Chapter 5

Regional cortical grey matter loss in Parkinson’s disease without dementia is independent from visual hallucinations

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Accepted for publication in Movement Disorders
5.1 Abstract

In our previous fMRI study, Parkinson’s disease (PD) patients with visual hallucinations (VH) showed reduced activations in ventral/lateral visual association cortices preceding image recognition, compared to both PD patients without VH and healthy controls. The primary aim of the current study was to investigate whether functional deficits are associated with grey matter volume changes. In addition, possible grey matter differences between all PD patients and healthy controls were assessed.

Using 3 Tesla MRI and voxel-based morphometry (VBM), we found no differences between PD patients with \( n=11 \) and without VH \( n=13 \). However, grey matter decreases of the 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 \( n=14 \).

This indicates that previously demonstrated functional deficits in PD patients with VH are not associated with grey matter loss. The strong left parietal reduction in both non-demented patient groups was hemisphere-specific and independent of the side of PD symptoms.
5.2 Introduction

Parkinson’s disease (PD) primarily affects the substantia nigra including its striatum projections (Lang and Lozano, 1998). Classically, cortical pathology has received little attention in PD (Selby, 1968). More recently, structural abnormalities have been described, although inconsistent and mainly focussed on cognitive impairment (Schneider et al., 1979; Dagher and Nagano-Saito, 2007). Functional imaging in non-demented PD patients, however, has revealed more consistent cortical impairment, both in motor and visual domains (Dagher and Nagano-Saito, 2007; Ma et al., 2007). Using fMRI, we recently specified a relation between visual cortex function and VH in non-demented PD patients by demonstrating reduced extrastriate visual activations preceding image recognition (Meppelink et al., 2009).

Now we aimed to gain further insight in possible occipito-temporal pathology associated with such VH using 3 Tesla MRI and voxel-based morphometry (VBM). VBM allows determination of cortex density and/or volume changes without a regional bias. It has been used before by one other group to address this topic (Ramirez-Ruiz et al., 2007b; Ibarretxe-Bilbao et al., 2009), but using 1.5 Tesla MRI. We also compared all PD patients with healthy controls to see whether regional cortex atrophy would match previously described reduced regional metabolism in PD.

5.3 Methods

5.3.1 Subjects

The thirty-eight included subjects were previously studied with fMRI (Meppelink et al., 2009) and divided in three groups: PD patients with VH, experienced at least weekly during the last month (n=11), patients without VH (n=13) and healthy controls (n=14). Patients met the criteria of the UK PD Society Brain Bank. Cognition was assessed with the Mini Mental State Examination (MMSE) (Folstein et al., 1975) and the SCOPA-cog (SCales of Outcomes in PArkinson’s disease, cognition)(Marinus et al., 2003). Severity of motor symptoms was rated with the Unified Parkinson’s Disease Rating Scale (UPDRS), part III. Severity of VH and executive functioning were assessed with the Neuropsychiatric Inventory (B: “Hallucinations”) and the Frontal As-
assessment Battery (FAB) (Dubois et al., 2000), respectively. Exclusion criteria were dementia (MMSE <24), neurological disorders other than PD, psychiatric disorders, visual acuity below 50 percent and visual field defects. The local Medical Ethical Committee approved the study. Participants signed an informed consent.

5.3.2 Voxel-based Morphometry

MRI was performed with a 3 Tesla scanner (Philips, Best, NL) using a standard 6 channel SENSE head coil. T1 weighted 3D anatomical images were defined by isotropic voxels 1 x 1 x 1 mm, matrix 256 x 256 and axial orientation.


Images were spatially normalised (T1 template Montreal Neurological Institute, MNI) and segmented into grey matter, white matter and cerebrospinal fluid. Grey matter images were modulated and smoothed (10 FWHM). We used modulated grey matter images, because modulation takes into account the deformation field generated during spatial normalization. In this way, the total amount of grey matter remains the same as it would be in the original images and grey matter volume changes rather than concentration differences can be assessed.

5.3.3 Statistical analyses

MMSE, FAB and UPDRS-III scores for PD patients were not normally distributed and therefore compared using the Mann-Whitney test. Education levels, total SCOPA-cog and SCOPA-cog subscores were compared with the Kruskal-Wallis test. Normally distributed age differences were tested with ANOVA. Grey matter volume changes were assessed with ANOVA (flexible factorial, main effect factor ‘group’). Total grey matter was calculated per subject and used as covariate to remove variance due to differences in head size. We compared PD with and without VH with each other and to healthy controls, and all PD versus healthy controls. Initial threshold was p<0.001, voxel-level, uncorrected. Clusters were considered statistically significant at brain-volume corrected cluster-level p<0.05. In addition, ROI’s were defined
with Marsbar in SPM5, based on previously reported activation decreases in PD with VH in the left fusiform gyrus (LFG).

