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PERSPECTIVE

Pathological Changes to the Subcortical Visual System and its Relationship to Visual Hallucinations in Dementia with Lewy Bodies

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Introduction

Recurrent complex visual hallucinations are a core clinical feature of dementia with Lewy bodies (DLB) and are typically well-formed, often consisting of figures, such as people or animals [1]. Despite the profound impact upon patients and caregivers in DLB, the aetiopathology of visual hallucinations remains largely unknown. In this article we discuss the anatomy of the human visual system, hypotheses of the genesis of visual hallucinations in DLB, and imaging and neuropathological studies that have attempted to understand visual hallucinations on a functional and anatomical basis.

The Human Visual System

Human visual input comes from the eye, where light is transduced by the photoreceptors of the retina and transmitted along the optic nerve. Retinal ganglion cells, whose axons comprise the optic nerve, transmit a neural representation of the observed visual field to the lateral geniculate nucleus (LGN) of the thalamus, the primary subcortical relay centre between the retina and visual cortex. The visual cortex then sends ascending visual information to one of two parallel post-striate pathways: one projecting dorsally, which is involved in spatial and movement perception, and one projecting ventrally, which is implicated in object perception [2].

An additional 'secondary' visual pathway originates in the retina, and projects parallel to the 'primary' retina-LGN-primary visual cortex pathway [3]. The secondary visual pathway projects from the retina to the superior colliculus and then innervates the pulvinar nucleus of the thalamus. From the pulvinar, one pathway continues to visual areas involved in motion processing. Another pathway from the pulvinar projects to widespread targets, including the cingulate gyrus, amygdala and insular cortex, and is thought to integrate sensory inputs with limbic influences.

Hypotheses of Visual Hallucinations

A key theme in visual hallucinations research has been the role of 'bottom-up' stimulus-driven contributors to visual hallucinations, and 'top-down' or expectancy- and experience-driven influences on visual hallucinations. Several hypotheses have been proposed, some of which are exclusively based on bottom-up or top-down influences, and others have aimed to incorporate both in a single model [4].

Cortical Release

This hypothesis suggests that visual hallucinations may occur due to impaired or degraded visual input resulting in compensatory changes in excitability in the afferent visual pathway from the retina to the primary visual cortex. This hypothesis has been based, to some extent, on the observation that hallucinations often occur in visually

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impaired but cognitively normal individuals in a phenomenon termed Charles Bonnet syndrome. However, phenotypic overlaps in the phenomenology between individuals with DLB and Charles Bonnet suggest this may also be applicable to DLB. In this hypothesis, impairments of retinal input, or in the visual pathway between the retina and primary visual cortex, contribute to a compensatory reduction in visual cortical inhibition and corresponding increases in excitability [4]. Under this proposed model, reduced inhibition, perhaps by compensatory changes to gamma-aminobutyric acid (GABA), contributes to increased visual cortical excitability underlying hallucinations [5].

Activation-Input-Modulation Model

Consciousness is proposed to be regulated by three factors of activation, input and modulation. Activation is information processing capacity, input involves gating the balance between external stimuli and internal representations, and modulation integrates both activation and input over time. In DLB, it is thought that input is altered, perhaps by impaired dopaminergic modulation of the retina, inducing the release of normally blocked internal representations of external objects and the experience of hallucinations, particularly misperceptions [4].

Blind to Blindsight

The secondary visual pathway, routed through the superior colliculus and pulvinar, is thought to mediate blindsight, the phenomenon of reacting to moving and affective stimuli in the absence of conscious perception. Impairment of the pathway underlying blindsight has been directly implicated in visual symptoms of Lewy body disease [3], as this pathway encodes important accessory information, such as motion, about the observed visual scene that helps direct cognitive resources such as attention, rather than information about the observed scene [4]. Dysfunction of this pathway could deprive the visual system of important accessory visual information, contributing to an over-reliance on top-down influences such as prior expectations that may also be dysfunctional in DLB.

