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Chapter 2

Compensatory fronto-parietal hyperactivation during set-shifting in unmedicated patients with Parkinson's disease

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ABSTRACT

Patients with Parkinson's disease (PD) often suffer from impairments in executive functions, such as mental rigidity, which can be measured as impaired set-shifting. Previous studies have shown that set-shifting deficits in patients with PD result from hypo-excitation of the caudate nucleus and lateral prefrontal cortices. The results of these studies may have been influenced by the inclusion of patients on dopaminergic medication, and by choosing set-shifting paradigms in which performance also depends on other cognitive mechanisms, such as matching-to-sample. To circumvent these potential confounding factors, we tested patients with PD that were not on dopamine replacement therapy, and we developed a new feedback-based paradigm to measure the cognitive construct set-shifting more accurately. In this case-control study, eighteen patients with PD and 35 well-matched healthy controls performed the set-shifting task, while task-related neural activation was recorded using functional magnetic resonance imaging. Behaviourally, PD patients, compared with healthy controls, made more errors during repeat trials, but not set-shift trials. The patients, compared with controls, showed increased task-related activation of the bilateral inferior parietal cortex, and the right superior frontal gyrus, and decreased activation of the right ventrolateral prefrontal cortex during set-shift trials. Our findings suggest that, despite decreased task-related activation of the right ventrolateral prefrontal cortex, these early-stage unmedicated patients with PD do not yet suffer from set-shifting deficits due to compensatory hyperactivation in the inferior parietal cortex and the superior frontal gyrus.

INTRODUCTION

Patients suffering from Parkinson's disease (PD) often show non-motor symptoms apart from their characteristic motor symptoms (i.e. bradykinesia, hypokinesia, rigidity, postural instability, and resting tremor) [3]. These non-motor symptoms include autonomic disturbances, neuropsychiatric symptoms, sleep disturbances, and cognitive impairments [11, 84]. Both motor and non-motor symptoms result from neuronal degeneration inflicted by α-synuclein pathology, [9] which severely affects, among others, the dopamine producing neurons in the substantia nigra pars compacta. This results in a decreased excitation of the striatum and the interconnected frontal-striatal circuits [32]. The fronto-striatal hypo-excitation presumably underlies the impairments in executive functions, such as mental rigidity, that are frequently present in patients with PD [14, 33, 93]. The cognitive construct mental rigidity is often measured using feedback-based set-shifting paradigms, such as the Wisconsin Card Sorting Task (WCST) [94].

Although set-shifting is usually associated with frontal lobe function, recent neuro-imaging studies have emphasized the involvement of parietal areas and the fronto-parietal network [95, 96]. There is, however, inconsistency across studies as to the involvement of the striatum and the anterior cingulate in set-shifting. Recent findings by Witt and Stevens [97] suggest that the involvement of these areas depends on paradigm design aspects, such as stimulus complexity, and not set-shifting *per se*. However, the participants in this study were young and healthy and it is unknown whether these results generalize to an older, or neurologically affected, population.

Monchi and colleagues applied a modified version of the WCST to investigate the neural substrate of the set-shifting deficits in PD patients [93, 98]. They found that patients, compared with healthy controls, made more errors during set-shift trials, and that these errors were associated with reduced recruitment of fronto-striatal areas, such as the caudate nucleus, the ventrolateral prefrontal cortex (VLPFC) and the dorsolateral prefrontal cortex (DLPFC) [93].

The literature has noted two potential confounding factors when attempting to investigate the neural substrate of set-shifting deficits in PD patients. First, paradigms designed to measure set-shifting may require other cognitive functions, such as matching-to-sample, visuospatial learning, working memory, and set formation [99]. Second, Cools and colleagues demonstrated that dopaminergic medication in patients with PD may alleviate impairments in set-shifting, presumably by increasing dopamine levels in the dorsal striatum [36]. To avoid this potentially confounding medication effect, patients may be tested during an OFF phase, i.e. when the most recent dose of dopaminergic medication was given a number of hours prior

to the investigation. This solution, however, also provides difficulties, as dopamine agonists and/or levodopa have long-lasting effects due to their long half-life [82, 83] and withdrawal can cause physical (e.g., rigidity, hypokinesia, and pain) and / or emotional distress (e.g., panic attacks, apathy, and cognitive rigidity) in the patients [84, 85].

To exclude these potential confounding factors, we here investigate the neural activity during a novel feedback-based set-shifting task in early-stage PD patients who were not yet on dopamine replacement therapy. We hypothesized that PD patients, when compared with controls, would show performance deficits associated with decreased task-related activation of the fronto-striatal and fronto-parietal areas.

MATERIAL AND METHODS

Participants

Twenty-two early-stage, non-demented, and unmedicated patients with PD and 40 well-matched healthy controls participated in this study. A number of participants was excluded from the final analyses due to 1) presence of a co-morbid psychiatric disorder (one patient), 2) scanner failure (one patient; one control), 3) more than 3 mm movement during the scanning session (two controls), and 4) extremely low accuracy on the task (more than two standard deviations from the median) in comparison with their own group (two patients; two controls), rendering our total sample size 18 patients with PD (mean age of 59 $\pm$ 10 years) and 35 age, gender, education, and handedness-matched healthy controls (mean age of 56 $\pm$ 10 years), who were recruited through advertisements, and with no history of alcohol abuse or neurological disorders (See Table 2.1).

Patients were diagnosed by neurologists specialized in movement disorders at the VUmc according to the UK PD Brain Bank criteria [100] for idiopathic PD, and we included as many patients as possible between February 2010 until November 2012. Patients were initially informed by the neurologist about this study and were, only after giving consent, approached by the investigator. Exclusion criteria were: i) usage of anti-parkinsonian medication, ii) additional neurological- or psychopathology, and iii) older than 75 years of age. No patients were using dopaminergic or cholinergic medication during the time of the investigation. One patient had previously used pramipexole, rasagiline, and levodopa-carbidopa during one year, but had abstained from dopaminergic medication two months prior to our study. The Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) [101] and Hoehn and Yahr (H&Y) stage [102] were administered to assess disease severity

and stage, respectively. All participants were screened for the presence of psychiatric disorders using the Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID-I) [103], general cognitive status using the Mini-Mental State Examination (MMSE) [104], depressive symptoms using the Beck Depression Inventory (BDI) [105], and anxiety using the Beck Anxiety Inventory (BAI) [106]. Handedness was assessed using the Edinburgh handedness inventory [107]. All participants provided informed consent, obtained according to the Declaration of Helsinki, and the study protocol was reviewed and approved by the Medical Ethical Committee of the VU University Medical Center.

