

## **How to understand it**

### **Visual Hallucinations**

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### **Key points**

- The commonest causes of complex visual hallucinations are Parkinson's disease and Dementia with Lewy Bodies.
- Silent people and animals are most often described
- Similar phenomena are seen in the Charles Bonnet Syndrome
- Peduncular hallucinations are occasionally described with structural lesions in the thalamus and midbrain.
- Drugs affecting dopaminergic, cholinergic or serotonergic transmission can provoke visual hallucinations
- Visual impairment, central neurotransmitter derangement and changes in thalamic connectivity may all be causally involved

## **Abstract**

Visual hallucinations have intrigued neurologists and physicians for generations due to their vivid nature and the fascinating descriptions provided by patients. They are most commonly associated with Parkinson's disease and Dementia with Lewy bodies, but are also described with visual loss, where they are known as Charles Bonnet Syndrome. More rarely, they can be found with other neurological conditions, such as thalamic or midbrain lesions when they are known as peduncular hallucinosis. This review considers mechanisms underlying visual hallucinations across diagnoses, including visual loss, network dysfunction across the brain, and changes in neurotransmitters. We propose a framework to explain why visual hallucinations are most commonly found in Parkinson's disease and Dementia with Lewy Bodies. We discuss treatment approaches to visual hallucinations in Parkinson's disease and Dementia with Lewy bodies based on these principles.

## **Introduction**

Visual hallucinations are the experience of seeing something that is not actually there. When they involve the perception of people or animals, they are often referred to as being complex, whereas if they involve simple geometrical patterns as seen for example in migraine they are called simple visual hallucinations. The experience of mistaking an object for an animal (for example seeing a pile of clothes as a dog), is known as an illusion or misperception. Another form of minor visual hallucinations includes passage hallucinations, where an object or animal is seen to briefly pass in the peripheral field<sup>1</sup>. Pareidolia is a closely related-phenomenon to visual hallucinations and is defined as a tendency to perceive a specific meaningful image in an ambiguous visual pattern. (See Box 1 for a glossary of terms relating to visual hallucinations).

It has been estimated that 60% of people with Parkinson's disease will experience complex visual hallucinations at some point during their illness<sup>2</sup>, and in the related Dementia with Lewy Bodies their presence is part of the diagnostic criteria<sup>3</sup>. The Charles Bonnet Syndrome is another common cause of complex visual hallucinations seen in neurological practice and occurs in up to 20% of patients with eye disease causing low vision<sup>4</sup>. We propose that a number of interconnected processes are responsible for visual hallucinations and that these may explain the high frequency in Parkinson's disease and Dementia with Lewy Bodies.

## **Case 1**

A 76 year old man who had Parkinson's disease for 2 years began to report seeing several people in the garden, dressed in dark clothes particularly in the evenings. They were described as strangers but were not at all frightening (Figure 1). He explained that he would often bring cups of tea out for them but that they never thanked him or engaged in conversation. At first he thought they were real people, but later came to accept that his mind was playing tricks with him and was no longer concerned about their presence.

Visual hallucinations associated with Parkinson's disease and Dementia with Lewy Bodies (DLB) frequently involve the perception of people or animals. They are usually non-threatening and are occasionally welcomed in the socially isolated. They are most likely to occur in the early evening or in dim light and often are seen in the same place<sup>1</sup>. They are now considered to be a harbinger of dementia in Parkinson's disease<sup>5</sup>.

## **Case 2**

A 94 year old woman described seeing thousands of small animals and children. They did not make sounds and they disappeared when she tried to touch them. She was aware that they were not real. She had a history of age-related macular degeneration but no other significant past medical history. She took no medications and lived independently. Neurological examination was unremarkable apart from significantly reduced visual acuities, at 20/400 in the right eye and 20/800 in the left eye. Cognitive examination was normal. On fundoscopy she had advanced geographic atrophy of both maculae<sup>6</sup>.

