Understanding cognitive heterogeneity in Parkinson's disease:

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Chapter 7

Gray matter differences contribute to variation in cognitive performance in Parkinson's disease

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ABSTRACT

A substantial proportion of patients with Parkinson's disease (PD) suffers from cognitive deficits, although there is a large variability in the severity of these impairments. While the cognitive deficits are often attributed to monoaminergic changes, there is evidence that alterations in structural brain volume also play a role. The aim of our study was to gain more insight into the variability of cognitive performance among PD patients by examining the relation between regional gray matter (GM) volume and cognitive performance.

We performed linear regression analyses between task performance and GM volume for six neuropsychological tasks within a group of 93 PD patients, and additionally compared them at a group level with matched healthy controls, using voxel-based morphometry (VBM).

Our most important findings were positive correlations between GM volume and cognitive performance for 1) parahippocampal gyrus and verbal memory, 2) medial temporal lobe and putamen and visuospatial memory, and 3) middle temporal gyrus and frontal lobe and verbal fluency. In addition, we found decreased GM volume in the frontal, parietal, and temporal cortices of PD patients compared with matched healthy controls.

We argue that the large variability in cognitive function across PD patients is partly mediated by GM volume differences in the implicated areas. Volume differences in these brain regions do not discriminate between patients and controls but explain cognitive variation within the patient population.

INTRODUCTION

Patients with Parkinson's disease (PD) often suffer from a variety of non-motor symptoms, such as neuropsychiatric disorders, sleep disturbances, and cognitive impairments [84]. There is, however, a large variability between PD patients in the severity of the cognitive deficits that include impairments in executive functions, memory and visuospatial functions [12, 14]. They are thought to arise from hypo-excitation of cortical and sub-cortical areas as a result of degeneration of monoaminergic nuclei in the brainstem [32]. Functional magnetic resonance imaging (fMRI) studies investigating executive dysfunction in PD have confirmed this theory by showing that deficits on planning and working memory tasks correlate with decreased activation of frontal-striatal areas [93]. Although the neurochemical substrates of the memory and visuospatial deficits are less well-formulated, cholinergic, serotonergic, and noradrenergic dysfunction appear to contribute [41, 261].

There is, however, accumulating evidence that besides functional changes in monoaminergic systems, morphological changes in the gray matter (GM) may also contribute to the cognitive deficits [262]. A valid method to investigate the relationship between cognitive functioning and regional volume changes in GM is voxel-based morphometry (VBM) [263]. VBM is an operator-independent, whole-brain voxel-based tool that can detect regional structural differences. Although the areas reported in previous VBM studies comparing groups of PD patients with healthy controls vary greatly across investigations, a consistent finding is that increased cognitive dysfunction and disease severity are associated with more pronounced GM atrophy [51, 54]. Pan and colleagues [264] performed a voxel-wise meta-analysis of 17 VBM studies comparing PD patients with healthy controls and found consistent GM volume decreases in the left inferior frontal gyrus, left superior temporal gyrus, and left insula. Ibarretxe-Bilbao and colleagues [262] reviewed studies that related GM volume changes with neuropsychological task performance in PD patients. They concluded that a correlation between memory deficits and medial temporal lobe volume loss was the most consistent finding, but that data involving other cognitive domains (e.g. visuospatial or executive functioning) were inconclusive. Both review articles attributed the discrepancies in the available literature to methodological issues, including 1) heterogeneity in clinical characteristics of the patient populations studied (e.g. disease severity or depression, 2) inconsistency in controlling for potential confounding factors, such as age, gender, and education, and 3) a lack of statistical power, due to relatively small sample sizes.

In summary, there is a large variability in cognitive performance among PD patients that might be related to differences in GM volume. This individual variabil-

ity, however, is lost in a comparison with healthy controls at a group level. We therefore investigated the relation between regional GM volume and task performance for six different neuropsychological tasks within a cohort of 93 PD patients. We expected a positive correlation between verbal memory performance and hippocampal volume, between visuospatial memory performance and parietal and temporal volume, and between executive performance and volumes of the frontal-striatal areas. We additionally compared regional GM volume between PD patients and matched healthy controls on a group level, to investigate whether task performance-related brain areas within the group of PD patients overlapped with between group differences in regional GM volume. We expected to find GM volume reductions in the temporal, insular, and frontal areas [264].