Table 2.1 Demographic, clinical, and behavioural characteristics

	HC (N = 35)	PD (N = 18)	p-value
Demographics			
Age (years)	56 ± 10 (39 – 75)	59 ± 10 (38 – 74)	.24[a]
Gender (% men)	22 (63%)	12 (67%)	.78[b]
Education[#]	6 (3 – 7)	6 (2 – 7)	.81[b]
Handedness (right)	31 (87%)	16 (89%)	.56[c]
Clinical measures			
MMSE	29 (27 – 30)	29 (24 – 30)	.23[b]
BDI	2 (0 – 10)	4.5 (0 – 11)	.01[b]
BAI	0 (0 – 11)	4 (0 – 16)	< .001[b]
UPDRS-III	NA	22 (2 – 35)	
H&Y stage	NA	2 (1 – 3)	
Behavioural measures			
RT correct repeat trials (ms)	822 ± 200 (503 – 1269)	1019 ± 283 (582 – 1638)	.005[a]
RT correct switch trials (ms)	902 ± 212 (519 – 1354)	1083 ± 336 (642 – 2057)	.02[a]
Failed switch trials (% of total)	.36 (0 – 4)	.5 (0 – 6)	.36[d]
Failed repeat trials (% of total)	.72 (0 – 4)	2.2 (0 – 19)	.004[d]
Switch costs (ms)	76 (-24 – 341)	48 (-121 – 420)	.32[d]
Normalized switch costs	.09 (-.03 - .47)	.05 (-.12 - .40)	.20[d]

Values are presented as mean ± standard deviation or median (range) unless indicated otherwise.
Abbreviations: *HC,* healthy controls; *PD,* patients with Parkinson's disease; *NA,* not applicable; *MMSE,* mini-mental state examination; *BDI,* Beck depression inventory; *BAI,* Beck anxiety inventory; *UPDRS,* unified Parkinson's disease rating scale; *H&Y,* Hoehn and Yahr.
[a] = Independent samples t-test
[b] = Pearson's χ^2 test
[c] = Fisher's exact test
[d] = Independent samples Mann-Whitney *U*-test
[#] = Education level was measured in 7 levels ranging from 1 (no finished education) to 7 (university training)

Set-Shifting Task

In our in-house developed set-shift task, programmed in E-Prime (version 2.0) and available on request to the authors, a fixation cross was permanently displayed at the centre of the screen (see Figure 2.1). An arrow appeared either on the right or on the left side of the cross, pointing in an upward or in a downward direction, leading to four possible stimulus-response combinations. The presented arrow could be categorized according to the *direction* in which it pointed (up / down) or according to its *location* in reference to the fixation cross (left / right). Participants had to respond to the feature of the stimulus that was relevant at the moment of presentation. A green feedback screen followed a correct response, a red feedback screen a false response. The relevant stimulus feature did not change for four to seven trials (the exact number was determined randomly to prevent anticipation). Then a red screen followed a correct response, indicating that the next stimulus had to be categorized according to the other classification rule. After a correct set-shift, a green feedback screen followed and the relevant stimulus feature did again not change for four to seven trials. This procedure continued until 40 correct set-shift trials were obtained. The total number of trials varied around 300, but depended on the number of errors.

The task was self-paced with a maximum stimulus duration of 4000 ms, and after each trial a feedback screen followed with a fixed duration of 2000 ms. When no response was given within the 4000 ms time window, there was a time-out followed by a red feedback screen. The inter-stimulus interval (ISI) between the feedback and stimulus presentation was jittered between 250 and 1000 ms for anti-aliasing purposes. All behavioural responses were recorded using an MRI compatible response-box (Cambridge Research Systems Ltd., UK).

We developed this task to resemble the WCST in its feedback-based approach, but to measure the cognitive construct of set-shifting more accurately. The stimuli were therefore kept constant over all trials to limit novelty or recognition effects, and we acquainted the participant with the paradigm by practising it extensively prior to the actual recording to exclude learning effects. We, furthermore, limited working memory load by only using two intrinsic stimulus features (i.e., direction and location), precluding the need for a reference stimulus and thus avoiding matching-to-sample effects. Last, to exclude potential confounding effects of motor activation on our fMRI data, we measured brain activation only while feedback was being presented, since no motor response was expected during, or directly following, the feedback.

