

University of Groningen

Visual hallucinations in Parkinson's disease

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Document Version

Publisher's PDF, also known as Version of record

Publication date:

2011

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Meppelink, A. M. (2011). *Visual hallucinations in Parkinson's disease: clinical and fMRI studies*. s.n.

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Chapter 1

General Introduction

THIS thesis' topic is visual hallucinations (VH) in Parkinson's disease (PD), studied clinically and with functional magnetic resonance imaging (fMRI). In this chapter, we will provide a brief introduction with background information on PD, basal ganglia circuits, VH in general, VH in PD, the visual system and attention.

1.1 Parkinson's disease

PD is a neurodegenerative disorder primarily affecting the neuromelanin containing dopaminergic neurons in the substantia nigra, that project to the striatum (Lang and Lozano, 1998). Clinically, it is characterized typically by motor symptoms like bradykinesia, akinesia, tremor, rigidity and gait disturbances. In addition, non-motor symptoms, like depression, sleep disorders, autonomic dysfunction, cognitive impairment and VH widely occur in PD. The latter is the main topic of this thesis and raises the question of cortical involvement in PD (see below). PD is the second most common neurodegenerative disease after Alzheimer's disease and has a prevalence of approximately 1.8 in 1000 in the European population, but about 10 times higher in the elderly (von Campenhausen et al., 2005). Several genes have been identified that can lead to familial PD (Tan and Skipper, 2007), but this genetic form of PD only constitutes a minor proportion of the total PD patient population. The cause of the disease in sporadic cases is unknown, but several pathophysiological mechanisms have been proposed. The generally accepted hypothesis is that PD results from an interaction between inherited predisposition and environmental or endogenous toxic agents, resulting in mitochondrial respiratory failure, oxidative stress and subsequent cell death of nigral neurons (Schapira et al., 1992). Neurodegeneration in PD might also result from a decreased activity of the ubiquitin-proteasome system, which degrades misfolded or excess protein. Accumulation of the protein α -synuclein and formation of α -synuclein inclusion bodies, called Lewy bodies, is one of the hallmarks of PD.

1.2 Basal ganglia circuits and cortical involvement

The degeneration of dopaminergic neurons of the substantia nigra pars compacta (SNc) and, to a lesser extent, of the ventral tegmental area (VTA) in PD, results in reduced dopamine in the basal ganglia (BG). 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). The functional-anatomical organization of the BG, with several feedback loops between nuclei in the BG and between the BG, thalamus and cortex, is in accordance with its role in complex behaviors. The BG receive input from the whole cortex and project, via the thalamus, back to the cortex, mainly the frontal lobe. They form a complex network of parallel and segregated cortico-basal ganglia-thalamo-cortical loops that can be clustered into three main functional categories; sensorimotor, cognitive and limbic.

The main input structure of the BG is the striatum, encompassing the caudate nucleus, putamen and nucleus accumbens. These input nuclei receive dopaminergic modulation from the SNc (nucleus caudatus 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. Both the internal globus pallidus and the SNr have an inhibitory connection to the thalamus. Dopamine from the mesencephalon that 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 premotor and prefrontal cortices and subsequent activation of behavioral output (see figure 1.1). 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.

1.3 Complex visual hallucinations

VH have been defined as involuntary visual perceptions in the waking state without external visual stimulation (Collerton et al., 2005). VH can be simple, characterized by the absence of form, or complex, with a clearly defined specific form. Complex VH can occur in many different pathological conditions like PD, schizophrenia, narcolepsy, hallucinogen-induced states, epilepsy and eye disease (Charles Bonnet Syndrome, CBS), amongst others (Manford and Andermann, 1998). Although the underlying pathology is different for every condition, complex hallucinatory experiences are phenomenologically quite

