◆ Human Brain Mapping 33:27–39 (2012) ◆

Levodopa and the Feedback Process on Set-Shifting in Parkinson's Disease

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Abstract: *Objective:* To study the interaction between levodopa and the feedback process on set-shifting in Parkinson's disease (PD). *Methods:* Functional magnetic resonance imaging (fMRI) studies were performed on 13 PD subjects and 17 age-matched healthy controls while they performed a modified card-sorting task. Experimental time periods were defined based on the types of feedback provided. PD subjects underwent the fMRI experiment twice, once during "off" medication (PDoff) and again after levodopa replacement (PDon). *Results:* Compared with normal subjects, the cognitive processing times were prolonged in PDoff but not in PDon subjects during learning through positive outcomes. The ability to set-shift through negative outcomes was not affected in PD subjects, even when "off" medication. Intergroup comparisons showed the lateral prefrontal cortex was deactivated in PDoff subjects during positive feedback learning, especially following internal feedback cues. The cortical activations were increased in the posterior brain regions in PDoff subjects following external feedback learning, especially when negative feedback cues were provided. Levodopa replacement did not completely restore the activation patterns in PD subjects to normal although activations in the corticostriatal loops were restored. *Conclusion:* PD subjects showed differential ability to set-shift, depending on the dopamine status as well as the types of feedback cues provided. PD subjects had difficulty performing set-shift tasks through positive outcomes when "off" medication, and showed improvement after levodopa replacement. The ability to set-shift through negative feedback was not affected in PD subjects even when "off" medication, possibly due to compensatory changes outside the nigrostriatal dopaminergic pathway. *Hum Brain Mapp 33:27–39, 2012.* © 2011 Wiley Periodicals, Inc.

Key words: executive functions; dopamine; functional magnetic resonance imaging

Contract grant sponsors: Ministry of Education (MOE) and the Agency of Science, Technology and Research (A*Star) of Singapore.

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Received for publication 31 March 2010; Revised 4 September 2010; Accepted 20 September 2010
DOI: 10.1002/hbm.21187
Published online 24 March 2011 in Wiley Online Library (wileyonlinelibrary.com).

INTRODUCTION

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder with both motor and cognitive manifestations. Executive dysfunction is one of the cognitive impairments seen in PD patients even in early stages of the disease [Hietanen and Teravainen, 1986; Lees and Smith, 1983; Muslimovic et al., 2005]. In particular, the ability to set-shift is impaired in PD subjects [Brown and Marsden, 1988a; Cools et al., 1984; Flowers and Robertson, 1985; Lees and Smith, 1983; Taylor et al., 1986]. However, the mechanisms mediating set-shift deficits in PD subjects have remained controversial. Cortical activations may be increased or decreased in PD subjects [Monchi et al., 2007] and levodopa replacement does not necessarily restore the cognitive networks in PD subjects to normal [Jubault et al., 2009]. Some authors have suggested that the increase in cortical activations observed in PD subjects represents the compensatory changes [Dagher et al., 2001; Samuel et al., 1997] whereas others have suggested that it implies direct involvement of the mesocortical dopaminergic substrates in mediating cognitive deficits in PD subjects [Monchi et al., 2007]. There is also evidence to suggest that set-shift deficits in PD subjects may be mediated via non-dopaminergic pathways [Kehagia et al., 2009; Lewis et al., 2005].

Using functional neuroimaging modalities, it has been shown that different areas in the frontal, parietal, and temporal regions may be activated during performance of a set-shift task [Wager et al., 2004], without necessarily involving the caudate nucleus [Monchi et al., 2006]. However, it is not known whether these activations were attributed to the set-shift process per se or due to a result of closely related executive functions such as working memory and the feedback process. There are considerable overlaps in brain areas activated in set-shifting tasks and working memory tasks [Wager et al., 2004], such as the medial prefrontal cortex (PFC), superior and inferior parietal, medial parietal and premotor cortices. The activation patterns observed during set-shifting may also be influenced by the feedback process inherent to the set-shift task [Monchi et al., 2001]. The ventrolateral prefrontal cortex (VLPFC), caudate nucleus, and thalamus were activated in normal subjects receiving negative feedback; the dorsolateral prefrontal cortex (DLPFC) was activated when either positive or negative feedback was received; and the putamen showed increased activity while matching after negative but not after positive feedback in the Wisconsin Card Sorting Task [Monchi et al., 2001].

To our knowledge, the interaction between levodopa and the feedback process on set-shifting is not well understood. Nevertheless, to perform a set-shift, there must first be attention attracted by an internal or external feedback mechanism to a specific perceptual dimension. This is usually followed by an internal monitoring process to ascertain which aspect of the dimension is "rewarded" and which is "punished" before a response selection is made [Robbins, 2007]. The set-shift process is thus influenced by multiple facets of executive functions: error and feedback monitoring, reward processing, and working memory. These cognitive functions are dependent on the proper functioning of the striatum and its dopaminergic projections [Holroyd and Coles, 2002; Lewis et al., 2004; Mcclure et al., 2004; Shohamy et al., 2004]. Furthermore, based on the computational models of basal ganglia feedback mechanisms, it has been suggested that PD subjects are better at learning through negative feedback during "off" medication and that levodopa reverses this bias, making PD subjects more responsive to positive outcomes [Frank et al., 2004]. With this background, we hypothesize that PD subjects will show differential ability to set-shift, depending on the dopamine status as well as the types of feedback cues provided. We hypothesize that the cortical activations observed in PD subjects in set-shifting may be attributed to the interactions between dopamine and the feedback mechanisms inherent to the set-shift tasks. In particular, we postulate that PD subjects will have difficulty performing set-shift tasks through positive outcomes when "off" medication and that their performances will improve after levodopa replacement. We also postulate that the ability to set-shift through negative feedback will not be affected in PD subjects (both "off" and "on" medication), possibly due to compensatory changes outside the nigrostriatal dopaminergic pathway (i.e., the mesocortical dopaminergic substrates or non-dopaminergic pathways).