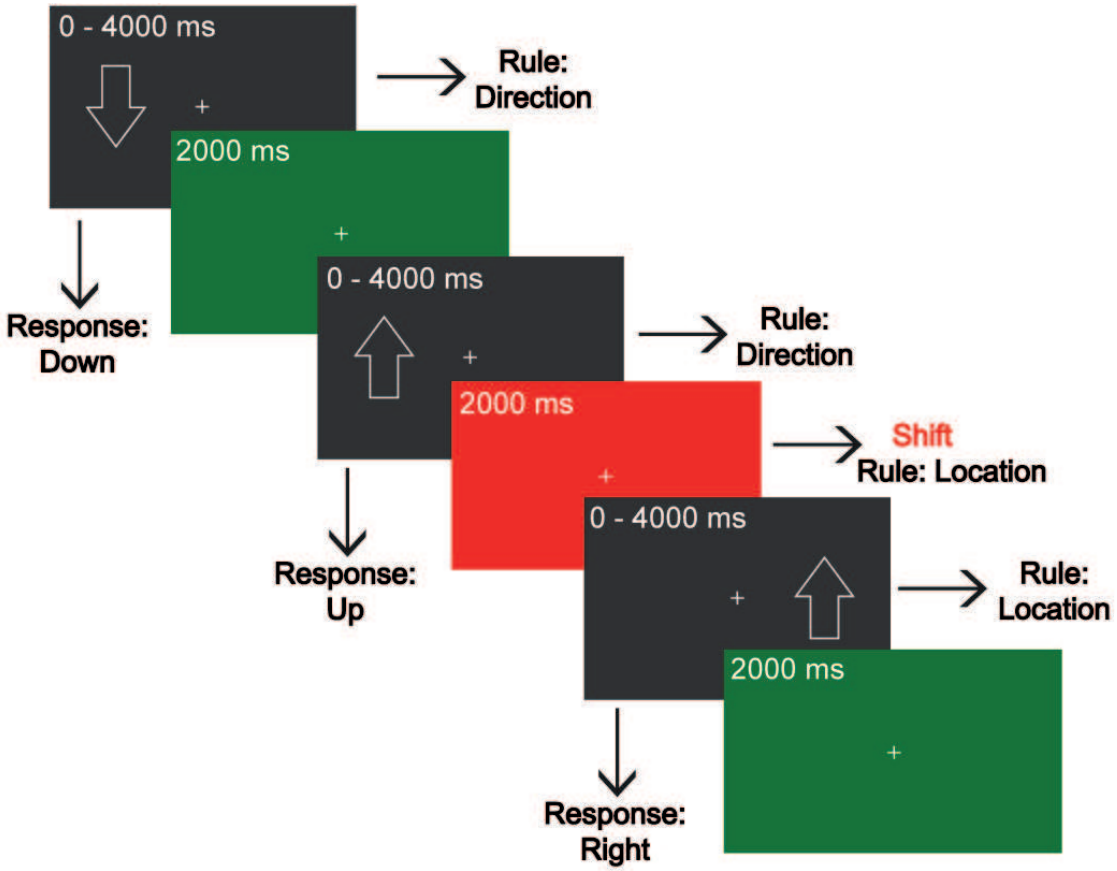


Figure 2.1 The set-shift paradigm Stimuli consisted of arrows that could appear in two different locations (left/right) and point in two different directions (up/down). The stimulus was presented on the screen for a maximum of 4000 ms and was terminated upon a button press. Each response was immediately followed by a green (correct response) or red feedback (incorrect response) screen for 2000 ms. The correct response depended on the relevant feature of the stimulus (i.e. location / direction). A red feedback screen following a correct response signalled a rule shift.

Image acquisition

Imaging was performed on a GE Signa HDxt 3-T MRI scanner (General Electric, Milwaukee) at the VU University Medical Center. Functional images were acquired with a gradient echo-planar imaging (EPI) sequence (TR = 2100 ms; TE = 30 ms; 64 x 64 matrix; field of view = 24 cm; flip angle = 80°) with 40 ascending slices per volume (3.75 x 3.75 mm in-plane resolution; slice thickness = 2.8 mm; inter-slice gap = 0.2 mm), which provided whole-brain coverage. Anatomical scanning included a sagittal three-dimensional gradient-echo T1-weighted sequence (256 x 256 matrix; voxel size = 1 x 0.977 x 0.977 mm; 172 sections).

Behavioural data analysis

Based on the response made by the participant, each trial was classified into the categories i) "correct repeat" if no set-shift was necessary and the stimulus was correctly categorized, ii) "successful shift" if the preceding feedback signalled a set-shift, and the response was correct, iii) "failed shift" if the preceding feedback signalled a set-shift, but was not executed, iv) "delayed shift" if a correct shift followed after a "failed shift", v) "failed repeat" if the participant shifted to the other classification rule without a set-shift signal, vi) "no shift / no repeat" when shifting back to the correct classification rule after a "failed repeat".

We computed the percentage failed shift and the percentage failed repeat trials from the absolute number of total trials to measure accuracy. We also calculated switch costs (= successful shift mean reaction time (RT) - correct repeat mean RT), a measure to assess the cognitive effort to perform a set-shift [108], although we did not *a priori* expect the groups to differ on this measure since switch costs are most sensitive in rule-based and not feedback-based paradigms. Because we anticipated a baseline difference in RT between the two groups, we also computed normalized switch costs (= switch costs / correct repeat mean RT). Independent samples *t*-tests were used to compare the test scores between the groups, and the Mann-Whitney *U* test in case of non-parametric distribution.

Image processing and analysis

All image pre-processing and analyses were conducted in SPM8. The EPI scans were slice-time corrected, realigned to the first image, unwarped using a least squares approach and a six parameter (rigid body) spatial transformation to correct for motion. They were subsequently warped to the Montreal Neurological Institute (MNI) T1-template, employing the individual T1-weighted image for estimation. Lastly, the images were smoothed with an eight mm Gaussian kernel.

As a second step, an event design matrix was created in order to examine the within-subject effects in a first-level general linear model (GLM). All trials were modelled at the onset of the feedback with a fixed duration of 2000 ms. The first regressor of interest was labelled "repeat" and consisted of correct repeat trials. The second regressor of interest was labelled "shift" and consisted of successful shift trials. Since participants, on average, only made a marginal number of errors, the failed repeat, delayed shift, failed shift, and no shift / no repeat trials were modelled into one regressor of no-interest. Also the six movement parameters generated during the realignment were modelled as regressors of no-interest. The defined contrasts we used at first level were correct shift > successful repeat ("shift>repeat") and successful repeat > correct shift ("repeat>shift").

Contrast images derived from the first level analyses were entered into second level (group) analyses, employing independent *t*-tests. Since both groups differed in RT on the shift and repeat trials, we included the RT on the shift trials as a covariate in the "shift>repeat" contrast, and RT on the repeat trials as a covariate in the "repeat>shift" contrast to correct for possible effects that were due to differences in RT between the groups. We furthermore performed a voxel-wise regression analysis on normalized switch costs - as a measure of task performance – for both groups separately, without the addition of RT on set-shift trials as covariate. Whole-brain statistical maps were thresholded at $p < .05$ corrected for family-wise errors (FWE) in the main effects of task. Group interaction effects were masked inclusively for the group specific main effects of task and thresholded at $p < .001$ (uncorrected).

Correlation with dopamine transporter binding

We obtained single photon emission computed tomography (SPECT) scans in 12 out of 18 PD patients with a [^{123}I]FP-CIT tracer binding to the dopamine transporter (DaT). We used these scans to calculate the age-corrected DaT binding ratios in the dorsal-medial striatum (procedure and calculation described elsewhere) [109]. To gain further insight into the relation between task performance, task-related neural activation, and levels of striatal dopamine, we computed Spearman correlations between the binding ratios with the RTs of the correct repeat and shift trials, switch costs, and normalized switch costs, and with the extracted parameter estimates of the peak voxels from the group-by-task interaction effects. All correlations were computed in SPSS 20.

RESULTS

Demographics and characteristics

The groups were matched with respect to age, gender, education, and handedness (see Table 2.1) and did not differ on MMSE scores ($U = 254$, $p = .23$). The PD patients had higher, but clinically irrelevant, BDI ($U = 447$, $p = .01$) and BAI scores ($U = 511$, $p < .001$) compared with healthy controls. Excluding the patient that had already used dopamine replacement therapy from our analyses did not significantly influence the behavioural or imaging outcomes (data not shown) and this patient was therefore included in all analyses.

Behavioural results

Main effect of task

We found that in our complete sample (N=53), while employing the non-parametric related samples Wilcoxon signed-rank test, that RTs on set-shift trials (Mdn = 893 ms) were significantly longer when compared with repeat trials (Mdn = 840 ms) ($Z = 5.10$; $p < .001$), but that participants made more errors on repeat (Mdn = 1.06%), when compared with set-shift trials (Mdn = 0.36%) ($Z = 4.14$; $p < .001$).

