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Attention and visual dysfunction in Parkinson's disease☆

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ABSTRACT

Visual processing extends from the retinal level to the ventral temporal lobe, and is modified by top-down and bottom-up processing. Complex visual hallucinations (VH) are commonly a feature of disorders which affect temporal lobe structures, frequently in association with impairment of ascending monoaminergic pathways. When Parkinson's disease (PD) is associated with VH, pathological changes characteristically affect the temporal lobes, a finding which is recapitulated by imaging findings. However, a major association of VH is with cognitive decline, and this is typically linked to deficits in attention and working memory, both of which are modulated by dopamine. Similarly, dopamine plays a crucial role in the function of prefrontal cortex, in addition to controlling access to consciousness via gating mechanisms that are dependent on the basal ganglia.

Visual hallucinations (VH) are one of the criteria for dementia with Lewy bodies (DLB), and are seen in a quarter of patients with Parkinson's disease (PD), but the pathophysiological mechanisms which combine to bring them to consciousness are poorly understood. Furthermore, evidence suggests that visual cognitive impairment is among the earliest non-motor features of PD [1]. The visual dysfunction seen in PD and DLB is complex and its investigation reveals much that is remarkable concerning the intricate processes that underlie vision and hallucinations.

Fundamentally, sensory information, regardless of the modality, requires bottom-up and top-down processing, a process by which basic afferent information is processed in progressive steps (bottom-up), but is modified by the demands of the organism, and influenced by attention and memory (top-down).

This review addresses specific features of top-down processing, in particular, the function of attention and working memory in the development of VH, outlining the role played by interactions between basal ganglia and frontal lobe in the maintenance of these functions, and how dysfunction of these systems allows for VH to arise. The review comprises three areas:

1. A brief overview of the basic functional anatomy of the visual system, emphasizing the role played by dopamine. More comprehensive reviews of this topic include those by Brandies et al. [2], Archibald et al. [3].
2. Implications from studies of the pathological and imaging findings in PD and DLB for the role of attentional processes in VH.
3. A review of top-down visual processing, emphasizing the critical role of the attentional mechanisms mediated by dopamine.

1. Functional anatomy of the visual system

Visual processing starts at retinal level, from where most of the information is relayed via the lateral geniculate nucleus (LGN) to the primary visual cortex (PVC), with a smaller input reaching the superior colliculus. Dopamine has been found to modulate visual processing at all of these structures. The role of the retinal dopaminergic system in visual performance has recently been reviewed elsewhere [2,3]. Visual functions that seem significantly modulated by dopamine at retinal level include contrast sensitivity, colour vision and motion perception. These functions, together with abnormalities observed with electroretinography and visual-evoked potentials, point to structural changes in the retina. However, the localization of the most basic sensory tasks to the retina does not seem to sufficiently account for the dysfunction observed in PD [3,4]. Further up the visual pathway, D1-like and D2-like receptor-families have been reported in all layers of the LGN of cats, rats and humans, where dopamine modulates retinogeniculate transmission [5–7]. Independent patterns of damage exist among the magno-, parvo- and koniocellular

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pathways in patients with PD, and these may be attributed to different patterns of dopaminergic modulation [8]. The presence of dopaminergic innervation of the PVC has been confirmed in both cats and humans [9,10]. Furthermore, given the specificity of the innervation (mainly to lamina VI), dopamine may also influence lamina VI output to lamina IV or the LGN, and thereby modify center-surround properties and spatial and temporal tuning. Over and above the local effects of dopaminergic modulation contributing to a range of deficits in the visual functions subserved by the retino-geniculo-calcarine pathways, the fact that more 'upstream' or 'central' areas also play an important role in these functions makes it difficult to dissect out the extent of the contribution made by upstream or downstream processing.

A number of regions for further processing of visual information have been identified that lie beyond the confines of what is typically viewed as primary visual and visual association cortices. Information from visual cortex is transmitted via dorsal and ventral streams, to the parietal and temporal lobes respectively [11]. The latter is particularly associated with visual recognition, and contains well defined areas which activate robustly in fMRI paradigms for a multiplicity of visual functions: recognition of faces (the fusiform face area, FFA); imaging of places (parahippocampal place area, PPA); processing of shapes (the lateral occipital complex, LOC, a complex at the junction of the inferior temporal cortices and the lateral occipital cortices), and the visual word form area in the left midfusiform gyrus. Information accessing these regions passes sequentially via areas V1 to V4, with increasing response to form and complexity of visual input, and concomitantly, an increasing degree of response to attentional input.