In 1769 Charles Bonnet described his blind grandfather's experience of visual hallucinations in the context of visual loss (Figure 2). Although a syndrome of visual loss with visual hallucinations in the absence of dementia is now considered to be suggestive of Charles Bonnet Syndrome (CBS), formal diagnostic criteria need to be devised. The level of impairment of visual acuity required to result in visual hallucinations is still unclear, and the possibility of mild cognitive impairment in many of the cases reported in the literature is unresolved. In the developed world it is most usually due to age related macular degeneration<sup>7</sup> but any cause of visual loss along the visual pathway can cause it, and retinal, optic nerve and occipital lesions with visual hallucinations have all been described<sup>8</sup>. Visual hallucinations due to eye disease are usually simple, unformed hallucinations such as are seen with posterior vitreous detachments and use of the term Charles Bonnet syndrome implies the presence of more complex images including people, faces and objects<sup>9</sup>.

## **Case 3**

In 1922 Jean Lhermitte (Figure 3) described the case of a 72 year old woman who presented to his clinic at La Salpêtrière hospital in Paris with double vision, headache and vomiting. She was noted to have a left abducens nerve paresis, pathologically brisk right sided tendon reflexes, and a right intention tremor. Cerebrospinal fluid examination was normal. Two months later, she developed a left ptosis and left oculomotor and trochlear nerve palsies, with right tongue deviation and right sided incoordination and weakness. It was at this juncture that she began to report seeing cats and chickens walking across the floor. When she tried to touch them they would disappear. She also described people dressed in bizarre costumes and children playing with dolls<sup>10</sup>.

Although a post mortem examination was not carried out, a similar patient with peduncular hallucinosis was described by Van Bogaert in 1927, with post mortem confirmation of a stroke involving the thalamus, cerebral peduncle, third nerve nucleus, superior colliculus, red nucleus, periaqueductal gray, decussation of the superior cerebellar peduncle and substantia nigra<sup>11</sup>. There are a number of more recent reports of structural lesions associated with peduncular hallucinations all involving the thalamus, pons or midbrain<sup>12</sup>.

These three vignettes illustrate that complex visual hallucinations with similar phenomenology involving living people and animals may occur in conditions with widely differing pathologies.

In sharp contrast visual hallucinations in schizophrenia are relatively uncommon and invariably are associated with auditory hallucinations although in affected individuals the visions may occur sometimes unaccompanied by voices<sup>13</sup>. Although they can also involve life-size images of faces, people or events, they are often more bizarre and frightening<sup>14</sup>, with poor insight<sup>15</sup>. Hallucinations induced by psychoactive substances (especially those active at serotonin receptors) are almost always in the visual domain<sup>16</sup>, and can include both geometric forms and complex hallucinations<sup>14</sup>.

## **Potential mechanisms involved in visual hallucinations**

### **Impaired visual processing**

In Charles Bonnet Syndrome it has been suggested that the absence of visual input, or deafferentation causes hallucinations through some form of cortical release<sup>17</sup>. This is based on the notion that bottom-up visual processing is usually inhibitory and when this is lost, for example as a consequence of blindness, spontaneous cortical activity is released. This notion, however, fails to explain why most blind people do not experience complex visual hallucinations, and gives no clues to the reason for the particular animate nature of the visions.

Patients with Parkinson's disease, and Dementia with Lewy Bodies, with visual hallucinations, are more likely to have visual deficits. Two large epidemiological studies have shown that visual deficits due to any cause were linked with poorer outcomes in PD, including depression, dementia and even death<sup>18,19</sup>. We have also recently shown that patients

with PD and visual dysfunction are more likely to have cognitive deficits at follow up, and more widespread changes in white matter structure<sup>20</sup>. Patients with PD-associated visual hallucinations, have deficits in higher-order vision compared with Parkinson's patients with no visual hallucinations<sup>21</sup>. A study from Canada has shown that Parkinson's patients with colour vision deficits are also more likely to develop dementia<sup>22</sup> and changes are even seen earlier in the visual pathway, with retinal thinning found in PD patients with visual hallucinations<sup>23</sup>. In DLB, impaired colour vision is specifically related to presence and severity of visual hallucinations<sup>24</sup>. It seems probable, therefore, that a connection between visual processing deficits in Parkinson's disease and DLB and visual hallucinations exists.