Group interaction effects

On average, PD patients (M = 1019 ms ± 283), compared with healthy controls (M = 822 ms ± 200), had significantly increased RTs on the correct repeat trials ($t(51) = -2.94$, $p = .01$). The patients (M = 1083 ms ± 336) were also significantly slower than controls (M = 902 ms ± 212) on successful shift trials ($t(51) = -2.40$, $p = .02$) (see Table 2.1 and Figure 2.2a).

Furthermore, patients (Mdn = 2.2 %) had a significantly higher percentage of failed repeat trials ($U = 467$, $p = .004$) when compared with controls (Mdn = 0.72%). However, patients (Mdn = 0.5) did not significantly differ from controls (Mdn = 0.36%) on the percentage of failed shift trials ($U = 363$, $p = .36$) (Table 2.1; Figure 2.2c).

Last, patients (median = 48 ms) and controls (Mdn = 76 ms) did not significantly differ on switch costs ($U = 263$, $p = .32$), nor was there a difference between patients (Mdn = 0.05) and controls (Mdn = 0.09) in normalized switch costs ($U = 247$, $p = .20$) (see Table 2.1 and Figure 2.2b and 2.2d, respectively).

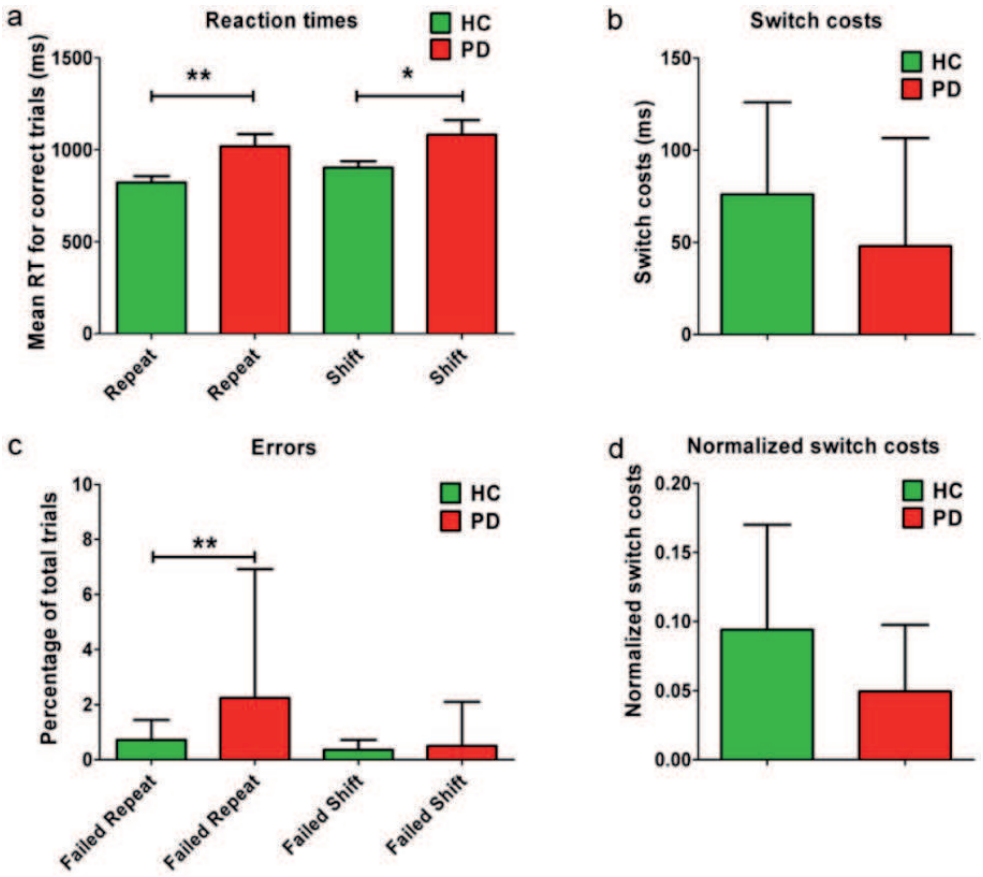


Figure 2.2 Behavioural results
a: PD patients, compared with controls, made more errors on repeat trials during the set-shift task.
b: the groups did not differ on switch costs.
c: the patients with PD were slower on correct repeat and shift trials.
d: the groups did not differ on normalized switch costs.
Panel a: mean with standard error of the mean
Panel b, c, and d: median with inter-quartile range
HC healthy controls; *PD* patients with Parkinson's disease

Imaging results

Main effect of task

We found a robust effect of task ("shift > repeat" contrast) in the bilateral superior, middle, and inferior frontal gyri, bilateral super parietal cortices, bilateral inferior parietal cortices, posterior cingulate gyrus, and left superior and right inferior temporal gyri (see Table 2.2 and Figure 2.3a for the healthy controls; see Table 2.3 and Figure 2.3b for the PD patients). The opposite contrast ("repeat > shift") showed activation in the left posterior and anterior cingulate gyri and the left anterior prefrontal cortex, (see Table 2.2 and Figure 2.3b).

