Impaired executive function signals in motor brain regions in Parkinson's disease ☆

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ARTICLE INFO

ABSTRACT

Recent evidence has shown that patients with Parkinson's disease (PD) often display deficits in executive functions, such as planning for future behavior, and these deficits may stem from pathologies in prefrontal cortex and basal ganglia circuits that are critical to executive control. Using the antisaccade task (look away from a visual stimulus), we show that when the preparatory 'readiness' to perform a given action is dissociated from the actual execution of that action, PD patients off and on dopamine medication display behavioral impairments and reduced cortical brain activation that cannot be explained by a pathology related to dysfunction in movement execution. Rather, they show that the appropriate *task set* signals were not in place in motor regions prior to execution, resulting in impairments in the control of subsequent voluntary movement. This is the first fMRI study of antisaccade deficits in Parkinson's disease, and importantly, the findings point to a critical role of the basal ganglia in translating signals related to rule representation (executive) into those governing voluntary motor behavior.

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Introduction

To perform a voluntary movement requires not only that the brain is functioning optimally to guide its execution, but that the brain is also properly *pre*set in order for the correct movement to be initiated. Presetting means the adoption of a *task set* (a rule about how to behave), which in the present study means preparing to execute a voluntary eye movement based on a colored cue. In Parkinson's disease (PD), the traditional focus has been on understanding the better-known deficits in motor execution and tremor (Betchen and Kaplitt, 2003), but recent evidence has pointed to the importance in understanding deficits in executive control that often surface in the disorder (Leh et al., 2010; Rodriguez-Oroz et al., 2009). Here, we provide direct evidence that these *cognitive* deficits related to task set establishment may be more important to the impaired control of voluntary movements in PD than previously thought.

We utilize a well-characterized measure of the ability for people to override an automatic response with an alternative, voluntary response that is more difficult to perform. Participants are required to refrain from initiating an automatic, visually-triggered eye-movement (a prosaccade) in the direction of an abruptly appearing visual stimulus, and to instead initiate a voluntary saccade in the opposite direction (an antisaccade) (Munoz and Everling, 2004). To do this successfully, a network of cortical and sub-cortical brain regions, including dorsolateral prefrontal cortex (DLPFC) (Guitton et al., 1985; Pierrot-Deseilligny et al., 1991), frontal, parietal and supplementary eye-fields (FEF, PEF and SEF) (Brown et al., 2007; Connolly et al., 2002; Curtis and D'Esposito, 2003; DeSouza et al., 2003; Ford et al., 2005), and the basal ganglia (BG) (Ford and Everling, 2009; Watanabe and Munoz, 2009, 2010) is required to come online prior to the appearance of the visual stimulus so that the motor system (i.e., FEF) is preset towards the appropriate action (Munoz and Everling, 2004).

We (Cameron et al., 2010; Chan et al., 2005) and others (Amador et al., 2006; Briand et al., 1999; Hood et al., 2007; Rivaud-Pechoux et al., 2007) have shown that PD patients display deficits in the antisaccade task, such that they are slower to initiate this voluntary response, and often execute a prosaccade in error with greater frequency. Recent evidence also shows that hypo-activation measured by functional Magnetic Resonance Imaging (fMRI) occurs

throughout the frontal cortex during voluntary saccade initiation in PD (Rieger et al., 2008), following general observation of hypo-activation in the brains of PD patients during complex tasks demanding attentional control (Dagher and Nagano-Saito, 2007). In the present study we reveal for the first time correlates of these well known antisaccade deficits in PD, and more importantly, provide evidence that hypo-activation in fMRI signals in PD occur more prominently in motor areas crucial to antisaccade generation during a *preparatory* stage, rather than during the execution of the actual response. We suggest that this corresponds to the failure to establish the appropriate task set, providing for a neural correlate of the behavioral deficits observed in PD when performing voluntary actions.

Methods

PD patients, on and off (>18 h from the previous dose) their regular dopaminergic medication (Table 1), and age-matched control subjects participated in a rapid event-related fMRI design with pro and anti *saccade* trials interleaved with pro and anti *instruction only* ('prep') trials (Fig. 1). This design allowed us to examine activation related to establishing an antisaccade task set (prep trials), separately from executing the antisaccade response, and to examine the effect of regular dopaminergic therapy on performance and fMRI activation. Correct anti trials were compared to pro trials and to errors on anti

trials, to examine the differential patterns in brain activation across the groups for these response types. All experiments were approved by the Research and Ethics Board of Queen's University, and adhered to the principles of the Canadian Tri-council Policy Statement on Ethical Conduct for Research Involving Humans, following the principles of the Declaration of Helsinki.

Participants

Twenty-eight patients with mild to moderate PD were recruited from the movement disorders clinic at the Kingston General Hospital by co-author GP, and were required to participate in two sessions (counterbalanced for medication order). Patients underwent an evaluation of motor function (Unified Parkinson's Disease Rating Scale), cognitive status (Mini-Mental State Examination) and depression (Beck Depression Inventory). Scores for each patient are shown in Table 1. Of this, 13 patients were utilized for full analysis because of the following exclusion criteria: patients could not score less than 26/30 on the MMSE, could not score higher than 15 on the BDI, were required to participate in two sessions of the experiment (on and off their regular dopaminergic medication), were able to successfully perform the task and provide online eye-tracking data, did not posses any visual abnormalities (e.g., macular degeneration or cataracts) or structural abnormalities other than diffuse white matter

Table 1
Clinical information for PD patients.

Patients	Sex	Age (yrs)	Off MEDS MMSE	BDI	UPDRS Part II (ADL)	Part III (motor)	Part V (Hoehn and Yahr)	Part VI (Schwab and England)	On MEDS MMSE	BDI	UPDRS Part II	Part III	Part V	Part VI	Med.	LED (mg)	Yrs since initial diagnosis
1	m	69	29	9	6	10	2.0	90	29		3	12	2.5	90	L	250	0.25
2	m	57	30	12	15	32	2.5	90	30		13	29	2.5	80	L	200	8.00
3	f	74	30	12	7	21	2.5	90	29	9	9	16	2.0	90	L, P	600	4.50
4	m	66	28	15	8	10	2.0	90	29	13	8	13	2.0	90	P	150	6.75
5	m	71	30	2	7	16	1.0	100	29	2	6	8	1.0	100	A, R	160	3.75
6	f	52	29	1	5	24	2.5	90	28	4	7	15	2.0	90	P	450	3.00
7	m	63	28	9	11	39	2.5	90	30	4	10	29	2.0	90	R	280	1.25
8	f	71	30	8	8	29	2.0	90	29	8	9	20	2.0	90	L, P	300	1.50
9	f	64	30	10	11	20	2.5	90	30	6	9	15	2.5	90	L	300	0.50
10	f	59	30	5	11	23	2.5	90	30	9	11	26	3.0	90	R	15	1.00
11	f	65	30	14	11	19	2.0	90	30	11	12	21	2.0	90	L, R	460	5.25
12	m	60	28	1	3	18	1.5	90	27	0	2	18	2.0	100	P	37.5	0.00
13	m	70	30	7	15	44	2.0	90	30	14	14	33	2.0	90	A, L, P	700	5.50
14mo	m	50	29	13	8	42	3.0	90	29	13	4	10	2.0	90	L, M	900	4.75
15md	m	67	30	4	3	10	1.0	100	–	–	–	–	–	–	–	0	0.00
16 t1	m	59	*29*	*12*	*16*	*31*	*3.0*	*90*	28	16	14	30	3.0	90	L	700	1.00
17 t1	f	68	*29*		*15*	*54*	*3.0*	*80*	30	8	7	13	2.0	90	L, R	335	11.50
18 t1	m	38	–	–	–	–	–	–	29		2	18	2.0		A, E, L, R, S	1831	5.50
19 t1	f	64	–	–	–	–	–	–	30		5	16	2.5	90	P	200	1.50
20 t2	m	54	30	5	11	26	2.0	90	30	15	11	37	2.0	90	P	125	0.25
21bdi	f	69	30	25	22	52	4.0	60	29	37	24	40	4.0	60	L, P	1575	5.25
22nv	m	51	30	0	8	22	2.0	90	30	0	8	29	2.0	90	P	150	0.25
23nv	m	77	27	9	13	40	3.0	90	29	7	7	23	2.0	90	E, L, S	1131	8.00
24nv	f	68	30	3	7	37	2.5	90	30	3	5	18	1.5	90	L, P	500	2.50
25f1	m	67	*27*	*7*	*11*	*39*	*3.0*	*90*	25	6	14	40	3.0	90	L, S	875	0.50
26f	f	75	–	–	–	–	–	–			14	27	3.0	80	L, P	675	8.75
27f	m	80	–	–	–	–	–	–			10	33	2.0	80	L		4.50
28f	m	70	–	–	–	–	–	–	27	7	11	37	2.0	90	L, M, R	1070	5.75
mean (n=28)	17 m; 11f	64.2	29.3	8.3	10.1	28.6	2.3	89.1	29.0	9.1	9.2	23.2	2.2	88.5			3.62
mean (n=13)	7 m; 6f	64.7	29.4	8.1	9.1	23.5	2.1	90.8	29.2	7.3	8.7	19.6	2.1	90.8			3.17
Controls mean (n=13)	7 m; 6f	64.8															