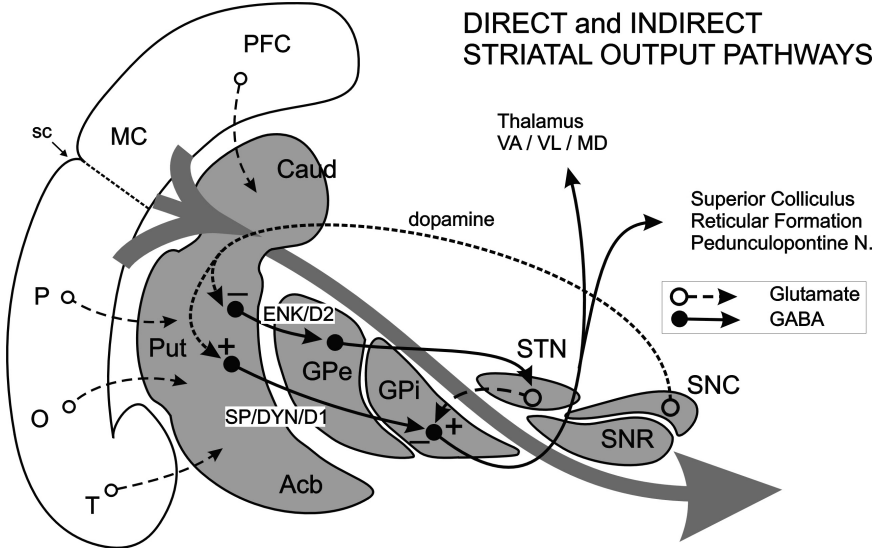


Figure 1.1: Direct and indirect striatal output pathways and the influence of dopamine on these routes, represented in a semi-sagittal scheme of the cerebral cortex and the basal ganglia. Abbreviations: Acb, nucleus accumbens; Caud, caudate nucleus; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; MC, primary motor cortex; MD, mediodorsal thalamic nucleus; O, occipital cortex; P, parietal cortex; PFC, prefrontal cortex; Put, putamen; sc, central sulcus; SNC, substantia nigra, pars compacta; SNR, substantia nigra, pars reticulata; STN, subthalamic nucleus; T, temporal cortex; VA, ventral anterior thalamic nucleus; VL, ventral lateral thalamic nucleus. (Groenewegen, 2009)

similar. In line with this, similar cortical activation patterns during VH have been demonstrated in schizophrenia, CBS and PD (Silbersweig et al., 1995; Ffytche et al., 1998; Kataoka et al., 2008). Disturbances at disparate sites and mutual connections between sites in a distributed network (Manford and Andermann, 1998), including visual cortices, prefrontal cortex and subcortical structures, involved in visual processing, attention and reality monitoring, might explain this. Phenomenology and pathophysiology of VH in PD are discussed below.

1.4 Visual hallucinations in Parkinson's disease

VH are common in PD with a prevalence of approximately 30 percent (Barnes and David, 2001). VH in PD typically comprise complex visual, commonly

moving images lasting for seconds to minutes. Animals, people and objects define the categories of images that are often perceived by hallucinating PD patients (Fenelon et al., 2000; Mosimann et al., 2006). Some have defined “minor forms” of hallucinations, which consist of a “sensation of presence”, a “sensation of a sideways passage” and illusions, in which an external stimulus is perceived but misinterpreted (Fenelon et al., 2000; Barnes and David, 2001; Fenelon et al., 2008). All above mentioned categories of hallucinations can occur in PD and often overlap, making it likely that they are related.

Though mostly these VH are non-threatening and insight is retained (Fenelon et al., 2000; Barnes and David, 2001), in 80 percent they progress to hallucinations with loss of insight or delusions and they constitute a risk factor for nursing home placement (Goetz and Stebbins, 1993; Lo et al., 2009).

The exact pathophysiological mechanism of VH in PD is unknown, but a combination of impaired visual processing and reduced attention has been proposed (Flowers and Robertson, 1995; Collerton et al., 2005). VH in PD have been commonly viewed as an adverse effect of dopaminergic treatment for PD, causing a relative overstimulation of the limbocortical dopaminergic receptors (Bosboom et al., 2004). All types of dopaminergic drugs are associated with the induction or exacerbation of VH, although the evidence is stronger for dopaminergic agonists than for levodopa (Baker et al., 2009; Diederich et al., 2009).

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 recent studies have reported a prevalence of 16-27 percent of VH in drug naïve PD patients (Biousse et al., 2004; Dotchin et al., 2009). This suggests that disease-related factors play a role in the genesis of VH in PD.

Clinical studies have shown that cognitive impairment in PD patients is associated with the occurrence of VH (Fenelon et al., 2000; Williams and Lees, 2005). Several cognitive domains (executive functioning, visuospatial abilities, attention) have been shown to be impaired in non-demented PD patients with VH, when compared to PD patients without VH (Imamura et al., 2007; Ramirez-Ruiz et al., 2007a). Other clinical factors that might be associated with VH in PD are disease duration (Fenelon et al., 2000), REM sleep behavioural dis-

order with vivid dreaming (Goetz et al., 2005) and visual disorders (Matsui et al., 2006b).