### **Changes in brain networks**

No consistent region of cerebral atrophy has been found in patients with visual hallucinations<sup>25</sup> and recent work has suggested that it is more likely that they arise from a shift in the relative weighting of different brain networks. We recently showed that patients with Parkinson's disease who had visual hallucinations were more dependent on prior knowledge compared with patients with no hallucinations, suggesting that information received from higher cognitive centres was more heavily weighted<sup>26</sup>.

The Default Mode Network (DMN) becomes activated during daydreaming and introspection. It has been suggested that it is over-activated in patients who develop visual hallucinations and that at the same time there is an associated failure in activating the dorsal attention network<sup>27</sup>. Reduced connectivity in a sub-network involved in the integration of information across the brain has also been reported in Parkinson's disease patients with hallucinations<sup>28</sup> (Figure 4).

The importance of brain networks, rather than particular brain regions, was also recently supported by a meta-analysis of peduncular hallucinosis<sup>12</sup>. Although traditionally thought of as arising from the pons, midbrain or thalamus the lesions causing peduncular hallucinosis were distributed heterogeneously with little overlap in location. The lesions however, did share functional localisation to extra-striate visual regions<sup>12</sup>.

### **The thalamus as a driver of network change**

The thalamus is a diencephalic hub that is critical for filtering sensory information. Although traditionally considered to be a relay station between different brain regions, its importance in controlling shifts between brain networks is now becoming clearer and it has recently been

suggested to be a driver of the network changes seen in patients who hallucinate<sup>29</sup>. Hypometabolism and atrophy of the thalamus have been found in patients with Parkinson's hallucinations<sup>30</sup> and also in patients with fronto-temporal dementia reporting hallucinations<sup>31</sup>. A reduced connectivity between the thalamus and the prefrontal cortex has also been reported in psychosis<sup>32</sup>. We recently reported that specific thalamic sub-nuclei are affected in people with Parkinson's disease who have visual hallucinations, with most changes occurring in the right medio-dorsal medial nucleus and the tracts connected to it<sup>33</sup>.

The model of thalamo-cortical dysrhythmia links thalamic dysfunction with network changes in the Default Mode Network (DMN)<sup>34</sup>. This proposes that hallucinations are driven by thalamic-driven decoupling of the DMN from fronto-parietal and attention networks and is accompanied by thalamic-driven theta EEG rhythms. This idea is largely based on studies showing that PDD and DLB are associated with progressive theta rhythms<sup>35</sup>, which in turn predict cognitive decline and fluctuations in PD.

## **Neurotransmitters affecting visual hallucinations**

### *Dopamine*

For many years after the introduction of dopaminergic therapy in the treatment of Parkinson's disease it was considered that visual hallucinations were a reversible drug related side effect rather than related to the disease process itself. The observation of 'off period' visual hallucinations in a few patients<sup>36</sup> and the emergence of Dementia with Lewy Bodies as an entity distinct from Alzheimer's disease or vascular dementia, where visual hallucinations were a striking feature, called this into question; and there are now clear reports of frequent visual hallucinations, including complex hallucinations in early stage Parkinson's patients who have not yet started dopaminergic treatment<sup>37,38</sup>. Nevertheless there is little doubt that dopaminergic therapy can lower the threshold for the emergence of visual hallucinations in Lewy body disease although there is no clear link with dosage<sup>39</sup>. Dopamine has a role in encoding the salience or importance of an object<sup>40</sup>. and dopaminergic therapy can also make hallucinations more distressing by enhancing the perceived salience of a given visual stimulus<sup>41</sup>.

### *Acetylcholine*

Visual hallucinations are a common adverse effect of anticholinergics in the elderly and after poisoning with solanaceous plants such as deadly nightshade. Acetylcholine is linked with enhancing the precision of sensory signals, possibly through nicotinic and muscarinic receptors as part of the thalamo-reticular nucleus. This helps to modulate sensory information by increasing relevant stimuli and suppressing signals thought to be noise<sup>42</sup>. A greater availability of acetylcholine might therefore enhance sensory precision and bottom-up information, making visual hallucinations less likely. This is likely to be the mechanism for particular benefit of Rivastigmine, an acetylcholinesterase inhibitor, on Parkinson's patients with visual hallucinations<sup>43</sup>.