2. Studies of the pathological and imaging findings in PD and DLB and their potential influence on attentional processes in VH

VH are a common feature of neurodegenerative conditions that are associated with dementia, the major pathological substrates for developing VH being PD and DLB, Alzheimer disease, and less commonly, the Parkinson-plus syndromes [12]. Regrettably, neuropathological findings often are only able to provide a final viewpoint of a very disordered nervous system. Consequently, inferences correlating disordered form and function need to be drawn carefully.

Patients with PD and cognitive impairment have elevated numbers of LBs in the amygdalae, basal nuclei and limbic cortex [13]. The amygdala is significantly affected in PD (Braak stage 4), and patients with amygdala pathology typically also have widespread cortical pathology [14]. The density of LBs in the basolateral nucleus of the amygdala has been reported to be significantly greater in patients with PD and associated VH [15], although in this study the VH group was older, had longer duration of disease, and the number of patients was quite small (7 cases with VH) [16]. The same investigators have also observed that patients with early onset of hallucinations had a higher overall LB burden, with regional increases in LBs in the parahippocampus and inferior temporal regions [16]. In this study, which combined patients with PD with dementia (PDD) and DLB, LBs were sparse in inferior parietal and occipital cortices, but high numbers were found in parahippocampus and amygdala in patients with VH [16]. In contrast, in a separate study of 10 patients with VH and PD, when compared to a group of PD patients matched for duration and age, the finding of an increase in the number of LBs in the amygdala was replicated, but there was also a widespread increase in the numbers of LBs in sections from the frontal, temporal and parietal lobes (Brodmann areas 9, 20 & 39) [17]. Similarly, in a study contrasting PD patients with and without VH, LB densities were higher in the middle frontal, anterior cingulate and transentorhinal cortices, but no difference was found in the LB count in the amygdalae [18].

Given the associations between impaired cognition and VH, as seen in both DLB and PD, it is important also to underscore that both conditions have deficits in attention [19]. Since the focus of this review is on attentional mechanisms and working memory, it is relevant to point out that there are significant correlations between dementia and LB load in the cingulate cortex, a structure which is critical in directed attention [20]. Furthermore, noting that striatal and limbic loops are also involved in working memory and attentional processes, it is perhaps under appreciated that α-synuclein staining is significantly increased in the striatum in both PDD and DLB [21], and that sizeable numbers of LBs and neurites are also found in the thalamic components of the limbic loop in PD [22].

Finally, with regard to monoaminergic pathways associated with arousal mechanisms, in addition to the well-known widespread cholinergic deficit in the cortex, PD is also characterized by α-synuclein pathology is found in the nucleus basalis of Meynert (NBM) [20], as is degeneration of the pedunculopontine nucleus, which projects to thalamus and other structures (reviewed in Ref. [23]).

Structural imaging has largely proven complementary to neuropathological findings in that patients with dementia and hallucinations have been shown to have hippocampal atrophy. Specifically, about a third of PD patients with VH, and nearly 80% of PDD patients, were found to have atrophy limited to the anterior hippocampus, noting that just over a quarter of PD patients *without* VH also had atrophy of this region [24]. In general, PD and PDD appear to have similar degrees of medial temporal atrophy [25], but to a lesser extent than DLB, whereas AD has the most severe degree of atrophy in the hippocampus and tempero-parietal cortex [26]. Although temporal atrophy may be similar, one group has reported that patients with DLB showed a greater degree of atrophy in the temporal, parietal, and occipital lobes than did patients with PDD [27]. The notion that VH parallel progression of disease is supported by a longitudinal study of PD patients with VH, which found widespread neocortical, paralimbic and limbic loss of cortical volume, and noted that 75% of the patients with VH developed dementia over a period of 2.5 years [28]. However, in patients who were not demented, reduced cortical volume in parietal, frontal, and temporal cortices is seen in PD patients with and without VH, and does not serve to distinguish between the two groups [29].

In addition, imaging has demonstrated that atrophy of midbrain and substantia innominata are found in DLB, likely reflecting involvement of the NBM and cholinergic nuclei in the midbrain [26], and PD patients also demonstrate atrophy of anterior cingulate and basal ganglia [30]. In a long term follow-up study of PD, dementia was associated with progressive involvement of the visual association and cingulate cortices, and with progression of dementia, there was increasing involvement of the thalamus and medial frontal lobes [31].