Neurochemically, several neurotransmitter systems have been postulated to be involved in the genesis of VH in PD. Apart from the before mentioned dopaminergic hypothesis, other mono-amines, like serotonin and adrenalin, and acetylcholine could play a role. According to the monoaminergic-cholinergic imbalance hypothesis, VH in PD are associated with a cholinergic deficit in combination with a relatively preserved (or overstimulated) dopamine system (Perry and Perry, 1995; Francis and Perry, 2007). This thesis' main topic of investigation is the association of VH in PD with impaired visual processing and decreased attention.

1.5 Visual processing and attention

1.5.1 Visual processing

In normal visual processing light is absorbed in the retina and transduced into electrical signals by the photoreceptors (rods and cones). Signals are transferred from the rods to the magnocellular ganglion cells and from the cones to the parvocellular and koniocellular ganglion cells. The axons of the ganglionic cells form the optic nerve and fibres of each eye partly cross at the chiasm to form the optic tract, carrying the representation of the contralateral visual field. The parvo- and koniocellular pathway are mainly involved in colour discrimination, while the magnocellular pathway is involved in achromatic contrast discrimination. The lateral geniculate nucleus (LGN) of the thalamus is the main relay between the retina and the visual cortex, but about 10 percent of retinal axons project to the superior colliculus, involved in head movements and saccadic eye movements. In addition, some axons of the retinal ganglionic cells project to the suprachiasmatic nucleus of the hypothalamus, involved in synchronizing biological rhythms, and the pretectum, controlling pupillary reflexes. The LGN consists of 6 different layers, with magnocellular projections to layers 1 and 2 and parvocellular projections to layers 3-6. Koniocellular cells project to the interlaminar zones between the 6 layers (Hendry and Yoshioka, 1994). 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-, parvo- and koniocellular axons project to different sublayers of V1, thus maintaining the segregation of these cellular pathways at this level of processing. Each half of the visual field is represented upside-down by the

contralateral striate cortex around the calcarine sulcus, the fovea being represented in the most posterior half of V1. After processing of visual stimuli in V1, information is conveyed through extrastriate areas to the occipito-parietal and occipito-temporal stream, also called the dorsal and ventral visual stream, respectively. Input to the occipito-parietal pathway (containing the motion sensitive area V5) derives mainly from the magnocellular cells, while input to the occipito-temporal pathway (with colour- and form-sensitive V4) derives from cells in both the magnocellular and parvocellular layers of the LGN (Ungerleider and Haxby, 1994). Retino-geniculate signals also project directly to V5, mostly via koniocellular neurons (Sincich et al., 2004). The ventral and lateral occipito-temporal 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).

1.5.2 Impaired visual processing and VH

Visual deprivation is a well known risk factor for the occurrence of VH. VH can occur in sighted subjects after prolonged blind-folding (Merabet et al., 2003) or in otherwise healthy subjects with visual impairment, also called the Charles Bonnet syndrome (CBS) (Merabet et al., 2003; Teunisse et al., 1996). A wide range of visual perceptual disturbances has been described in PD, attributing the underlying causes to different levels of the visual-cognitive system, from retina to frontal cortex. PD patients regularly complain of difficulty reading and blurred vision, despite normal visual acuity (Pieri et al., 2000; Biousse et al., 2004). Abnormalities in early visual processing have been shown to occur in PD patients studying Visual Evoked Potentials and contrast sensitivity, reflecting dopaminergic malfunction in the amacrine cells of the retina (Bodis-Wollner, 1990). Also, autopsy studies have shown reduced retinal dopamine (DA) levels of unmedicated PD patients, but normal DA levels in PD patients that received levodopa until death (Harnois and Di Paolo, 1990). Colour 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).

Several studies have shown that visual perceptual impairments in PD are as-

sociated with the occurrence of VH. Matsui and colleagues showed that VH in PD were closely related to impaired visual acuity (Matsui et al., 2006b). Furthermore, it was shown that contrast sensitivity and colour discrimination were significantly more impaired in PD patients with VH, compared to PD patients without VH, regardless of visual acuity (Diederich et al., 1998; Davidsdottir et al., 2005). Other visual disturbances associated with VH in PD include visual space perception (Ramirez-Ruiz et al., 2007a) and visual object perception (Barnes et al., 2003; Ramirez-Ruiz et al., 2006).