METHODS

Subjects

We recruited 13 clinically definite PD subjects (7 men, 6 women, mean age 61.9 ± 7.4 years) according to the diagnostic criteria of Calne et al. [1992], and 17 age-matched healthy subjects (9 men, 8 women, mean age 60.5 ± 9.2 years). All were right-handed ethnic Chinese. PD subjects had mild to moderate disease severity (Hoehn and Yahr Stage 1 to 3), with mean disease duration of 4.9 ± 3.5 years. All PD subjects were on levodopa (mean dose 322.3 ± 102.0 mg/day), with three subjects on bromocriptine (mean dose 26.3 ± 26.5 mg/day), four subjects on ropinirole (mean dose 2.8 ± 1.6 mg/day), four subjects on benzhexol (mean dose 2.5 ± 1.0 mg/day), two subjects on amantadine (mean dose 150.0 ± 70.7 mg/day), six subjects on selegiline (mean dose 10 ± 0 mg/day), and one subject on COMT inhibitor (400 mg/day). Subjects with atypical parkinsonism, dementia, psychiatric illness, severe motor fluctuation, color blindness, on dopamine blocking agents, or with contraindications to functional magnetic resonance imaging (fMRI) scanning were excluded from the study. Normal subjects on medications that might exert a dopaminergic effect were also excluded from the study. All PD subjects underwent the fMRI experiment twice in a day: one after overnight withdrawal of antiparkinson medication for at least 12 h (PDoff), and the other during "on" medication (PDon) at 40 min after being served the usual

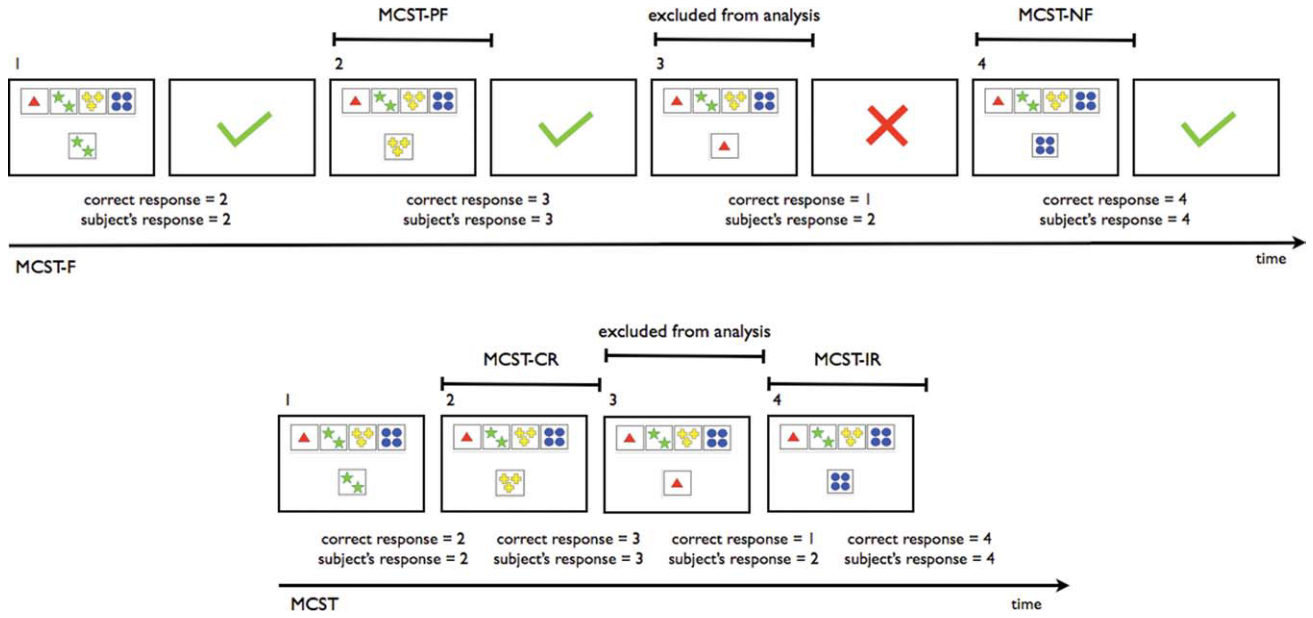

Figure 1.

Modified Card Sorting Task (MCST). Subjects were asked to match the stimulus card at the bottom of the computer screen to one of the four index cards displayed in the top half of the screen. The sorting principle was derived from a comparison of attributes (color, number, or shape) between the stimulus and index cards. Only the control condition blocks were shown in this figure, where an exact match existed between the stimulus and one of the index cards. In the continuous shift blocks (not shown in this figure), the stimulus card contained only one attribute shared with one of the four index cards. The matching attributes of consecutive trials varied in a random order, such that a shift was implicitly given by the task. In the MCST trials, external feedback was not provided after a response was made. Subjects had to perform the tasks through implicit or internal learning without external feedback guidance. In MCST-F trials, external feedback was provided after each response. A green tick was displayed when the response was correct, and a red cross was shown when the response was incorrect. All error trials were removed from the fMRI analysis (e.g., trial number 3). Four experimental time periods were defined for the remaining correct trials: (1) MCST-PF, correct trials just after receiving a positive external feedback, (2) MCST-NF, correct trials just after receiving a negative external feedback, (3) MCST-CR, correct trials just after a correct response was made in MCST trials, and (4) MCST-IR, correct trials just after an incorrect response was made in MCST trials.

morning dose of levodopa (mean morning dose 92.3 ± 18.8 mg). The study was approved by the Institution Ethics and Review Board and all subjects gave written informed consent.

Quantitative Motor Assessments and Cognitive Tasks

Subjects were briefed on the scanning procedures and experimental conditions, and allowed up to 30 min to practice on the cognitive tasks outside the scanner until their performance had reached a plateau. All subjects achieved at least 60% accuracy rates on the tasks during the practice session. The Unified Parkinson's Disease Rating Scale (UPDRS) motor score and quantitative motor assessments were acquired prior to each fMRI experiment. Details of methods and analysis of timed motor testing using the basic element of performance (BEP) module (Human Performance Measurement Inc., Texas) were described elsewhere [Au et al., 2008]. In brief, subjects were measured on the index finger tapping (FT) speed, alternating hand (AH) movement speed, finger tapping speed between two targets separated by a distance of 30 cm (MS), and visuomotor reaction speed (RT). The scores on both sides were added, and the values of FT, AH, and MS were summed to give an overall upper limb motor performance index (UL Index). The higher the UL index, the better was the motor performance.

The cognitive task was performed using a modification of the Montreal Card Sorting Task [Monchi et al., 2006]. In the Modified Card Sorting Task (MCST), external feedback was not provided so that subjects performed the MCST tasks through implicit (or internal) learning without external feedback guidance (see Fig. 1). In the MCST with feedback (MCST-F), external feedback was provided similar to the Montreal Card Sorting Task. However, instead of a

change in screen brightness which might be implicit to the subjects, a red cross was displayed on screen after an incorrect response and a green tick was displayed when the response was correct. The feedback was thus explicit and remained on screen for 0.5 s. The external feedback served as external visual cues to guide subjects on the task performance.

