Visual hallucinations in Parkinson's disease

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Chapter 9

General Discussion

9.1 Introduction

THE hypothesis that VH in PD are associated with impaired visual perception and attention was investigated in this thesis.
Below, the results of our clinical and imaging studies will be discussed in a broader perspective, related to visual processing and attention in PD. In addition, possible mechanisms of impaired visual perception and attention leading to VH will be considered, using a functional network approach. We will focus on two important aspects; 1) bottom-up and top-down processing and 2) modulation and selection. Interactions between and impairments in PD of processing, modulation and selection of visual stimuli will be described on a functional anatomical level, leading to a model on VH in PD that reveals future research areas of interest on pathogenesis and treatment of VH in PD.

9.2 Bottom-up processing

9.2.1 Early visual processing

Visual processing begins in the retina, where light is absorbed and transduced into electrical signals by the photoreceptors. The retina is part of the central nervous system and contains three functional classes of neurons; photoreceptors, interneurons (bipolar, horizontal and amacrine cells) and ganglion cells. Retinal signaling occurs in vertical and horizontal directions. Vertical neurotransmission takes place from photoreceptor to bipolar cell to ganglion cell. Axons of the ganglion cells form the optic nerve and fibers of each eye partly cross at the chiasm to form the optic tract, carrying the representation of the contralateral visual field. The human retina contains two types of photoreceptors; the cones, mediating bright-light, chromatic vision, and the rods, mediating low-light, achromatic vision. Cones are mainly present in the central part (fovea) of the retina and project to parvocellular and koniocellular ganglion cells, while rods are distributed in the peripheral retina and project to magnocellular ganglion cells. In this way already at the level of the retina, a functional segregation into a parvocellular processing stream, involved mainly in color vision, and a magnocellular stream, involved in motion perception, exists (Kandel, 2000). Horizontal transmission, through amacrine and horizontal cells, involves the combining of signals from several photoreceptors to

the ganglion cells, thus shaping the temporal and spatial qualities of chromatic and achromatic vision. Glutamate is the principal neurotransmitter of vertical transmission, while GABA and glycine mainly mediate horizontal transmission. In addition, dopaminergic (DA) neurons have been identified in the human retina (Frederick et al., 1982). These DA amacrine cells exhibit widespread dendritic arborizations and long axons ensuring overlap with other amacrine cells and bipolar cells. The density of DA amacrine cells is highest in the peripheral retina, paralleling the distribution of rods (Harris et al., 1992). In line with this, DA amacrine cells amplify contrast sensitivity through modulation of vertical transmission (Bodis-Wollner, 2009; Archibald et al., 2009).

9.2.2 Cortical visual processing

The optic tract projects to the lateral geniculate nucleus (LGN) of the thalamus, which is the main relay between the retina and the visual cortex. About 10 percent of retinal axons project to the superior colliculus (SC), involved in head movements and saccadic eye movements. In addition, some retinal axons project to the suprachiasmatic nucleus of the hypothalamus, involved in synchronizing biological rhythms, the pretectum in the midbrain, controlling pupillary reflexes, and the pulvinar nucleus of the thalamus. From the LGN, optic radiations project to the primary visual cortex (V1) in the occipital lobe. V1 is also called the striate cortex, because of the presence of a stripe of white matter, the stria of Gennari, in layer 4. Magno- and parvocellular axons project to different sublayers of LGN and V1, thus maintaining the segregation of these cellular pathways at successive levels of neuronal processing. Each half of the visual field is represented upside-down in the striate cortex around the contralateral calcarine sulcus, the fovea being represented in the most posterior half of V1.
After processing of visual stimuli in V1, information is conveyed "bottom-up" via area V2 to the occipito-parietal (containing the motion sensitive area V5) and occipito-temporal (with color- and form-sensitive V4) cortex, also called the dorsal and ventral visual stream, respectively. Input to the occipito-parietal pathway derives mainly from the magnocellular cells, while input to the occipito-temporal pathway derives from cells in both the magnocellular and parvocellular layers of the LGN (Ungerleider and Haxby, 1994). Retinogeniculate signals also project directly to V5, mostly via koniocellular neurons (Sincich et al., 2004). Area V6, located at the medial parieto-occipital region, is also involved in motion perception (Pitzalis et al., 2010). The dorsal route is