Symbols and definitions: A, anticholinergic (trihexyphenidyl); ADL, Activities Of Daily Living; BDI, Beck Depression Inventory; E, entacapone; L, levodopa/carbidopa; LED, Levodopa Equivalent Dose; M, monoamine oxidase inhibitor (rasagiline); Med., medications; MMSE, Mini Mental State Examination; P, pramipexole dihydrochloride; R, ropinirole HCl; S, amantadine; UPDRS, Unified Parkinson's Disease Rating Scale; Yrs, years; '–', not applicable; (blank), not assessed. Exclusions: mo, motion>2 mm (both sessions); md, no medication history (participated in off meds session only); t1, failed eye tracking in 1 session (*italicized*) (subjects 18 and 19 were not required to participate in second session); t2, failed eye tracking in both sessions; bdi, Beck Depression Inventory scores>15; nv, neurological or visual confounds (atrophy in oculomotor regions, macular degeneration, or cataracts); f1, could not perform task off meds (*italicized*); f, could not perform task on meds (not required to participate in off meds session).
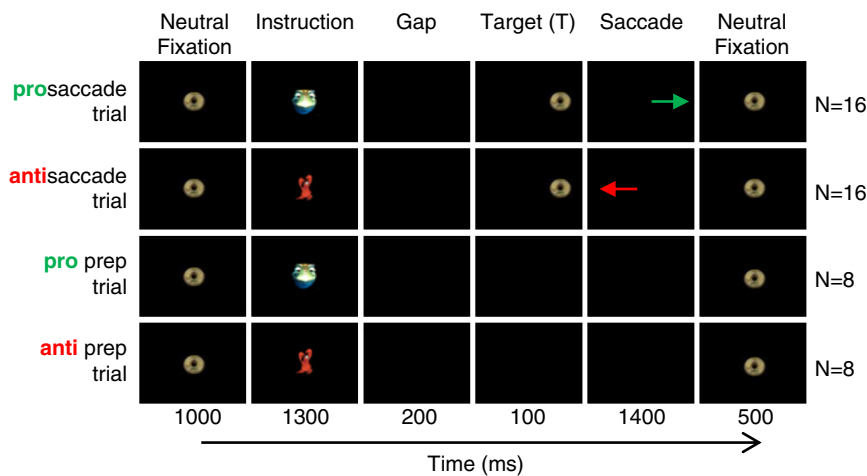
Fig. 1. Representation of stimuli and timing of events in the 4 trial types. Trials were pseudorandomly presented and intermixed with periods of fixation on the Neutral Fixation stimulus that were 1.5, 3 and 4.5 s in length. (Arrows in saccade trials were not actually displayed).

hypodensities not occurring in the saccade regions of interest (defined below), and did not move more than 2 mm from starting position in the fMRI scans. Individual reasons for exclusion are listed in Table 1. In the end, the 13 'core' patients consisted of 7 males, with a mean age of 64.7 years, range of 52–74, and a mean maximum movement in any direction of 1.03 mm (off-meds), and 1.04 mm (on-meds) in the fMRI scans. (Note that some patients that did not meet the exclusion criteria were utilized for additional correlational analyses to improve power (Fig. 7), providing they met the diagnosis for PD and could perform the task in one or both sessions successfully). Each core patient was age-matched to a control subject that fit the criteria for exclusion described above, and that did not possess any neurological/psychiatric disorders as assessed by experimenter questioning and the use of the MMSE or Montreal Cognitive Assessment exam. The control subjects (13) consisted of 7 males, with a mean age of 64.8 years, range of 51–74, and a mean maximum movement in any direction of 0.96 mm in the functional runs.

Experimental design

64 trials were presented in a given run (totaling 277.5 s) and were presented in a rapid event-related fMRI design (Fig. 1). Each run contained a pseudorandom presentation of 16 'prosaccade' trials, 16 'antisaccade' trials, 8 'pro prep' trials (instruction only), 8 'anti prep' trials, and 16 'fixation' only trials. Prosaccade and antisaccade trials began with 1000 ms of fixation on a central fixation stimulus (approximately 2° of visual angle). This neutral fixation stimulus was a hollow gold coin. The pro or anti instruction was then presented for 1300 ms, and was either a green stimulus (a turtle), or a red stimulus (a lobster), of the same size. (These stimuli were chosen based on the conduction of this identical experiment for comparison across other neurological disorders which included child-age participants). A gap of 200 ms in the central stimulus subsequently occurred prior to the presentation of the peripheral, 'target' stimulus (gold coin) for 100 ms at 6 or 7° to the left or right of fixation. The gap was employed to push the subjects towards automatic responding, by increasing the occurrence of short-latency 'express' prosaccades (described in the Results section) (Dorris et al., 1997; Fischer and Weber, 1997). Following the presentation of the target, 1400 ms of darkness occurred, in which subjects were required to initiate a saccade to the location of the target on a prosaccade trial, or to its mirror location on an antisaccade trial. If they executed the incorrect response (a direction error), they were instructed to correct themselves. A period of 500 ms of neutral fixation was then included to return the subjects' fixation to center. Subjects were encouraged to wait for this fixation

stimulus before returning their gaze. 'Prep' trials were identical, but did not include the presentation of the target, and thus contained a period of 1700 ms of darkness following the instruction, and subjects were required to remain fixated at center. Under this design, saccade and prep trials were 4500 ms (3 TRs of 1.5 s, described below) in length. Trials containing only the neutral fixation point were also included, such that 8 of these trials were 1 TR in length, 4 were 2 TRs and 4 were 3 TRs in length. The inclusion of prep trials and fixation trials of varying length were necessary for the fMRI analysis (Dale, 1999; Ollinger et al., 2001). All runs began with an additional period of fixation for 3 s (to account for the fMRI signal to reach stead-state longitudinal magnetization), and ended with a period of fixation for 16.5 s, to allow for the return of the hemodynamic response signal to the baseline level of activation. Each subject performed between 6 and 8 runs.

Eye position data was recorded at 120 Hz using an ISCAN ETL-400 camera (Burlington, MA, USA). The camera was positioned next to a screen (located at the head end of the magnet), approximately 50 cm from the magnet bore to view the right eye of the subject in a mirror placed on the head coil. An infrared fiber-optic illuminator was fixed to the head coil. This illuminated the subject's right eye from an angle of approximately 45° below the eye. Prior to the first functional scan, calibration of the eye tracker was conducted using a nine-point calibration routine. Visual stimuli were generated using E-Prime (Psychology Software Tools Inc., Pittsburgh, PA, USA) running on a PC, and an NEC LT265 DLP video projector (Tokyo, Japan) was used to back-project the image onto the screen. The projector had a refresh rate of 60 Hz.

Functional images were acquired with 24 horizontal slices (3.3 mm thick) covering the brain from the top and including the frontal/prefrontal, parietal, visual areas, and BG to the level of the ventral striatum. Each functional volume consisted of a $T2^*$-weighted echo-planar images (EPI) sensitive to blood oxygen-level dependent (BOLD) contrast (Kwong et al., 1992; Ogawa et al., 1990) acquired in an interleaved fashion (repetition time, TR = 1500 ms; echo time, TE = 30 ms; flip angle, FA = 72°, field-of-view, FOV = 211 × 211 mm, matrix size 64 × 64, 3.3 mm isovoxel resolution, 185 volumes). High-resolution MP-RAGE 3D T1-weighted scans were acquired for anatomical localization (TE = 2.2 ms, TR = 1760 ms, FA = 9°; 176 slices, 1 mm thick).

Data analysis

Behavioral data were analyzed with custom MATLAB v7.04 programs (The MathWorks Inc., Natick, MA) and imaging data were analyzed using BrainVoyager QX v2.1 (Brain Innovation, Maastricht,

The Netherlands) and SPSS Statistics version 17.0 (IBM, Chicago, IL). Correct trials were separated from incorrect trials, consisting of: direction errors on saccade trials, SRTs<90 ms (anticipatory errors), SRTs>1000 ms, saccades in the wrong direction *after* a correct response, and saccades during prep and fixation trials or periods. The first two imaging volumes were removed for steady state magnetization, and then pre-processing steps were performed including rigid-body 3D motion correction to the first of the remaining volumes in each run, slice scan-time correction with a cubic-spline interpolation, temporal filtering (high-pass filter with cut-off of 3 cycles/run and linear trend removal), and 3D spatial smoothing with a 4 mm FWHM Gaussian kernel. A 'deconvolution' analysis was then performed in BrainVoyager, such that the hemodynamic response was estimated using stick predictors in a 13-point time series with a temporal resolution of approximately 1TR (1.5 s) that was aligned with the start of each trial (actual times displayed in seconds in Figs. 3B, 6). This process was used to model the hemodynamic response for each trial type and cover the temporal extent of a typical hemodynamic response of approximately 20 s (20 s /13 ≈ 1.5 s). The trial types of interest consisted of: correct anti prep, correct pro prep, correct anti saccade, and correct pro saccade. Correctly performed fixation trials were not modeled explicitly so as to provide a baseline measure (Ollinger et al., 2001). All incorrect trials were classified together in the design matrix as an additional trial type of no interest, in order so that they would not contaminate the estimation of the BOLD signal for correct trials (Brown et al., 2007).