In both MCST and MCST-F, four index cards were displayed in a row in the top half of the computer screen. Starting from the left, the screen showed one red triangle, two green stars, three yellow crosses, and four blue circles. On each classification trial, a stimulus card was presented in the middle of the screen below the index cards. Subjects were asked to match stimulus cards to the four index cards, using one of the attributes: number, color, or shape; the sorting principle was derived from a comparison of attributes between the stimulus and index cards.

The original Montreal Card Sorting Task was designed with four test conditions: control (C), continuous shift (S), retrieval with shift (RS), and retrieval without shift (R) [Monchi et al., 2006]. We had adapted the same paradigm in our card-sorting task, and in this study considered only the C and S conditions in order not to include the cognitive planning component from set-shifting [Monchi et al., 2006, 2007). In the C condition, there existed an exact match between the stimulus and one of the index cards. This condition served as the baseline for perceptual, motor, identity matching, and response selection components inherent to the card sorting task [Lie et al., 2006]. In the S condition, the stimulus card contained only one attribute (color, number, or shape) shared with one of the four index cards. Therefore, only a single response was possible on each trial. The matching attributes of consecutive trials varied in a random order such that the shift was implicitly given by the task [Monchi et al., 2006]. There were eight trials in each block of C and S condition. The condition blocks appeared randomly for four times. Stimulus would remain on screen until a response was received. The maximum response time allowed for each trial was 7.5 s. The MCST-F block appeared in random either before or after the MCST block.

FMRI Scanning

Structural three-dimensional (3D) MR scans of the whole brain were acquired using a 3 Tesla whole-body MRI scanner (Achieva 3.0, Philips Medical Systems, Best, The Netherlands). One hundred and eighty axial slices of T1-weighted 3D anatomical images (MPRAGE sequence) were acquired (TR = 6.7 ms, TE = 3.0 ms, FOV = 230 × 230 mm^2, matrix = 256 × 256, thickness = 0.9 mm, voxel size = 0.90 × 0.90 × 0.90 mm^3). Functional images were then obtained with a T2-weighted gradient echo, echo planar imaging (EPI sequence, 36 contiguous oblique axial 3 mm slices, TR = 2,000 ms, TE = 30 ms, FOV = 230 × 230 mm^2, acquisition matrix = 128 × 128, voxel size = 1.8 × 1.8 × 3 mm^3 with blood oxygenation level dependent [BOLD] contrast). Visual stimuli were projected on a screen and the experiment was controlled by EPrime software, mediated by the scanner-compatible IFIS System outside the scanning room. Subjects were asked to respond to the visual stimuli by pressing one of the four keys on a keyboard provided to indicate answers for "one," "two," "three," and "four," corresponding to one of the four index cards. The left middle finger corresponded to "one red triangle," the left index finger to "two green stars," the right index finger to "three yellow crosses," and the right middle finger to "four blue circles."

Statistical Analysis

Statistical analyses of quantitative motor parameters and behavioral data were performed using SPSS version 11. Student's *t*-tests were performed at a significance level of 0.05. FMRI data were analyzed using the Statistical Parametric Mapping software (SPM2/SPM5) and the standard procedures [Friston et al., 1995b]. All functional images were first corrected for head movement by using least-squares minimization [Friston et al., 1995a] and then corrected for slice timing. After coregistration to the subject's 3D T1-weighted anatomical MR image, functional images were spatially normalized into the SPM standard space with the anatomical image as a guide. Images were then resampled at 2 mm, using Sinc interpolation, and smoothed with a 3D Gaussian kernel with FWHM = 8 mm to decrease spatial noise. For an individual subject, the signal changes in BOLD contrast associated with the performance of tasks were assessed on a voxel-by-voxel basis, using the general linear model and the theory of Gaussian fields as implemented in SPM. The multivariate regression analysis used canonical haemodynamic response function with time and dispersion derivatives as basis function, and corrected for temporal and spatial autocorrelations in the fMRI data. For every single condition, all error trials were removed from the fMRI analysis. The start time and the length of each correct trial were explicitly included in the design matrix. The S minus C contrast was generated to look for activated regions specific to continuous set-shifting without cognitive planning [Monchi et al., 2007]. Four experimental time periods based on the feedback mechanism in action were defined: matching following positive external feedback (MCST-PF), matching following negative external feedback (MCST-NF), matching following positive internal feedback (i.e., after a correct response was made in MCST [MCST-CR]), and matching following negative internal feedback (i.e., after an incorrect response was made in MCST [MCST-IR]). Group analyses were done using random effect analysis (RFX) implemented in SPM5. The analysis used full-factorial design consisting of three factors with following levels: three groups (Normal vs. PDoff vs. PDon); two matching types (S vs. C); and four response types (CR vs. IR vs. PF vs.

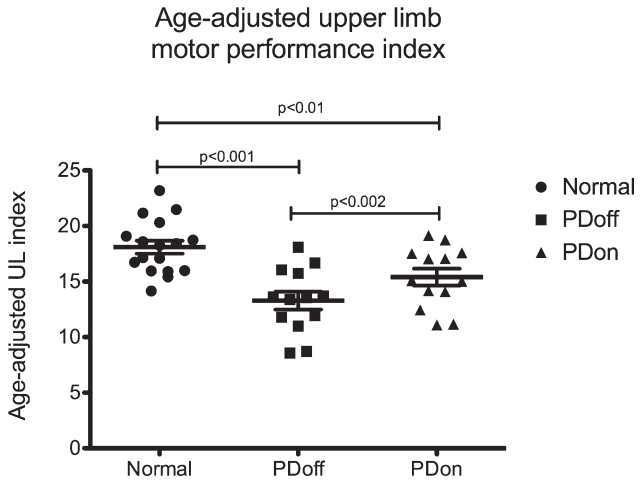

Figure 2.

Age-adjusted upper limb motor performance index amongst PD and healthy subjects. Normal, healthy subjects; PDoff, PD subjects during "off" medication, PDon, PD subjects after levodopa replacement. Error bar = Standard Error of Mean (SEM).