also called 'vision-for-action', because of its important role in real-time actions to visual targets (Goodale et al., 2004). In accordance with this is the functional connectivity between parietal cortex and dorsolateral prefrontal cortex related to grasping (Hattori et al., 2009). The ventral and lateral occipito-temporal cortical areas are important in perceiving and recognizing visual objects (Grill-Spector, 2003; Downing et al., 2006). Several subregions in the occipito-temporal cortex exist that respond more strongly to specific object categories, such as the fusiform face area for faces and the parahippocampal place area for scenes (Kanwisher et al., 1997; Epstein et al., 1999b). Other regions that are important in visual object recognition are the fusiform gyrus (including the fusiform face area), the lingual gyrus, the lateral occipital complex and the middle temporal gyrus (Malach et al., 1995; Downing et al., 2006). The ventral route has been logically called 'vision-for-perception' and was suggested to mediate memory-driven actions (Goodale et al., 2004).

9.2.3 Visual impairments in Parkinson's disease

Abnormalities in early visual processing have been shown to occur in PD patients studying Visual Evoked Potentials (VEPs). Furthermore, contrast sensitivity was especially reduced in the peripheral retina in PD, possibly reflecting malfunction of the DA amacrine cells (Bodis-Wollner, 1990; Harris et al., 1992). Direct functional evidence of retinal involvement in PD was shown using pattern electroretinography, assessing spatial tuning (Tagliati et al., 1996). Autopsy studies have shown reduced retinal dopamine levels of unmedicated PD patients, but normal levels in PD patients that received levodopa until death (Harnois and Di Paolo, 1990).
Apart from DA amacrine cell dysfunction, multiple early visual pathways are affected in PD as well, including independent damage of the magno- and parvocellular pathways (Silva et al., 2005). Furthermore, a recent study showed inner retinal layer thinning in PD (Hajee et al., 2009). Color discrimination can be reduced in PD, but probably only a subset of PD patients may show chromatic deficits (Buttner et al., 1995; Pieri et al., 2000; Silva et al., 2005). Magnocellular impairment, leading to reduced achromatic contrast sensitivity, seems more generally associated with PD disease duration (Silva et al., 2005). Levodopa as well as apomorphine have been shown to improve both achromatic and chromatic contrast discrimination, although it is unclear if this is a retinal or a cortical effect (Buttner et al., 1994, 2000; Geerligs et al., 2009). For a comprehensive review on the retina in PD, see Archibald et al. (2009).

In addition to retinal dysfunction, higher visual function deficits occur in PD. Pre-attentive visual processing of orientation differences, without need for attentive visual search to perform the task, was shown to be impaired in non-demented PD patients, while attentive visual search was similar compared to healthy controls (Lieb et al., 1999). Another, more recent study also showed that visual perceptual impairments in PD patients are mainly pre-attentive or bottom-up. When saliency of stimuli in a visual search paradigm was decreased and no prior information (top-down, see below) about the identity of the object of interest was provided, PD patients scored worse than healthy controls (Horowitz et al., 2006). These data suggest pathological involvement of the striate and extrastriate visual cortex in PD, which is in accordance with neuroimaging studies showing hypoperfusion in the occipital and parietal cortex in non-demented PD patients (Abe et al., 2003). Given the fact that visual deprivation may lead to VH (Charles Bonnet Syndrome, CBS), both retinal and early visual cortex dysfunction might play a role in the generation of VH.

9.3 Top-down visual processing and attention

9.3.1 Top-down visual processing

Success in visual object recognition also depends on attentive, 'top-down' influences that predict likely object identities. Top-down factors become increasingly important in circumstances of impoverished visual input, for example when images are noisy or partially degraded (Eger et al., 2006; Bar et al., 2006). It is thought that a partially analyzed version of the input image is rapidly projected from early visual areas to the prefrontal cortex, where it activates an "initial guess", which is projected back to the temporal cortex (Bar et al., 2006). There, it is integrated in bottom-up visual processing.
It is largely unknown through which pathways the feedforward information to the prefrontal cortex is conveyed. A magnocellular pathway via the superior longitudinal fasciculus of the dorsal stream was suggested (Kveraga et al., 2007), but also occipito-pulvinar-frontal projections and SC-amygdala-frontal projections might be involved. The latter route is primarily involved in the processing of threatening, fearful stimuli (Reinders et al., 2006). Another possibility is the inferior fronto-occipital fasciculus (IFOF), which projects from the inferior/lateral occipital lobe to inferior- and dorsolateral regions of the frontal lobe. Recently demonstrated reductions in white matter connectivity of the IFOF associated with an age-related decline in face perception were

proposed to reflect top-down visual processing deficits (Thomas et al., 2008).