The Dorsal Attentional Network

Another account of visual hallucinations suggests that DLB patients may have difficulty in engaging the dorsal attention network to direct attention towards novel visual stimuli on the basis of salience and behavioural relevance [6]. Instead they rely on the self-referential default mode network, a brain network involved in self-referential and memory retrieval, thus biasing the visual system toward 'top-down' influences on perception.

Perception and Attention Deficit

Normal visual perception is thought to be a complex interplay between visual input and internal top-down representations of objects and visual scenes termed proto-objects, formed as a result of experience and deployed on the basis of expectations [7]. The Perceptual and Attention Deficit model suggests that deficient visual input and attention bias the visual system to the selection of incorrect proto-objects. Crucially, the visual scene remains intact, thus the hallucinated object is congruent with the visual scene, as observed in DLB [4].

Neuroimaging Studies in DLB

To investigate the afferent visual pathway we examined the LGN, the primary thalamic relay structure between the retina and visual cortex, using a cohort of patients who were imaged using functional magnetic resonance imaging (fMRI) in response to flashing checkerboard visual stimuli [8]. This study demonstrated no significant difference between control and DLB cases in response to the observed stimulus, suggesting that the major relay structure between the retina and primary visual cortex is intact.

In the primary visual cortex, we used the phenomenon of phosphenes – flashes of light elicited by transcranial magnetic stimulation (TMS) over the occiput – to investigate cortical excitability in DLB [9]. This study demonstrated no differences between DLB cases and controls in the degree of stimulation necessary to elicit phosphenes, as a surrogate of cortical excitability. However, visual hallucination severity was correlated with the degree of stimulation necessary to elicit phosphenes [9]. Using a combination of TMS and blood oxygen level dependent (BOLD) fMRI in response to visual stimuli, we observed that phosphene threshold was positively correlated with BOLD activity in early visual areas in aged control cases [10]. This observation intuitively implies that individuals with sensitive visual systems require less stimulation to respond to an observed stimulus. However, we observed the opposite relationship in DLB, suggesting this dynamic has broken down. In controls, the positive relationship between BOLD activity (a summative measure of both excitatory and inhibitory activity) and phosphene threshold (a function of the balance between inhibitory and excitatory activity) means that inhibition must outweigh excitation, whereas in DLB, this would mean inhibition is reduced relative to excitation.

Fewer neuroimaging studies have evaluated the secondary visual pathway. However, our collaborators Marco Onofrj and Laura Bonnani have demonstrated a relationship between increased diffusivity of particular sub-regions of the pulvinar, as a marker of reduced tissue integrity, and clinical markers of the severity and frequency of visual hallucinations [11].

Neuropathological Studies on the Visual System in DLB

Histological Studies

The characteristic neuropathological feature of DLB is the presence of intracytoplasmic inclusions of aggregated α-synuclein, termed Lewy bodies, within vulnerable neurons [1]. Amyloid-β and tau are also frequently observed in brains of individuals with DLB and, although not a diagnostic feature, may influence the clinical phenotype.

Post-mortem analysis of the LGN of aged control, DLB and Alzheimer's disease (AD) cases using stereological assessment of neuronal number and densitometry to determine the extent of neuropathological lesion formation, indicated no significant difference between control and DLB cases. Notably, there was a complete absence of Lewy body pathology in all cases. In contrast, non-hallucinating AD cases (four tau Braak V and three Braak VI) had a significant reduction in parvocellular neuron number in the LGN compared to control cases [8]. In the primary visual cortex we reported an absence of Lewy body pathology, neuronal loss and atrophy in DLB cases compared to aged controls [12]. In contrast, we demonstrated atrophic neuronal soma in layer four of the primary visual cortex, the layer that receives input from the LGN, in non-hallucinating AD cases (five tau Braak V and six Braak VI) compared to controls.