### *Serotonin*

The serotonergic system influences both early and late stages of sensory processing, as well as affecting behavioral responses to visual information<sup>44</sup>. Particular receptors that are involved in visual processing include 5HT<sub>2A</sub>, which are strongly expressed in the visual cortex, and 5HT<sub>3</sub> receptors, which modulate the release of other neurotransmitters, especially acetylcholine, dopamine and glutamate. Many psychedelic drugs including LSD 25 induce hallucinations through their effects on 5HT<sub>2A</sub> receptors. There has also been interest in agents active at serotonergic receptors as potential treatments for visual hallucinations. Clozapine has activity at serotonergic receptors<sup>45</sup> and pimavanserin is a 5HT<sub>2A</sub> inverse agonist, now licensed for use in the US, as a treatment for psychosis and visual hallucinations in Parkinson's disease<sup>46</sup>. It has been claimed that it is more effective in patients with greater cognitive impairment<sup>47</sup>. Ondansetron is a 5HT<sub>3</sub> antagonist that is licensed for use as an anti-emetic. Open label studies previously showed some potential benefits in Parkinson's hallucinations<sup>48</sup>, but the higher cost at the time of those studies, meant that larger trials were not conducted. However, it now has a lower cost, and a randomized controlled trial of ondansetron is underway to formally test its effectiveness in Parkinson's hallucinations ([TOP HAT | Psychiatry - UCL – University College London](#)).

### **A combination of factors at play?**

The fact that visual hallucinations are commonly seen in Parkinson's disease and Dementia with Lewy bodies, but only rarely seen in other neurodegenerative conditions with different pathological signatures and regions of selective vulnerability is of considerable interest. It may be that a combination of dysfunction across lower precision ascending sensory inputs combined with neurotransmitter imbalance in subcortical structures and loss of network



integrity promotes visual hallucinations. The observation that visual hallucinations are a strong predictor of poor outcomes in Parkinson's disease, including dementia and death, raises the possibility that more extensive network involvement including thalamic dysfunction has already occurred in these susceptible individuals.

### **Practical management of visual hallucinations in Parkinson's disease and Dementia with Lewy Bodies**

No symptomatic treatment is required in the large majority of patients with Parkinson's disease who develop visual hallucinations other than a recommendation that the home is well lit in the evenings. Some patients report that if they stare at the people they see, or if they talk to them they can make the apparitions disappear.

Frightening, threatening visual hallucinations often associated with paranoia and delirium on the other hand are a medical emergency and may require urgent hospital admission. In this situation the first step is always to carefully examine the patient and exclude and treat intercurrent urinary or respiratory tract infections, metabolic abnormalities, refractory constipation and enquire about any recent falls. If the patient is receiving anticholinergic drugs then these should be slowly reduced before starting to cut back on dopaminergic medication. Adjuvant dopaminergic therapies including dopamine agonists and both monoamine oxidase and COMT inhibitors should be tailed off in steps over ten days. If necessary the dose of levodopa may need to be increased if severe immobility ensues. If the patients is receiving opioids or other medications known to provoke visual hallucinations these should also be stopped.

Cholinesterase inhibitors can be effective in reducing the frequency and intensity of visual hallucinations. The evidence for benefit is best for rivastigmine and donepezil but if this is ineffective or poorly tolerated, memantine and galantamine can also be tried<sup>49</sup>. In some cases, persistent and distressing visual hallucinations require antipsychotic medication. These should be used with caution as they are linked with higher rates of morbidity and mortality, with side effects including worsening of Parkinsonism and cognitive function as well as falls and sedation. Current NICE guidance recommends quetiapine as first-line treatment, despite weak evidence for its efficacy, due to its relatively good safety profile. Treatment is best started with a very small dose of 12.5mg at night and built up slowly until the psychosis has settled following which an attempt should be made to slowly withdraw it.