9.3.2 Attention

When multiple stimuli appear simultaneously in the visual field, they interact in a mutually suppressive way, competing for representation in the visual cortex. Selective attention biases competition among stimuli in the visual scene for representation in the visual cortex by coordinating selective visual information processing (Desimone and Duncan, 1995; Serences and Yantis, 2006). Cortical and subcortical areas exerting this bias in competition are source regions of attentional control, while visual cortex areas in which activity is modulated are target regions of attentional control. Attentional influence can be implemented by both top-down signals, depending on goals and expectations, and bottom-up signals that depend on the physical salience of the stimulus. Neurophysiological data confirm that both voluntary and stimulus-driven factors influence neuronal activity of target regions, the relative impact of the latter decreasing as incoming information ascends the cortical hierarchy from V1 to prefrontal cortex (Treue, 2003).
Stimulus-driven bias, for example 'pop-out' of a distinguishable stimulus from other stimuli, leads to increased activation in striate and extrastriate cortices (Beck and Kastner, 2005, 2009). The same effect is seen when attention is directed selectively to a specific feature or location of an image in target brain regions that are involved in the processing of the feature, for example activation of the fusiform gyrus when attending to changes in shape (Corbetta et al., 1991; Kastner et al., 1998). Using fMRI, we have shown similar activations in a blind patient with CBS of both the visual motion area V5/MT and the fusiform gyrus by attending to either motion or color features of her visual hallucinations (Meppelink et al., 2010). So, attention can increase the signal to noise ratio in specific cortical target areas both in a bottom-up and a top-down manner.
Cortical sources of attention include the prefrontal cortex (frontal eye fields, cingulate cortex) and the posterior parietal cortex. During selective attention, increased perfusion of posterior parietal and prefrontal cortices was seen (Fink et al., 1997). Right inferior parietal gyrus and right prefrontal activation were shown during a sustained attention task, with relative deactivations over time, that were associated with increased reaction times (Coull et al., 1998). Several studies showed transient activation of the superior parietal cortex when shifts of attention were made, regardless of the type of the attentional deploy-

ment (Liu et al., 2005; Serences and Yantis, 2006). This transient, domain-independent 'switch signal' might enable a new attentional state, without carrying information about the parameters of the new state (Serences and Yantis, 2006). Thus, regions in both frontal and parietal cortex are likely candidates for the source of the biasing signal that, according to biased competition theory (Desimone and Duncan, 1995), resolves competition in the visual cortex (Beck and Kastner, 2009).

Subcortical structures, including the basal ganglia and the thalamus, also play a role in selective attention and higher order visual processing. In the thalamus, two nuclei apart from the LGN are important in this respect; the pulvinar and the thalamic reticular nucleus (TRN). The pulvinar is highly connected with visual and attentional areas (Leh et al., 2008). Cortico-pulvino-cortical connections exist between parietal and frontal cortices and between occipital and inferior temporal areas, while fronto-parietal areas also connect to occipito-temporal areas via a cortico-colliculo-pulvino-cortical pathway (Saalmann and Kastner, 2009). In addition, the pulvinar receives input from the TRN, which is reciprocally connected to both LGN and pulvinar and provides inhibitory input to both. Considering these extensive connections, the pulvinar can be considered as a subcortical component of the attention network in the brain. Selective attention has been shown to increase activation or metabolism in the intact human pulvinar (LaBerge and Buchsbaum, 1990; Kastner et al., 2004; Smith et al., 2009), while pulvinar lesions in humans have been associated with deficits in selective attention (Snow et al., 2009). The described increase of activation or metabolism in the pulvinar during tasks requiring selective attention was proposed to reflect inhibition of irrelevant stimuli and facilitation of behaviorally relevant stimuli (Robinson and Petersen, 1992). The pulvinar, as well as the LGN, are regulated by the TRN, which also receives input from the SC and the striate, extrastriate and prefrontal cortices. After integration of these inputs, the TRN is in a position to regulate information transmission in the LGN and pulvinar, according to the behavioral context (Saalmann and Kastner, 2009). Enhanced visual attention inhibits TRN activity, releasing inhibition of TRN to the LGN (McAlonan et al., 2008), providing support for its 'guardian' role of the thalamic "gateway tot the cortex" (Crick, 1984; McAlonan et al., 2008; Mayo, 2009).