Main contrast analysis

A random-effects multi-subject general linear model (GLM) with a Z-normalization was run using the 5th to 7th time points (7.7, 9.3 and 10.8 s) from the onset of a saccade trial, to account for a reliable measure surrounding peak activation from trial onset as determined by preliminary examination. Data from correctly performed prosaccade trials was subtracted from correctly performed antisaccade trials, and group-level statistical maps were generated at a threshold of $P<0.01$ (T value = 3.06), corrected for multiple comparisons across the voxel population at $P<0.01$ (8 contiguous voxels). For each group, these statistical maps are superimposed on the average of the subjects' 3D anatomical data transformed into Talairach coordinate space (Fig. 3A). These statistical maps constitute the *main contrast*, and were used for subsequent Region of Interest (ROI) analysis pertaining to task set establishment, and response execution in saccade ROIs. ROI analysis was done in this fashion because the antisaccade requires additional control mechanisms (automatic response suppression, attention redirection, saccade 'vector inversion' to a location void of a stimulus) on top of more automatic prosaccade processes (Munoz and Everling, 2004), and so the contrast of antisaccade to prosaccade trials allows us to define ROI's where greater activation magnitudes on antisaccade trials is hypothesized to reflect these additional mechanisms.

ROI analysis

Two ROI analyses were conducted using random-effects GLMs to extract beta-weight parameter estimates of BOLD signal change from each of the saccade ROIs. These ROIs were selected as the 125 contiguous voxels (5×5×5) within a cubic cluster centered on the point of peak activation from the main contrast in the DLPFC, FEF, SEF, PEF and caudate nucleus (CN), defined by anatomical landmarks and known locations in Talairach space. For analysis pertaining to preparatory effects (Figs. 4A, 5A), the mean of the beta values from the 5th and 6th time points relative to prep trial onset was used to account for a measure of the peak preparatory activation. For analysis of saccade execution processes (Figs. 4B, 5B), the time points were shifted by 1.5 s to include only the 6th and 7th time points, as the onset of the peripheral target occurs 1.5 s (one time point) after the appearance of the instruction (Brown et al., 2007).

Direction error analysis

A comparison of BOLD signal time courses (13 time points) on correct and erroneously executed antisaccade trials (anti direction errors) was also conducted (Fig. 6), and for this, direction errors on both pro and antisaccade trials were incorporated as distinct events in an ROI analysis. The initial prosaccade was corrected on the majority of anti direction error trials (PD off-meds: 91%, PD on-meds: 92%, Controls: 91%) and therefore all anti direction error trials were included.

Statistical analysis

For behavioral data, one-way ANOVAs were performed across the three groups for pro and antisaccade responses separately (to confirm whether this study would reveal the known antisaccade performance deficits in PD, but also, possible differences in prosaccade performance), and t-tests were performed between two groups (illustrated in Fig. 2, and listed in full in Supplementary Table 1). Partial eta squared (η^2) and Hedges' g values are provided for effect sizes for ANOVAs and t-tests, respectively. One-way ANOVAs were also performed for fMRI ROI analyses across the three groups for pro and anti trials separately (Fig. 4), with independent t-tests performed between two groups (Supplementary Table 1). Note that because of the deconvolution design, a full factorial (ANOVA) analysis was not conducted to produce pro and anti contrast maps; this method would not provide sensible interpretations because each time point is modeled separately in the GLM, resulting in interactions between time points in the same response type (e.g., see Fig. 3B). Instead, anti processes were contrasted to pro processes within each group to produce contrast maps (Figs. 3, 5, Supplementary Figs. 1, 3, 4), which is a common approach in the saccade field. Our hypothesis was that there would be differences across the groups in anti activation magnitudes in the ROI analysis (Fig. 4), corresponding to impaired antisaccade generation in PD; however, we also investigated if there were differences in pro activation magnitudes. We were not interested in task (pro, anti) by group interactions, because the ROI's were already defined by an antisaccade–prosaccade contrast within each group, and because these interactions would not identify group deficits related specifically to antisaccade generation. Linear regressions were performed for correlations (Correlational analysis section and Medication effects section), and the t-test values on the coefficients are reported.

Results

Behavior

Fig. 2 illustrates the antisaccade deficits we observed in PD that were identical to those described previously (Amador et al., 2006; Briand et al., 1999; Cameron et al., 2010; Chan et al., 2005; Hood et al., 2007), providing the basis for an fMRI investigation of well-characterized antisaccade impairments in PD. Specifically, PD patients executed a higher proportion of anti direction errors (Fig. 2B, exemplified in Fig. 2A), and appeared to be overall slower at antisaccade initiation (increased saccade reaction time (SRT)) (Fig. 2D). Interestingly, *superior* prosaccade performance, in terms of fewer percentage direction errors, was observed in PD in comparison to controls (Fig. 2B), which was consistent with our recent study that also utilized an interleaved design containing trials that varied in the degree of executive control (Cameron et al., 2010). When a difference in % direction errors between pro and antisaccade trials in the current study was calculated (Fig. 2C), the result approached significance across the groups, $F(2,36)=2.80, P=0.07, \eta^2=0.13$. (The results from independent t-tests between two groups are illustrated throughout Fig. 2). PD patients also appeared to be faster at initiating a prosaccade, but slower at initiating an antisaccade (as described above) (Fig. 2D),
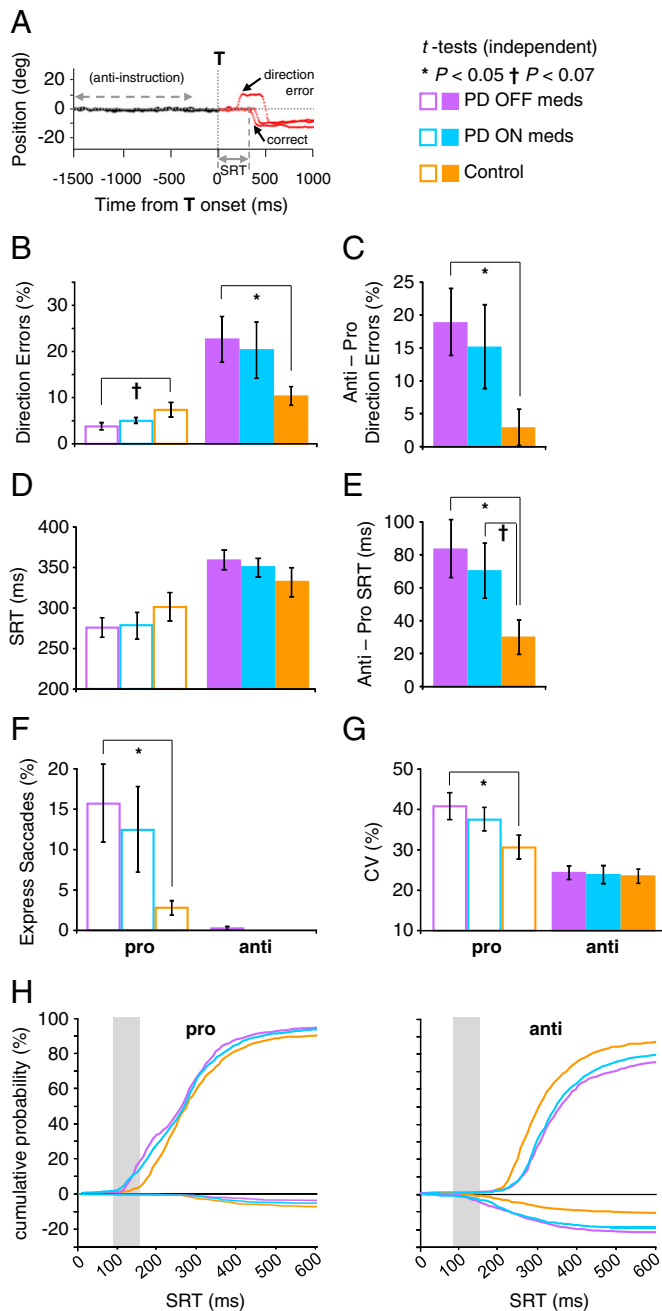
Fig. 2. Behavior. (A) Sample eye traces comparing correct antisaccade trials and anti-saccade direction error trials. (B) Mean percentage direction errors (initial saccade away from T on prosaccade trial, towards T on antisaccade trial). (C) Mean % anti direction errors–% pro direction errors. (D) Mean saccade reaction time (SRT) on correct trials. (E) Mean anti SRT–pro SRT. (F) Mean percentage 'express' saccades (90<SRT<160 ms). (G) Mean intrasubject coefficient of variation (CV) in SRT (standard deviation/mean×100). Error bars correspond to standard error of the mean (SE). (H) Cumulative probabilities of saccade distributions for all three groups (pooled SRT across subjects). Positive Y values indicate correct saccades, while negative Y values indicate direction errors (colored to indicate saccade type executed, e.g., anti or pro). Gray shaded region highlights the region calculated as 'express saccades' (90<SRT<160 ms).