5.4 Results

No differences existed between the three groups regarding age (F=0.62, p=0.54), gender ($\chi^2=2.55$, p=0.28) and education level ($\chi^2=0.35$, p=0.84). Mean (SD) PD disease duration was 8.0 (4.7) in PD with VH and 7.9 (2.4) in PD without VH. PD groups were similar regarding MMSE scores (z=-1.45, p=0.15).

Total SCOPA-cog scores differed between groups ($\chi^2=9.0$, p=0.01), with verbal memory being the only significant subscore ($\chi^2=8.37$, p=0.02; attention: $\chi^2=0.81$, p=0.67; executive functioning: $\chi^2=2.63$, p=0.27; visuospatial: $\chi^2=0.18$, p=0.18). Mann-Whitney test revealed significant differences on verbal memory between PD with VH versus controls (z=-2.66, p=0.008). Differences were not significant between PD without VH versus either PD with VH (z=-1.66, p=0.10) or controls (z=-1.67, p=0.09). FAB-scores were lower in PD patients with VH, compared to patients without VH (z=-2.29, p=0.02). UPDRS-III scores did not differ (z=-0.70, p=0.48).

Voxel-based comparison between grey matter images of PD patients with VH and without VH did not show any differences between the two groups, ROI analysis of the LFG showed no differences either (data not shown). In comparison with healthy controls, however, each of the two PD patient groups, i.e. with or without VH, showed grey matter decreases in prefrontal, parietal and temporal cortices (Fig.5.1B,C).

The combined PD group (=PDtotal) showed grey matter reductions in prefrontal and parietal cortices (bilaterally), the left temporal lobe, left middle occipital gyrus and right (pre-) Supplementary Motor Area (SMA) (Fig.5.1A). Table 5.1 reports significant regions of grey matter decrease (p<0.05, cluster-level, brain-volume corrected).

Parietal grey matter reductions were most apparent in the left hemisphere (Fig.5.1, Table 5.1). In order to explore a possible relation with contralateral symptom dominance, a PD symptom lateralization index was calculated defined by negative values for left-sided dominance, positive values for right dominance and zero for absent lateralization. Adding this index as a covariate in the analysis had no effect on the results, indicating that the observed lateralization was hemisphere-specific, independent from the side of symptom dominance. Because PD patients with and without VH differed on the FAB-
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Figure 5.1: Regional cortical grey matter changes in PD patients. Grey matter reductions in PDtotal, compared to healthy controls (A), PD without VH, compared to healthy controls (B) and PD with VH, compared to healthy controls (C) at a threshold of p < 0.001 (uncorrected), k=20. Regional grey matter reductions are rendered on a standard MNI brain. R = right, P = posterior.

scores, these were also added as a covariate, without effect on SPM results either.

5.5 Discussion

5.5.1 Equal grey matter in PD with and without VH

Reduced cortical grey matter volume was a general PD characteristic, without differences between patients with or without VH. This indicates that the functional differences we previously found between these two patient groups, i.e. reduced activation of ventral/lateral extrastriate visual cortices in PD with VH
Table 5.1: Demographic and illness characteristics of PD patients with visual hallucinations (PD + VH; n=14), PD patients without VH (PD - VH; n=14) and healthy controls (HC; n=14)
(Meppelink et al., 2009), were not associated with local cortical atrophy. This seeming discrepancy with Ramirez-Ruiz and colleagues, who associated VH in PD with grey matter reductions in the lingual gyrus and superior parietal lobe (Ramirez-Ruiz et al., 2007b), is likely explained by the advanced disease stage in their study. Although they included Hoehn and Yahr stage as a covariate in their analysis, this only corrects for differences between their two PD groups and not between their patients and ours. VH-related functional impairment without anatomy changes in our patients suggests specific neurochemical deficits preceding structural changes. Cholinergic deficit might be considered in this respect, possibly causing impaired selection of subcortical information streams, subsequently predisposing to hallucinations (Perry and Perry, 1995). Higher density of Lewy bodies in the temporal lobe might also play a role (Harding et al., 2002).