Temporal and occipital extrastriate cortices, as well as before-mentioned visually related ventrolateral prefrontal regions project to the body and tail of the caudate nucleus of the striatum. The striatum, encompassing the caudate nucleus, putamen and nucleus accumbens, is the main input structure of the

basal ganglia (BG). The striatum receives input from the entire cortex as well as modulatory dopaminergic input from the substantia nigra pars compacta (SNc; caudate nucleus and putamen) and the VTA (nucleus accumbens), both localized in the ventral mesencephalon. The striatum projects to the output nuclei of the BG, the internal globus pallidus and the substantia nigra pars reticulata (SNr), via a direct pathway and via an indirect pathway. This indirect pathway also encompasses intrinsic nuclei of the BG; the external globus pallidus and the subthalamic nucleus (Mink, 1996). Both the internal globus pallidus and the SNr have an inhibitory connection to the thalamus, which in turn has excitatory projections back to the cortex, mainly the frontal lobe (Wolters et al., 2007). The BG play an important role in motor, cognitive and affective behavioral functions. The mechanism by which the BG contribute to these functions, seems to be through the selection of an appropriate response in a particular context and, in parallel, the suppression of inadequate responses (Redgrave et al., 1999; de Jong and Paans, 2007). They form a complex network of parallel, functionally segregated cortico-basal ganglia-thalamo-cortical loops.
In the visual corticostriatal loop, the SNr receives input from ventral extrastriate cortices by way of the visual striatum (body and tail of the caudate nucleus) that projects back to visual extrastriate cortices via the thalamus (Middleton and Strick, 1996). This visual loop may contribute to selection of a particular interpretation of an ambiguous visual scene or updating visual working memory (Groenewegen, 2009). Human fMRI studies show activation of the body and tail of the caudate during visual categorization (Seger and Cincotta, 2005). In addition, the visual loop may enable selection of appropriate motor programs on the basis of current visual processing, via output projections from the visual to the motor loop (Ashby et al., 2007). Specific BG structures and distinct thalamic nuclei thus play an important role in both selecting visual information to be brought in attentional focus and movements to be prepared for distinct action.

9.4 Parkinson's disease and visual hallucinations

9.4.1 Impaired visual processing

Reduced contrast sensitivity, impaired color discrimination as well as visual acuity, factors that are at least partly caused by retinal defects, have been associated with VH in PD (Diederich et al., 1998; Holroyd et al., 2001; Matsui

et al., 2006b). Apart from impaired early visual processing, several studies have shown that VH in PD are associated with impaired visual perception, due to deficits at later processing stages (Barnes et al., 2003; Ramirez-Ruiz et al., 2006, 2007a). We and others have shown that object and space perception in PD patients with VH is more impaired compared to PD patients without VH (Koerts et al., 2010). In addition, we have shown that the speed of identifying distinct images emerging from visual noise is decreased in PD patients with VH, compared to both PD patients without VH and healthy controls (Meppelink et al., 2008).
Functional imaging studies have shown that the primary visual cortex is equally affected in PD patients with VH as compared to PD patients without VH (Boecker et al., 2007; Oishi et al., 2005). Visual association cortices, on the other hand, showed reduction of either activation, perfusion or metabolism during rest or simple visual stimulation in PD patients with VH, as compared to PD patients without VH (Okada et al., 1999; Oishi et al., 2005; Matsui et al., 2006a; Stebbins et al., 2004; Boecker et al., 2007). Using similar images emerging from visual noise as described above (Meppelink et al., 2008) during fMRI, we have shown decreased activation of occipital and temporal extrastriate visual cortices, including the fusiform gyrus, before image recognition in PD patients with VH, compared to both PD patients without VH and healthy controls (Meppelink et al., 2009). This is in line with the previously described perfusion, activation and metabolism reductions in visual association cortices in these patients, as was shown by several groups (Okada et al., 1999; Oishi et al., 2005; Matsui et al., 2006a; Stebbins et al., 2004; Boecker et al., 2007).

9.4.2 Impaired attentive top-down processing

During visual search, PD patients relied more on top-down processing to compensate for their bottom-up visual processing deficits, when compared to healthy controls (Horowitz et al., 2006). PD patients with VH, with relatively more visual impairments compared to PD without VH, might therefore rely even more on top-down processing. Hypothetically, this could lead to excessive compensatory top-down visual processing and internal image generation, giving rise to VH. Involvement of top-down areas during VH was shown by several groups. Increased perfusion of the cingulate cortex and striatum was observed as a common feature during hallucinations in patients with schizophrenia, while the content of the hallucinations, being visual or auditory, was related to specific cortical activation (Silbersweig et al., 1995). Similarly, increased

prefrontal perfusion or activation was seen in one PD patient and in some CBS patients during VH (Kataoka et al., 2008; Ffytche et al., 1998). Apart from activation of these top-down areas, all three studies also showed activation of visual association cortices during VH. Interestingly, it was shown in CBS that the content of VH reflected the functional specialization of regions in the extrastriate visual cortex (Ffytche et al., 1998).