1.5.3 Attention

Attention is a heterogeneous process and one can attend to a stimulus (object, location or moment) in different ways, leading to several sub-processes of attention. In selective (or focussed) attention priority is given to one stimulus in favour of another, while sustained attention and divided attention encompass attending to one stimulus or dividing attention between two or more different stimuli, respectively, over an increasing period of time. Attending to specific features of a visual image elicits activations in brain regions that are involved in the processing of these features, for example activation of the fusiform gyrus when attending to changes in shape (Corbetta et al., 1991). Attentive, i.e. “top-down”, processes are considered to play an important role in the identification of objects in suboptimal visual circumstances (Bar et al., 2006). Interestingly, VH in PD tend to occur in these suboptimal visual circumstances, mostly during the evening (Fenelon et al., 2000).

1.5.4 Impaired attention and VH

Cognitive dysfunction is common in PD patients and consists mainly of impairment of executive function and attention (Muslimovic et al., 2005; Verleden et al., 2007). In a recent study, it was shown that about a quarter of de novo diagnosed PD patients without dementia were cognitively impaired, defined as impairment on at least three neuropsychological tests. All cognitively impaired PD patients had attentional and executive deficits (Muslimovic et al., 2005). Although only few studies on attention in PD exist, it seems that executive and attentional functions are more impaired in non-demented PD patients with VH than in non-demented PD patients without VH (Grossi et al., 2005; Imamura et al., 2007; Barnes and Boubert, 2008).

The influence of executive dysfunction is widespread and might therefore ex-

plain a considerable part of previous behavioral and imaging results regarding visual perception and attention. The Mini Mental State Examination (MMSE) was developed as a screening test for Alzheimer's type dementia (Folstein et al., 1975), but seems less sensitive to cognitive impairment in PD. The Frontal Assessment Battery (FAB) was developed to assess frontal lobe function to identify a dysexecutive syndrome (Dubois et al., 2000). Even in PD patients with dementia, MMSE scores can be relatively spared, while scores on the FAB are decreased and thus seem to better reflect cognitive impairments in PD patients. For this reason, an effort was made to match participating patients of the studies described in this thesis on both MMSE and FAB.

1.6 Therapeutic options for treatment of VH

1.6.1 Non-pharmacological interventions

Effective non-pharmacological interventions to improve VH in PD include correction of reduced visual acuity (glasses) or, when indicated, removing cataract (Matsui et al., 2006b). Coping strategies for PD patients with VH include looking in another direction or at another object, turning on the light during the night or speaking to the spouse or caregiver in order to check the non-reality of the phenomenon (Diederich et al., 2003, 2009).

1.6.2 Dopaminergic modulation

Typical neuroleptics have been used in the past at low doses to reduce hallucinations and other psychotic symptoms in PD, but have the disadvantage of worsening motor function. Newer, so called "atypical", neuroleptics have the potential to treat hallucinations in PD with less negative effects on motor function. The only atypical neuroleptic with confirmed benefit without worsening motor function is clozapine, which exhibits weak antagonism for the D2 dopamine receptor subtype. In addition, it blocks other neurotransmitter receptors, including the serotonergic 2A receptor (Schotte et al., 1993).

1.6.3 Cholinergic modulation

Other studies have shown that, apart from the dopaminergic neurotransmitter system, the cholinergic system is likely to be involved in the pathogenesis of

VH in PD (Perry and Perry, 1995). The cholinergic system plays an important role in awareness. A decrease in the cortical acetylcholine (ACh) 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 visual hallucinations can be induced by anti-cholinergics, while cholinesterase inhibitors (ChE-I) ameliorate cognitive dysfunction and VH in PD (Burn et al., 2006; Wesnes et al., 2005). The cholinergic innervation of the human cortex is derived from cholinergic cell groups in the basal forebrain. The nucleus basalis of Meynert (nbM) contains cholinergic neurons that project to the entire cerebral cortex, including primary and associative visual cortical regions (Mesulam and Geula, 1994). Hilker and colleagues have shown that non-demented PD patients have reduced acetylcholinesterase binding, reflecting reduced cholinergic activity, in occipital and temporal cortical regions, while PD patients with dementia (PDD) have a more extensive cholinergic deficit, especially in the middle temporal gyrus, compared to healthy controls (Hilker et al., 2005).