NF), for a total of 24 treatment combinations. We evaluated the effects of levodopa on set-shifting through intergroup comparisons within each of the task conditions (MCST-PF, MCST-NF, MCST-CR, MCST-IR). The effects of feedback were analyzed through comparisons of contrasts between MCST and MCST-F within each subject group. Model parameters were estimated using ReML (Restricted Maximum Likelihood). Significant haemodynamic changes for each contrast were assessed using the *t*-statistical parametric maps. We reported activations below a threshold of $P < 0.005$ (uncorrected) for multiple comparisons corresponding to $t > 2.59$ above a cluster size of greater than 30 voxels. Activations that reached $P < 0.05$ (corrected) were indicated in the tables by footnotes "a" and "b" for False Discovery Rate (FDR) and Family-wise Error (FWE) corrections, respectively. Locations of significant activations were identified by anatomical automatic labeling (AAL) with cluster approach [Tzourio-Mazoyer et al., 2002]. Labels with the highest percentage per cluster were chosen, excluding those labeled "outside" by AAL.

RESULTS

Quantitative Motor Parameters

As expected, normal subjects had better motor performance than PD subjects (see Fig. 2). Levodopa replacement improved the UL index within the PD group ($P < 0.002$). The corresponding UPDRS motor score also improved from 21 ± 9 to 10 ± 5 ($P < 0.001$). Despite the differences in motor performance, there were no significant differences in visuomotor reaction speed across subject groups (Control group: 9.7 ± 1.5 per second, PDoff: 9.0 ± 1.3 per second, PDon: 9.0 ± 1.6 per second).

Task Accuracy and Response Times

The set-shift accuracy rates were comparable across subject groups, regardless of levodopa replacement. The presence of external feedback cues improved the accuracy rates within S conditions in PD subjects (PDoff, $P < 0.005$; PDon, $P < 0.01$) but not in the normal group. The response times, however, were unaffected by the presence of the external feedback cues. Intergroup comparisons showed a trend towards longer MCST-PF and MCST-CR response times in PDoff compared with normal subjects (Fig. 3A). The corresponding response times of PDon subjects were comparable to those of normal subjects. There were no significant differences in MCST-NF and MCST-IR response times across subject groups (Fig. 3B).

FMRI Data

The S minus C contrasts were obtained for all subject groups to identify the activation areas during set-shifting (Tables I and II). Overall, PD and normal subjects showed activations in one or more of the following areas during set-shifting: frontal, parietal, and temporal cortices. Activation areas were fewer in matched trials following positive outcomes (MCST-PF, MCST-CR) than in matched trials following negative outcomes (MCST-NF, MCST-IR).

Activations during set-shifting following positive outcomes (MCST-PF and MCST-CR)

There was a paucity of activation areas in normal and PDon subjects but not in PDoff subjects, during MCST-PF (Table I). In MCST-CR, only the right DLPFC and thalamus were activated in normal subjects, with an absence of activation areas in the PD group (with and without medication).

Activations during set-shifting following negative outcomes (MCST-NF and MCST-IR)

In MCST-NF, the right DLPFC was activated in normal and PDon subjects but not in PDoff subjects (Table II). On the other hand, the caudate nucleus was weakly activated in PDoff ($t = 2.9$, $P = 0.002$) but not in PDon and normal subjects. Posteriorly, normal subjects activated the parieto-temporal areas, mainly on the left side. PDoff subjects activated mainly the midline structures such as the cingulate cortex and precuneus. PDon subjects activated the right posterior parietal cortex (PPC) and bilateral temporal lobes. In MCST-IR, normal subjects activated the left DLPFC, together with strategic areas over the left parieto-occipital region and left superior temporal pole. Activation areas in PDoff subjects were limited to the right insula only. PDon subjects showed diffuse activations over frontal and posterior brain regions.

Effects of external feedback vs. internal feedback learning

Normal subjects activated the corticostriatal loop, such as the left medial PFC, right caudate, left thalamus, and

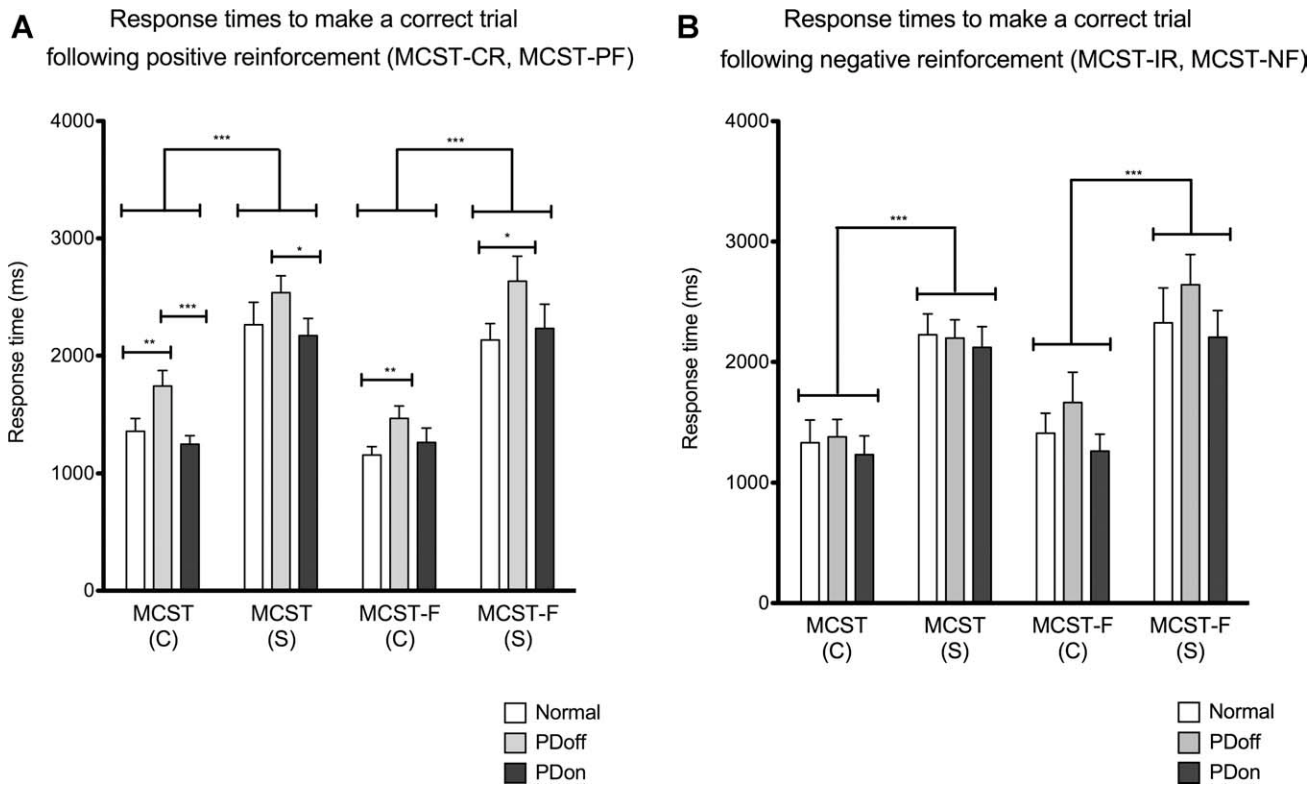

Figure 3.
Response times to make a correct trial following (**A**) positive reinforcement (MCST-CR, MCST-PF), and (**B**) negative reinforcement (MCST-IR, MCST-NF). Asterisks (*, **, ***) denote significance level at $P < 0.05$, $P < 0.01$, and $P < 0.001$ respectively. Error bar = Standard Error of Mean (SEM).