Clozapine is active at serotonergic (5HT<sub>2A</sub>, 5HT<sub>2C</sub>, 5HT<sub>6</sub> and 5HT<sub>7</sub>) receptors, as well as having affinity for dopaminergic receptors and has much better evidence for efficacy than quetiapine. However, due to concerns of agranulocytosis, it can only be prescribed in specialist mental health settings and requires daily heart rate and blood pressure checks initially and weekly blood tests for the first 18 weeks. In any patient who fails to benefit from quetiapine it should be started at a dose of 6.25 mg and increased up to a maximum dose of 50mg daily.

Other treatment approaches are currently being evaluated for visual hallucinations. These include the use of anti-depressants and also apomorphine. Interventions such as electroconvulsive therapy, transcranial magnetic stimulation and transcranial direct current stimulation are also being investigated (see<sup>50</sup> for a more detailed review on these techniques).

### **Summary**

The phenomenology of visual hallucinations seen in Parkinson's disease and Dementia with Lewy bodies closely resembles the Charles Bonnet syndrome and the peduncular hallucinosis of Lhermitte and is distinct from the complex visual hallucinations reported in other neurological and psychiatric conditions. A combination of visual perceptual impairment, defective modulation of thalamocortical circuitry and involvement of ascending cholinergic and serotonergic transmitter pathways may be responsible.

### **Figure Legends**

#### **Figure 1**

A painting by a man in his 80s with DLB. He had visual impairment due to cataract as well as hearing disability. His symptoms were of visual hallucinations, episodic confusion and great tiredness, courtesy of Dr Sibylle Mayer, Skane University Hospital and Dr Elisabet Londos.

#### **Figure 2**

A lithograph of Charles Bonnet. Reproduced from<sup>51</sup> with permission.

#### **Figure 3**

Photograph of Jacques Jean Lhermitte. The words under the photograph are: À mon collègue et ami le Docteur Subirana. Bien cordial souvenir de la visite a Paris. (To my colleague and friend Dr Subirana. Cordial memories of the visit to Paris.) Reproduced with permission from

the Spanish Society of Neurology's museum and historical archive (Sociedad Española de Neurología Museo Archivo Histórico).

#### **Figure 4**

Network based statistics analysis comparing the structural brain networks of patients with Parkinson's disease and visual hallucinations compared to Parkinson's disease without hallucinations. A subnetwork of reduced connectivity is shown. (Reproduced from<sup>28</sup>, open license.).

#### **Table 1. Conditions frequently associated with complex visual hallucinations**

#### **Box 1. Glossary of terms linked to visual hallucinations**

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#### **Further reading**

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### Box 1 Glossary of terms linked to visual hallucinations

- Complex visual hallucination: visual hallucination of a formed object, usually a person or an animal.
- Extracampine hallucination: the sense of a person being present, without seeing them.
- Minor hallucination: a term that includes visual illusions, passage hallucinations and extracampine hallucinations.
- Pareidolia: seeing meaningful objects (usually faces) in patterned surfaces or scenes.
- Passage hallucination: seeing an object fleetingly in the periphery, where that object is not there.
- Visual hallucination: the experience of seeing something in the absence of an external stimulus

- Visual illusion: mistaking one object for another, for example seeing a towel on the floor as a dog.

**Table 1. Conditions associated with visual hallucinations**

<b>Neurological causes</b>	Parkinson's disease Lewy body dementia (including Dementia with Lewy bodies and Parkinson's disease dementia) Fronto-temporal dementia Strokes: brainstem or thalamic lesions: peduncular hallucinosis Strokes: due to occipital lobe infarcts Occipital Epilepsy Migraine coma Posterior Reversible Encephalopathy Syndrome Creutzfeldt-Jakob Disease
<b>Psychiatric causes</b>	Schizophrenia (much less common than auditory hallucinations )
<b>Ophthalmic causes</b>	Charles Bonnet Syndrome
<b>Drugs Medications</b>	Levodopa Dopamine agonists Anticholinergics Opiates ACE inhibitors Baclofen withdrawal Alcohol intoxication or withdrawal Barbiturate and benzodiazepine withdrawal
<b>Psychoactive drugs</b>	Lysergic acid diethylamine (LSD) Psilocybin Mescaline Cannabis DMT Phencyclidine (Angel Dust)
<b>Miscellaneous</b>	Narcolepsy-Cataplexy syndrome Bereavement Sensory deprivation: shipwreck survivors