METHODS

Participants

Data were obtained from 93 PD patients of the outpatient clinic for Movement Disorders at the VU University Medical Center (VUmc), Amsterdam, The Netherlands. The MRI scans, neuropsychological and clinical assessments used in this study were obtained as part of the routine diagnostic medical evaluation. All patients fulfilled the UK PD Brain Bank criteria [100] and gave a written informed consent to store and use their medical information for scientific research. Of the 93 PD patients, 75 patients did not show evident cognitive impairments, 8 patients fulfilled the criteria for mild cognitive impairment (MCI), and 4 patients were diagnosed with Parkinson's disease dementia (PDD). Six patients were not classified. Educational level was categorized according to a Dutch classification system (Verhage system) consisting of 7 categories ranging from 1 (did not finish primary school) to 7 (university degree) [265]. Disease stage and severity of motor symptoms were assessed using the modified Hoehn and Yahr scale [102] and the Unified Parkinson's Disease Rating Scale (UPDRS-III) [101] respectively. Levodopa equivalent daily dose (LEDD) was calculated as described elsewhere [73]. Depressive symptoms and anxiety were assessed using the Beck Depression Inventory (BDI) [266] and Beck Anxiety Inventory (BAI) [106], respectively.

A sample of forty-six healthy controls was selected from parallel studies performed at the VUmc using the same MRI scanner to match our sample of PD patients with respect to age and gender. Due to the retrospective nature of the study, the neuropsychological test scores were only obtained for the PD patients, not for the healthy controls. The study was approved by the local ethics committee of the VUmc.

Neuropsychological assessment

We used both the total immediate and the delayed recall score (30 minutes after the last immediate recall trial) of the Dutch version of the Rey Auditory Verbal Learning Task (RAVLT) [267] to assess verbal memory. We assessed visuospatial memory by using the 3 minutes delayed recall condition on the Rey-Osterrieth Complex Figure Test (ROCFT) [268], while excluding the immediate copy condition due to ceiling effects. Four tasks were used to assess distinct aspects of executive functioning. Interference susceptibility was measured by the mean time needed for card III of the Stroop Color-Word Test [269] minus the average completion time of Card I (speed of word reading) and II (speed of color naming). For the Trail Making Test (TMT) [270] we subtracted the completion time on TMT-A from the completion time of TMT-B (TMTB-A) [271]. Semantic verbal fluency performance was measured using a categoric word fluency task (naming as many "animals" as possible in 60 seconds), and phonemic verbal fluency with a letter fluency task (naming as many words in 60 seconds starting with a D, A, and T respectively). The summed score of the three trials was used to assess phonemic verbal fluency.

Missing values for the neuropsychological tests were due to insufficient time, motor and speech difficulties, fatigue, lack of motivation, or language problems.

MRI acquisition and preprocessing

All MRI scans were acquired using a GE Signa HDxt 3.0 T MRI-scanner (General Electric, Milwaukee, Wisconsin, USA) with an 8-channel head coil. Structural images were obtained using a sagittal 3-dimensional gradient-echo T1-weighted sequence (matrix = 256 x 256; field of view = 25 cm; slice thickness = 1 mm; voxel size = 1 x 0.98 x 0.98 mm; TR = 7.8 ms; TE = 3.0 ms; view angle = 12º).

Imaging data were preprocessed using VBM in SPM8 (Wellcome Trust Centre for Neuroimaging, University College London; http://www.fil.ion.ucl.ac.uk/spm). Scans were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), and transformed to DARTEL space, using 'New Segment' with 30 mm bias full width at half-maximum. For each of the six neuropsychological tests, and for the comparison with the healthy controls, a separate group-specific template was created using DARTEL default settings [272] and flow fields were calculated accordingly. Next, the templates were normalized by warping them to MNI stereotactic space (Montreal Neurological Institute), modulated, and smoothed using a 10 mm Gaussian kernel.