right supplementary motor area (SMA) during set-shifting through internal feedback (MCST minus MCST-F) (Table III), whereas the presence of an external feedback cue (MCST-F minus MCST) activated more of the mesocortical substrates (DLPFC, middle cingulate cortex [MCC], and insula on the right side) (Table IV). PDoff subjects had diffuse cortical activations during set-shifting through external feedback. Following levodopa replacement, the cortical activations were focused mainly over the anterior brain regions during set-shifting through external feedback.

TABLE I. Significantly activated regions in continuous shift (S) minus control (C) contrasts in set-shifting task: MCST-PF (with positive feedback) and MCST-CR (with correct responses)

	Normal			PDoff		
Area	*x*, *y*, *z*	*t*-stats	Cluster size	*x*, *y*, *z*	*t*-stats	Cluster size
MCST-PF						
VLPFC_R				52, 20, 20	3.56	63
PCN_L	−26, −52, 8	3.11	45			
MTG_R				46, −58, −4	3.19	34
MCST-CR						
DLPFC_R	24, −10, 58	3.96	101			
Thalamus_R	12, −8, −4	3.65	58			

The PDon group had no significant activations.
L, left; R, right; DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; PCN, precuneus; MTG, middle temporal gyrus. Locations identified by anatomical automatic labeling with cluster approach. Peak threshold levels at $P < 0.005$ (uncorrected). Number denotes *t*-statistics. Cluster size = number of activated voxels.

TABLE II. Significantly activated regions in continuous shift (S) minus control (C) contrasts in set-shifting task: MCST-NF (with negative feedback) and MCST-IR (with incorrect responses)

	Normal			PDoff			PDon		
Area	*x*, *y*, *z*	*t*-stats	Cluster size	*x*, *y*, *z*	*t*-stats	Cluster size	*x*, *y*, *z*	*t*-stats	Cluster size
MCST-NF									
DLPFC_R	30, 56, 8	6[a,b]	25071				32, 26, 34	3.43	77
VLPFC_L							−50, 14, 8	3.05	30
VLPFC_R							52, 12, 32	5.96[a,b]	230
Medial PFC_L				6, 50, 28	3.85	457			
PMC_L				−42, −4, 40	3.5	75			
ACC_R				12, 44, 12	3.16	53			
MCC_L	−8, −40, −52	3.51[a]	37	−16, −32, 46	3.38	120			
				−8, 14, 44	3.69	213			
MCC_R	10, −28, 46	3.65[a]	245				10, 14, 40	3.8	95
Insula_L							−26, 26, −4	3.78	99
SSC_L	−32, −38, 52	3.39[a]	33						
SSC_R	40, −32, 46	3.14[a]	36						
AG_R				42, −56, 34	3.74	90			
PPC_R							40, −46, 44	3.36	52
PCN_L	−18, −56, 38	3.69[a]	174	−10, −46, 50	3.07	31			
PCN_R				4, −60, 22	3.26	99			
STG_R							56, −46, 24	3.11	40
MTG_L							−52, −52, 22	3.27	30
ITG_L	−46, −58, −14	4.71[a,b]	88						
Caudate_R				16, 6, 14	2.9	37			
MCST-IR									
DLPFC_L	−12, 32, 50	3.3	43				−18, −10, 56	3.24	54
DLPFC_R							18, 14, 44	3.14	79
Lateral OBF_R							36, 30, −10	3.41	39
SMA_R							16, −16, 54	3.2	50
Insula_L							−28, 16, −18	3.52	85
Insula_R				38, −2, 2	4.05	50			
AG_L	−50, −54, 32	3.64	42						
STP_L	−48, 18, −26	3.39	63						
HC_R							26, −46, 0	2.98	42
PHG_L							−14, −28, −16	4.22	87
PHG_R							20, −26, −16	4.34	106
OC_L	−48, −70, 2	3.77	40						

L, left; R, right; DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; lateral OBF, lateral orbitofrontal cortex; medial PFC, medial prefrontal cortex; PMC, primary motor cortex; SMA, supplementary motor area; ACC, anterior cingulate cortex; MCC, middle cingulate cortex; SSC, somatosensory cortex; AG, angular gyrus; PPC, posterior parietal cortex; PCN, precuneus; STP, superior temporal pole; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus; HC, hippocampus; PHG, parahippocampal gyrus; OC, occipital cortex. Locations identified by anatomical automatic labeling with cluster approach. Peak threshold levels at $P < 0.005$ (uncorrected). Number denotes *t*-statistics. Cluster size = number of activated voxels.

[a]Activations that reach $P < 0.05$ with FDR corrections.

[b]Activations that reach $P < 0.05$ with FWE corrections.

Intergroup comparisons during internal feedback learning

Inter-group comparisons during MCST-CR showed cortical deactivations in the hypodopaminergic state (Fig. 4A). Compared with normal subjects, the deactivations in the right DLPFC were greater in PDoff ($t = 4.16$, $P < 0.0001$) than in PDon subjects ($t = 3.71$, $P < 0.0001$). Inter-group comparisons during MCST-IR showed greater activity in the PD group compared with normal subjects, especially when levodopa replacement was given. The left PPC and the right middle temporal gyrus were activated more in the PD group than in normal controls. Greater activity was also noted in PDon than in normal subjects over diffuse cortical areas, including the right caudate nucleus. Within the PD group, the corticostriatal loop activity was restored after levodopa replacement: bilateral DLPFC, right putamen, and right SMA. The posterior cingulate cortex and striate cortex on the right side were activated more in PDoff than PDon subjects.