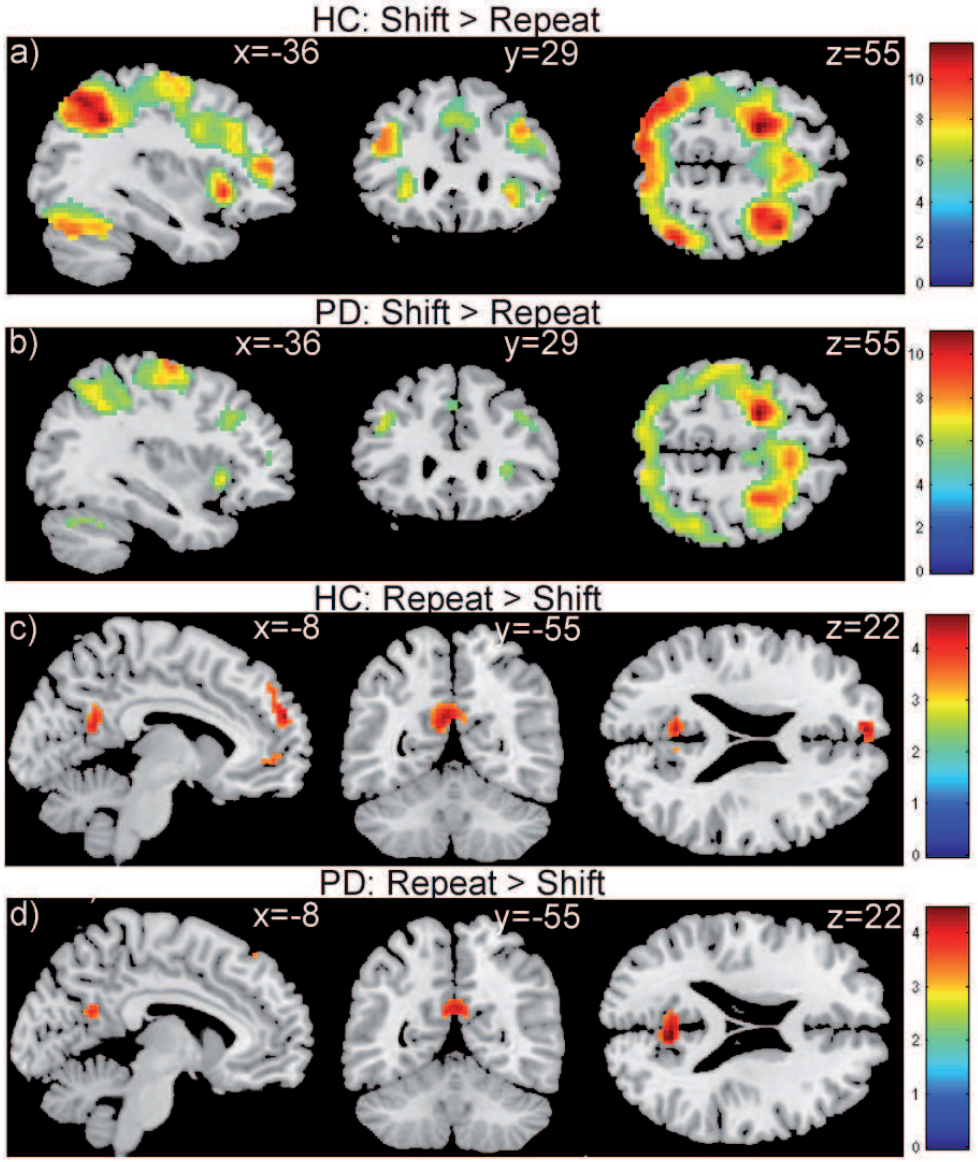


Figure 2.3 Main effect of task for the healthy controls (N=35) and PD patients (N=18)
T-statistic image of the contrast shift > repeat for the healthy controls (panel a) and PD patients (panel b), and for the contrast repeat > shift for the controls (panel c) and PD patients (panel d), corrected for the RT on shift and repeat trials, respectively. Threshold at p = .05, whole-brain family-wise error-corrected for the shift > repeat, and p = .001 (uncorrected) for the repeat > shift contrast, overlain on ch2better MNI template with MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron). The coloured bar indicates the Z-values.

Table 2.2 Main effect of task for the healthy controls (N=35)

L/R	BA	Area	t-value	Cluster size	Peak coordinates (MNI)		
					X	Y	Z
HC: Shift > Repeat							
L	6	Superior frontal gyrus	11.15	12404	-24	2	58
L	6		11.58		-24	-7	55
R	6		11.02		30	-4	58
R	6		10.93		35	5	55
L	9		11.02		-48	8	37
R	47	Inferior frontal gyrus	11.52		30	20	-8
L	47		11.42		-33	20	-2
R	47		11.60		39	20	-8
L	7	Superior parietal cortex	10.93		-30	-73	46
L	7		11.23		-35	-61	49
L	7		10.68		-30	-73	40
L	7		11.70		-3	-79	46
R	40	Inferior parietal cortex	11.59		48	-55	46
L	40		11.57		-33	-52	40
L	40		11.55		-48	-52	49
L	40		10.97		-45	-61	49
R	23	Posterior cingulate gyrus	6.10	59	3	-28	31
HC: Repeat > Shift							
L	10	Medial frontal gyrus	4.64	54	-6	56	25
L	9		3.78		-6	50	40
L	24	Anterior cingulate gyrus	4.44	40	-3	38	1
L	32		3.97		-6	50	-2
L	31	Posterior cingulate gyrus	4.33	56	-6	-55	25
L	8	Medial frontal gyrus	3.47	2	-12	41	46

HC Shift > Repeat; Brain areas significant at a threshold of $p = .05$ (FWE-corrected)
HC Repeat > Shift; Brain areas significant at a threshold of $p = .001$ (uncorrected)
Abbreviation: *HC,* healthy controls

Table 2.3 Main effect of task for the patients with Parkinson's disease (N=18)

L/R	BA	Area	t-value	Cluster size	Peak coordinates (MNI)		
					X	Y	Z
		PD: Shift > Repeat					
L	6	Superior frontal gyrus	11.03	4681	-24	-7	55
L	6		9.64		-30	-7	67
R	6		9.32		27	-10	58
R	6		8.35		24	5	61
R	6		8.30		6	11	52
L	9	Middle frontal gyrus	8.48		-51	8	37
R	7	Superior parietal cortex	7.97		9	-82	46
L	7		7.86		-9	-76	46
L	40	Inferior parietal cortex	8.43		-48	-52	46
R	40		8.08		39	-40	43
L	40		8.03		-45	-34	49
L	40		7.29		-39	-55	49
L	40		7.24		-33	-52	40
R	2	Postcentral gyrus	7.44		63	-22	34
L	2		7.26		-60	-22	31
L	4	Precentral gyrus	7.41		-33	-16	55
L	9	Middle frontal gyrus	5.36	10	42	8	37
R	10	Frontopolar PFC	6.33	53	39	41	25
R	10		5.92	34	33	53	4
R	10		5.54		30	53	13
L	10		5.82	21	-30	53	16
R	47	Inferior frontal gyrus	7.14	133	30	20	-8
R	47		6.99		39	20	-8
R	47		6.82		30	26	4
L	47		6.83	68	-36	20	-2
R	6	Superior frontal gyrus	5.92	22	60	2	31
R	37	Fusiform gyrus	7.32	355	48	-58	-20
R	-	Posterior cerebellum	7.20		9	-73	-29
R	-		7.12		27	-70	-29
R	-	Thalamus	5.60	17	12	-19	10
L	-	Posterior cerebellum	6.42	131	-30	-58	-29
L	37	Fusiform gyrus	6.31		-48	-61	-17
R	21	Middle temporal gyrus	5.92	13	60	-25	-11
R	21		5.07	1	48	-22	-14
L	19		4.94	1	-33	-82	22
R	18	Lingual gyrus	6.49	207	9	-85	-8
L	17		6.09		-12	-94	-14
R	18		5.88		12	-76	1