Frontal and parietal cortices may show compensatory increased activation during visual processing or, on the contrary, less activation, due to involvement of these top-down attentive areas in addition to bottom-up processing areas. One study showed increased activation of the inferior frontal gyrus and the caudate nucleus during simple visual stimulation in PD with VH, compared to PD without VH (Stebbins et al., 2004). Although this may reflect increased top-down involvement, the simple nature of the task makes this less likely. During visual processing of more complex, gradually revealed images we did not find support for the hypothesis of compensatory increased top-down activations during or before image recognition in PD patients with VH. In contrast, in the period before image recognition decreased activation of the right superior and middle frontal gyrus was seen in PD patients with VH, compared to PD patients without VH. In addition, a decreased activation of the inferior parietal cortex was seen in PD patients with VH, compared to healthy controls only (Meppelink et al., 2009).
A recent fMRI study has also shown reduced activation of the right ventrolateral prefrontal cortex during face perception in cognitively impaired PD patients with VH, compared to both PD without VH and healthy controls (Ramirez-Ruiz et al., 2008). Dysfunction of the lateral prefrontal cortex was proposed to reflect a deficit in suppression of irrelevant stimuli, which might predispose to VH. Another implication of the reduced activation of ventrolateral prefrontal cortex in PD patients with VH is that these patients may have reduced tendency to address external stimuli. While lateral prefrontal regions are associated with externally cued behavior, medial prefrontal activation is associated with internally guided behavior (de Jong and Paans, 2007). The superior frontal gyrus plays a role in endogenous allocation and maintenance of visual attention and was shown to be involved in the inhibition of internally represented information (Corbetta et al., 2002; de Jong and Paans, 2007). The process of distinguishing between internally- and externally- generated information is also called reality monitoring. Reduced activations of the anterior medial part of the superior frontal gyrus (i.e. medial anterior prefrontal cortex) during a reality monitoring task was associated with proneness to psychotic symptoms in healthy volunteers (Simons et al., 2008). Barnes

and colleagues have shown that PD patients with VH, when compared to PD patients without VH, had a greater propensity to report imaged stimuli as real percepts, which was interpreted as a reality-monitoring deficit (Barnes et al., 2003). In line with this, reduced activation or metabolism of the pulvinar was associated with an increased proneness to hallucinations in healthy subjects and in patients with schizophrenia (Ku et al., 2008; Hazlett et al., 2004). This suggests that the process of inhibiting irrelevant information of the pulvinar is less activated in an individual that is prone to VH, although no data on the pulvinar in PD exist.
Relatively reduced activation of prefrontal and/or posterior parietal cortex in PD patients with VH might also reflect attentional impairments. This is in line with recent publications describing a decrease in selective attention as well as sustained attention in PD patients with VH, when compared to PD patients without VH, who again performed worse than healthy controls (Barnes and Boubert, 2008; Meppelink et al., 2008).
Concluding, VH in PD are associated with impairment of both bottom-up and top-down visual processing and attention. The influence of modulatory neurotransmitter systems on these deficits and on what level they might occur in PD are discussed below.

9.5 Modulation of cortical and subcortical processing streams

Connections between or within cortical areas use mainly glutamate (excitatory) and GABA (inhibitory) in their synapses, while thalamic projections are also glutaminergic. In contrast, ascending modulatory systems use monoaminergic [dopamine, (nor)epinephrin, serotonin] and cholinergic (acetylcholine) neurotransmitters, amongst others. Modulatory projections to the cortex and subcortical areas are widespread and play a role in arousal, attention and selection. We will discuss the role of ascending cholinergic projections on attention, sleep and dreaming and the role of dopaminergic projections on selection and visual processing, with the focus on VH in PD.

9.5.1 Dopaminergic projections

Dopamine from neurons in the mesencephalon, which is released in the striatum, stimulates the direct pathway via D1 dopamine receptors and inhibits

the indirect pathway via the D2 dopamine receptors. The net result is a disinhibition of the thalamus, leading to activation of the cortex and thus selection of (motor or behavioral) programs. In PD, less dopamine is delivered to the striatum, resulting in reduced stimulation of the direct pathway and reduced inhibition of the indirect pathway. The consequence of these effects is an increased inhibition of the thalamus and thus reduced motor or behavioral output.