3. Top-down influences on object recognition and categorization in PD

Noting the previously mentioned caveat regarding the difficulty of dissecting out the role of dopamine in bottom-up and top-down processing, several studies have identified impaired object recognition and semantic categorization among patients with PD, and have implicated dopamine in the modulation of these functions. Patients with early PD have been found to have impairments in perceptual and semantic categorization [32,33]: Antal et al. [32] have suggested that recognition involves feature extraction (e.g. wheels, windows, etc.), with the neostriatum integral to the process of selecting and weighing up of task relevant features,

a process which is impaired in PD. Levodopa naïve patients have been shown to require more information to identify specific semantic visual categories, a feature which resolves with dopamine replacement [34]. Specifically, identification of objects within categories that share several universal features, such as animals, were most affected in PD, perhaps due to the increase in possible interpretations that results in a greater number of representations competing for selection (see below).

In keeping with this, Barnes et al. [35] demonstrated impaired recognition, on four separate tests, of silhouettes of common objects and animals among PD patients and concluded that these result from an inability to resolve visual ambiguities.

Koerts et al. documented similar perceptual impairmentsamong patients with VH [36]. The contribution of impaired object recognition, misperception and subsequent visual illusions to the genesis of complex visual hallucinations has recently been reviewed elsewhere (see Refs. [37,38])

4. Dopaminergic modulation of visual working memory

Working memory is regarded as the process whereby information is maintained on-line for a short period of time, making it available for manipulation. Functionally, WM can be divided into auditory and visual subtypes, with the latter further divided into visual-spatial WM and visual-object WM. Experimental setups aimed at testing various visual functions usually include an assessment of visual working memory, either explicitly (e.g. in a delayed match-to-target test) or implicitly (e.g. during visual search tasks). Several of the areas proposed to be involved in WM are modulated by the dopaminergic system. At cortical level, it appears that D1 receptors are primarily involved with the modulation of visual-spatial WM, whereas D2 receptors modulate visual-object WM [39,40].

The prefrontal cortex (PFC) is integral to the maintenance of information in visual working memory. The PFC does not appear to store the information itself [41], but plays an important role during processing and encoding of information, as well as directing attention within WM [42]. It also serves to protect the information in WM, with this 'maintenance' of information modulated by dopamine [43–45]. Furthermore, the effect of dopamine on various PFC functions has been demonstrated to have an 'inverted-U' shape, in that there exists an optimal level from which a significant increase or decrease in dopamine leads to impaired function. As WM and attention are differentially modulated by dopamine levels in the PFC, the optimum for a given task might represent a compromise between these two functions [46].

PD is well known to be associated with cognitive inflexibility and working memory deficits [47,48]. Studies assessing the relative involvement of the WM subsystems in PD patients have yielded conflicting results, although it appears that impairment of visual-spatial WM is more severe and occurs earlier in the course of the illness [49]. Interestingly, these deficits can be found before the involvement of the dopaminergic inputs to the PFC are affected by disease progression [50]. Whereas the PFC is important in the maintenance of WM, the striatum is crucial for updating WM, as well as maintaining a high ratio of task-related to unrelated neuronal activity in cortical regions [51–54] Based on the inverse relationship that exists between striatal and frontal dopaminergic activity, it has been suggested that the combination of decreased striatal dopamine activity and increased dopamine activity in the PFC may result in 'hyperfrontality' in early PD [55]. This may bring about enhanced maintenance of information in visual WM among PD patients who are not on treatment. However, the same mechanism may lead to difficulties with set shifting and a reduction in the ability to update or manipulate information in WM [48,51,55–57]. Restoration of striatal dopamine reverses these findings, and PD patients then perform similarly to controls [47,55]. The relationship between WM, set shifting and resistance to irrelevant visual information also suggests a significant overlap between the concepts of visual working memory, selective visual attention and the (visual) contents of consciousness, which will be elaborated on below.

5. Selective attention, cognitive control and consciousness

Despite the variety of visual abnormalities that seem to result from dopaminergic dysregulation, a major component of the dysfunction is likely to result from loss of control over what visual information should be used for further processing and decision making.