L/R	BA	Area	t-value	Cluster size	Peak coordinates (MNI)		
					X	Y	Z
R	22	Superior temporal gyrus	5.48	6	63	-46	16
R	19	Parahippocampal gyrus	5.25	1	15	-43	-8
L	44	Precentral gyrus	5.20	5	-51	5	13
L	-	Sub-thalamic nucleus	5.18	4	-9	-16	-8
R	-	Putamen	5.16	6	15	8	4
L	-	Thalamus	4.97	2	-12	-19	10
		PD: Repeat > Shift					
R	31	Posterior cingulate gyrus	4.47	58	6	-58	22
L	8	Medial frontal gyrus	4.13	5	-12	41	49
L	8		3.31	1	-6	38	55

PD Shift > Repeat; Brain areas significant at a threshold of $p = .05$ (FWE-corrected)
PD Repeat > Shift; Brain areas significant at a threshold of $p = .001$ (uncorrected)
Abbreviation: *PD,* patients with Parkinson's disease

Group interaction effects

Patients with PD, compared with healthy controls, showed decreased activation of the right inferior frontal gyrus on successful shift trials when compared with correct repeat trials (see Table 2.3 and Figure 2.4a) and increased activation of the right superior frontal gyrus, bilateral inferior parietal gyrus, and right superior temporal gyrus (see Table 2.4 and Figure 2.4b).

Table 2.4 Group*task interaction effects: Shift > Repeat

L/R	BA	Area	t-value	Cluster size	Peak coordinates (MNI)		
					X	Y	Z
		HC > PD, Shift > Repeat					
R	47	Inferior frontal gyrus	3.44	3	51	29	-2
		PD > HC, Shift > Repeat					
R	6	Superior frontal gyrus	3.61	10	24	8	61
R	43	Postcentral gyrus	3.95	14	63	-19	22
L	1		3.71	9	-54	-22	52
L	1		3.67	7	-63	-19	28
R	2		3.53	7	63	-22	34
R	22	Superior temporal gyrus	3.27	1	63	-43	16

Significant at $p = .001$ (uncorrected) threshold
Abbreviations: *HC,* healthy controls; *PD,* patients with Parkinson's disease; *BA*, Brodmann area.

Correlation with normalized switch costs

In patients, normalized switch costs correlated negatively with task-related frontal activation, including the right fronto-polar cortex, right superior frontal gyrus, left inferior frontal gyrus, and bilateral anterior cingulate gyri (see Table 2.4 and Figure 2.4c). In controls, normalized switch costs correlated negatively with activation of the right superior parietal cortex (see Table 2.4).

Table 2.5 Relationship of task performance with brain activation

L/R	BA	Area	t-value	r	Cluster size	Peak coordinates (MNI)		
						X	Y	Z
			HC					
R	7	SPC	3.44	-.53**	1	15	-73	61
			PD					
R	10	Frontopolar PFC	4.33	-.71**	5	30	50	4
R	6	Superior frontal gyrus	4.12	-.69**	2	39	2	64
R	47	Inferior frontal gyrus	4.01	-.67**	3	39	38	-5
L	47		3.80	-.61**	1	-51	29	-2
L	44	Frontal operculum	3.73	-.63**	1	54	14	16
L	13	Insula	3.95	-.53**	1	-33	17	10
R	32	Anterior cingulate gyrus	3.99	-.65**	5	9	32	31
L	32		3.74	-.65**	1	-9	38	4

Brain areas significant at a threshold of $p = .001$ (uncorrected)
r denotes the Pearson correlations between peak-voxel parameter estimate and normalized switch costs
Abbreviations: *HC,* healthy controls; *PD,* patients with Parkinson's disease; *BA*, Brodmann area; *SPC*, superior parietal cortex; *PFC* prefrontal cortex.
** Correlation is significant at a $p = .01$ level (2-tailed)

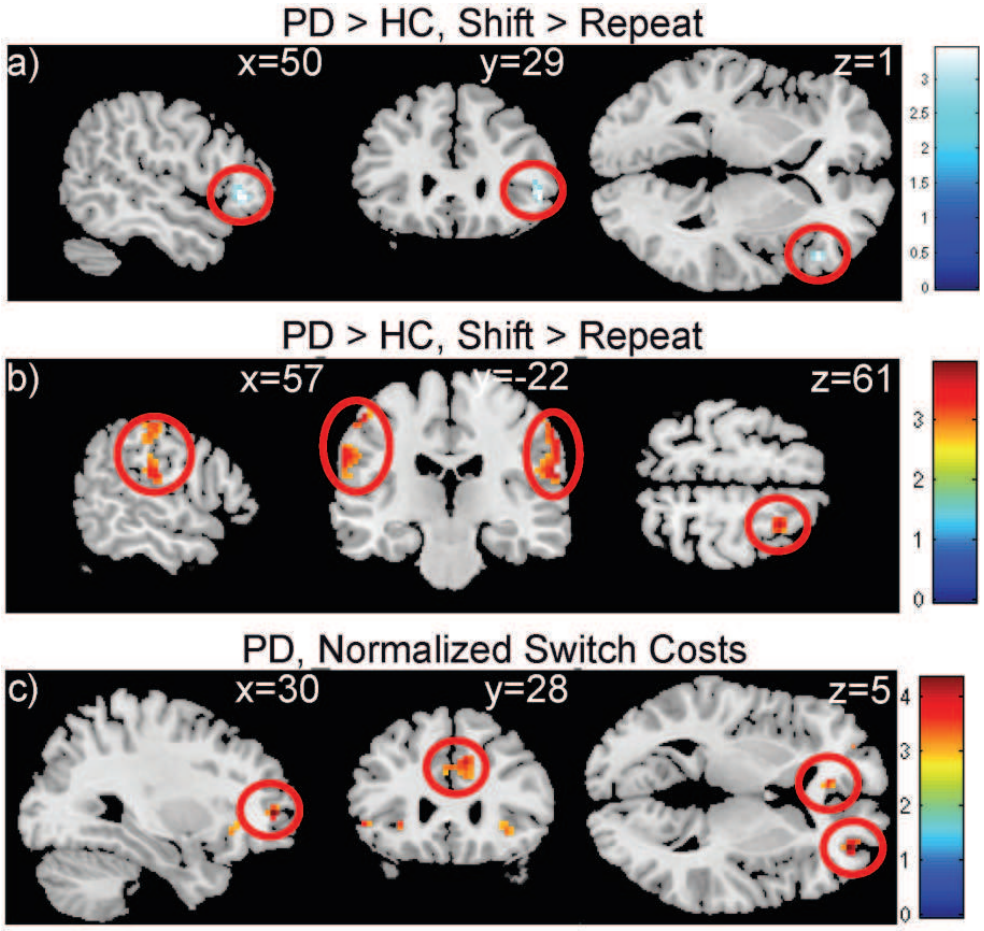


Figure 2.4 Group interaction effects and relationship with normalized switch costs
a: decreased right VLPFC activation in patients with PD compared with controls during correct set-shift trials
b: increased activation in the bilateral IPC and right superior frontal gyrus in patients with PD compared with controls
c: Results from the regression analysis between neural activation during the correct set-shift trials and normalized switch costs within the PD patients (N=18)
Image thresholds are set at p = .005 (uncorrected) for illustrative purposes, overlain on ch2better MNI template with MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron). Coordinates are in MNI space. Warm colours indicate increased activation, cool colours decreased activation. The coloured bar indicates the Z-values.