Our post-mortem analysis of the superior colliculus demonstrated that it is affected by Lewy body pathology and this was concentrated in the intermediate and deep layers, with the superficial layer largely spared, and neuronal loss only affecting the intermediate layer [13]. AD cases had neuronal loss in all layers of the superior colliculus. The superficial layer of the superior colliculus has connectivity with both the LGN and visual cortex, both of which are typically spared Lewy body pathology and neuronal loss in DLB [8, 12]. In contrast, the intermediate layer of the superior colliculus has an important role in visual target selection and directing visual attention towards behaviourally salient objects. Therefore, these results are consistent with our findings from the LGN and visual cortex, with DLB cases showing specific neuronal loss in non-primary visual regions compared to more widespread neuronal loss in AD.

We have also reported mild Lewy body pathology in the pulvinar as particularly affecting the medial aspect of the nucleus [14]. However, neuronal loss as determined by stereology was specifically found in the lateral aspect, a sub-region connected to the primary visual cortex that strongly regulates visual cortical activity on the basis of attentional demands [15]. Although AD cases also had neuronal loss in the lateral pulvinar, DLB had a greater degree of neuronal loss than AD cases in the lateral pulvinar, a notable finding in a stereological study conducted outside of the midbrain [16].

Overall, these studies have demonstrated relatively specific topographies of Lewy body pathology and neuronal loss in the visual system in DLB, with neurodegeneration particularly apparent in areas involved in regulating visual perception, particularly with regard to attention. In contrast, AD cases had more widespread neuronal loss and AD-type pathology was more widely distributed throughout the visual system. In DLB cases, Lewy body pathology and neuronal loss were typically found in secondary visual pathway structures, namely the superior colliculus and pulvinar, rather than in the LGN and primary visual cortex of the primary visual pathway.

Molecular Studies

Although we have reported the primary visual cortex as spared histological signs of neurodegeneration post-mortem [12], there is physiological evidence from patients that it is functionally altered in DLB in a manner permissive to the genesis of visual hallucinations [9, 10]. To explore changes to the primary visual cortex in DLB, we obtained tissue homogenates from DLB cases post-mortem for DNA microarray analysis. Microarray and subsequent confirmatory RNA and protein analyses demonstrated alterations to proteins involved in synaptic transmission, particularly involving reductions in the inhibitory neurotransmitter GABA [12]. We speculated that GABA-ergic changes may be a downstream result of neurodegeneration elsewhere, with the aim of compensating for altered input to the primary visual cortex. Our finding of reduced inhibitory activity in the visual cortex in DLB post-mortem is consistent with our previous findings of decreased excitability in the visual cortex *intra vitam* [9].

Although we have reported neuronal loss in the pulvinar in DLB [14], and others have reported a relationship between pulvinar degeneration and visual hallucinations [11], Lewy body pathology in this area is relatively mild and the sub-regions most severely affected by α-synuclein aggregation did not manifest neuronal loss. Therefore, it is difficult to attribute the neuronal loss in the pulvinar to the

manifest burden of Lewy body pathology. Therefore, we speculated that other factors must account for the reported neurodegeneration. RNA sequencing analysis of tissue lysates from the pulvinar, followed by confirmatory protein quantification assays and histology, demonstrated profound reductions of synaptic markers and increases in reactive astrocytic proteins [17]. We observed no relationship between astrocytic markers and Lewy body pathology but we did find a negative association between synaptic and astrocytic markers. As the pulvinar is a cerebral hub region that receives input from across the cortex, we speculated that alterations to the pulvinar result from neurodegenerative changes elsewhere. Reactive astrocytes have been previously reported in regions with high densities of Lewy bodies in Lewy body disease and may be activated by the actions of α-synuclein on currently unidentified receptors. Nevertheless, α-synuclein can activate astrocytes, inducing release of pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-2 and IL-4, creating a toxic environment for synaptic organisation and function [18].