Statistical analyses and covariates

TMTB-A scores and Stroop interference scores were log-transformed and the RAVLT delayed recall scores were square root-transformed to correct the non-normal distribution.

Voxel-wise whole-brain regression analyses were performed using the GM images as criterion variable and neuropsychological test scores as predictor variable. We included age, gender, education (entered as a dummy variable; low educational level, Verhage 1-5, and high educational level, Verhage 6-7), and total GM volume as covariates in all our VBM regression analyses within the PD group. No disease related covariates were included, since their addition to the standard four covariates only marginally enhanced the prediction of the test scores.

Using a 2-sample t-test analysis, with total GM volume as covariate, we studied regional volume differences between PD patients and the healthy controls.

Our statistical threshold was set at $p < .001$ (uncorrected) to avoid false-negative findings, and we used an extent threshold of 50 voxels and absolute masking at a threshold of 0.2 to correct for false-positive findings. Regression coefficients and corresponding p-values were calculated and displayed in Statistical Parametric Maps, from which the peak-voxel values were extracted. These were used to correlate GM volume with the cognitive test scores in SPSS 15.0 (SPSS, Chicago, IL, USA). Brain regions were identified using the WFU-Pick Atlas [151].

Table 7.1: Demographic and clinical characteristics of the whole PD and HC study population, and of the PD sub-groups per neuropsychological task

	PD Total	RAVLT	ROCFT	Stroop Interference	TMTB-A	Category Fluency	Letter Fluency	HC
Number of patients	93	88	83	86	79	85	80	46
Age (years, range)*	63 ± 10 (27-88)	63 ± 10 (27-88)	62 ± 10 (27-88)	62 ± 10 (27-88)	62 ± 10 (27-88)	63 ± 11 (27-88)	62 ± 10 (27-84)	61 ± 8 (47-77)
Gender (male), n (%)**	61 (65.6%)	56 (63.6%)	53 (63.9%)	54 (62.8%)	48 (60.8%)	56 (65.9%)	52 (65.0%)	28 (61%)
UPDRS-III	24.5 ± 10.3	24.2 ± 9.6	23.4 ± 9.2	24.0 ± 9.6	24.1 ± 9.7	24.7 ± 9.9	23.9 ± 9.6	NA
H&Y stage	2.0 (1.0-4.0)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (1.0-4.0)	2.0 (1.0-3.0)	NA
DRP, n (%)	32 (34.4%)	30 (34.1%)	27 (32.5%)	29 (33.7%)	28 (35.4%)	27 (31.8%)	26 (32.5%)	NA
LEDD, (mg/day)[a]	509 (100-1590)	492 (100-1590)	522 (150-1590)	495 (100-1590)	509 (150-1590)	525 (100-1590)	489 (100-1590)	NA
Education[b]	5 (1-7)	5 (1-7)	5 (1-7)	5 (1-7)	5 (2-7)	5 (1-7)	6 (1-7)	NO
BDI	8 (0-32)	8 (0-28)	8 (0-28)	8 (0-28)	8 (0-28)	8 (0-26)	8 (0-28)	NO
BAI	10 (0-45)	10 (0-45)	10 (0-45)	10 (0-45)	11 (1-45)	10 (0-45)	10 (0-45)	NO
Total GM (ml)	723 ± 72	721 ± 74	723 ± 75	717 ± 73	722 ± 76	724 ± 75	724 ± 72	706 ± 68

Values are presented as mean ± SD or median (range) unless otherwise indicated

* Two-sample t-test (PD total vs HC; p = .23)

** Pearson's chi-squared test (PD total vs HC; p = .58)

[a] Average is calculated for patients that were using dopaminergic medication

[b] Using a 7-point scale, 1 indicates did not finish primary school, 7 indicates university degree

UPDRS Unified Parkinson's Disease Rating scale, *H&Y stage* Hoehn and Yahr stage, *DRP* Dopamine replacement therapy, *LEDD* Levodopa Equivalency Daily Dose, *BDI* Beck Depression Inventory, *BAI* Beck Anxiety Inventory, *GM* gray matter volume, *RAVLT* Rey Auditory Verbal Learning Test, *ROCFT* Rey-Osterrieth Complex Figure Test, *TMT* Trail Making Test, *HC* Healthy Controls

