BRAIN
SCIENTIFIC COMMENTARY

Using network approaches to unravel the mysteries of visual hallucinations in Lewy body dementia

This scientific commentary refers to 'Functional and structural brain network correlates of visual hallucinations in Lewy body dementia' by Mehraram *et al.* (https://doi.org/10.1093/brain/awac094).

In Lewy body dementia (LBD), which includes both dementia with Lewy bodies and Parkinson's disease dementia, visual hallucinations are common as well as distressing. They are linked to poorer outcomes, including dementia and nursing home admission, but remain poorly understood. Patients with LBD and regular visual hallucinations tend to be frailer and less able to attend for study visits than other patients, making hallucinations particularly challenging to investigate. The hallucinations themselves are also usually transient and often occur in familiar places, such as the patient's own home, rather than in the laboratory. As a result, most studies of hallucinations—including that of Mehraram and co-workers[1] in this issue of *Brain*—examine the trait of having visual hallucinations rather than brain changes during hallucinations *per se*.

Some consider visual hallucinations to result from a breakdown of the normal processes involved in perception. The experience of seeing can be conceptualized as an interplay between bottom-up sensory information from the eyes and early visual processing regions, and top-down information, or visual priors and expectancies.[2] Visual hallucinations are thought to arise when an impairment of bottom-up information occurs in combination with over-reliance on top-down processes[3] (Fig. 1). In Parkinson's disease-associated hallucinations, for example, dysfunctional visual processing is apparent from the results of behavioural studies and from imaging showing hypometabolism in occipital and temporal-parietal regions.[4] An over-reliance on visual priors, supporting excess top-down processing, has also been demonstrated behaviourally.[5]

Top-down and bottom-up information are at least partly operationalized through connections between distinct brain regions at different levels of the cortical hierarchy. Network-based approaches examining the complex functional and structural interactions across regions can therefore be helpful. Studies examining functional connectivity using resting state functional MRI show changes in the relative balance of attentional networks in patients with Parkinson's disease and visual hallucinations, specifically increased activation of the default mode network and reduced activation of the dorsal attentional network.[6] Structural connectivity is also altered at whole brain level in patients with Parkinson's disease-associated hallucinations, particularly among highly interconnected regions that are crucial in switching the brain between different functional states.[7]

Changes in neurotransmission, most notably cholinergic transmission, have additionally been implicated in visual hallucinations. Patients with hallucinations often improve after treatment with cholinesterase inhibitors, while studies show that the main cortical source of cholinergic transmission, the nucleus basalis of Meynert (NBM), is particularly affected in patients with LBD and visual hallucinations. However, dopamine and serotonin are also likely to be involved. Precisely how neurotransmitter changes map onto top-down/bottom-up mechanistic models of visual hallucinations has yet to be fully resolved, although there is evidence that cholinergic transmission may enhance the precision of sensory signals.

To address these issues, Mehraram *et al.*[1] used EEG and diffusion-weighted imaging to examine functional and structural connectivity changes concurrently in 42 patients with LBD, of whom 25 experienced visual hallucinations. They applied network-based statistics to functional networks derived from alpha-band EEG source localization (shown to be preferentially affected in DLB). The results revealed that hallucinators had reduced functional connectivity both within the visual ventral network and between the visual ventral and default mode networks, with the occipital lobe most affected. These findings lend further support to involvement of bottom-up processing pathways in visual hallucinations in LBD and are also consistent with potential changes in top-down processing.

Next, Mehraram *et al.*[1] examined structural connectivity between the affected networks. They used diffusion tensor imaging to calculate the number of streamline connections between the thalamus, basal forebrain and cortical regions where they had shown reduced functional connectivity. Patients with hallucinations showed a reduced number of streamlines between the NBM and the cortex, and between the thalamus and cortex, compared to non-hallucinators. Both these regions have previously been implicated in hallucinations in patients with Parkinson's disease: reduced structural connectivity between the NBM and parietal-occipital regions was observed in a tract-of-interest analysis,[8] and we have shown reduced thalamo-cortical connectivity at baseline and longitudinally, with the mediodorsal thalamus preferentially affected.[9] The finding by Mehraram *et al.*[1] of reduced streamlines between NBM and cortex provides further support for