In summary, despite relatively low or absent levels of neurodegenerative pathology, the pulvinar and primary visual cortex manifest substantial changes on the molecular level in DLB. In both instances we suggest there is evidence to indicate that such changes, which are proposed to contribute to visual hallucinations, occur as a downstream result of neurodegenerative pathological changes elsewhere in the brain.

Discussion

Our studies of the subcortical visual pathways have demonstrated relatively specific topographies of Lewy body pathology and neuronal loss in the visual system in DLB (Fig. 1). In contrast, AD cases have more widespread neuronal loss and AD-type pathology is more widely distributed throughout the visual system. In DLB cases, Lewy body pathology and neuronal loss are typically found in secondary visual pathway structures, namely the superior colliculus and pulvinar, compared to the LGN and primary visual cortex of the primary visual pathway. However, despite low or absent levels of Lewy body pathology in the pulvinar and primary visual cortex, both regions manifest substantial changes on the molecular level in DLB brain tissue which are consistent with functional findings obtained *intra vitam*.

The absence of Lewy body pathology or neuronal loss in a particular brain region does not necessarily imply it is physiologically intact. If visual hallucinations result purely from degeneration of the visual system, then one would expect visual hallucinations to be at least as frequent in AD as they evidence more widespread patterns of pathological changes, yet visual hallucinations are more commonly found in DLB than AD. Therefore, we suggest that visual hallucinations in DLB are not simply the result of the observed pattern of degeneration within the visual system, but also physiological changes that occur in regions spared neurodegeneration. For example, while we noted an absence of Lewy body pathology and neuronal loss in the visual cortex in DLB [12], we observed alterations in markers of inhibitory neurotransmission post-mortem and increased excitability in this region *intra vitam* that correlated with the severity of visual hallucinations [9, 10]. Furthermore, we observed neuronal and synaptic loss in the pulvinar [14, 17], a region that regulates visual cortical activity, demonstrating a potential mechanism for how degeneration of a regulatory structure may induce physiological changes in the regions whose activity it regulates.

In the superior colliculus, we demonstrated that neuronal density in the superficial layer of the superior colliculus, a region typically spared Lewy body pathology, was positively correlated with clinical markers of the severity and frequency of hallucinations [13]. While counterintuitive, the relative preservation of the superficial layer, in the context of neuronal loss in the intermediate layer, may contribute a vulnerability to visual hallucinations. The superficial layer receives feedback modulation through vertical pathways from the intermediate and deep layers, which can enhance or inhibit responses to observed visual stimuli. As a result, the superficial layer may erroneously enhance or inhibit visual responses due to altered modulatory influences from the dysfunctional intermediate layer.

Since functional changes in non-degenerated brain regions may be permissive, and widespread degeneration prohibitive, to the generation of visual hallucinations, a key question is why some brain regions are not subject to neurodegenerative pathology in DLB. Pathological vulnerability may be explained in the context of a 'prion-like' spread of pathology originating at a predilection site and spreading on the basis of anatomical connectivity. However, some regions highly interconnected with early predilection sites do not typically manifest Lewy body pathology [19], indicating that anatomical connectivity is not the sole determinant of vulnerability. We have recently demonstrated that the primary visual cortex, a region with remarkable resilience to Lewy body formation, contains strikingly lower levels of physiological α-synuclein in the brains of the cognitively intact elderly post-mortem [20]. Therefore, normal expression levels of physiological α-synuclein may contribute to the topography of regions that are resilient to Lewy body formation but which nonetheless remain vulnerable to physiological changes resulting from degeneration elsewhere.