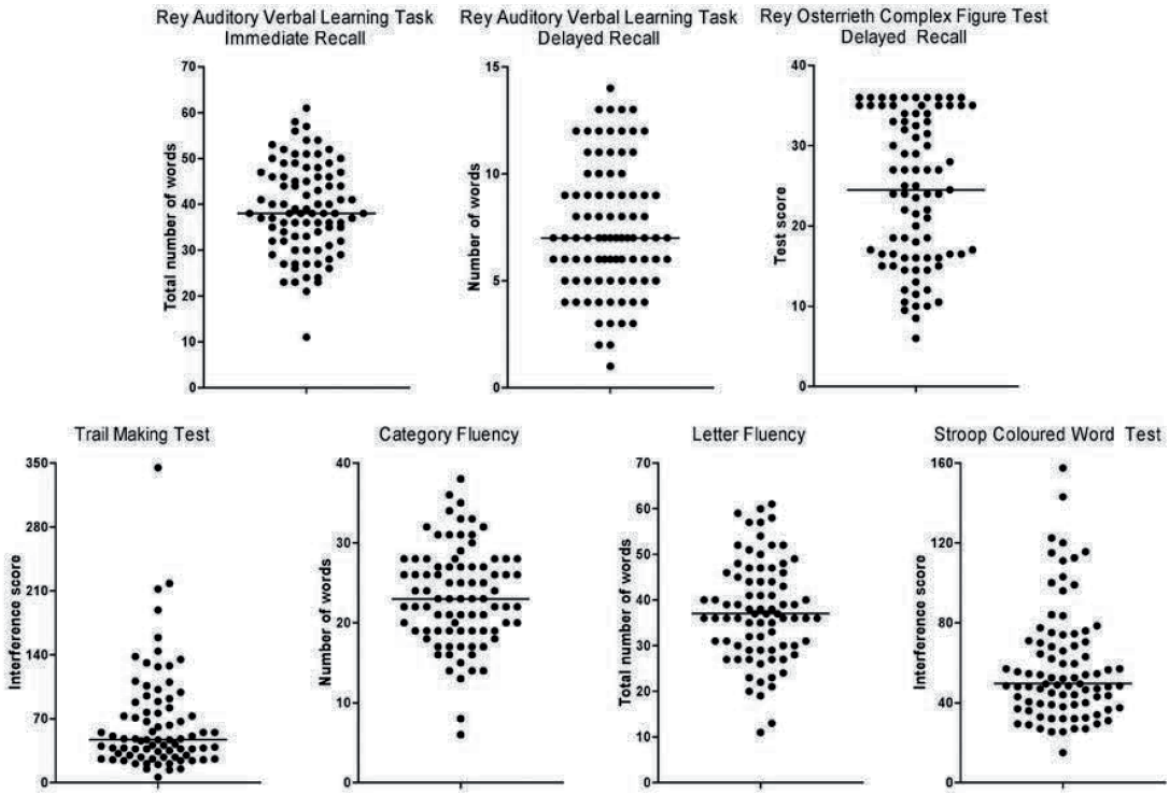

Figure 7.1 Raw test scores per neuropsychological task
The horizontal line represents the median test score

RESULTS

Within-group regression analyses

Demographic and clinical characteristics per task are summarized in Table 7.1 and the raw test scores per neuropsychological task are depicted in Figure 7.1.

Visuospatial memory and learning

We found a positive correlation between ROCFT recall scores and GM volume in the left and right middle temporal gyri, right putamen and globus pallidus and right post-central gyrus (Table 7.2; Figure 7.2, panel a).

We found a positive correlation between the total immediate recall scores on the RAVLT test and GM volume of the right parahippocampal gyrus and left occipital lobe (Table 7.2; Figure 7.2, panel b), and for the delayed recall an association with GM volume in the left precuneus and the right parahippocampal gyrus (Table 7.2; Figure 7.2, panel c).