Taking the ventral visual pathway as an example, information can be processed up to higher levels without subjects reporting detection of the visual stimulus [58,59]. During processing, a clear divergence occurs from 270 ms onwards, when the perceived stimulus leads to widespread parieto-frontal activation and synchrony [60]. This is often modeled by representing the parieto-frontal 'network' as a 'global workspace', with information entering this workspace being buffered from sensory stimulation and being able tobe maintained at will [61].

A selection problem results as soon as more than one system competes for control/access to a limited resource [62]. The workspace has a limited capacity, and given the enormity of sensory input coupled with 'internal' representations, there are innumerable systems competing for access to it. To ensure the process is functional, 'top-down' biasing signals promote representations that contribute to the demands of the current task or goal(Fig. 1).If stimulus strength is particularly strong, salient or emotionally charged, it may force entry to the network in a bottom-up fashion, regardless of the demands of the current tasks. For visual representations to influence subsequent behavior in a meaningful way, or for the visual information to be stored or manipulated, it needs to gain access to this 'network'. Once visual information has done so, it needs to be protected from interfering stimuli and updated or manipulated so as to achieve the current goal.

Several of the models for selective attention, working memory, and consciousness involve such a global competition for access to a 'workspace', along with a mechanism for 'gating' access in a biased manner [63]. The PFC, parietal cortex and basal ganglia are widely regarded as being responsible for the biased selection of representations into the workspace and subsequently, for protecting or updating the information. Crucially, dopamine, especially in the striatum, is a major modulator in these models. Redgrave et al. [62,64] have argued that the basal ganglia, along with the dopaminergic system, evolved as 'central selector', which acts to disinhibit winning competitors whilst inhibiting the losers. In this regard, the functioning of the basal ganglia as 'selector' is synonymous with its function as the 'gating mechanism' [65–67] and its role in 'protection against interference' [68,69]with regards to WM.

These ideas are easily reconcilable with the concept of selective visual attention [70,71]. Information relevant to the current task or goal, as well as the visual information currently in WM, provides a top-down biasing signal, which allows for independent enhancement of specific features or locations of objects [72], thereby enhancing the representation to be attended to, and maintaining it as the target of attention.

By biasing activity in the initial visual pathway as well as related cortical areas, the PFC controls the updating of task representations, and also optimizes the functioning of WM [73–75]. Recently, it has also become clear that this process does not end when information is encoded in WM, but continues throughout maintenance of WM,

