a consequence of dopaminergic therapy, evidence now suggests that there is no clear association between levodopa dose and VH, although dopamine agonists as a class are associated with a small increased risk of VH [2, 27]. There are historical reports of hallucinations complicating late-stage PD in the pre-levodopa era, and DLB patients frequently experience florid VH without previous exposure to dopaminergic therapy. Anticholinergic medication may potentiate VH [28] and further evidence against a ‘pure’ dopaminergic hypothesis is provided by the improvements seen in PDD hallucinators when treated with cholinesterase inhibitors.

**Sleep Disturbance**
Several studies have suggested that REM sleep behavioural disorder (RBD) is an independent risk factor, along with cognitive impairment, for developing VH in PD [16]. However, clear correlation between RBD, VH and motor and non-motor outcome has not been confirmed in other studies. Goetz et al. [29] found that although sleep disorders (sleep fragmentation, vivid dreams/nightmares, acting out of dreams) co-occurred with VH in a 10-year longitudinal study of PD patients, they did not predict their development.

**Other Psychiatric Symptoms**
Mood disorder, and delusional syndromes may co-exist with hallucinations; perhaps reflecting the role of other factors. Insight, for example, may be compromised by cognitive function [11]. Delusional misidentifications, for example Capgras and Fregoli type syndromes, may similarly reflect the combination of cognitive and perceptual factors.
Pathophysiology

Neuroimaging
Different modes of neuroimaging have been used to examine the structural and functional consequences of neurodegeneration in PD and PDD. Figure 1 summarises these findings.

Bruck et al. [30] demonstrated hippocampal and prefrontal cortex atrophy in non-demented PD patients compared with healthy controls, the former being associated with memory deficits and the latter with attentional impairments on cognitive testing [30]. More diffuse, but subtle, atrophy has also been detected in superior parietal, occipital, fusiform and parahippocampal regions of non-demented PD patients, correlating with visuospatial and visuoperceptual impairments [31]. Greater reductions in grey matter density in limbic, paralimbic and neocortical regions are evident in PD hallucinators compared with non-hallucinators, suggesting a link not just with cognitive profile but also visual symptoms [32, 33].

Atrophy is more pronounced in studies of PDD and DLB. Hippocampal, parahippocampal, frontal, parietal and occipital regions are all affected [34], although those cortical areas involved in dorsal and ventral stream visual processing seem particularly vulnerable [35, 36]. Diffusion tensor imaging, which provides a measure of the integrity of neural connectivity, suggests that communication between precuneus, posterior cingulate and posterior parietal regions is damaged in PDD and DLB [37, 38].

Single-photon emission computed tomography (SPECT) studies, measuring regional perfusion, provide functional as well as structural measure of cortical integrity. SPECT studies in DLB and PDD have demonstrated reductions in occipital and posterior parietal perfusion [39, 40] associated with cognitive and behavioural features such as attentional deficits and hallucinations [41]. In addition to this occipitoparietal change, greater hypoperfusion in inferior temporal and fusiform regions is described in hallucinators compared with non-hallucinators [42, 43]. Subtle perfusion changes are even demonstrable in parieto-occipital regions in PD patients with mild cognitive impairment compared with cognitively normal PD patients [44]. MR spectroscopy and positron emission tomography highlight reductions in metabolic activity in occipital [45], temporal and frontal areas [46].

fMRI has been employed to study the neuroanatomical substrate of cognitive impairment and associated symptoms in PD. During stroboscopic and kinematic stimulation of the visual pathway, PD hallucinators show an altered pattern of activation in the visual pathways, with reduced activity in occipital and parietal, and increased activation in frontal, subcortical and visual association areas compared with non-hallucinators [47]. DLB patients demonstrate reduced activation in ventral occipitotemporal regions for face perception tasks and reduced activation of lateral occipitotemporal cortex for visual motion tasks [48]. Results from face recognition and visual pop-out tasks in PD hallucinators and non-hallucinators highlight the role
Bruck (2004) - hippocampal and pre-frontal cortex atrophy in PD vs HC. Former assoc. with memory deficits and latter with attentional problems

Ramirez-Ruiz (2007) - reduction in grey matter density in superior parietal and left lingual regions in PD hallucinators vs non-hallucinators

Pereira (2009) - sup parietal, sup occipital, middle occipital, fusiform & parahippocampal atrophy in PD. Correlated with visuospatial and visuo perceptual impairments

Ibarretxe-Bilbao (2009) - atrophy in limbic, paralimbic and neocortical (frontal, parietal) areas in PD hallucinators vs non-hallucinators and controls. Atrophy progressive in hallucinators and correlated with cognitive deficits