resulting in a significant SRT difference between pro and antisaccade trials across the groups, $F(2,36) = 3.34$, $P<0.05$, $\eta^2 = 0.16$ (Fig. 2E). PD patients also displayed a higher proportion of pro 'express saccades' than the controls (Fig. 2F), which are the shortest-latency population of automatic saccades to a visual stimulus, with latencies typically described between 90 and 140 ms (Dorris et al., 1997; Fischer et al.,

1993), but with the upper boundary dependent on the participants age and laboratory conditions (Peltsch et al., 2011). The upper boundary was set at<160 ms in the current study, based on an observed separation between two SRT distribution sub-populations at this epoch in all three groups (not shown). It was also observed that PD patients were more variable in prosaccade SRT (Fig. 2G), as reported previously (Chan et al., 2005). Finally, the cumulative distributions of reaction times for correct and direction error trials summarizes the saccade behavior in each group (Fig. 2H); PD patients off-meds displayed the largest prosaccade 'bias' in reaction time (e.g., slower antisaccade SRT, but faster prosaccade SRT with a higher percentage of 'express' saccades and, interestingly, another population of short-latency prosaccades<200 ms in SRT) which contributes to their increased execution of inappropriate prosaccades on antisaccade trials.

Overall the behavior we observed was consistent with previous studies, highlighting the fact that PD patients are biased towards executing the more automatic prosaccade, and against the more voluntary antisaccade. Note however that medication did not result in significant improvements in performance, though it did make the behavior of PD patients more like the control subjects' than in their off-meds state.

fMRI

As described above, we based the fMRI analysis on comparing antisaccade to prosaccade processes, with the hypothesis that activation should be greater in saccade areas on anti trials, because antisaccades require additional executive processes critical to implementing the voluntary components of antisaccade generation (automatic response suppression, attention redirection, saccade vector inversion) that are not required on prosaccade trials (Munoz and Everling, 2004). Furthermore, we hypothesized that these processes should not be successfully implemented when an anti direction error is generated.

Main contrast

An initial contrast of correct antisaccade trials minus correct pro-saccade trials was made for all three groups (Fig. 3A) in order to identify regions previously shown with fMRI to display greater activation for antisaccades compared to prosaccades: DLPFC, FEF, SEF, PEF and caudate nucleus (CN) (Brown et al., 2006; Connolly et al., 2002, 2005; Curtis and D'Esposito, 2003; DeSouza et al., 2003; Luna et al., 1998; Luna et al., 1998; Sweeney et al., 1996). Fig. 3B exemplifies how this contrast was made using the 5th, 6th and 7th time points (see Methods subsection Main contrast analysis) for one of these regions. Talairach locations of the peak locations in all regions exceeding the statistical threshold are provided in Table 2. Having confirmed that greater activation for antisaccade generation compared to prosaccade generation occurs in these 5 ROIs in all three groups, we subsequently extracted the magnitudes of BOLD activations from two critical sub-processes of pro and antisaccade generation: task set establishment and response execution.

ROI analysis

Prep trials contain the task set component only, and we expected the prep trials to comprise the same preparatory state that would also be present in the first part of the saccade trials before the target was presented (Fig. 1). Therefore, prep trial activation should reveal the same underlying component of task set in the same ROIs defined by the main contrast. A random effects analysis of the peak locations within the DLPFC, SEF, FEF, PEF and CN ROIs, was conducted for pro and anti prep trials (Fig. 4A). (Unless indicated by 'R' for 'right', values from bilateral activations were averaged.) One-way ANOVAs revealed that significant or marginally significant group differences resulted for pro prep in CN, $F(2,36) = 5.75$, $P<0.01$, $\eta^2 = 0.24$ and SEF, $F(2,36) = 2.37$, $P = 0.1$, $\eta^2 = 0.12$, and significant or marginally
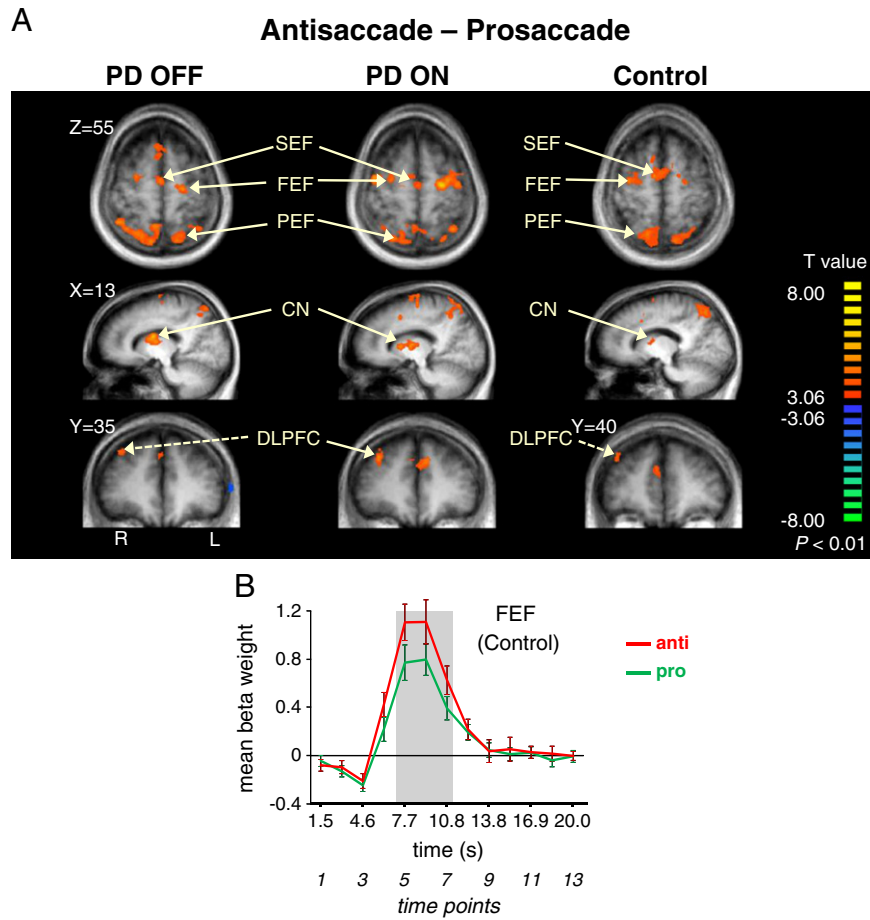
Fig. 3. Saccade trial contrast map. (A) Contrast of prosaccade trials subtracted from antisaccade trials (Fig. 1), thresholded at $P<0.01$, and cluster size corrected at $P<0.01$ (8 contiguous voxels). Significantly greater BOLD activation is shown in the saccade regions of interest for antisaccades ('hot' colors) as labeled. Dotted lines indicate putative DLPFC regions. Coordinate values of planes in Talairach space are indicated. (B) Representation of mean BOLD signal time course for pro and antisaccade trials from FEF region in control subjects in A. Shaded area corresponds to a region of peak activation from trial onset. The three time points (5,6,7) under the shaded area were used to compute the contrast maps in A. Error bars correspond to standard error of the mean (SE), R = right, L = left.

significant differences resulted for anti prep in CN, $F(2,36)=7.27$, $P<0.01$, $\eta^2=0.29$, PEF, $F(2,36)=3.19$, $P=0.05$, $\eta^2=0.15$ and SEF, $F(2,36)=2.64$, $P=0.09$, $\eta^2=0.13$. Subsequently, independent t-tests were performed to compare one group to another (uncorrected; shown in Fig. 4). Note that in general, the two frontal motor areas involved in antisaccade programming, SEF and FEF (Everling and Munoz, 2000; Schlag-Rey et al., 1997) had greater activation for both pro and anti preparation in the controls. A similar trend was shown in the PEF and CN.

The activation patterns related only to the saccade execution components were calculated using the same ROIs defined in the main contrast; however, prep trial activation was first subtracted from saccade trial activation, prior to pro being subtracted from anti, to isolate the components related to target appearance and saccade execution (Fig. 4B). No statistical differences between the group responses were observed, $F(2,36)=2.50$, $P>0.09$, other than between PD patients that were off- and on-meds in PEF for prosaccades ($P<0.05$, t-test, Fig. 4B).

Taken together, there were several differences in the ROI activation patterns between the groups that occurred during task set establishment, whereas there was only one difference between the groups found during saccade execution.