Executive functioning

Performance on the Category Fluency task correlated positively with GM volume in the left orbital and left middle temporal gyrus (Table 7.2; Figure 7.2, panel d), and performance on the Letter Fluency task correlated positively with GM volume in the right parahippocampal gyrus and right superior frontal gyrus (Table 7.2; Figure 7.2, panel e).

Performance on the TMT correlated positively with GM volume in the right inferior parietal lobe (Table 7.2; Figure 7.2, panel f). No significant correlations were found for task performance on the Stroop task and regional GM volume.

Between-group comparison

The group comparison between our total sample of PD patients and matched healthy controls (see Table 7.1 for demographics), showed significant GM volume reductions in the right inferior parietal lobe, right inferior and middle temporal lobe, left precentral gyrus, right superior and middle frontal gyrus, and right cerebellum in patients compared with controls (Table 7.2; Figure 7.2, panel g).

Table 7.2 Summary of the results from the linear regression analyses and from the comparison between healthy controls and Parkinson's disease patients.

Cluster size (voxels)	*T*	r	Peak coordinates (MNI)			Brain region
			X	Y	Z	
Correlations with ROCFT recall scores (corrected for tGM, gender, education, age)						
156	4.07	.38	-44	-59	1	L middle temporal gyrus
735	3.61	.34	22	4	-4	R putamen + globus pallidus
256	3.50	.33	51	-11	43	R post central gyrus
258	3.32	.32	54	-26	-6	R middle temporal gyrus
Correlations with RAVLT total immediate recall scores (corrected for tGM, gender, education, age)						
549	4.61	.39	38	-26	-15	R hippocampal gyrus
312	3.83	.33	-15	-89	-8	L occipital lobe / lingual gyrus
Correlations with RAVLT delayed recall scores (corrected for tGM, gender, education, age)						
679	3.86	.31	-19	-66	27	L precuneus
87	3.49	.31	38	-28	-13	R hippocampal gyrus
Correlations with Stroop Interference scores (corrected for tGM, gender, education, age)						
No significant results						
Correlations with TMTB-A scores (corrected for tGM, gender, education, age)						
190	3.72	-.34	55	-44	43	R inferior parietal lobe

Cluster size (voxels)	*T*	r	Peak coordinates (MNI)			Brain region
			X	Y	Z	
Correlations with Category Fluency scores (corrected for tGM, gender, education, age)						
100	3.77	.31	-11	29	-26	L rectal gyrus
449	3.28	.34	-64	-42	1	L middle temporal gyrus
Correlations with Letter Fluency scores (corrected for tGM, gender, education, age)						
63	3.63	.36	36	-26	-20	R parahippocampal gyrus
78	3.38	.34	7	52	31	R superior frontal gyrus
HC > PD (corrected for tGM)						
415	4.14	NA	38	-64	40	R inferior parietal lobe
1072	3.97	NA	62	-21	-23	R inferior temporal gyrus
772	3.95	NA	-47	-8	49	L precentral gyrus
639	3.77	NA	62	-56	-9	R inferior temporal gyrus
715	3.50	NA	6	21	61	R superior frontal gyrus
50	3.48	NA	29	35	46	R middle frontal gyrus
126	3.46	NA	59	9	-21	R middle temporal gyrus
287	3.45	NA	26	-87	-39	R posterior cerebellum
PD > HC (corrected for tGM)						
No significant results						

Results depicted $p_{uncorr} < .001$, extent threshold 50 voxels
T = t-statistic
r = Pearson's correlation coefficient
tGM total gray matter volume, *RAVLT* Rey Auditory Verbal Learning Test, *ROCFT* Rey-Osterrieth Complex Figure Test, *TMT* Trail Making Test, *PD* Parkinson's disease, *HC* healthy controls, *NA* not applicable