Ramirez-Ruiz (2007) - reduction in grey matter density in superior parietal and left lingual regions in PD hallucinators vs non-hallucinators

Burton (2004) - diffuse atrophy inc. hippocampal and parahippocampal, occipital, right frontal & left parietal in PDD & DLB

Beyer (2007) - diffuse atrophy in occipital, temporal and parietal regions in PDD & DLB

Matsui (2007), Firbank (2007) - diffusion tensor imaging suggests reductions in connectivity between precuneus, posterior cingulate and posterior parietal regions in PDD & DLB

Ramirez-Ruiz (2005) - neocortical atrophy inc. right fusiform and right temporo-occipital regions in PDD

Fig. 1. Imaging studies. In this depiction, the lobes of the brain have been flattened out to allow a better appreciation of the principal regions affected in Lewy body disorders. Each symbol relates to a separate study; more symbols indicate more severe pathology or dysfunction. Note the bias toward involvement of the medial temporal, occipitoparietal and prefrontal regions, which holds even in those studies focussing on early stage disease. HC = Healthy controls; PIGD = postural instability gait difficulty; TD = tremor dominant; PD-MCI = PD-mild cognitive impairment; PPC = posterior parietal cortex.
Veeral Perception and Visual Hallucinations in Lewy Body Disorders

**Perfusion imaging - PD, PDD and DLB**

- Abe (2003) - reduced regional cortical blood flow (rCBF) in occipital and PPC (PD vs HC)
- O'Brien (2005) - cognitive and behavioural features associated with perfusion changes in post. cingulate, thalamus and inferior occipital regions (PDD & DLB)
- Matusi (2006) - PD and PDD hallucinators and non-hallucinators. Reduced perfusion in inferior parietal lobe, inferior temporal gyrus, precuneus and occipital lobe
- Oishi (2005) - hypoperfusion in right fusiform region and hyper-perfusion in sup. and middle temporal gyri in PD hallucinators
- Mito (2006) - reduced perfusion in anterior cingulate and occipital cortex, more marked in PIGD vs TD phenotype
- Nobili (2009) - PD-MCI vs PD demonstrates reduced perfusion in posterior parietal cortex, right occipital region and precuneus

**Functional MRI - PD, PDD and DLB**

- Sauer (2006) - fMRI during face perception and visual motion tasks. Reduced activation in DLB (ef.AD) in ventral occipital-temporal regions for former and lateral occipital-temporal regions for latter
- Holroyd (2006) - PD hallucinators and non-hallucinators. Increased activation in association visual cortex and reduced activation in primary visual cortex
- Meppelink (2009) - Visual pop-out task demonstrates reductions in occipital and ventral stream activation in PD hallucinators. Also subtle parietal and frontal hypoactivation.
- Stebbins (2004) - stroboscopic and kinematic stimuli in PD hallucinators and non-hallucinators. Altered pattern of activation with posterior activation in non-hallucinators and frontal/sub-cortical activation in hallucinators
- Ramirez-Ruiz (2008) - face recognition task in PD hallucinators and non-hallucinators. Reduced activation of right pre-frontal areas and anterior cingulate and increased activation of right inferior frontal gyrus in hallucinators
of pre-frontal, cingulate and temporal regions in this task, with hallucinators showing reductions in activation [49, 50].

Neuropathology
In PD and PDD/DLB, there is structural and neurochemical pathology in virtually all parts of the visual system from the retina to frontal cortex, as well as in the brainstem and thalamic regulatory systems which project to visual areas [5]. Cholinergic and dopaminergic deficits are particularly consistent. Two studies have examined the neuropathology in Lewy body dementia (PDD and DLB) specifically with VH. Consistent with both is an association between α-synuclein burden in the medial temporal lobe (particularly the amygdala) and VH in life [51, 52]. Synuclein and amyloid may thus disrupt a distributed system beyond its capability to self-stabilise, rather than having an effect in a critical location.

Models of Visual Hallucinations
In recent years, a number of models have been proposed which link disturbances in brain function with VH. Current models of normal visual perception see the subjective experience of vision as resulting from an internal, sparse, functional, predictive, dynamic representation of the visual input that the brain would receive if that representation were correct. Given this conceptualization, it is perhaps not surprising that disturbance in any part of this system can produce misperceptions. With potentially different causes in different patients, or even within the same one, there may thus not be a single final pathway for hallucinations in PD.