Classically, VH in PD have been viewed as an adverse effect of dopaminergic treatment for PD, causing a relative overstimulation of the mesolimbic dopaminergic receptors (Bosboom et al., 2004). The exact mechanism of this overstimulation in PD is unknown. In schizophrenia, increased ventral striatal and cingulate activity was shown, together with activations in distinct auditory- and visual cortical regions during respectively auditory- and visual hallucinations (Silbersweig et al., 1995). With fMRI, increased caudate activation has been demonstrated during visual stimulation in PD patients with VH, compared to PD patients without VH, thus showing some resemblance with the above described functional imaging findings in schizophrenia (Stebbins et al., 2004).

Limbic and paralimbic structures in the temporal lobe project to the ventral striatum. Together with dopaminergic input from the VTA, these projections seem to modulate the responsiveness of the ventral striatum to stimulation of other, prefrontal afferents (Epstein et al., 1999a). Antipsychotic drugs exert their effect mainly via blockade of the D2 subtype dopamine receptor, located at dopaminergic neurons in the midbrain, including the VTA, the stiatum and the prefrontal cortex (Westerink, 2002). The opposite effect, i.e. stimulation of dopamine receptors, might increase activation in VTA, ventral striatum, prefrontal and (para)limbic areas and might induce psychotic symptoms in schizophrenia (with an overactive dopamine system) or PD (due to extrinsic factors as levodopa or dopamine agonists). Alternatively, excessive stimulation of DA receptors in the visual striatum may lead to a net decrease of SNr activity and an abnormal increase in thalamic input to the temporal cortex (Middleton and Strick, 1996). VH in patients with dementia with Lewy bodies were associated with decreased dopamine transporter (DAT) binding in the caudate nucleus (Roselli et al., 2009). Reduced DAT binding in PD was shown to be associated with higher DA turnover which may lead to higher oscillations in synaptic DA, leading to transient states of intrinsic overstimulation (Sossi et al., 2007; Roselli et al., 2009). Extrinsic overstimulation may occur after administration of dopaminergic drugs.

All types of dopaminergic drugs are associated with the induction or exac-

erbation of VH, although the evidence is stronger for dopaminergic agonists than for levodopa (Baker et al., 2009; Diederich et al., 2009).
However, the hypothesis that VH in PD are simply caused by dopaminergic overstimulation has been challenged by several observations. First, a majority of PD patients on dopaminergic treatment do not report VH, while several studies report that the mean levodopa-equivalent dose is equal in PD patients with and without VH (Fenelon et al., 2000; Merims et al., 2004). Second, high-dose challenge with levodopa in non-demented PD patients with daily VH does not precipitate hallucinations (Goetz et al., 1998). Moreover, VH have already been reported in the pre-levodopa era (Fenelon et al., 2006) and have also been reported in typical PD patients in areas where levodopa treatment was not available (Dotchin et al., 2009). So, although the striatum and the dopaminergic system seem to be involved in the pathophysiology of VH in PD, evidence points to a broader involvement of several systems interacting.

9.5.2 Cholinergic modulation from the brainstem: PPN

Apart from involvement of DA neurons in the SN and later also the VTA, several other brainstem nuclei, including the dorsal vagal nucleus, raphe nucleus, locus coeruleus and pedunculopontine nucleus (PPN) (Zweig et al., 1989) are affected in PD. The PPN is connected with the SC, SN, BG, thalamus, hypothalamus, cortex and other brainstem nuclei (raphe nucleus and locus coeruleus, a.o.) and exerts enhancing influence on many processes, including locomotor activity, sleep, attention and visual processing (Kobayashi and Isa, 2002). Apart from cholinergic neurons, the PPN contains also a substantial amount of glutaminergic neurons, that project to and activate the nucleus basalis of Meynert (NbM, see below).
Regarding the enhancing role of the PPN on the thalamus, degeneration of the PPN was hypothesized to contribute to the presence of cognitive fluctuations, VH and/or sleep disturbances in α-synuclein pathology related neurodegenerative diseases, like PD. PPN cholinergic activity increases during REM sleep, together with attenuation of raphe serotonergic activity, leads to ponto-geniculate-occipital (PGO) wave production (Rye, 1997; Steriade, 2004). REM sleep behavioral disorder (RBD), consisting of loss of muscle atonia during sleep and vivid dreaming, frequently occurs in PD and might be related to the occurrence of VH. Although several studies have shown an association between RBD and VH in PD, the largest prospective longitudinal study in PD did not confirm this and only showed a relation of VH with vivid dreaming

(Goetz et al., 2005). Moreover, PPN cell loss in DLB and multi system atrophy (MSA) was not associated with either VH, cognitive impairment or RBD (Schmeichel et al., 2008). This suggests that the degeneration of the PPN in PD may only partially explain alterations in cortical arousal and visual processing and is probably not directly involved in emergence of either RBD or VH.