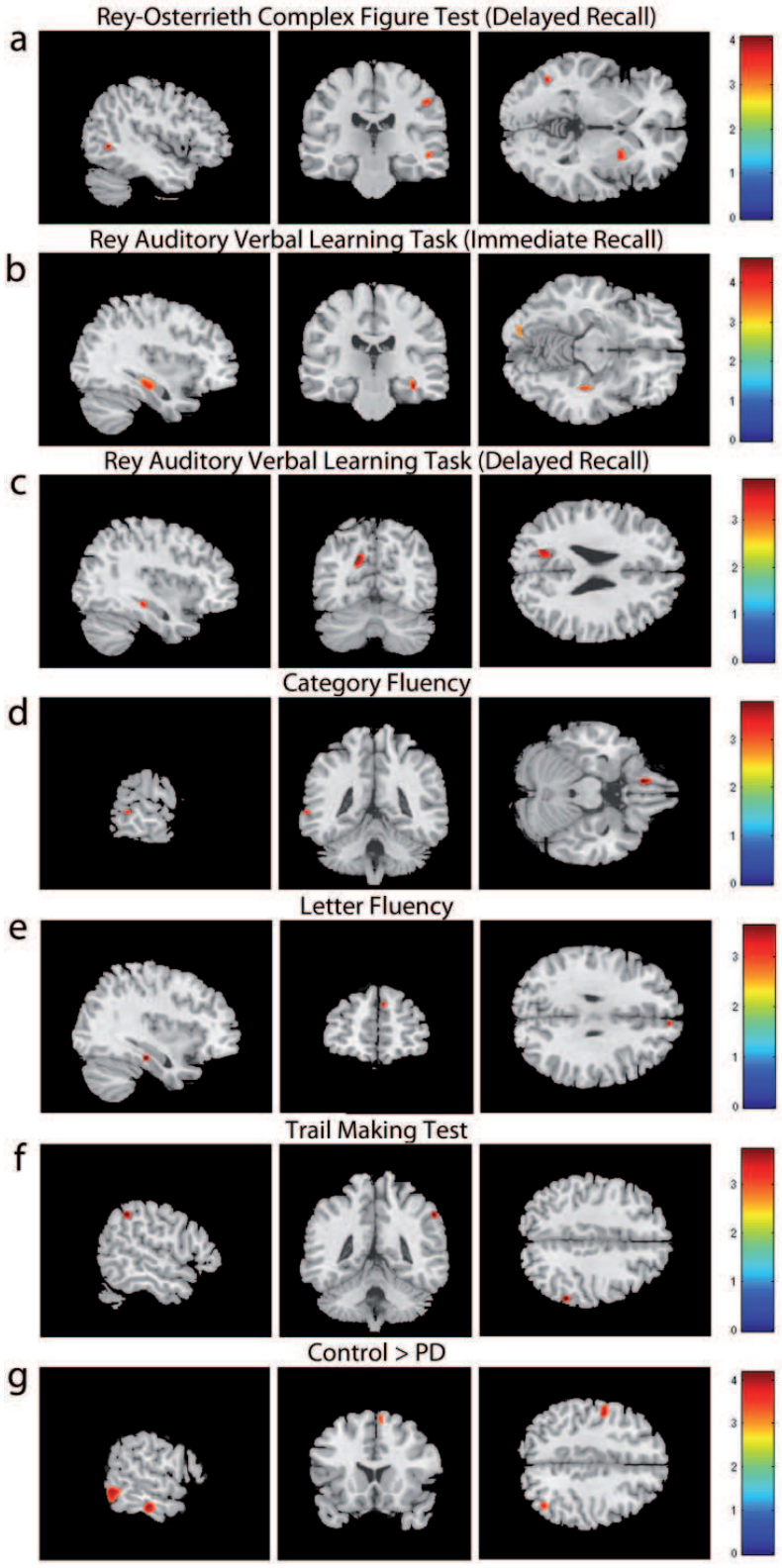

Figure 7.2 Results from the linear regression analyses between neuropsychological test scores and gray matter volume within the Parkinson's disease patients group, and of the gray matter volume comparison between the healthy controls and Parkinson's disease patients
The coloured bar indicates the Z-values

DISCUSSION

In this VBM study we investigated cognitive heterogeneity within a large group of PD patients. We found that the variation in cognitive function was associated with differences in GM volume of the implicated brain regions and that these variations do not overlap with brain regions showing volume differences between patients and controls.