1.7 Brain imaging methods

1.7.1 Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI) is a tool to acquire detailed images of the human brain in vivo, making use of the magnetic properties of different tissues. Hydrogen atoms in the brain tissue align with the static magnetic field inside the scanner, called longitudinal magnetization. A dynamic magnetic field is subsequently applied in which hydrogen atoms are excited by radio frequency pulses in a direction perpendicular to the static magnetic field, called transverse magnetization. When the radio frequency is turned off, hydrogen atoms return to equilibrium, emitting energy that gives rise to the MRI signal. Recovery of the longitudinal signal (T1) or decay of the transverse signal (T2) can be measured, signal strength depending on tissue characteristics in which the atoms reside. Signal strength is also affected by changes in homogeneity of the local magnetic field due to changes in blood oxygenation (T2*), used in functional MRI (Huettel et al., 2004).

1.7.2 Basic principles of functional MRI

Functional MRI (fMRI) is a technique that uses magnetic properties of blood to determine indirectly which brain regions are active. When a certain brain region becomes activated, for example during a specific task, blood flow increases and oxygen rich blood (containing oxyhemoglobin) is supplied to this region, replacing the deoxygenated blood (containing deoxyhemoglobin). This response is called the hemodynamic response and can be measured over time: the Hemodynamic Response Function (HRF). For reasons unknown, more oxygenated blood is supplied than needed (Fox and Raichle, 1986), the so-called overshoot. So even when activated tissues use the supplied oxygen, the overshoot causes a local relative increase in oxygenated blood. Deoxyhemoglobin has paramagnetic properties, which means that it introduces inhomogeneity into the nearby magnetic field. Oxyhemoglobin, on the other hand, is weakly diamagnetic and has little effect on the local magnetic field, leading to an increased signal (Pauling and Coryell, 1936).

The fMRI signal that arises is an indirect measure of neuronal activity and is also called the Blood Oxygenation Level Dependent (BOLD) signal. Cerebral activation during a specific task is compared to another task or with baseline. Every 2-3 seconds whole brain volume images can be acquired, consisting of so-called voxels (volume pixels) of approximately 3 mm^3 . Voxels that show differences during a task condition can be displayed as a map (image) of t -values, using Statistical Parametric Mapping (SPM) (Friston et al., 1995).

1.8 Outline of the thesis

This thesis' topic is visual hallucinations (VH) in Parkinson's disease (PD). The main objectives of this thesis were to investigate: 1) the association between VH in PD and impairments of visual processing and attention and 2) cerebral functional organization underlying visual processing in PD patients with VH. In addition, the influence of pharmacological and non-pharmacological interventions on visual processing in PD and on VH in CBS, respectively, is explored.

This thesis is divided in two parts. In the first part (chapters 2, 3, 4 and 5), underlying mechanisms of VH in PD are investigated. In **chapter 2** we investigated visual perception of gradually revealed images and sustained attention in PD patients with VH, compared to PD patients without VH and to healthy controls. In **chapter 3** visual object and space perception was investigated in the same subjects. To gain further insight in underlying mechanisms of VH in

PD, we investigated cerebral activation patterns with fMRI before and during recognition of gradually revealed images in these patients, compared to PD patients without VH and to controls (**chapter 4**). In **chapter 5** we used Voxel Based Morphometry (VBM) to investigate whether the functional differences in PD patients with VH (from chapter 4) were associated with structural, i.e. grey matter volume, changes.

The second part (chapters 6, 7 and 8) focuses on therapeutic interventions in patients with VH. **Chapter 6** describes preliminary data on the effect of the cholinesterase-inhibitor rivastigmine on visual object processing in healthy controls. **Chapter 7** is a pilot study in which the effect of apomorphine on visual perception and attention in PD patients with VH is described. **Chapter 8** describes fMRI correlates of VH in one patient with CBS and the influence of repetitive transcranial magnetic stimulation (rTMS). In **chapter 9** the results of our clinical and imaging studies are discussed in a broader perspective, focusing on possible mechanisms of impaired visual perception and attention leading to VH in PD, using a functional network approach.