Visual hallucinations in Parkinson's disease
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Summary and conclusion
This thesis’ topic addresses underlying mechanisms of 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) the underlying functional cerebral architecture explored by fMRI using visual activation paradigms in PD patients with VH. In addition, we explored the influence of pharmacological and non-pharmacological interventions on visual processing in PD and on VH in CBS, respectively. The results of these clinical and imaging studies were discussed in a wider perspective in the previous chapter. In the following section the results of each objective will be summarized and briefly discussed.

Impaired visual processing and attention in PD with VH

In chapter 2 and 3 we investigated the hypothesis that VH in PD are associated with impaired visual perception and attention. Importantly, the patients that participated in these studies were matched for education level and executive functioning, which was an important strategy to exclude such confounding factors that might otherwise influence performance on tests of visual perception and attention. In chapter 2 visual processing of gradually revealed images of animals, objects and people and sustained attention was demonstrated to be significantly slower in PD patients with VH than both PD patients without VH and healthy controls. Although recognition was slower, all images were correctly recognized. In addition, PD patients with VH showed decreased sustained attention compared to PD patients without VH, while the latter performed worse than healthy controls. In chapter 3 visual object and space perception was investigated in the same subjects. PD patients with VH showed impairment of both object and space perception, although such impairment was only statistically significant for some subtests, when compared to PD patients without VH and healthy controls.

Impaired object and space perception in PD patients with VH was associated with a decrease of sustained visual attention, while slower image recognition in PD patients with VH was not. These clinical studies thus confirmed our hypothesis that VH in PD are indeed associated with deficits in visual processing and attention. Impairment of both object- and space perception suggests involvement of the parvo- as well as the magnocellular pathways to the ventral and dorsal visual streams, respectively (see chapter 9). We proposed that reduced speed of identifying distinct images emerging from visual noise in specifically PD patients with VH reflects impaired bottom-up processing in these patients. Hypothetically, this may lead to a higher demand on the top-down system, resulting in activation of visual images by a kind of over-
compensation, causing VH in PD.

**Functional and anatomical imaging in PD with VH**

To gain further insight in underlying mechanisms of VH in PD, we investigated cerebral activation patterns with fMRI before and during recognition of the described gradually revealed images in these patients, compared to PD patients without VH and controls (chapter 4). We started with the hypothesis that PD patients with VH would show reduced activations of ventral visual association cortices before image recognition complemented by compensatory frontal or parietal activations, reflecting increased top-down processing. We indeed demonstrated that PD patients with VH were characterized by a pattern of decreased activation of lateral occipital cortex and extrastriate temporal visual cortices before image recognition. Contrary to our initial ideas, reduced (instead of increased) activation in a wider network included the lateral prefrontal cortex which suggested that cortical regions involved in top-down processing are additionally impaired. No differences were seen between PD patients without VH and healthy controls, implying a specific association of activation changes with VH and not with PD in general. No arguments for compensatory increases of activation in PD patients with VH were found, and thus no support for a link between vulnerability for VH and increased reliance on top-down processing during visual perception. Because none of the participating subjects experienced VH during scanning, the gradually revealed images were an indirect way to measure functional cerebral impairments associated with VH. Although the ventral/lateral temporal cortex and part of the prefrontal cortex were relatively impaired in PD patients with VH, one may still assume that activation increases occur in these regions during VH in these patients. Joint activation of frontal and visual association cortices during VH was shown in one patient with PD and in schizophrenia (Kataoka et al. 2008, Silbersweig et al. 1995), while activation of ventral visual association cortices during VH was demonstrated in CBS (ffytche 1998). Thus, disease-related factors like impaired visual perception, reflected in cortical activation reductions are associated with VH in PD. Underlying these functional deficits may be grey matter volume changes (see below), deposition of Lewy bodies or decreased cholinergic innervation (see below).