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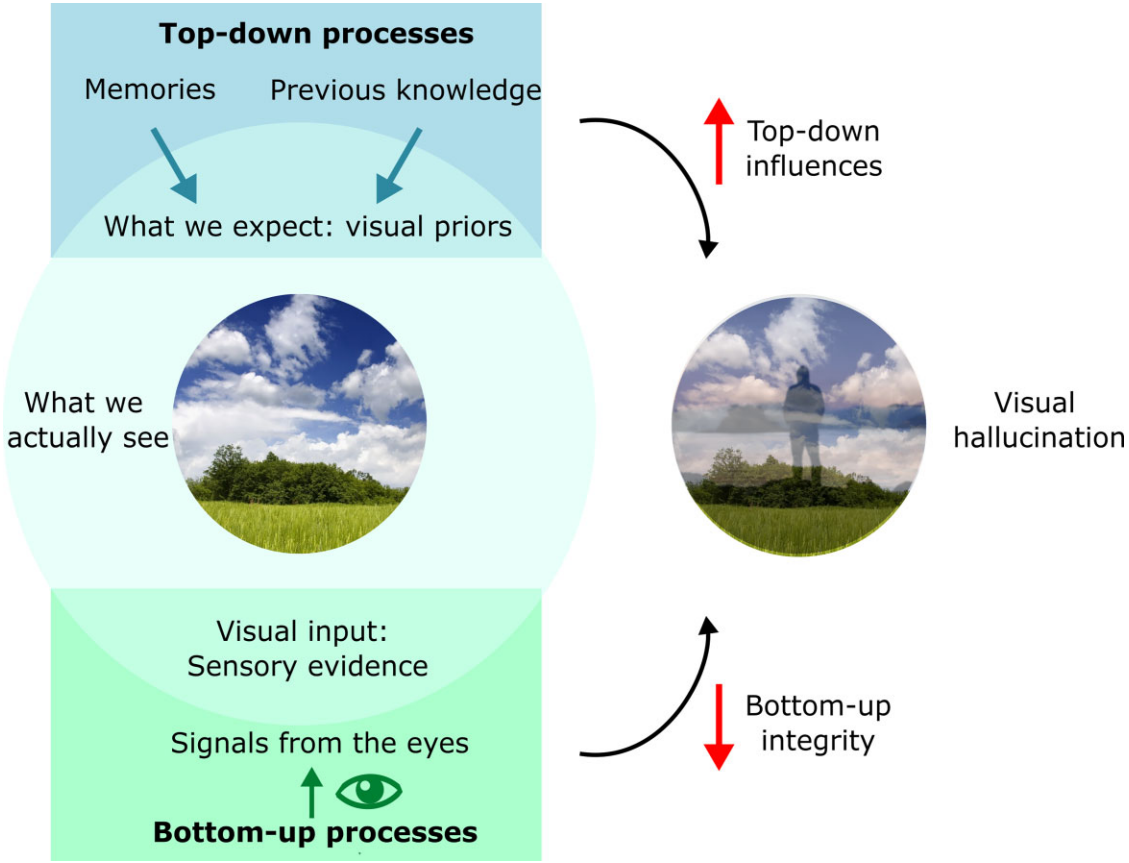

Figure 1 The origins of visual hallucinations. *Left*: Normal perception reflects a combination of bottom-up sensory input from the eyes, and top-down processes such as memories and previous knowledge that form expectations or visual priors. *Right*: Visual hallucinations are thought to arise due to a combination of reduced integrity of bottom-up sensory information from the eyes and visual processing streams; and excess weighting of top-down information. Image credits: Original images by Benson (Stockvault) and Gantas Vaičiulėnas (Pexels).

changes in cholinergic pathways, although other neurotransmitters are also likely to be involved.

Intriguingly, Mehraram *et al.*[1] found that the structural connectivity between NBM and cortex, defined by the number of streamlines, was correlated with functional connectivity in non-hallucinators but not in hallucinators. Structural and functional connectivity show a specific pattern of coupling in the healthy brain, with regions higher in the cortical hierarchy showing less strong coupling than unimodal (sensory) regions such as the visual cortex. Alterations in the physiological pattern of structural—functional decoupling have been observed in the presence of neurological and psychiatric disease as well as specifically in Lewy body disease,[9] albeit this has not yet been shown in relation to hallucinations. The lack of correlation between structural and functional NBM—cortex connectivity in hallucinators implies a loss of physiological structural–functional coupling in this group. Mehraram *et al.*[1] did not replicate this finding using other metrics of white matter integrity such as mean diffusivity or fractional anisotropy of the defined tracts, limiting the interpretation of this result. However, structure–function coupling is postulated to play a key role in sensory processing and cognition, with greater coupling associated with improved executive function. This study potentially adds further evidence for how the complex relationship between structural and functional connectivity becomes altered in LBD hallucinations.

A key limitation is that the approach used does not allow the directionality or causal influence of either the functional or structural connectivity alterations to be assessed. Although networks involved in top-down and bottom-up processing were both implicated in visual hallucinations in this work, it is not possible to draw any conclusions about the direction of involvement, and specifically whether bottom-up, top-down or a combination of both pathways are affected. To address this question, techniques such as dynamic causal modelling are needed, which examine the casual influence of one brain region over another, and which are designed to measure effective (i.e. directional) connectivity.

Ultra-high field 7 T MRI with its greater anatomical precision, capable of resolving cortical layers, offers a complementary approach to assess directional involvement of brain networks in LBD hallucinations. Top-down and bottom-up circuits in health are arranged into distinct layers of grey matter, with bottom-up circuits terminating in middle layers and feedback top-down circuits terminating in superficial and deeper layers.[10] Structural and functional layer-specific metrics from 7 T MRI have provided important insights in health and could be used to assess how the balance between top-down and bottom-up influences becomes disrupted to produce hallucinations, and at which level of the cortical hierarchy this happens.

Using advanced approaches such as those applied by Mehraram *et al.*,[1] and emerging imaging techniques, we are beginning to gain a more detailed and mechanistic understanding of the previously elusive yet fascinating visual hallucinations of LBD. In time, these may yield therapeutic targets for this common and often upsetting symptom.

Angeliki Zarkali[1] and Rimona S. Weil[1,2]

1 Dementia Research Centre, UCL, London, UK
2 Wellcome Centre for Human Neuroimaging, UCL, London, UK

Correspondence to: Rimona Weil
E-mail: r.weil@ucl.ac.uk

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Competing interests

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