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Conflict of interest statement:

Dr Weil received personal fees from GE Healthcare.

Provenance and peer review: Submitted and externally reviewed

Date first submitted: 17/6/2020

Date submitted after peer review: 23/6/2020

Acceptance date: 23/6/2020

Published online: 13/7/20

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To cite: Weil R, Reeves S. ACNR 2020;19(4):20-22

Hallucinations in Parkinson's disease: new insights into mechanisms and treatments

Abstract

Hallucinations are common in Parkinson's disease and can be distressing to patients and their families. They are associated with higher rates of nursing home placement and with increased mortality. Their underlying mechanisms have been elusive, but recent advances in network imaging provides some intriguing insights into possible underlying drivers. Treatment is complicated by risk of worsening Parkinson's motor symptoms and by higher rates of mortality with antipsychotics, but new therapeutic avenues are emerging that offer potential hope.

Visual hallucinations are common in Parkinson's disease, affecting up to 75% of patients over the disease course. The emergence of visual hallucinations has a significant impact on the quality of life of both patients and their families: they are strongly associated with cognitive decline and increased mortality and they are the strongest predictor of earlier placement in care homes.¹

Although often initially benign and even entertaining, they can become distressing with disease progression, when insight is lost, and when associated with depression or delusions. They almost invariably involve perception of people and animals, often in vivid detail, with patients describing scenes of Victorian women and small children playing. They often occur at specific times of day, usually in the evening, and in specific places, usually in the patient's own home. At early stages of disease, patients can describe minor hallucinations with misinterpretation of innocuous objects such as piles of clothes as dogs and cats. They also experience passage hallucinations, which involve the illusion of objects passing across the peripheries of vision² and extracampine hallucinations, or the sense of a presence.

Less frequently, patients have hallucinations in other modalities as the illness progresses, although these are usually less well-formed. For example, auditory hallucinations in people with Parkinson's disease are largely non-verbal, with muffled, undistinguishable sounds. Occasionally patients describe tactile, gustatory or olfactory hallucinations, which tend to co-occur with visual hallucinations.

Visual hallucinations pose a particular challenge in Parkinson's disease as the very treatments for motor symptoms in Parkinson's disease can also trigger and worsen hallucinations. Finding treatment for hallucinations

that are both effective and safe is an area of great unmet need as antipsychotic drugs worsen Parkinson's symptoms, are associated with cognitive deterioration and an increased risk of stroke and death.³

Mechanisms

Network changes and thalamic drivers

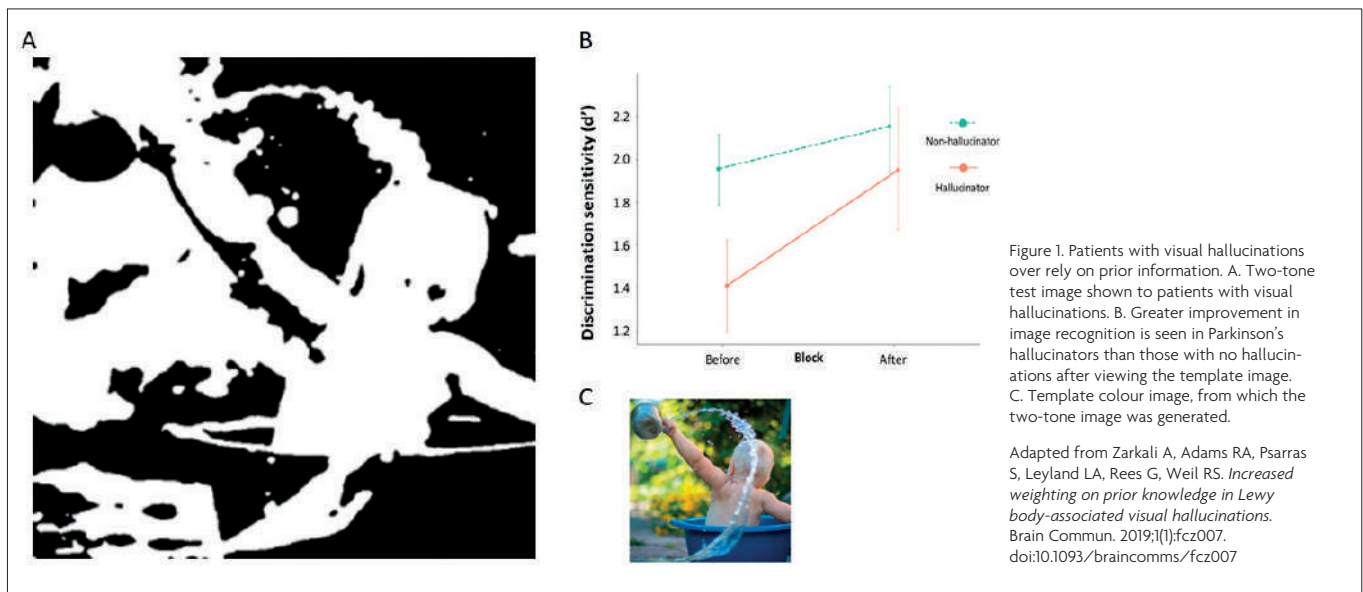
Visual hallucinations have fascinated neurologists and neuroscientists for many years, with their tantalisingly rich and often narrative detail. Due to their transient nature, they have been challenging to investigate, with no clear mechanism found, but many theories have been proposed. Previous models for visual hallucinations considered them as "cortical release" phenomena, where spontaneous activity occurs in the absence of visual stimuli. Alternative models suggested that hallucinations arise due to incorrect binding of objects into visual scenes.⁴