Correlations with DaT SPECT binding ratios in dorsal-medial striatum

In our post hoc analyses (sub-sample of 12 PD patients), we found that the DaT binding ratio correlated negatively at trend-level with the mean RT on the successful switch trials (rho = -.50; p = .10) and with task-related activation of the right superior frontal gyrus (rho = -.53; p = .08).

As a post-hoc analysis, we investigated the functional connectivity between the areas in which we found the hyper- and hypo-activity, by extracting the parameter estimates of the four implicated areas (i.e. bilateral IPC, right SFG and right VLPFC) and computing Spearman correlations between these estimates for each group separately. We found a positive correlation between the right IPC and right VLPFC (rho = .51; p = .002) for the healthy controls, but not for the PD patients (rho = -.16; p = .53), and Fisher's Z-test for correlations showed that this was a significant between-group difference (Z = 2.31; p = .02). We also found a positive correlation between the right IPC and the right SFG for the PD patients (rho = .57; p = .01) but not for controls (rho = .25; p = .15), but this between-group difference did not reach significance (Z = 1.25; p = .21). Last, we found a correlation between the two parietal cortices in both the PD patients (rho = .75; p < .001) and controls (rho = .39; p = .02).

DISCUSSION

We investigated the neural correlates of set-shifting in a group of unmedicated early-stage patients with PD, compared with a matched healthy control group, using a feedback-based set-shifting paradigm with high construct validity. We found that PD patients, compared with controls, made more errors during repeat trials. During set-shifting PD patients showed decreased recruitment of the right inferior frontal gyrus, and hyper-activated the bilateral parietal cortices, right superior frontal gyrus, and right superior temporal gyrus.

Because performance on the set-shift trials of the patients and controls was equal, we conclude that our early-stage patients with PD did not show a clear set-shifting impairment. This might be explained by the fact that task performance on previous employed set-shifting tasks in PD also depended on other cognitive mechanisms, such as matching-to-sample, working memory, and visuospatial learning, and therefore not resulted from set-shifting deficits *per se* [99]. Alternative explanations for the absence of a set-shifting deficit in our patients relate to their early disease stage, relatively high education level that might have served as a protective mechanism to postpone cognitive decline [25], or the simplicity of our paradigm.

The patients with PD had a higher percentage of failed repeat trials, which was unexpected and might indicate a compensatory behavioural strategy by anticipating an upcoming set-shift trial. In a post-hoc analysis, however, we found that the median location of the failed repeat trials in the sequence did not differ between patients and controls (data not shown), thus diminishing the possibility of a compensatory strategy. Also, since patients with PD suffer from attentional problems [12] it is conceivable that they were not able to continuously maintain their atten-

tion during the parts of the task that were little challenging, resulting in errors during repeat trials.

The patients performed more slowly on both the correct repeat and correct shift trials, probably due to a combination of a slowed motor response as a consequence of bradykinesia [3], and a general cognitive slowing [110]. We found no group differences in switch costs or normalized switch costs. This was not surprising, since switch costs are most sensitive as an indication of cognitive effort to set-shift in rule-based paradigms [108], while our paradigm was feedback-based.

It has been shown that PD patients without medication have an equal, or better, performance on tasks on which performance is based on learning through negative feedback [37, 111, 112]. A different study employed a modified card sorting task (MCST), an adapted version of the WCST, and provided explicit feedback after each response. They found that the ability to set-shift through negative feedback was not affected in PD subjects even when in an OFF phase [113]. Our lack of a set-shifting deficit could, according to these results, thus be explained by the fact that PD patients in an OFF phase learn better through errors / negative feedback. However, we have tried to minimize the effects of learning by training our participants extensively prior to the actual recording in the MRI scanner. They were consequently expecting the negative feedback and knew how to interpret it (i.e. the wrong categorization rule is being applied). We therefore argue that learning effects only had a minimal effect on task-performance or neuronal activation, and that the equal behavioural performance results from equal set-shifting abilities.

We furthermore compared performance on our in-house developed test with the behavioral results of the validated intra-dimensional–extra-dimensional (ID-ED) set shifting test, a subtask of the Cambridge Neuropsychological Test Automated Battery (CANTAB) [114, 115] (see supplementary figure 2.1 and supplementary table 2.1). We found on the ID/ED task no set-shifting deficits and increased RTs for the PD patients compared with controls, which is in line with the results from our own task.

We found robust task-related activation of fronto-parietal areas during the set-shift trials, across both groups, especially in the bilateral superior frontal gyrus, bilateral inferior parietal cortices, and bilateral prefrontal areas. These activation patterns are in accordance with meta-analyses on set-shifting [95, 96] and can thus be interpreted as a validation of our paradigm. We did not find activation of the caudate nucleus or anterior cingulate cortex in our main effect of task. This is in accordance with the results from Witt and Stevens [97], who concluded that striatal and cingulate activation are related to the complexity of the paradigm, and not to set-shifting *per se*, which is in line with the straightforwardness of our paradigm.

The relative simplicity of our paradigm may also explain the fact that during repeat trials, compared with shift trials, activation was limited to the brain regions that overlap with the default-mode network (DMN) [116], a brain network that becomes active during rest [117] or during low-demanding baseline conditions [118]. This contrasts with previous studies [93, 98, 119] reporting prefrontal and parietal activation during non-set-shift trials in more complex set-shifting paradigms.