9.5.3 Cholinergic modulation from the forebrain: NbM

Attention is closely related to the cholinergic system (Sarter et al., 2001). Post-mortem studies in PD have shown loss of cortical cholinergic neurons and associated degeneration of the NbM, or Ch4 group (Mesulam, 2004), in the basal forebrain (Perry et al., 1985). Recent in vivo cholinergic tracer studies have shown cholinergic denervation of the occipital and parietal cortex in non-demented PD patients, while others have shown an association of cholinergic denervation with impaired attention (Hilker et al., 2005; Shimada et al., 2009; Bohnen et al., 2006). The cholinergic system plays an important role in awareness. A decrease in the cortical acetylcholine levels impairs the selection of subcortical information streams, causing unselected and chaotic cortical activation, which may predispose to hallucinations (Perry and Perry, 1995). Clinical evidence shows that VH can be induced by anti-cholinergics, while cholinesterase inhibitors ameliorate cognitive dysfunction and VH in PD (Burn et al., 2006; Wesnes et al., 2005).
A recent study indirectly showed lower cortical acetylcholine in PD patients withVH, compared to PD patients without VH, using short-latency afferent inhibition (SAI) (Manganelli et al., 2009).

9.5.4 Other modulatory systems

A recent study showed that PD patients with VH had increased serotonin 2A receptor binding. In combination with the high affinity for serotonin 2A receptors of clozapine, regularly used to effectively treat VH in PD, suggests a role for this system as well (Schotte et al., 1993; Ballanger et al., 2010). The role of glutaminergic neurotransmission on VH in PD is still unclear, although the glutamate receptor antagonist memantine may improve cognition and VH in patients with PDD (Litvinenko et al., 2010).

9.6 VH in PD: from phenomenology to functional anatomy

Regarding the phenomenology of VH in PD and the above summarized impairments in visual processing, attention and modulation, possible mechanisms on its pathophysiology and directions for future research are discussed here.

9.6.1 Visual processing and attention

VH in PD typically consist of complex visual images, implying involvement, i.e. activation, of extrastriate visual cortices during VH. Decreased metabolism or activation during rest or visual perception, respectively, does not contradict with this. On the contrary, basal reduced activity in visual cortices could lead to 'release' of higher order visual cortices, like in CBS, although the cause of underlying visual dysfunction is different. It was shown before that perfusion of the inferior frontal gyrus was increased during VH of a spider in one Parkinson's disease patient, together with increased perfusion of visual association areas (Kataoka et al., 2008). A comparable cerebral activation pattern was seen during hallucinations in patients with schizophrenia (Silbersweig et al., 1995).

It is unclear however, what cortical region initiates activation increases within the visual perceptual network of temporal, frontal and perhaps parietal cortical activation during VH. An intra-operative stimulation study in epilepsy patients showed that stimulation of the prefrontal cortex (inferior frontal gyrus) can evoke complex VH, probably by propagation of activity from the prefrontal cortex along white matter tracts [uncinate fasciculus (Catani and Mesulam, 2008)] to the ventral occipito-temporal lobe (Blanke et al., 2000). Furthermore orbitofrontal seizures can present with complex VH, probably also by propagation of epileptic activity to temporal regions (La Vega-Talbot et al., 2006).