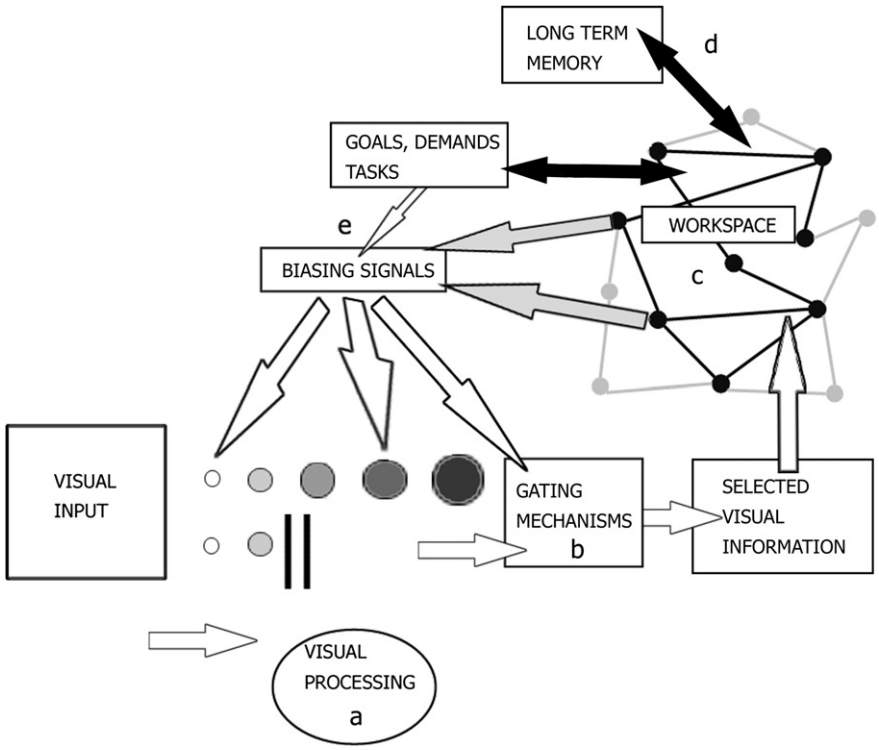

Fig. 1. (a) Visual information is processed in a feed forward fashion yielding competing representations. (b) 'Gating' or 'selection' of visual information relevant to the current goals/demands takes place, and the selected information enters the 'workspace' of working memory or consciousness (c) Information is distributed globally, and is protected from interference by the gating mechanism. Information can be stored, analyzed further, manipulated or replaced. (d) Information from long term memory, executive centers dictating current goals and other specialized modules can also enter the workspace or modify the information (e) The resulting contents of working memory/consciousness, together with executive centers keeping track of the current goals, provide biasing signals both to the early visual processing pathways as well as the gating mechanism.

manipulation of information and subsequent behavior. Some have suggested that the concept of selective attention is inseparable from working memory [41,76], with the 'higher' cortical areas traditionally viewed as the source of top-down attention (PFC and parietal cortex) constantly interacting with areas involved in visual perception during the maintenance or manipulation of items in WM [77]. (See Ref. [78] for a review on the interaction between WM and selective attention).

As mentioned previously, the network involved in conscious processing is also modeled as a workspace with biased competition for access. This overlap between consciousness, working memory and selective attention has been highlighted by others [63], and the suggestion that dopamine plays a crucial goal in gating the information that enters consciousness is intriguing. It is clear that PD patients have problems with 'top-down' attention [79], and it can be inferred that altered regulation of dopamine function causes a loss or inflexibility of task relevant top-down biasing signals. This potentially results either in important visual information failing to gain access to WM, or that the information currently occupying the 'workspace' fails to be protected from interference, which in turn brings about deranged subsequent biasing signals. This effect of altered dopaminergic regulation is also reconcilable with models of VH that envisage a disturbance of external perceptions vs internal representations [80]or between the dorsal attention network and the default mode and ventral attention networks [38], both of which involve visual representations entering consciousness that would normally be processed unconsciously.

The disruption of top-down biasing signals that occurs secondary to dopaminergic dysfunction is likely to be central to the issue of visual dysfunction in PD, and has widespread implications:

i impaired feature extraction and semantic categorization lead to deficits in object recognition;
ii impaired visual processing results in sub-optimal use of WM capacity and impaired performance on WM tasks; misperceived objects might lead to illusions;
iii impaired buffering of information in working memory from both external and internal representations might contribute to the genesis of visual hallucinations.

An additional, and likely critical factor may be that there are fundamental alterations in consciousness in PD, Experimental work on the attentional blink (AB) supports this suggestion. During AB experiments, subjects are asked to identify two targets (T1 and T2) during rapid serial visual presentation [81]. Distractors are presented shortly before and after the targets. When the two targets are separated by 200–500ms, subjects often fail to identify T2. The AB is likely to result from loss of cognitive control because of exogenous set shifting and/or impaired buffering of the information from exogenous stimuli [82]. Dopamine has been shown to modulate the processes that underlie the attentional blink [83]. In the absence of optimal dopamine, irrelevant visual information gaining access to the workspace results in set shifting and disrupts the current contents of WM or consciousness. The resulting increase in processing time of T1 correlates inversely with the proportion of T2 representations that are seen [84,85].

6. Conclusion

Visual dysfunction, of which visual hallucinations are particularly prominent, is a common feature of Parkinson's disease. Given the widespread modulatory action of dopamine on multiple aspects of

the visual system, this is to be expected. However, the pathophysiology of the observed dysfunction is still poorly understood, and although specific anatomical sites and pathological findings have been linked to visual hallucinations in PD, these are often insufficient on their own to result in VH. VH are typically found in patients with widespread pathology, mirrored by associated cognitive impairment, of which impaired selective attention and WM are likely to be of critical importance in their contribution to the genesis of VH. Several lines of evidence support the view that a deficit in attention and WM function contribute to a loss of control over the 'gating' or 'selection' of visual information, and is linked to dopaminergic dysregulation in the striatum and prefrontal cortex. Furthermore, interactions between the PFC and the basal ganglia, which are modulated by dopamine to determine access to the parieto-frontal network, are important contributors to this system. This loss of control in these higher order systems over the nature of the visual information to be used for further processing is likely to a major contributor to much of the visual dysfunction observed in PD.

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