Advances in computational modelling and network neuroscience have opened up approaches to understanding the brain in new ways. Recent models suggest that Parkinson's hallucinations could arise due to a shift in dominance of difference networks. Specifically, there is thought to be a breakdown in those networks directed to attention and perception, and overactivity of the default mode network (DMN),^{5,6} a large-scale network that becomes activated during rest, and in day dreaming and mind-wandering. Indeed abnormal levels of default mode network activation are seen in patients with Parkinson's hallucinations.⁷

Related to this is the theory that hallucinations arise as a result of failure to integrate sensory information with prior knowledge⁸ and we recently showed that patients with Parkinson's who hallucinate over rely on prior knowledge compared with those that do not hallucinate (See Figure 1).⁹ In this way, hallucinations arise due to over interpretation of visual input. The thalamus is likely to be important as a driver of shifting network control, and release of DMN inhibition.⁶ Consistent with this, we recently showed reduced white matter connectivity in posterior thalamic projections in patients with Parkinson's hallucinations.¹⁰

Neurotransmitters and hallucinations

The role of dopamine in the pathophysiology of psychotic symptoms has long been studied. In Parkinson's disease, it is recognised that visual hallucinations increase with the dose and duration of levodopa treatment,¹¹ and that dopamine agonists are linked with higher rates of visual hallucinations.¹² It has been suggested that hypersensitisation of nigrostriatal dopa-



minergic neurones by anti-Parkinson's drugs is an important extrinsic contributor to visual hallucinations.¹³

Visual processing involves a complex interplay between dopaminergic, serotonergic, cholinergic, and GABAergic neurones¹⁴ and disruption of this dynamic balance, due to intrinsic, disease-related changes underpins the emergence of visual hallucinations in Parkinson's disease. The distinct contribution of each neurotransmitter has however proved difficult to disentangle, due to the overlapping functional networks involved in the interpretation of visual stimuli.¹⁴

Perceptual inference (filling in the gaps in what our senses tell us) relies on the brain's ability to make accurate predictions about the reliability of sensory data. The thalamoreticular nucleus, a shell of GABA-releasing neurones surrounding the thalamic circuits, plays a key role in perceptual inference, as it modulates information flow to facilitate salient stimuli and suppress less relevant stimuli.¹⁵ Acetyl choline is a critical modulator of the thalamoreticular nucleus via nicotinic alpha 7 and muscarinic M2 receptors, and acts as a 'sensory precision signal'.¹⁶

The serotonergic system is involved in early sensory processing, complex visual processing and (with noradrenaline), modulates behavioural responses (inhibition/arousal) to visual inputs.¹⁴ This multiplicity of function reflects the widely distributed network and functional diversity of receptors which modulate the activity of sensory cortices, the thalamoreticular nucleus and thalamocortical circuitry. Receptor subtypes that are most closely involved in visual processing include 5HT1A (expressed on cortical pyramidal neurones), 5HT1B and 5HT2A (densely expressed in the primary visual cortex), and 5HT3 receptors (expressed on GABAergic neurones) which modulate the release of acetyl choline, dopamine and glutamate.^{14,17}

Viewed in the context of 'network control',

the early disruption of serotonergic and cholinergic neurotransmission that occurs in Parkinson's disease may play a key role in thalamic driven decoupling of the DMN¹⁷ and this is a major area of research interest.

Treatment approaches

The general principle for treating visual hallucinations in Parkinson's disease is to look for recent triggers, such as infection, or recent medication changes. The next step is to reduce or stop medications that could be worsening hallucinations and only then to consider specific treatments.¹⁸ Importantly, specific interventions for visual hallucinations should only be initiated if patients are bothered by the experiences, as in most cases, side effects can outweigh benefits of treatment.