Direct prep trial and execution period contrasts

To complement the above analysis, we also contrasted pro and anti prep trial and execution period activations directly. The importance of

direct contrasts is that they allow us to directly identify ROIs showing greater activation for anti task set compared to pro task set, or anti execution compared to pro execution, as the ROIs identified from the main contrast (Fig. 3A) contain both components. These results show that there was greater activation for anti preparation throughout in the frontal ROIs (FEF, SEF, DLPFC) in controls and in PD on-meds (Fig. 5A, Talairach locations of peak activations given in Table 3), but not in PD off-meds. For PD patients that were off-meds, greater anti prep activation was seen in the CN instead. Table 3 lists all brain regions that showed greater activation for anti or pro preparation in each group. However, there were no significant increases in anti execution compared to pro execution in any of the frontal ROIs, other than in a putative left DLPFC region in the PD off-meds group, and in the left FEF in controls (Fig. 5B, Table 4). Thus, the significant differences across the groups between pro and antisaccade processes at the contrast level were also more apparent during task set establishment.

Anti direction error analysis

To determine if greater preparatory activation correlated to better antisaccade performance, the BOLD response curves in the ROIs on correct and direction error trials were compared, which also allowed us to determine if any differences arose for the time points corresponding more to preparation (e.g., time point 5) than to the execution component (e.g., time point 7). BOLD response curves were
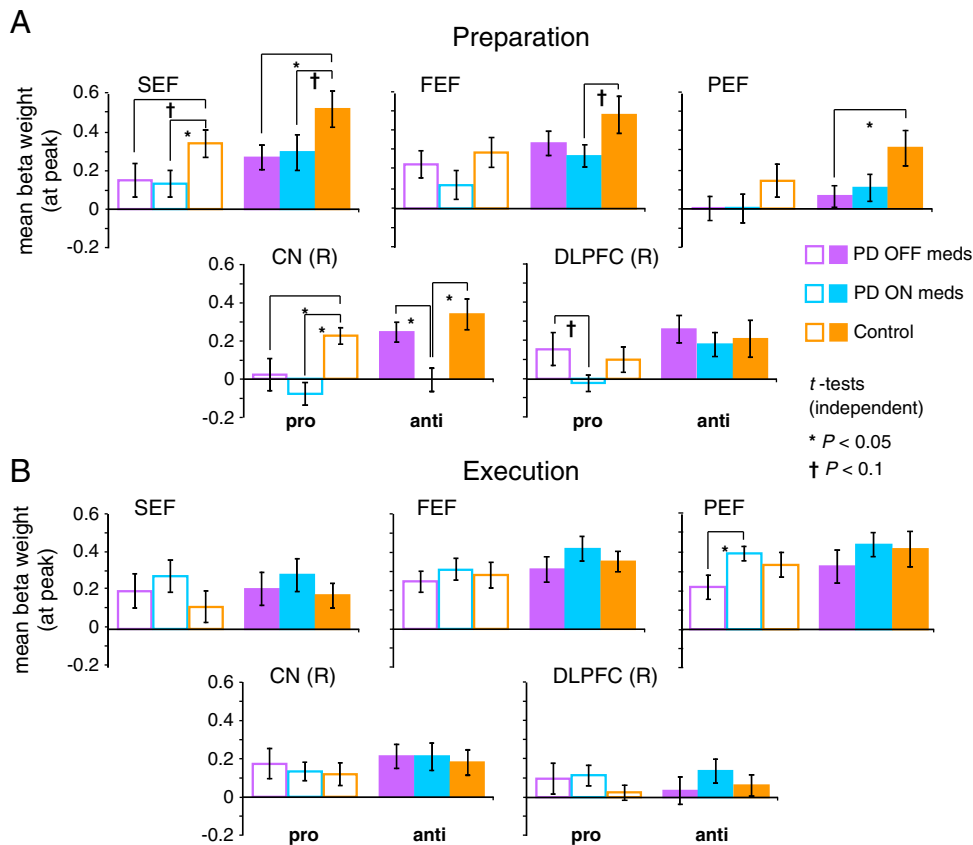
Fig. 4. Region of interest (ROI) analysis for saccade preparation and saccade execution. (A) Mean beta weight values for time points 5 and 6 from an analysis of pro prep and anti prep trials for 125 cubic voxels surrounding peak activations in the saccade ROIs in Fig. 3A. (Bilateral activations were averaged unless indicated. Note that 'DLPFC(R)' includes putative right DLPFC in PD OFF and control groups). Error bars correspond to standard error of the mean (SE). (B) Mean beta weight values for time points 6 and 7 for the saccade execution period (saccade trials–prep trials).

extracted from a random effects analysis from the main contrast ROIs (Fig. 3A). It can be seen in Fig. 6 that PD patients off-meds displayed enhanced early activation on correct antisaccade trials in the putative right DLPFC region, but not in the frontal motor regions (SEF and FEF). In contrast, controls and PD patients on-meds did show trends for enhanced activation in SEF and FEF for correct antisaccade trials. Because the differences occurred most prominently at the 5th time point (7.7 s) from trial onset, repeated measures ANOVAs with the factors of 'time point' (4th, 5th, 6th) and 'performance' (correct and error) were conducted to assess the statistical significance of this enhanced activation. The results revealed that in control subjects only, FEF activation for correct antisaccades was significantly greater across these three time points compared to erroneous antisaccades, $F(1,12) = 4.98$, $P<0.05$, $\eta^2 = 0.29$ (Fig. 6). No other tests reached significance, $F(1,12)<2.68$, $P>0.1$, other than in the putative right DLPFC in PD off-meds, $F(1,12) = 4.89$, $P<0.05$, $\eta^2 = 0.29$. Note that this same analysis was conducted from peak activation locations in ROIs defined by antisaccade trials compared to baseline (fixation), but the results revealed similar results overall (e.g., enhanced FEF activation for correct antisaccade trials in controls only) and so are not reported. The prosaccade and antisaccade contrast maps relative to baseline are shown in Supplementary Fig. 1.

Correlational analysis

To determine whether differences in the magnitudes of anti task set activation across subjects correlated to behavior and UPDRS scores for PD patients (Table 1), beta weights from the 5th and 6th time points of anti prep trials were extracted from an ROI analysis of the

peak locations of FEF in antisaccade activation maps defined for each subject separately (not shown). The 5th, 6th and 7th time points were used to define the subject specific FEF ROI. The analysis was conducted on FEF because of the findings described above, and our knowledge of the role of FEF neuronal populations in antisaccade generation (Everling and Munoz, 2000).

It can be seen that PD patients that were off-meds displayed trends for negative correlations of anti preparatory activation with anti direction errors, as well as with measures of disease state based on UPDRS scores (Fig. 7). Additional participants were included where appropriate (see Fig. 7 caption and Table 1), and separate linear regressions are displayed for the larger dataset (dotted line) as well as the core 13 (solid line). The correlation involving UPDRS Part III (N = 18) approached significance for PD off-meds, $t(16) = -1.90$, $P=0.075$, as did the correlation involving SRT for the control group which included an additional 4 participants from our database (N = 17), $t(15) = -1.85$, $P = 0.08$. No correlations were significantly different from one another, (Fisher's z-test, $Z<1.12$, $P>0.26$). In general, the higher the preparatory activation, the less severe was the disease state for PD patients that were off-meds, and the better the subject's performance was.

To support this observation, we converted the heterogeneous medication regimens of the on-meds group into Levodopa Equivalent Doses (LED), based on the methods of Tomlinson et al. (2010). Because LDOPA was not prescribed to patients unless a therapeutic benefit from taking dopamine agonists primarily was not sufficient, we hypothesized that there would be a negative correlation of anti prep activation with LED, but positive correlations with behavior (direction errors and SRT) reflecting the fact that a greater LED might correspond to patients whose disease state was greater. As expected, there

Table 2

Talairach coordinates (X,Y,Z) of peak activations in GLM contrast maps for Antisaccade–Prosaccade contrast (Fig. 3A) (saccade ROIs in bold).

Group and region	X	Y	Z	T value	Volume of cluster (voxels)
PD OFF					
Right DLPFC (putative)	36	32	43	4.19	12
Right FEF†	24	−7	58	5.33	43
Left FEF	−21	−16	55	5.52	23
SEF†	0	−10	52	6.04	31
Right CN	12	−1	19	8.74	114
Left PEF††	−15	−64	46	5.97	158
Right PEF††	9	−67	55	5.11	25
Right medial frontal gyrus†	3	41	40	7.50	428
Left claustrum	−30	5	10	5.28	42
Left putamen	−24	−4	13	5.29	47
Right inferior parietal lobule	60	−37	25	7.40	57
Left superior parietal lobule	−39	−55	52	4.67	22
Right superior parietal lobule††	30	−58	52	6.16	352
*Right cuneus	3	−76	13	−4.61	47
PD ON					
Right DLPFC	33	32	40	5.63	38
Right FEF	21	−7	67	10.04	486
(superior frontal sulcus)†					
Right FEF (lateral)†	39	−7	52	6.18	29
Left FEF	−24	−13	55	7.56	209
SEF†	−3	−4	49	5.50	37
Right CN	9	11	7	6.69	193
Left PEF††	−12	−64	43	7.95	236
Right PEF††	24	−64	55	5.79	44
Right insula	30	23	13	4.72	33
Left putamen	−21	5	4	4.78	26
Right precentral gyrus	48	2	34	6.12	49
Left cingulate cortex	−3	−2	31	6.09	26
Left thalamus	−12	−16	7	4.53	18
Right inferior parietal lobule††	42	−31	37	8.54	1,183
Control					
Right DLPFC (putative)	36	47	40	4.38	17
Right FEF	27	−10	49	5.22	104
Left FEF	−21	−10	55	4.69	35
SEF	9	−4	55	5.50	215
Right CN	15	−1	13	3.98	17
Left PEF	−33	−61	49	6.04	99
Right PEF	12	−67	49	5.12	146
Right medial frontal gyrus	6	38	31	4.45	22
Right insula	33	17	16	4.34	35
Left insula	−39	17	4	4.29	14
Right medial frontal gyrus	21	5	52	4.45	17
Right inferior parietal lobule	60	−37	31	4.44	15
Right inferior parietal lobule	30	−46	43	5.71	69
Left inferior parietal lobule	−39	−46	43	3.95	30