TABLE III. Significantly activated regions in MCST minus MCST-F contrasts in set-shifting task

	Normal			PDon		
Areas	*x*, *y*, *z*	*t*-stats	Cluster size	*x*, *y*, *z*	*t*-stats	Cluster size
Medial PFC_L	−8, 32, 48	3.63[a]	103			
RO_L	−46, 4, 8	3.94[a]	153			
SMA_R	10, −4, 56	3.95[a]	136			
MCC_L				−14, 0, 36	2.87	32
PCN_R				26, −48, 0	3.05	30
STP_L	−54, 14, −14	3.89[a]	30			
STG_R	34, −20, −20	4.62[a,b]	513	48, −6, −8	3.87	58
MTG_L	−56, −22, −8	3.85[a]	133	−58, −12, −10	3.11	125
MTG_R	62, −42, −6	4.29[a]	290			
FUG_L	−36, −22, −20	3.56[a]	42			
AMG_L	−18, 0, −22	4.95[a,b]	39			
EC_L	−18, −66, 2	3.82[a]	72	−22, −40, −2	3.58	227
Caudate_R	6, 18, −6	4.02[a]	452			
Thalamus_L	−14, −22, −2	3.2	48	−2, −22, 24	3.53	106

The PDoff group had significant activations only in the right DLPFC ($x = 48$, $y = 12$, $z = 46$, *t*-stats = 3.69, cluster size = 43).
Abbreviations as in Table I and II. FUG, fusiform gyrus; AMG, amygdala; RO, rolandic operculum; EC, extrastriate cortex. Locations identified by anatomical automatic labeling with cluster approach. Peak threshold levels at $P < 0.005$ (uncorrected). Number denotes *t*-statistics. Cluster size = number of activated voxels.
[a]Activations that reach $P < 0.05$ with FDR corrections.
[b]Activations that reach $P < 0.05$ with FWE corrections.

Intergroup comparisons during external feedback learning

The right VLPFC was deactivated in the hypodopaminergic state during MCST-PF (activations in normal > PDoff, $t = 3.16$, $P = 0.001$; activations in PDon > PDoff, $t = 3.38$, $P < 0.0001$). Comparing PDon to normal subjects, no significant differences in activity were noted in the PFC. Intergroup comparisons during MCST-NF showed increase activity in DLPFC without caudate activations in PDon compared with normal subjects (Fig. 4B). On the other hand, PDoff subjects showed activity in the caudate nucleus without activating the DLPFC. Besides the DLPFC, the areas that were deactivated in the PD group compared to normal subjects included the anterior cingulate cortex, MCC, supramarginal gyrus, and inferior temporal gyrus. Increased activations were noted in the temporo-parieto-occipital lobe in PDoff compared with normal subjects, and in the lateral orbitofrontal cortex, angular gyrus, and midline structures of PDoff compared with PDon subjects.

DISCUSSION

By introducing a card-sorting paradigm with and without external feedback cues, we were able to show the modulation effects of both levodopa and the feedback processes on set-shifting. Our results showed that PD subjects during "off" medication were less efficient in performing set-shift tasks compared with normal controls during both internal and external positive feedback learning. Levodopa replacement improved the cognitive processing speeds in our PD subjects without significant improvement in task accuracy. On the other hand, the ability to set-shift through negative outcomes was not affected in PD subjects, both during "off" and "on" medication states. Taken together, these findings are in accordance with the observations by Frank et al. [2004] in that PD subjects during "off" medication are better at learning through errors whereas PD subjects after levodopa replacement are more responsive to positive outcomes. Although the improvement in bradykinesia following levodopa replacement may improve the overall task response time, there were no significant differences in the visuomotor reaction speeds across subject groups. That is, the speed at which a subject initiated a motor response following a visual stimulus was relatively unaffected by levodopa. Hence, the changes in task response times reflected differences in cognitive processing speeds and not improvements in motor speeds alone. Our work based on in vivo fMRI experiments confirm the findings of Frank et al. [2004] based on computational modeling and cognitive procedural learning tasks.

Studies have shown that PD subjects perform cognitive tasks better through external feedback rather than through internal attentional control [Brown and Marsden, 1988a,b; Fimm et al., 1994; Horstink et al., 1990; Hsieh et al., 1995]. Likewise, PD subjects in our study showed improvement in task accuracy following external feedback learning without significant effects on the task response times. In addition, our findings showed that the ability to set-shift depended not only on the functioning DLPFC but also on

TABLE IV. Significantly activated regions in MCST-F minus MCST contrasts in set-shifting task

	Normal			PDoff			PDon		
Areas	x,y,z	*t*-stats	Cluster size	x,y,z	*t*-stats	Cluster size	x,y,z	*t*-stats	Cluster size
DLPFC_R	26, 28, 44	3.28[a]	30						
VLPFC_L							−46, 16, 6	4.15[a]	180
VLPFC_R							52, 12, 32	5.31[a,b]	220
PMC_L				−42, −4, 38	3.46	106			
RO_R							44, −16, 18	3.41	41
SMA_L				−8, 14, 44	2.91	31			
ACC_L				−16, 54, 14	3.71	481			
MCC_L				−16, −34, 46	3.53	144			
MCC_R	10, −30, 48	3.31[a]	63						
	8, −44, 36	3.07[a]	42						
Insula_L				−28, 36, 2	4.84[a,b]	393			
Insula_R	30, 12, −16	3.72[a]	72	38, −30, 24	3.05	31			
SSC_R	40, −32, 44	3.1[a]	38	40, −26, 36	3.26	35			
AG_R				42, −56, 34	3.65	62			
SMG_L				−50, −42, 28	3.81	141			
PPC_R							40, −48, 44	3.6	88
PCN_L				−8, −46, 50	3.14	40			
PCN_R				6, −60, 22	3.01	58			
ITG_L	−44, −58, −14	3.53[a]	61						
ITG_R	46, −50, −10	3[a]	42						
OC_L				−38, −70, 24	3.43	116			
SC_R							18, −84, 36	3.74	100
Caudate_R				18, 8, 14	3.32	164			
Thalamus_L				−24, −30, 16	3.44	99			
Thalamus_R							6, −22, 2	3.08	35

Abbreviations as in Table I, II, and III. SMG, supramarginal gyrus; SC, striate cortex. Locations identified by anatomical automatic labeling with cluster approach. Peak threshold levels at $P < 0.005$ (uncorrected). Number denotes *t*-statistics. Cluster size = number of activated voxels.

[a]Activations that reach $P < 0.05$ with FDR corrections.