There is no evidence base for the order of withdrawal, and best practise is to withdraw whatever triggered the hallucinations. With no clear trigger, withdrawal should start with the least efficacious. A useful order has been recently provided: anticholinergics, followed by amantadine, rasagaline, dopamine agonists, monoamine oxidase (MAO) B inhibitors, entacapone and then levodopa.^{19,20}

Cholinesterase inhibitors are widely thought to reduce hallucinations. However, there are no supportive randomised controlled trial (RCT) data where visual hallucinations have been the treatment indication or primary outcome. The best evidence for their benefit is the observation that Rivastigmine improved cognitive performance most in those patients with visual hallucinations.²¹

Treatment options for persistent hallucinations are limited to antipsychotic drugs, which are associated with significant side-effects (falls, sedation, worsening of cognitive and motor function) and increased mortality. National Institute of Clinical Excellence (NICE 2017, www.nice.org.uk/) guidance supports use of quetiapine, as it is safer than other atypical antipsychotics (odds ratio of mortality 2.16 compared to 2.79 for olanza-

pine).³ However the evidence for its use is weak as RCTs have shown no superiority over placebo, apart from one study which excluded patients with delusions.²²

Clozapine has the strongest evidence for efficacy in treating distressing hallucinations in Parkinson's disease. Two good size RCTs have shown effectiveness in reducing hallucinations and associated delusions, with no worsening of Parkinson's motor symptoms, following very low dose treatment (10% of the dose used to treat schizophrenia).^{23,24} However, concern of agranulocytosis, daily pulse and blood pressure checks, and weekly blood monitoring for the first 18 weeks, make this impractical outside of specialist mental health settings.

Serotonergic agents have attracted considerable attention as candidate drug treatments for hallucinations, as they offer an alternative approach that is not mediated via direct antagonism of dopamine D2/3 receptors. The 5HT2A inverse agonist, Pimavanserin, was recently shown in a large randomised controlled trial to improve psychosis and visual hallucinations in Parkinson's disease,²⁵ with greatest improvement observed in patients with poorer cognition.²⁶ Initial concerns of higher rates of mortality were shown to be no higher than those in this already frail patient group.²⁷

An alternative serotonergic agent is the 5HT3 antagonist, ondansetron, which is already in use and licensed as an anti-emetic. Ondansetron showed early promise in the early 1990s as treatment of severe, persistent visual hallucinations in a case series of people with Parkinson's disease²⁸ and a subsequent open study, with marked improvement in hallucinations and delusions.²⁹ At the time, the then high cost of ondansetron prevented further studies, but this is no longer the case and the first placebo-controlled trial of ondansetron as a Parkinson's hallucinations treatment (TOP HAT) is planned for Autumn 2020, funded by Parkinson's UK.

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REGULARS — BOOK REVIEWS

Oxford Handbook of Rehabilitation Medicine. 3rd Edition

In the best tradition of Oxford Handbooks, this is a small book that packs a heavy punch. This third edition represents a significant expansion in scope and detail compared to the second edition of 2009. With over 650 pages miraculously compressed into less than two and a half centimetres, this edition adeptly fulfils its role in providing for jobbing clinicians a succinct, easily navigable overview of key clinical topics at their fingertips.

The volume is structured in two sections, the first of which 'Common Clinical Approaches' provides 25 chapters on cross-cutting areas from Communication, to Chronic Pain, Sexual Function and Mobility and Gait. Section 2 addresses 'Condition-Specific Approaches' in 16 chapters including Traumatic Brain Injury, Multiple Sclerosis, Prolonged Disorders of Consciousness and Amputee Rehabilitation. Where there is overlap, this is usefully signposted within the text, directing the reader to other relevant chapters. The text is helpfully presented, easy to scan and interspersed with many useful illustrations and diagrams.

The devotion of two chapters to musculoskeletal conditions, as well as the inclusion of Cancer Rehabilitation and Geriatric Rehabilitation reflects the editors' timely desire to see the focus of rehabilitation as a medical specialty in the UK broaden to address conditions of greatest population burden. They will also be useful to rehabilitation practitioners in the

traditional areas of neurological and spinal cord rehabilitation who find themselves working with increasingly complex conditions and co-morbidities.

Between the second and third editions the title has shifted from Clinical Rehabilitation to Rehabilitation Medicine, which is indicative of a change of emphasis towards greater rigorous pathophysiological detail and is accompanied by an authoritative, brisk editorial style. Medics, from students and junior doctors to specialists in Rehabilitation Medicine (but also Geriatrics, Neurology, Stroke Medicine and beyond) will be the main users of this handbook, but it also has much to offer to the whole multi-professional rehabilitation team.

The chapter authors are largely drawn from the UK and Australia, and sections on models of care and organisation of services reflect those settings. Inevitably, some details have already been superseded by new guidelines, for example that in TIA risk stratification, but in general this edition does an excellent job of succinctly bringing the reader up to date, and signposting further reading.

In its main aim of concisely presenting both the core principles and practical clinical details of Rehabilitation Medicine practice across an expanded scope of conditions, this handbook has certainly succeeded and it will undoubtedly become a familiar sight in MDT rooms and doctors' offices across the rehabilitation landscape.



Editors: Manoj Sivan, Margaret Phillips, Ian Baguley, Melissa Nott
Published by: Oxford University Press
Paperback price: £34.99
Pages: 658
ISBN: 9780198785477
Reviewed by: Stephen Halpin, Senior Clinical Research Fellow and Consultant in Rehabilitation Medicine, Academic Department of Rehabilitation Medicine, University of Leeds.