Symbols and definitions: DLPFC, dorsolateral prefrontal cortex; CN, caudate nucleus; FEF, SEF, PEF, frontal, supplementary, parietal eye fields; *, pro>anti; †,††, saccade ROI included in larger cluster area indicated by identical symbols (>300 voxels).

was a trend for a negative correlation between LED and FEF mean beta weight in the 13 participants (Fig. 7), however it did not reach significance ($P = 0.13$). A positive correlation of LED with SRT did reach significance with $N = 20$ participants (not shown), $R^2 = 0.22$, $t(18) = 2.23$, $P < 0.05$, but correlations with anti direction errors did not ($P > 0.27$). However, anti direction errors were affected by one outlier (91% direction errors), which when removed, also yielded a significant positive correlation of anti direction errors with LED for the 12 (remaining) core participants, $R^2 = 0.42$, $t(10) = 2.67$, $P < 0.05$, and for 19 patients, $R^2 = 0.21$, $t(17) = 2.06$, $P = 0.05$. This suggests worse performance in patients who were taking greater amounts of medication, reflecting a relationship to disease state. Indeed, we also observed positive correlations between UPDRS Part III (motor) scores and antisaccade SRT in PD patients off-meds, $R^2 = 0.43$, $t(11) = 2.90$, $P < 0.05$ and on-meds, $R^2 = 0.48$, $t(11) = 3.17$, $P < 0.01$; $R^2 = 0.52$, $t(18) = 4.45$, $P < 0.01$. Correlations involving UPDRS Part III scores and anti direction errors did not approach significance ($P > 0.40$).

Medication effects

Following these findings, we analyzed medication effects with more detail, by dividing the patients into those regularly taking levodopa ('LDOPA') ($N = 7$), and those not regularly taking ('no-LDOPA') ($N = 6$) (Table 1). Doing so roughly divided the group into half and provided enough participants in each sub-group for random effects analyses. This also allowed us to further examine disease severity indirectly (because LDOPA was not prescribed to patients unless the therapeutic benefit from taking dopamine agonists primarily was not sufficient). As confirmed from Table 1, the mean UPDRS motor scores for the PD patients not taking LDOPA was lower (21.7 off-meds session; 18.2 on-meds session) than for the patients taking LDOPA (25.0 off-meds; 20.9 on-meds session).

The results from behavioral comparisons between these groups are illustrated in Supplementary Analysis, and in Supplementary Fig. 2. Results from fMRI contrasts (conducted in identical fashions as in Figs. 3 and 5) are described in Supplementary Analysis, and in Supplementary Figs. 3 and 4. We also directly contrasted anti and pro activations *across* the two medication groups (Supplementary Figs. 5 and 6). In general, the 'LDOPA group', on-meds, displayed similar cortical activation patterns to the control subjects and Figs. 3 and 5, but interestingly they did not perform the antisaccade task as well as the controls, or even the 'no-LDOPA group' (Supplementary Fig. 2A). Most interestingly, an emerging trend showed that, in general, CN activation was greater for antisaccades off-meds in the no-LDOPA group (Supplementary Figs. 5 and 6), but DLPFC activation was greater in the LDOPA group, on-meds (Supplementary Figs. 3 ,4 and 6). Moreover, despite the greater DLPFC activation on-meds, the LDOPA group did not get as much of a performance benefit from taking medication (Supplementary Fig. 2A).

To further explore these findings, we examined correlations between anti prep CN activation and anti prep FEF activation (derived from the beta values in Fig. 4) when patients were off-meds, and between anti prep DLPFC and FEF activation when patients were on-meds. A positive correlation resulted between the no-LDOPA group's off-meds activation in RCN and FEF, $R^2 = 0.42$ that interestingly, reached significance when correlated with left FEF only ($R^2 = 0.75$, $t(4) = 3.42$, $P < 0.05$) (Fig. 8). Only a weakly positive trend was seen in the LDOPA group off-meds between RCN and FEF, $R^2 = 0.17$. However, there was a *negative* correlation between RDLPFC and FEF activation in the LDOPA group on-meds, $R^2 = 0.22$, that was again stronger, and significant, with left FEF ($R^2 = 0.66$, $t(5) = -3.09$, $P < 0.05$) (Fig. 8). For controls, it can be seen that strong positive correlations resulted between RCN and FEF (bilateral) ($R^2 = 0.65$, $t(11) = 4.46$, $P < 0.01$), and RDLPFC and FEF (bilateral) ($R^2 = 0.45$, $t(11) = 3.00$, $P < 0.05$) (Fig. 8) suggesting that the negative DLPFC–FEF correlations in PD patients taking LDOPA reflected something aberrant to performance, and the lateralization effect in these correlations was specific to the participants with PD. The DLPFC–FEF correlations between the LDOPA group and controls were significantly different for both FEF bilateral (Fisher's z-test, $Z = 2.23$, $P < 0.05$), and FEF left ($Z = 2.96$, $P < 0.01$).

Discussion

Here, we propose that in Parkinson's disease (PD), reduced brain activation in the frontal cortex corresponds to ineffective pre-setting of networks important to voluntary saccade generation. First, whereas controls showed greater activation for anti preparation throughout the cortical saccade network in the anti prep compared to pro prep contrast (Fig. 5A), PD patients off medication did not. Second, a reduced enhancement of an early rise in preparatory activation in FEF on correct antisaccade trials compared to incorrect antisaccade trials was also observed in PD compared to the controls (Fig. 6), providing an important neural correlate to performance in a motor command region. Finally, medication led to improved performance trends,
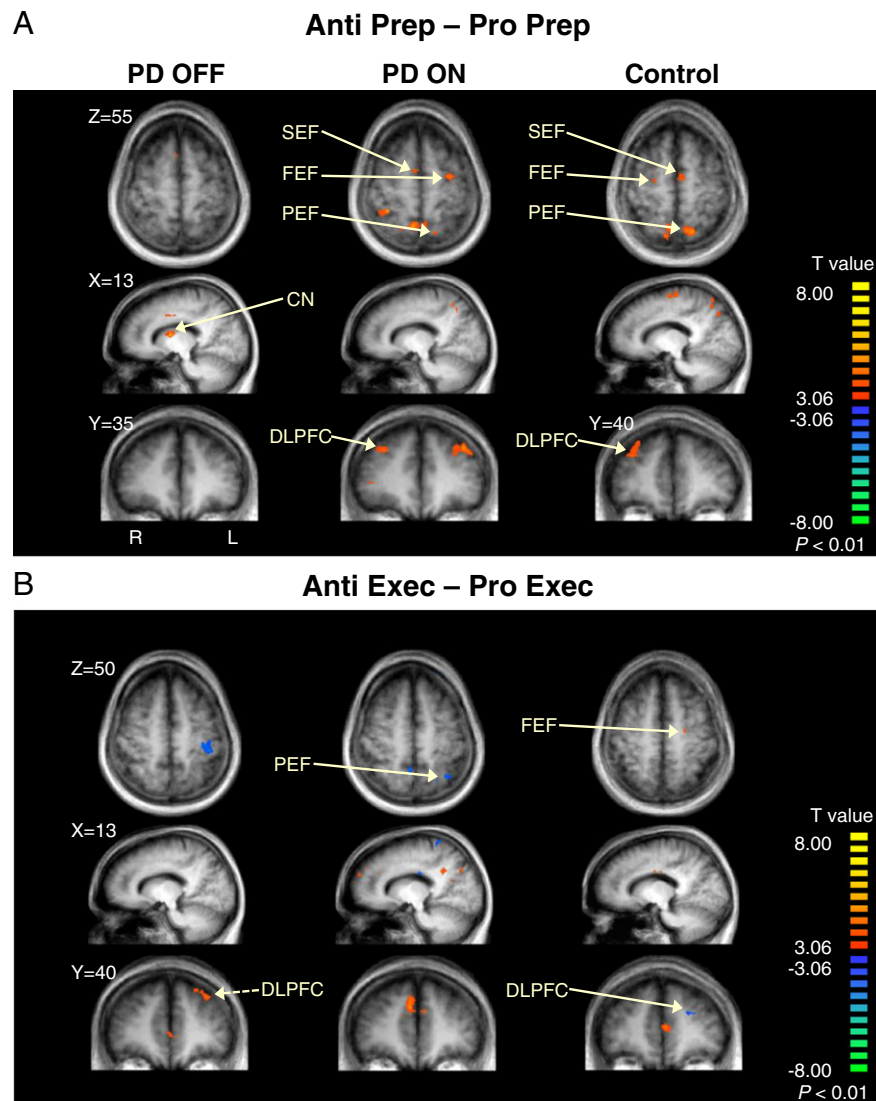
Fig. 5. Saccade preparation and saccade execution contrast maps. (A) Preparation contrast: anti prep–pro prep, thresholded at $P<0.01$, and cluster size corrected at $P<0.01$ (8 contiguous voxels). The 5th and 6th time points relative to trial onset were used. The 5 saccade ROIs are indicated. (B) Execution contrast: (antisaccade–anti prep)–(prosaccade–pro prep). The 6th and 7th time points from trial onset were used. Dotted line indicates putative DLPFC region.