[b]Activations that reach $P < 0.05$ with FWE corrections.

the interaction between the PFC and the other cortical areas. These interactions were modulated by the dopamine status of the subjects as well as the types of feedback cues provided. Overall, normal subjects in our study activated a set of cortical areas in the frontal, parietal, and temporal regions during set-shifting, similar to those reported in other studies [Lie et al., 2006; Monchi et al., 2007; Nagahama et al., 1996; Rogers et al., 2000; Wager et al., 2004]. In addition, our study showed that the corticostriatal loops (medial PFC, SMA, caudate nucleus) were activated during internal feedback learning whereas the mesocortical substrates (DLPFC, cingulate cortex, insula) were activated in the presence of external feedback cues. Intergroup comparisons showed the lateral prefrontal cortex was deactivated in PDoff subjects during positive feedback learning, especially following internal feedback cues. The cortical activations were increased in the posterior brain regions in PDoff subjects following external feedback learning, especially when negative feedback cues were provided. Levodopa replacement did not completely restore the activation patterns of PD subjects to normal although most activations in the corticostriatal loops were restored.

Our study, in particular, showed that both PD and normal subjects had reduced cortical activations during matching following positive outcomes (MCST-CR, MCST-PF), and increased cortical activations during matching following negative outcomes (MCST-IR, MCST-NF). While the increase in cortical activations has been associated with poor task performance [Wager et al., 2005] and the exploratory phase of feedback learning [Sailer et al., 2007], it may also be a compensatory mechanism triggered by individual subjects to cope with the set-shift demands [Dagher et al., 2001; Samuel et al., 1997]. In particular, cortical activations were increased in our PD subjects compared with normal controls during MCST-NF without compromising the task performance. Studies on primates have shown a phasic rise in dopamine levels when a reward is presented, and a phasic fall in dopamine levels when an error is made [Schultz et al., 1997]. The phasic changes in dopamine levels in response to the different feedback cues will lead to different cortical activations, depending on whether the mesocortical or the nigrostriatal pathways are affected [Cohen and Frank, 2009; Frank, 2005; Guthrie et al., 2009]. Our findings suggest that the

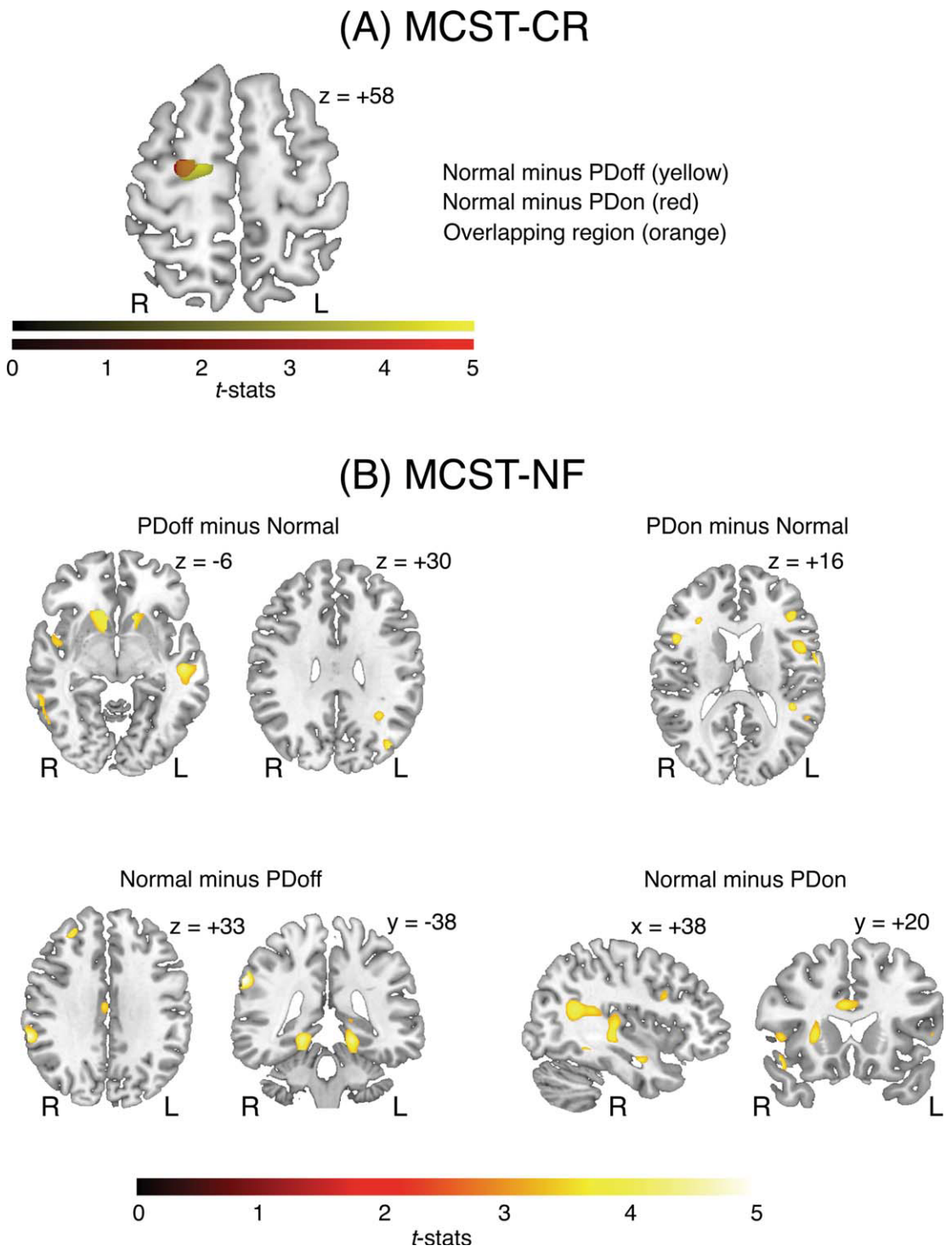

Figure 4.

Intergroup comparisons of fMRI activation patterns in (**A**) MCST-CR, and (**B**) MCST-NF. A: Deactivations were noted in the right DLPFC in the hypodopaminergic state during MCST-CR. Compared with normal subjects, the deactivations were greater in PDoff ($t = 4.16$, $P < 0.0001$) than in PDon subjects ($t = 3.71$, $P < 0.0001$). B: In MCST-NF, greater activations were observed in the PDoff group compared to normal subjects in the caudate nucleus and posterior brain regions, without activating the DLPFC. On the other hand, greater activations were observed in the PDon group compared to normal subjects in the DLPFC, without caudate activations. Both PDoff and PDon groups showed deactivations in the cingulate cortex, supramarginal gyrus, and inferior temporal gyrus, when compared with normal subjects. The significance values are given as color-coded *t*-statistics.

increase in cortical activations observed in MCST-NF is mediated via the mesocortical pathways [Cools et al., 2002; Mattay et al., 2002; Monchi et al., 2007] through phasic decrease in dopamine levels following an error response [Schultz et al., 1997]. Dopamine deficiency in the mesocortical pathway leads to cortical disinhibition with a loss of focusing effect of neural activity in the frontal lobe (and hence increased cortical activations) [Cools et al., 2002; Mattay et al., 2002; Monchi et al., 2007]. Set-shift deficits observed in PDoff subjects in our study during learning through positive outcomes were explained by deactivations in the lateral PFC as compared with normal subjects. In particular, the right DLPFC was deactivated in MCST-CR and the right VLPFC was deactivated in MCST-PF. The reduced activations in the lateral PFC may be explained by nigrostriatal dopamine deficiency with an increase in thalamocortical inhibition [Albin et al., 1989; Alexander et al., 1986; Cools, 2006; Owen et al., 1998].