Arnulf et al. [53] proposed the first PD-specific model in 2000 suggesting that hallucinations reflected the intrusion of dreams into the waking state. In spite of the associations of VH with disturbed sleep and dreaming, more recent evidence suggests that these may reflect co- incidental disturbances in closely related but separate systems rather than causal links. Phenomenological differences between dreams and hallucinations further suggest that other models may fit the data better [54].

In 2005, Collerton et al. [13] and Diederich et al. [55] separately published similar interactive models which locate the generation of VH in the faulty interaction between top down internal representations and bottom up sensory input.

Collerton and collaborators developed the Perception and Attention Deficit (PAD) Model to account for VH across many disorders: a combination of attentional and perceptual impairments leads to the intrusion of an expected but incorrect perception which is not then disconfirmed because of poor perceptual function. Thus, the perception with a hallucinatory element is possible because it provides a better match for distorted visual input than does a purely veridical perception. Other risk factors, for example alertness, poor vision, and medication act through these attentional and perceptual pathways. The cognitive data noted earlier, which indicate that
attentional and perceptual impairments are associated with hallucinations, provide some support for the PAD model. It is also broadly consistent with functional imaging data suggesting abnormalities in the ventral visual stream, but there are conflicting results from imaging of frontal cortex, perhaps reflecting the difficulty in capturing the dynamic changes associated with specific hallucinations instead of the relatively static factors which generally increase the risk of hallucinating. Because of the intermittent nature of hallucinations, virtually all studies have been of subjects who are prone to hallucinations but who are not actively hallucinating at the time of imaging.

Diederich’s Activation, Input, Modulation Disturbance Model [28, 55] suggests more direct roles for alertness and sensory input than does PAD, but similarly locates the disturbance at the interface between internal and external factors within the perceptual process. Given the conceptual overlap between these two models, similar levels of experimental support exist for both.

**Treatment**

Reduction or cessation of medications, particularly those with cholinergic effects, is the first consideration when managing hallucinosis in most disorders [56]. In Lewy body disorders, it is usually possible to rationalise anti-parkinsonian therapy, aiming to remove those drugs with the greatest tendency to cause neuropsychiatric disturbance (anti-cholinergics, amantadine). It may also be appropriate to simplify the therapeutic schedule by stopping weak anti-parkinsonian medications, such as monoamine oxidase type B inhibitors (selegiline, rasagiline), and aiming for levodopa monotherapy wherever possible. With such changes, a worsening of motor symptoms is to be expected, and patients and carers must be counselled accordingly. It some patients, motor fluctuations may necessitate the institution or continuance of catechol-O-methyl transferase inhibitors (entacapone, tolcapone). There is no clear link between levodopa dose and the development of VH, but the direct synthetic dopamine agonists as a class do appear to be associated with VH as well as a wide range of behavioural symptoms. Very few PDD/DLB patients tolerate direct dopamine agonists (e.g. pramipexole, ropinirole), and for this reason they should be avoided.

If medication reduction is impossible or ineffective, atypical antipsychotics may be effective. Clozapine has the best evidence base, but its use is limited by side effects and the risk of agranulocytosis [28]. Clozapine is also licensed in the US for the treatment of tremor and can have a beneficial effect on motor symptoms in some PD patients. Cholinesterase inhibitors are effective in PDD by enhancing cognition and reducing psychiatric symptoms [57]. Hallucinators respond better than non-hallucinators to rivastigmine, perhaps reflecting the relatively greater cortical cholinergic deficits in those PDD and DLB patients with hallucinations [57]. Cholinesterase inhibitors may therefore have a role as ‘antipsychotic’ medication in PDD patients. There is no
evidence base for the use of cholinesterase inhibitors to treat hallucinations in PD patients without dementia or with milder cognitive impairments.

Practical manipulations such as improving lighting or vision, and modifying sleep or activity patterns may be tried [56]. There is no systematic evidence of effectiveness, but patients often use such techniques themselves [58], and there is little likelihood of harm. Cognitive behavioural treatments analogous to those used in psychosis may be useful to reduce the distress associated with hallucinations, but they lack a current evidence base.

Future Directions

Future progress is likely to come from combined methods which link a specific focus on a particular visual symptom with risk factors, structural and functional imaging, and treatment effects. Clinicians may benefit from improved clinical scales for the assessment of visual symptoms in PD patients with or without dementia. Furthermore, clinical algorithms on how to diagnose and treat visual symptoms in PDD and DLB are likely to improve diagnostic accuracy and management. More effective treatments that do not compromise motor function are needed.

References


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