however not to the levels attained by controls; it also produced altered activation patterns between DLPFC, CN and FEF when PD patients were divided based on medication regimen, suggesting a decoupling between these regions. From these findings, we propose that PD patients were less efficient at establishing voluntary task set in networks important to controlling a voluntary motor behavior. This is consistent with a general view that decreased cortical functioning can occur in PD, as the result of disrupted *dis*-inhibitory mechanism of the BG direct pathway on thalamo-cortical excitation (Dagher and Nagano-Saito, 2007; Mink, 1996; Nambu, 2005).

There were two main observations from our results that permit us to make the inference that PD patients have impaired dis-inhibitory mechanisms affecting antisaccade task set. First, it has been shown consistently that antisaccade activation in the 5 saccade ROIs we studied is greater than prosaccade activation (Brown et al., 2006, 2007; Connolly et al., 2002, 2005; Curtis and Connolly, 2008; Curtis and D'Esposito, 2003; DeSouza et al., 2003; Ford et al., 2005; Luna et al., 1998; Sweeney et al., 1996), and this greater activation is presumed to reflect, in part, the executive processes (e.g., response inhibition, top-down attentional direction) necessary for generating a correct antisaccade (Munoz and Everling, 2004). Importantly, it is known that the prefrontal and premotor cortices containing DLPFC,

SEF and FEF are influenced by BG output (Alexander et al., 1986). Throughout these saccade ROIs, we observed that control subjects typically showed higher levels of preparatory activation on both pro and anti trials (Fig. 4A), suggesting that they were better able to establish a task set based on a given instruction. Second, the measures of the preparatory component of activation for correct antisaccades were greater in magnitude compared to those for antisaccade direction errors in FEF for control subjects (Fig. 6), and anti prep trial activation was greater, in general, than pro prep trial activation for control subjects, and for PD patients on-meds to some extent (Figs. 4A, 5A). Overall, this suggests that controls were best able to *utilize* the instruction-related information to configure the appropriate task set in the oculomotor network required for optimal behavioral performance.

To understand what antisaccade task set may be at the neural level, knowledge from monkey neurophysiology provides a sensible interpretation based on how neurons in FEF are configured to appropriate levels of activity prior to the generation of a desired behavior. FEF has a specialized role in generating voluntary saccade motor commands (Hanes and Schall, 1996), and it also contains mechanisms to suppress automatic saccades, via enhanced activity in a distinct population of 'fixation' neurons along with reduced activity in 'saccade'

Table 3
Talairach coordinates (X,Y,Z) of peak activations in GLM contrast maps for Anti Prep–Pro Prep contrast (Fig. 5A) (saccade ROIs in bold).

Group and region	X	Y	Z	T value	Volume of cluster (voxels)
PD OFF					
Right CN	12	2	13	6.71	49
Left PEF	−24	−64	46	5.31	14
Superior frontal gyrus	0	11	49	5.08	54
Right anterior cingulate cortex	9	−4	43	4.72	18
Left inferior parietal lobule	−39	−37	40	4.43	15
Right inferior parietal lobule	36	−49	37	5.30	56
Right precuneus	27	−70	37	5.31	14
PD ON					
Right DLPFC	33	29	37	4.91	20
Left DLPFC	−36	35	40	5.60	66
Right FEF	24	−10	49	5.26	64
Right FEF (superior frontal sulcus)	18	−10	70	4.96	14
Left FEF	−30	−7	46	5.13	14
Left FEF (lateral)	−45	−7	46	3.98	18
Left FEF (superior frontal sulcus)	−18	−16	67	4.92	36
SEF	3	−1	58	3.6	22
Left PEF	−15	−55	46	5.50	30
Right middle frontal gyrus	30	41	25	7.65	14
Right inferior frontal gyrus	42	41	7	4.94	13
Right anterior cingulate cortex	6	23	34	5.67	25
Left claustrum	−27	26	10	4.95	16
Right claustrum	27	17	13	5.60	30
Left putamen	−24	5	7	6.21	97
Right precentral gyrus (inf. lat.)	54	2	13	4.71	35
Right inferior parietal lobule	30	−40	55	4.34	77
Left inferior parietal lobule	−36	−43	46	4.85	31
Right supramarginal gyrus	60	−46	28	5.74	101
Right parahippocampal gyrus	39	−49	4	4.30	16
Left superior temporal gyrus	−60	−49	22	5.53	11
Right precuneus	3	−55	46	6.16	186
Right middle temporal gyrus	27	−55	31	4.01	17
Control					
Right DLPFC	30	41	43	4.08	19
Right FEF (superior frontal sulcus)	21	−16	70	5.58	84
SEF	−6	−10	52	4.58	35
Left PEF	−15	−61	52	5.83	54
Superior frontal gyrus	0	32	43	4.78	29
Right middle frontal gyrus	45	23	40	3.95	19
*Left posterior cingulate gyrus	−21	−28	31	−5.09	18
Right inferior parietal lobule	48	−31	31	4.39	26
Right precuneus	9	−55	55	5.50	61

Symbols and definitions: DLPFC, dorsolateral prefrontal cortex; CN, caudate nucleus; FEF, SEF, PEF, frontal, supplementary, parietal eye fields; *, pro > anti.

Table 4
Talairach coordinates (X,Y,Z) of peak activations in GLM contrast maps for Anti Exec–Pro Exec contrast (Fig. 5B) (saccade ROIs in bold).

Group and region	X	Y	Z	T value	Volume of cluster (voxels)
PD OFF					
Left DLPFC (putative)	−30	44	40	5.37	21
Medial frontal gyrus	0	44	13	4.25	15
*Left insula	−36	26	19	−5.18	68
*Left inferior frontal gyrus	−42	−1	19	−5.89	25
*Left superior temporal gyrus	−54	−22	7	−4.59	25
*Left postcentral gyrus	−34	−25	52	−5.42	34
*Right superior temporal gyrus	45	−55	31	−5.60	68
*Left superior temporal gyrus	−51	−55	22	−7.28	30
*Left inferior parietal lobule	−45	−64	40	−5.28	26
PD ON					
Right medial frontal gyrus	6	44	31	5.86	70
Left medial frontal gyrus	−9	53	1	6.91	25
Right superior frontal gyrus	21	53	25	4.19	25
Right middle frontal gyrus	42	11	43	4.62	28
*Right corpus callosum	6	−7	25	−6.67	28
*Left corpus callosum	−9	−34	16	−4.37	14
*Left insula (dorsal)	−30	−10	25	−5.50	33
Posterior cingulate cortex	0	−25	31	4.94	26
*Left paracentral lobule	−9	−40	61	−5.37	57
*Left inferior parietal lobule	−42	−43	40	−8.29	37
Right posterior cingulate cortex	9	−46	28	4.99	56
*Right parahippocampal cortex	36	−49	4	−4.79	35
*Left precuneus	−6	−55	55	−5.57	58
*Left inferior parietal lobule	−36	−58	46	−5.01	19
Right superior occipital gyrus	−36	−76	28	4.68	35
Right cuneus	3	−79	34	6.26	37
*Middle occipital gyrus	21	−85	16	−5.25	33
*Left cuneus	−18	−88	28	−5.43	17
Control					
Left FEF	−24	−10	46	5.49	26
*Left anterior frontal cortex	−15	53	4	−5.07	17
*Left middle frontal gyrus	−21	32	28	−4.87	34
Left anterior cingulate cortex	−3	32	16	5.87	43
Right anterior cingulate cortex	3	20	34	4.42	14
Right corpus callosum	9	−7	31	4.79	34
*Left cuneus	−9	−79	22	−5.89	18

DLPFC, dorsolateral prefrontal cortex; CN, caudate nucleus; FEF, SEF, PEF, frontal, supplementary, parietal eye fields; Exec = execution period (Saccade−Prep); *, pro > anti.

neurons, during the antisaccade instruction period (Everling and Munoz, 2000; Munoz and Everling, 2004). Therefore, execution of a successful antisaccade requires that firing rates of fixation and saccade neurons are configured to appropriate levels prior to responding, representing a neural correlate of antisaccade task set. Note that while similar patterns of greater activation for anti preparation compared to pro preparation in the saccade network were also observed in PD patients on-meds (Fig. 5A), PD patients on-meds did not perform the antisaccade task as well as the control subjects (Fig. 2). Correspondingly, they did not show the same *magnitudes* of antisaccade preparatory activation in FEF compared to control subjects (Fig. 4A), nor did they show the same degree of enhanced preparatory activation on correct trials compared to error trials (Fig. 6), suggesting that FEF neurons were not as effectively configured.