When a mental shift in task strategies is required, such as matching following an incorrect response (MCST-IR), we noted activations in the left DLPFC together with strategic areas over the left hemisphere (angular gyrus, superior temporal pole, occipital lobe). These cortical interactions were absent in PDoff subjects, likely due to nigrostriatal dopamine deficiency with reduced DLPFC activation [Albin et al., 1989; Nagano-Saito et al., 2008]. However, we noted PDoff subjects were able to compensate by activating the right insula to cope with the set-shift demands [Soros et al., 2007; Taylor et al., 2009]. Intergroup comparisons indicated that the PD group was able to activate greater resources in the PPC than normal subjects. Both PPC and insula have been reported to mediate attentional set-shifting [Fox et al., 2003; Sylvester et al., 2003]. The involvement of these areas may suggest possible non-dopaminergic pathways in mediating set-shifting [Kehagia et al., 2009; Lewis et al., 2005]. On the other hand, although activations in the corticostriatal loops (DLPFC, SMA, putamen) were restored in PD subjects following levodopa replacement, the activation patterns in PD subjects did not return completely to normal. There were diffuse cortical activations in PDon subjects in the PFC and posterior brain regions compared to either PDoff or normal subjects. With no significant differences in task performance across subject groups in MCST-IR in our study, the increase in cortical activations in PDon subjects may suggest a less efficient compensatory mechanism in PD subjects after levodopa replacement. Possible explanations may include functional disconnectivity in the cortical regions as a result of oversaturating the relatively intact mesocortical dopaminergic networks with levodopa [Rowe et al., 2008], i.e., the inverted U-shape dose response between dopamine and cognitive function [Cools, 2006; Tunbridge et al., 2006; Williams-Gray et al., 2008]. Others have suggested that it is the phasic changes in dopamine levels, which modulate the cortical activations, and the levodopa replacement likely blunted the phasic dopaminergic response [Frank, 2005; Guthrie et al., 2009]. It is also possible that the cognitive processes involved in this domain are not subject to dopaminergic depletion at all [Kehagia et al., 2009; Lewis et al., 2005]. In any case, the increase in cortical activations observed in PDon compared with normal subjects in MCST-IR, despite having comparable set-shift performance in our study, suggests a less efficient functional network in PDon subjects to cope with the set-shift demands [Fimm et al., 1994].

There were several limitations to our study. Our sample population could be small and restricted to PD subjects who were stable responders to levodopa treatment. There could be differences in brain activation patterns and learning strategies in treatment naive subjects and motor fluctuators [Kulisevsky, 2000; Kulisevsky et al., 1996]. Future studies could evaluate the effects of levodopa treatment in these groups of patients. In our study, PD subjects performed the fMRI experiments twice within one day. There were concerns that fatigue and "learning effects" may confound the fMRI data. However, we did not notice any significant difference in the visuomotor reaction time across subject groups, which is a surrogate measure of attention and concentration. In order to minimize these effects, we had all subjects trained adequately on the tasks to ensure that the learning had reached a plateau before scanning. Moreover, the task conditions were presented at random order for both fMRI experiments so that 'learning effects' were kept to a minimum.

The order in which PD subjects were scanned was not counterbalanced in our study due to local logistic requirements for PD subjects to have both "off" and "on" scans performed in a day. While we acknowledge that the order in which PD subjects were scanned ("off" medication followed by "on" medication) may offer significant confound in terms of the "order effect" [Konishi et al., 2008], the changes in activation patterns observed in our study from PDoff to PDon were different from those reported in normal subjects with initial versus subsequent shifts on the Wisconsin Card Sorting Task [Konishi et al., 2008]. Moreover, the activation patterns of PDon minus PDoff subjects were different across task conditions, with corresponding behavioral results consistent with those reported by Frank et al. [2004]. Therefore, even though underlying "order effect" cannot be completely excluded, our findings do suggest possible interactions between levodopa and the feedback process on set-shifting. Nonetheless, the "order effect" will need further evaluation in future studies.

The use of dopamine agonists in some of our PD subjects may confound the interpretation of the results in this study, since dopamine agonists may have an effect on executive functions [Costa et al., 2009]. Fortunately, the plasma elimination half-lives of the dopamine agonists used by our PD subjects were relatively short (3–8 h for bromocriptine, 3–6 h for ropinirole) [Foley et al., 2004], and the 12-h overnight withdrawal of antiparkinson medication is generally acceptable to define the clinically "off" state in PD subjects [Langston et al., 1992].

In conclusion, we observed differences in set-shift task performance and brain activation patterns across subject

groups, modulated by the dopamine status of the subjects and also the types of feedback provided. The ability to set-shift in subjects depended not only on the DLPFC [Goel and Vartanian, 2005; Nagahama et al., 1996; Wager et al., 2005], but also on the interactions between the PFC and the posterior brain regions [Cole and Schneider, 2007; Hampshire and Owen, 2006; Nagahama et al., 1999; Rogers et al., 2000; Wager et al., 2004]. Our findings showed that PD subjects had impaired set-shifting through positive outcomes during "off" medication, which was mediated via reduced lateral PFC activations. We also observed that the ability to set-shift through negative feedback was not affected in PD subjects (both "off" and "on" medication), possibly due to compensatory changes outside the nigrostriatal dopaminergic pathway (i.e., the mesocortical dopaminergic substrates or non-dopaminergic pathways) as suggested by the fMRI findings in our study.

ACKNOWLEDGMENTS

The authors thank Ms. Irene Seah for her assistance in recruiting subjects and performing the quantitative motor assessments, Ms. Keren-Happuch E. Fan Fen for performing the behavioral tasks, and Dr. Oury Monchi for his advice on the experimental design. Dr. Paulito Palmes is supported by funding from the Singapore Millennium Foundation Limited.

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