PD patients, compared with healthy controls, showed a small but significant cluster of reduced activation in the right inferior frontal gyrus (VLPFC) when preparing a set-shift. This finding concurs with the results by Monchi and colleagues [93]. It is also known that the PFC in PD patients is a vulnerable area due to the striatal dopamine depletion [6, 32], and that particularly context-switching paradigms exert cognitive strain on inferior frontal areas [96]. Our finding fits these previous results. Monchi and colleagues [93] also observed decreased task-related activation of the DLPFC and caudate nucleus in patients compared with controls, which is probably related to the complexity of their set-shifting paradigm, involving additional executive processes.

We found that patients, compared with controls, had increased activation in the inferior parietal cortex and superior frontal gyrus while preparing a set-shift. We hypothesize that patients with PD recruited these areas more extensively in order to compensate for the decreased activation in the VLPFC. These results fit with previous task-related fMRI studies in PD patients that reported increased, and presumably compensatory, neural activation [113, 120, 121]. The interpretation is also in accordance with a recently postulated hypothesis [80] stating that brain areas become less synchronized due to the dopamine depletion and therefore exchange less information. We speculate that, as a consequence of the decreased synchronization, the individual task-related areas have to work harder to maintain normal task performance levels. This hypothesis was further strengthened by the post-hoc analysis which showed a positive correlation between the right IPC and right VLPFC in activity in controls, but not patients. Importantly, since our cohort of PD patients was not using medication, we can exclude potential confounding effects of anti-parkinsonian drugs [36]. This thus provides us with a unique and unbiased image of the effect of PD on both set-shifting performance and task-related neuronal activation.

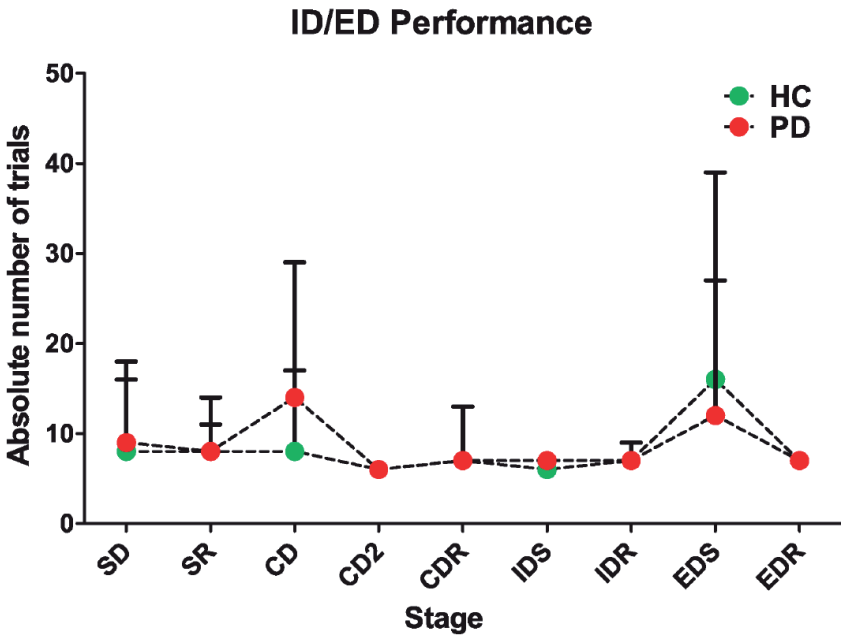
In PD patients, but not controls, we found that activation throughout mainly prefrontal areas correlated with reduced normalized switch costs. This strengthens our

interpretation that set-shifting capacity in the PD patients critically depends on cortical activation of the prefrontal cortex [93, 95, 97, 98], a vulnerable area in PD.

We found trend-significant, moderately strong negative correlations between DaT binding ratios and task-related activation of the superior frontal gyrus. This suggest that striatal dopaminergic depletion may result in increased activation of the superior frontal gyrus, which is in line with our hypothesis on the compensatory role of the superior frontal gyrus. However, since our sub-sample consisted of only 12 patients this finding should be interpreted with caution. The trend-significant negative relation between DaT binding and the RT on switch trials is not necessarily meaningful since it potentially reflects general bradykinesia or cognitive slowing, which happened to be supra-threshold for the switch trials and sub-threshold for repeat trials and should therefore also be evaluated with care.

The current study has some methodological strengths, such as the relatively large sample sizes, the unmedicated status of the PD patients, and the high construct validity of the set-shifting paradigm. These factors, however, also limit comparability to earlier studies. We suggest that the relatively low difficulty level of our task, owing to its selective sensitivity to the switching process, may not have been challenging enough to differentiate patients from controls. We also argue that this issue underlies the subtle, although relevant, group-by-task interaction effects that were found. Other important methodological issues to consider are the absence of an a priori validation of our task against an existing set-shifting paradigm and the use of a red feedback screen to indicate two different events (i.e. set shift and negative feedback).

We measured task-related brain activity in a large group of unmedicated early-stage patients with PD and matched healthy controls while performing a simplified set-shifting paradigm. We found that the patients made more non-set-shift errors, but not failed shifts. The PD patients showed decreased task-related recruitment of the right VLPFC and we hypothesize that the hypo-activation of the VLPFC represents a neural failure that was compensated for by an increased recruitment of the fronto-parietal network, mainly involving the inferior parietal cortex and superior frontal gyrus, and that this compensation underlies the preserved set-shift accuracy.



Supplementary figure 2.1 Behavioural task performance on the ID/ED task for both groups.
The median absolute number of trials per stage (error bar represents the interquartile range) for the healthy controls and PD patients while performing the intra-dimensional extra-dimensional (ID/ED) task. By employing a mixed model ANOVA, we found a significant effect for stage ($F(4,208) = 9.71$; $p < .001$), but not for group ($F(1,51) = .46$; $p = .50$) or a group*level interaction ($F(4,208) = .46$; $p = .77$).
Abbreviations: *SD* simple discrimination; *SR* simple reversal; *CD* compound discrimination; *CD2* compound discrimination 2; *CDR* compound discrimination reversal; *IDS* intra-dimensional shift; *IDR* intra-dimensional reversal; *EDS* extra-dimensional shift; *EDR* extra-dimensional reversal.

Supplementary table 2.1 Behavioral measures of task performance of the healthy controls and PD patients while performing the intra-dimensional extra-dimensional (ID/ED) task.

ID/ED task measures	HC (N=35)	PD (N=18)	
Attrition rate	9 (1 – 9)	9 (1 – 9)	.32[a]
Total number of trials	84 (50 – 207)	82 (50 – 129)	.83[b]
Number of errors non-switch trials	15 (2 – 84)	21 (5 – 57)	.66[b]
RT on all correct trials (ms)	2002 (885 – 7971)	3038 (1106 – 5574)	.008[b]

[a] = Fisher's exact test
[b] = Mann-Whitney U test