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. In addition, we assessed possible grey matter differences between all PD patients and healthy
controls. In this study we have found no differences between PD patients with and without VH. However, grey matter decreases of bilateral prefrontal and parietal cortex, left anterior superior temporal and left middle occipital gyrus were found in the total group of PD patients, compared to controls. Most extensive grey matter volume reductions were found in the left parietal cortex in both non-demented patient groups, which was hemisphere-specific and independent of the side of PD symptoms. These results indicate that the functional deficits that we were able to identify in PD patients with VH are not associated with grey matter loss. Given the early stage of non-motor functional deterioration in our PD group with VH, functional deficit was regarded to possibly precede structural changes. We hypothesized that the strong left parietal reduction in both PD patient groups might reflect a secondary effect of basal ganglia disease, leading to impaired recruitment of internally guided motor programs and subsequent reduction of sustained skilled purposeful movements.

Pharmacological and non-pharmacological interventions

The second part of this thesis (chapters 6, 7 and 8) focused on therapeutic interventions in patients with VH. Chapter 6 described preliminary data of our follow-up study on cerebral activation during visual object processing from chapter 4. We hypothesized that the reduced activations in ventral/lateral visual association cortices in PD patients with VH, compared to both PD patients without VH and healthy controls, might result from decreased cholinergic input to these regions. This idea is consistent with the beneficial effects of cholinesterase-inhibitors, like rivastigmine, on VH in PD and PD dementia. Therefore, administration of rivastigmine was expected to ‘normalize’ occipital and temporal cortex activation during image perception in PD patients with VH. We assessed cerebral activation patterns with fMRI during image recognition in healthy controls and PD patients with VH in two sessions; one after administration of placebo and one after rivastigmine (double-blind, pseudo-randomized design). Healthy controls showed robust bilateral fusiform- and lingual gyri activation in both treatments, while rivastigmine (compared to placebo) resulted in activation increases of the superior frontal gyrus, anterior cingulate and insula. PD patients with VH showed less robust activation than controls, without significant differences between treatment conditions. However, non-significant activation increases after rivastigmine were seen in bilateral (para)hippocampus, posterior superior frontal gyrus and striate and extrastriate visual cortices. The latter may reflect ‘normalization’ of impaired visual cortex activation in PD with VH by rivastigmine. Extension of these preliminary data is necessary to confirm this effect. This study is ongoing.
Chapter 7 describes a small study investigating the effect of apomorphine on visual perception and attention in PD patients with VH. In our study, administration of apomorphine resulted in an increase of contrast sensitivity, possibly by stimulating retinal dopamine receptors, but prolonged reaction times in a selective attention task. These data may lead to the hypothesis that apomorphine improves VH in PD in some patients with mainly visual perceptive problems, but may also worsen VH in other patients, with mainly attentional impairments. In chapter 8, we describe a patient with a CBS-like syndrome due to retinal impairment, experiencing continuously present visual sensations of motion and colour. By instructing her to focus attention to 1) either one of these visual sensations or 2) a control condition during fMRI, we were able to discriminate cerebral activation patterns related to the two types of visual sensations. Activation patterns in motion-sensitive area V5 were subsequently used for neuronavigation to localize the position for rTMS. No clear effects were seen using inhibitory frequency rTMS, neither on V5 nor V1. Nevertheless, this study provided clear support for the concept that areas dedicated to visual motion and color processing were activated in a top-down fashion and that this procedure may help targeting for rTMS.

In chapter 9 the results of our clinical and imaging studies were discussed in a broader perspective, focusing on interacting mechanisms of impaired visual perception and attention possibly leading to VH in PD. In this respect, we followed a functional network approach, focussing on two basic principles of cerebral organization; 1) bottom-up and top-down processing and 2) modulation and selection within such processing streams, including the description of cortical and subcortical interactions. Interactions between and impairments in PD of such processing, modulation and selection of visual stimuli were described on a functional anatomical level, leading to a model on VH in PD that provides a starting point for future research topics concerning pathogenesis and treatment of VH in PD.

Final conclusions
VH in PD are associated with impaired visual processing and reduced attention. Reduced activation of visual association cortices before image recognition reflects vulnerability for VH in PD. The demonstrated functional deficits in PD patients with VH were not a result of grey matter volume loss, but might precede such anatomical change.