Many patients hallucinate animals, people or objects in a behaviorally correct context. The often stereotypical environment where these VH occur (for example only in their own home) suggests that veridical visual information (i.e. the environment) elicits or at least facilitates a certain false perception (the VH). This strongly suggests involvement of the prefrontal cortex, where an 'initial guess' of objects' identities, based on a coarse representation of the object or the scene, can be projected to temporal association cortices (Bar et al., 2006). This frontal activation mainly occurs when visual input is suboptimal,

which is again in accordance with visual perceptual impairments in PD with VH. Also, VH in PD mainly occur in the evening or night, when visual input is often reduced because of dim light. However, this typical circadian pattern is only present in part of the patients and does not account for VH during the day, suggesting that other mechanism additionally play a role (see below).
VH in PD are mostly very realistic, unlike hallucinations in CBS, often consisting of fairy tale figures or Lilliputian figures (Teunisse et al., 1996). Distinguishing between externally and internally generated images, i.e. reality monitoring, was shown to be impaired in PD patients with VH (Barnes et al., 2003). The superior frontal gyrus, especially the medial part, plays an important role in this process and might be (partly) dysfunctional in PD with VH. A subcortical component of reality monitoring might be the pulvinar nucleus of the thalamus, which was shown to be activated when healthy subjects realized that an imposed illusion was not real. Future research might involve reality monitoring tasks during functional imaging in PD patients with VH, focusing on medial prefrontal and pulvinar (de)activation. Imaging during VH might reveal the time course of activation in cortical and subcortical structures, but is notoriously difficult, because VH in PD are usually infrequent and transient. Alternatively, if VH always occur in a specific visual scene, photographs of that scene might evoke VH and can be used during functional imaging.

9.6.2 Modulation and selection

Selection of an appropriate visual image also involves the basal ganglia, projecting to extrastriate cortices via the thalamus. Dopaminergic modulation facilitates processing in cortico-basal ganglia-thalamo-cortical loops. Overstimulation, either intrinsic or extrinsic, might activate either the visual or the limbic (projecting to the prefrontal cortex) loop, which may lead to VH. Concurrent reduction of cholinergic modulation might lead to inappropriate activation of visual networks that are normally (with normal cholinergic input) inhibited through attention, focusing only at behaviorally relevant information. Attentional impairments in PD are associated with VH and might fluctuate during the day, like typically seen in dementia with Lewy bodies. Reduced NbM cholinergic output to the cortex, either secondary to reduced glutaminergic input from the PPN or due to cell loss in the NbM, is associated with attentional impairments in PD.
In combination with other pontine nuclei, like the raphe (serotonin) and the coeruleus (noradrenergic), and hypothalamic nuclei, the PPN plays an impor-

tant role in the regulation of circadian rhythms like sleep and wakefulness. During REM sleep, levels of cortical ACh are similar to those during waking and twice or more the levels observed during slow-wave sleep (Rye, 1997; Steriade, 2004). No direct association between PPN cell loss, RBD and VH seems to exist. Possibly however, consciousness changes at sleep onset and during NREM sleep are more comparable with states in which VH in PD occur. In line with generation of hypnogogic hallucinations in healthy subjects, dysregulation of circadian rhythms in PD might predispose to VH. Narcolepsy, characterized by sleep attacks, VH and abnormalities of the sleep-wake cycle, is caused by a loss of hypocretin neurons in the hypothalamus (Thannickal et al., 2000). Recently it was shown that PD is also characterized by a massive loss of hypocretin neurons, which was associated with the clinical stage of PD (Thannickal et al., 2007). Because VH in PD also occur in more advanced disease stages, future research should explore a possible relation with a more severe hypocretin cell loss in PD patients experiencing VH. Increased inhibition of thalamocortical processing by the TRN in combination with reduced cholinergic input to the cortex might lead to increased intrinsic excitation of the cortex.

9.7 Conclusions

Impairments of visual processing and attention in PD occur at different levels of the visual information processing system and are associated with the occurrence of VH. Visual impairments may be bottom-up, from retina to extrastriate visual cortex, and top-down, involving prefrontal and parietal cortices, and might be caused by a combination of reduced retinal dopamine, damage to magno- and parvocellular pathways, cortical Lewy bodies and/or atrophy. In addition, changed modulation of the cortex and the thalamus by brainstem and basal forebrain neurotransmitter systems can lead to dysregulation of circadian rhythms and faulty selection in cortico-basal-ganglia-thalamo-cortical circuits. The combination of impaired visual processing, fluctuating attention accompanying dysregulated circadian rhythms and decreased reality monitoring can give rise to internally generated images that are perceived as real perceptions, i.e. visual hallucinations. Obviously, not all these deficits have to be present in one individual with PD for VH to occur. It is of clinical relevance to investigate which of the aforementioned domains is impaired in a patient, to decide what treatment will be most beneficial.
Future research in PD with VH should direct 1) the role of cortical choliner-

gic deficits on impaired visual processing and attention, 2) reality monitoring focussing on prefrontal and pulvinar activations and 3) the influence of brainstem pathology, attention and circadian rhythms.