In non-demented PD patients, VH have been associated with cognitive impairment (Fenelon et al., 2000; Williams and Lees, 2005; Imamura et al., 2007; Ramirez-Ruiz et al., 2007a; Meppelink et al., 2008) and may predict dementia (Aarsland et al., 2003; Santangelo et al., 2007). In pathologically proven PD, VH were an initial milestone of advanced disease independent from disease duration (Kempster et al., 2007). The association between VH and cognitive decline in PD is consistent with enhanced brain atrophy in PD patients with VH, particularly when dementia follows (Ibarretxe-Bilbao et al., 2009). In this respect, our PD patients with VH might show cognitive impairment and atrophy in follow-up assessments.

### 5.5.2 Grey matter reductions in PD

Although we saw no grey matter differences between the two non-demented PD patient groups, PDTotal showed grey matter reductions in specific parietal, temporal, occipital and frontal regions, compared to healthy controls. These reductions were more extensive than previously described, possibly explained by higher sensitivity of 3 Tesla imaging. Frontal and temporal cortex atrophy in non-demented PD patients has been described before with 1.5 Tesla MRI (Burton et al., 2004; Ramirez-Ruiz et al., 2007b; Pereira et al., 2009; Summerfield et al., 2005; Beyer et al., 2007; Tir et al., 2009), but not consistently (Nagano-Saito et al., 2005; Feldmann et al., 2008) and depending on cognitive impairment (Nagano-Saito et al., 2005) or depression (Feldmann et al., 2008). Medial frontal atrophy in our study particularly concerned the rostral (or pre-) SMA, which is consistent with functional cortical impairment in PD.
due to loss of basal ganglia-thalamus output (Playford et al., 1992; Cunning-
ton et al., 2001). Associated frontal and parietal grey matter reductions may
further reflect impaired neuronal circuitry implicated in both motor- and cog-
nITIVE functions (de Jong et al., 1996; Ma et al., 2007; Huang et al., 2007).

To explain cortical volume reduction, a first consideration is disease-inflicted
cell loss. This might e.g. be a consequence of α-synuclein pathology (Jellinger,
2009b), although subsequent cortical Lewy body deposition in non-demented
PD remains an issue of debate (Jellinger, 2009a; Braak et al., 2004, 2005;
Colosimo et al., 2003; Parkkinen et al., 2008). Tissue pathology, however,
does not explain the left-sided predominance of parietal atrophy we found be-
cause it was not contralateral to the side of dominant symptoms. Volume
reduction might alternatively be a dynamic consequence of reduced neuronal
activity, leading to reduced dendritic spine volume or astroglial volume reduc-
tion (Draganski et al., 2004). The opposite effect, i.e. action-induced volume
increase, has been demonstrated (Draganski and May, 2008).

Bilateral parietal atrophy in PD has been described before, also with left-sided
dominance (Pereira et al., 2009). To provide a functional explanation for left-
sided parietal atrophy, possible associations between parietal motor functions
(Binkofski et al., 1999) and PD symptoms need to be considered. Left parietal
processing of body scheme- or self-referenced (motor) information subserves
prehension (Binkofski et al., 1999; de Jong et al., 2001) and contributes to the
initiation of new motor programs (de Jong et al., 1999, 2001), while deficit may
result in ideomotor apraxia (Wheaton and Hallett, 2007). Although apraxia is
not a key symptom of PD, reduced internally-driven performance would fit the
hypothesis of ‘de-learning’ skilled movements in PD. Atrophy would thus be
secondary to reduced purposeful action, in which a general intentional drive
is impaired due to basal ganglia disease. Such dynamic volume change has
been demonstrated by the opposite effect: grey matter of visual motion area
MT/V5 and the left parietal cortex thickens after learning a new skill such as
juggling (Draganski et al., 2004); left frontoparietal cortex volume enlarges in
skilled golfers (Jancke et al., 2009). Finally, although PD patients, especially
those with VH, scored lower at the verbal memory subtask of the SCOPA-cog,
we regard it unlikely that the left lateralized parietal atrophy reflects impair-
ment of language-related function.
5.6 Conclusions

Compared to healthy controls, gray matter was equally reduced in PD patients with and without VH, indicating that previously found VH-related functional deficits in these patients were not associated with detectable anatomical changes. Hemisphere-specific left parietal atrophy in PDtotal might reflect a secondary effect of basal ganglia disease, leading to impaired recruitment of internally guided motor programs.

5.7 Acknowledgements

We would like to thank professor K.L. Leenders for critically reading previous versions of this manuscript.