The relation between learning, for both immediate and delayed recall, and medial temporal lobe volume has been consistently described in previous studies in PD patients [262]. In this study we found a correlation between right parahippocampal volume and verbal memory, although classically the left hippocampus is most strongly associated with verbal learning [273]. The relationship between occipital cortex and precuneus volume and immediate and delayed recall, respectively, was unexpected. Both brain areas are implicated in memory function, but mainly in visual and episodic memory [274, 275].

We found a positive correlation between visuospatial memory performance and GM volume of the left and right middle temporal gyri. The absence of a correlation with parietal volumes might be explained by the fact that this task relies more strongly on memory than on visuospatial construction. The correlation between visuospatial memory and putamen/pallidum volume was unexpected. Muslimovic and colleagues [14] tested a large group of PD patients neuropsychologically and argued that visuospatial task performance is influenced by executive functions. This fits our results, since both putamen and pallidum are implicated in executive functions [32]. Volume differences in these structures may thus contribute to variation in visuospatial memory performance.

When correlating response inhibition performance with GM volume, no effects passed the statistical threshold. This might be explained by the high correlations between age, GM volume, and task performance. By including age into our regression model, we might have also removed unique variance from GM volume and task performance, thus masking a potential effect of interest.

We found a positive correlation between performance on the letter fluency task and GM volume in the right superior frontal and parahippocampal gyrus, which is in line with studies in healthy controls [276] and patients [277, 278]. We furthermore found a positive correlation between performance on the category word fluency task and GM volume in the left middle temporal and rectal gyrus, replicating findings from a previous VBM study in PD patients [279]. Decreased cognitive flexibility correlated with decreased GM volume in the right inferior parietal lobe. This finding fits recent neuroimaging studies that show the importance of non-frontal areas, such as the parietal lobe, for intact executive functions [280].

We found, as hypothesized, areas of lower GM volume in the right parietal, temporal, and frontal areas when comparing our PD group with healthy controls [264]. The areas showing group differences were relatively small, which is in accordance with other studies that compared PD patients with a similar cognitive status [51, 54] and disease severity [46, 281] with matched healthy controls.

We found that in PD patients, better performance on the neuropsychological tasks was associated with larger GM volume in the middle and medial temporal lobe, putamen/pallidum, parietal, and prefrontal cortex. PD patients perform, on average, lower on tasks that measure executive functions, memory, and visuospatial tasks in comparison to matched healthy controls. There is, however, a large variability in cognitive performance between PD patients [12]. Cognitive deficits are believed to arise from monoaminergic changes in, most notably, the striatum and the hippocampus. Although we did not find reduced GM volume in the hippocampus or putamen in the comparison between PD patients and healthy controls, our task performance-related correlations indicate that (medial) temporal and putaminal GM volume may contribute to the level of cognitive performance within the group of PD patients. Although temporal volume differences between patients and controls do not exactly overlap with the temporal regions showing a volume relationship with cognitive performance, one might theorize that volume loss in these areas can interfere with the task performance-related areas and thus contribute to cognitive deficits. We hypothesize that patients with greater GM volumes in these areas may have an advantage by way of greater cognitive reserve and would therefore display less cognitive deficits.

Our study has some limitations. The first is the lack of neuropsychological test data of the control group. Although PD patients, as a rule, score lower on these tasks than healthy controls [14] we were in the current setup not able to make statements on the specificity of the correlations for PD between test scores and GM volume. A second limitation is more general to this type of studies. The multicolinearity between different covariates, such as age, gender, education, and test performance with GM volume makes it difficult to assess the influence of each of these covariates on the dependent variable [282]. By including all of these covariates in our regression analyses we may have been overly conservative. We believe, however, that this strictness renders our eventual findings more robust and reliable.

In conclusion, we suggest that variation in cognitive functioning in PD can, at least partly, be explained by differences in GM volume of implicated brain regions and that these variations in regional GM volume are subtle and do not differentiate between patients and controls.