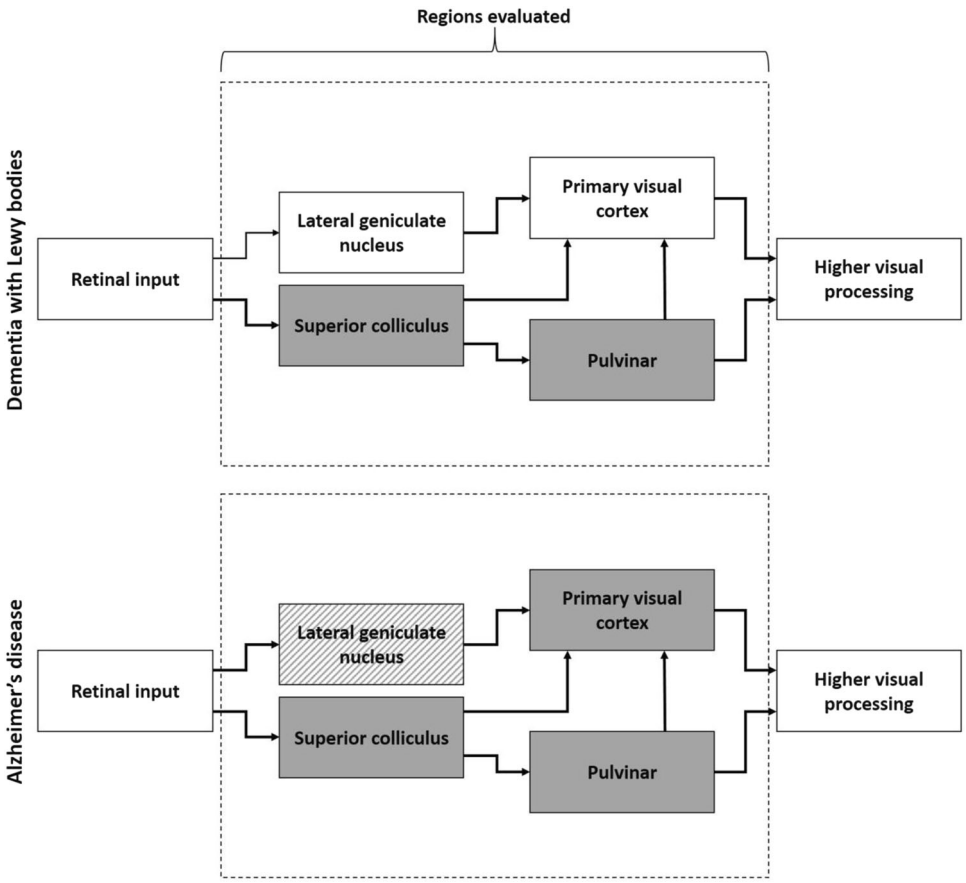

Fig. 1 Schematic demonstrating the subcortical visual pathway structures evaluated in dementia with Lewy bodies (DLB) and Alzheimer's disease (AD). Shaded areas are subject to both neurodegenerative pathology (Lewy bodies in DLB or tau in AD) and neuronal loss/atrophy. Partially shaded areas are subject only to neuronal loss. Note that secondary visual areas subject to degeneration in DLB, superior colliculus and pulvinar, also project to primary visual structures, consistent with their regulatory roles.

Overall, the combination of our physiological and neuropathological studies indicates that a particular pattern of preserved and impaired functionality may be needed in order to generate visual hallucinations. All of the models reviewed earlier suggest that combined changes in several aspects of visual processing are necessary for these phenomena. This overlap between pathological findings and modelling suggests that this will be a fruitful approach to explore in future research studies.

Conclusion

The visual system shows relatively focal neurodegeneration in DLB. The specific topography of degeneration, and physiological changes in pathologically 'preserved' regions, may both be critical to the manifestation of visual hallucinations. Pathological susceptibility may be mediated by numerous factors, but physiological α-synuclein expression levels appear important. In AD, more widespread degeneration of the visual system may preclude physiological dysfunction due to a lack of anatomically preserved but physiologically altered regions necessary to elicit visual hallucinations. These findings suggest that evaluation of regions beyond those with high burdens of Lewy body pathology may be important to identify changes that may occur downstream of neurodegeneration, but may be critical to the manifestation of visual hallucinations.

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