Our understanding of the nature of the BOLD signal relates to the proposal that enhanced fixation and reduced saccade neuron activity should correspond with increased BOLD activation in a given brain area. The BOLD signal correlates with synaptic activity (input), as well as (and perhaps more than) the spiking activity (output) of a region (Logothetis and Wandell, 2004; Logothetis et al., 2001). From this, one could predict that the proper presetting of FEF neural

activity could be the result of incoming neural signals, and thus, reduced BOLD activation in FEF could correspond with reduced input signals critical to establishing the correct preparatory levels in FEF neurons. However, where these *task set* signals originate is unknown, given the complex relationship between BG, DLPFC and FEF networks.

One possibility is that they are carried directly by DLPFC inputs to FEF (Munoz and Everling, 2004). While the motor, premotor (FEF and SEF), and prefrontal (DLPFC) cortices are all influenced by BG output (Alexander et al., 1986), the latter (DLPFC) is associated with general executive control (Gazzaley and D'Esposito, 2007; Miller and Cohen, 2001). The DLPFC is believed to be a crucial brain region involved in establishing an antisaccade task set, because patients with DLPFC lesions make more direction errors on antisaccade trials (Guitton et al., 1985). Patients with PD also display a variety of deficits in executive control, which mirror those of prefrontal cortical dysfunction (Monchi et al., 2004; Owen, 2004; Rodriguez-Oroz et al., 2009; Williams-Gray et al., 2006), however, it has also been shown that PD patients off medication can show enhanced prefrontal function depending on task demands (Cools et al., 2010). We observed that enhanced DLPFC activation for anti prep trials compared to pro prep trials was *not* present in the PD off-meds group (Fig. 5A), suggesting that the *resolution* of the instruction into the establishment of an appropriate task set was less efficient in PD patients when off medication. This follows a hypothesis that DLPFC is important to establishing appropriate voluntary task set signals. However, we did observe that there was enhanced activation in putative DLPFC for correct compared to erroneous antisaccade trials in PD patients off-meds
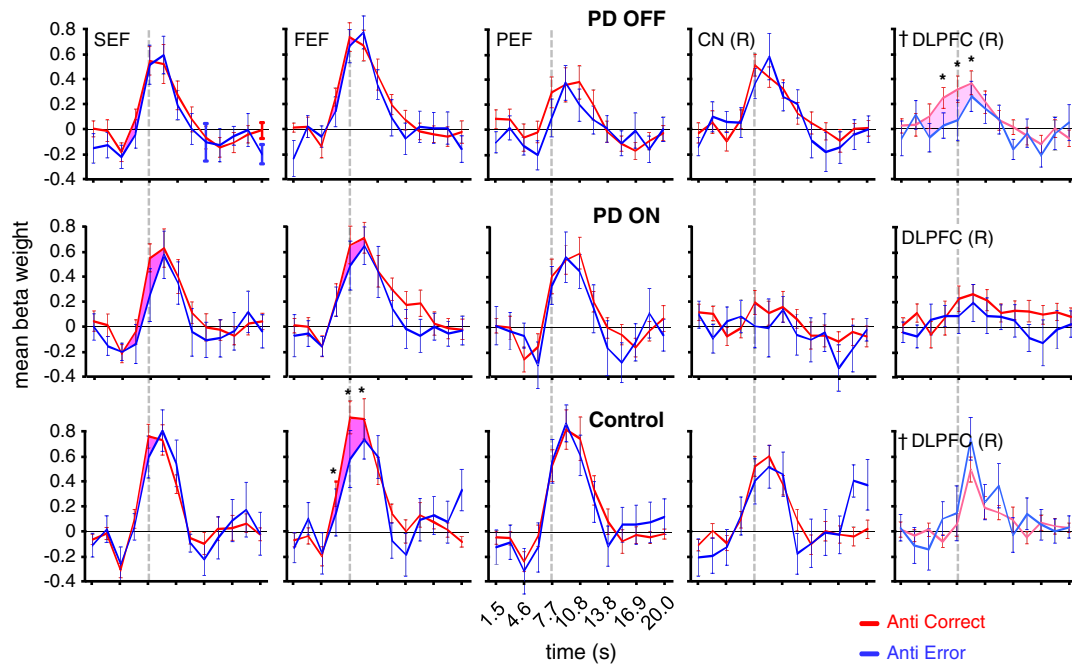
Fig. 6. Comparison of BOLD activation on correct and erroneous antisaccade trials, extracted from the 125 cubic voxels surrounding peak activations in the 5 saccade ROIs (Fig. 3A). Light gray dotted lines indicate 5th time point, with pink shading used to highlight enhanced activation around the 5th time point on correct anti trials in frontal regions (SEF, FEF and putative DLPFC). †DLPFC(R) corresponds to putative right DLPFC regions (Fig. 3A dotted lines). Error bars correspond to standard error of the mean (SE). *P<0.05 (ANOVA) between correct anti trials and anti direction errors.

(Fig. 6), and we did also see that putative left DLPFC showed enhanced anti compared to pro execution activation in PD patients off-meds (Fig. 5B), though we hypothesize that enhanced activation during the execution component occurs too late to be related to successful task performance. This supports another possibility (though not independent), that for *task set* signals to be translated to FEF, a 'boosting' mechanism, derived from BG-mediated dis-inhibition of thalamo-FEF signals is required (Alexander et al., 1986; Hikosaka and Isoda, 2010; Mink, 1996; Munoz and Everling, 2004), and this mechanism would be expected to be impaired in PD, where decreased striatal dopamine is thought to result in a shift towards increased BG inhibitory output. Similar to this hypothesis, is a case in which task set signals originate in DLPFC inputs to FEF, however the establishment of the appropriate task set signals in DLPFC is also dependent on the assistance of BG-mediated dis-inhibition.

To reconcile these possibilities, we examined the effects of medication in PD patients more specifically because this was what produced interesting CN and DLPFC activation patterns (Figs. 4–6). In doing so, we also took advantage of the fact that we were comparing people with a less advanced disease state to a more advanced state. Our interpretations based on group medication effects are explained in the following section, and do suggest the importance of the requirement of functioning BG signals to properly establish task set signals in FEF.

Medication effects

While medication appeared to improve behavioral performance, it did not result in a statistical improvement (Fig. 2). Patients *not* taking LDOPA did show improved performance trends on antisaccade trials when taking medication, but those taking LDOPA did not (see Supplementary Fig. 2). This is interesting, because it has been shown in another study of 14 PD patients taking LDOPA with dopamine agonists that medication did reduce antisaccade direction error rate (Hood et al., 2007). A likely possibility for this discrepancy, is that our task was more complex because anti and pro trials were interleaved, and the prep trials introduced an added complexity of not responding

on every trial. Cognitive inflexibility in PD patients is a known problem (Cools, 2006; Monchi et al., 2004; Rodriguez-Oroz et al., 2009), and we have observed that PD patients on-meds (including LDOPA) do display greater difficulty in antisaccade preparation when moving from blocked designs to interleaved trials containing unpredictable changes in task requirement (Cameron et al., 2010). Thus, it would not be surprising that a group of patients taking LDOPA would show improved performance in simpler tasks only.

When fMRI contrasts between anti and pro processes within medication groups were produced (Supplementary Figs. 3 and 4), as well as contrasts between groups for anti processes (Supplementary Figs. 5 and 6), it was revealed that greater anti activation in CN generally resulted for the no-LDOPA group off-meds, while greater DLPFC activation resulted for the LDOPA group on-meds. Recall that only the no-LDOPA group received a marginal benefit of decreased anti-saccade error rates when on-meds (Supplementary Fig. 2), suggesting that enhancing DLPFC activation does not, on its own, correlate with improved performance. Greater DLPFC activations in the LDOPA group, off- or on-meds, could reflect a compensatory component to BG impairment that is simply not effective. Indeed, it has been observed by others that PD patients can show increased PFC activation independent of BG activation (Leh et al., 2010), This also fits with the finding that greater putative DLPFC activation was seen in correct compared to erroneous antisaccade trials off-meds (Fig. 6), but overall, PD patients off-meds performed the worst. We did not, however, observe a further behavioral detriment when the LDOPA group took their medication (Supplementary Fig. 2), so we cannot assume to have an 'overdosing' effect of dopamine in DLPFC (Cools, 2006; Williams and Goldman-Rakic, 1995). What can be stated clearly however, is that despite the observed increases in DLPFC activation, there was not a corresponding increase in FEF activation during critical components of preparation (Fig. 6, Supplementary Figs. 4–6), suggesting DLPFC activation in PD may not relate to establishing necessary task set signals in FEF. We propose that it is critical that task set signals result in effective FEF neuronal configuration, which we suggest depends on functional BG dis-inhibitory mechanisms.
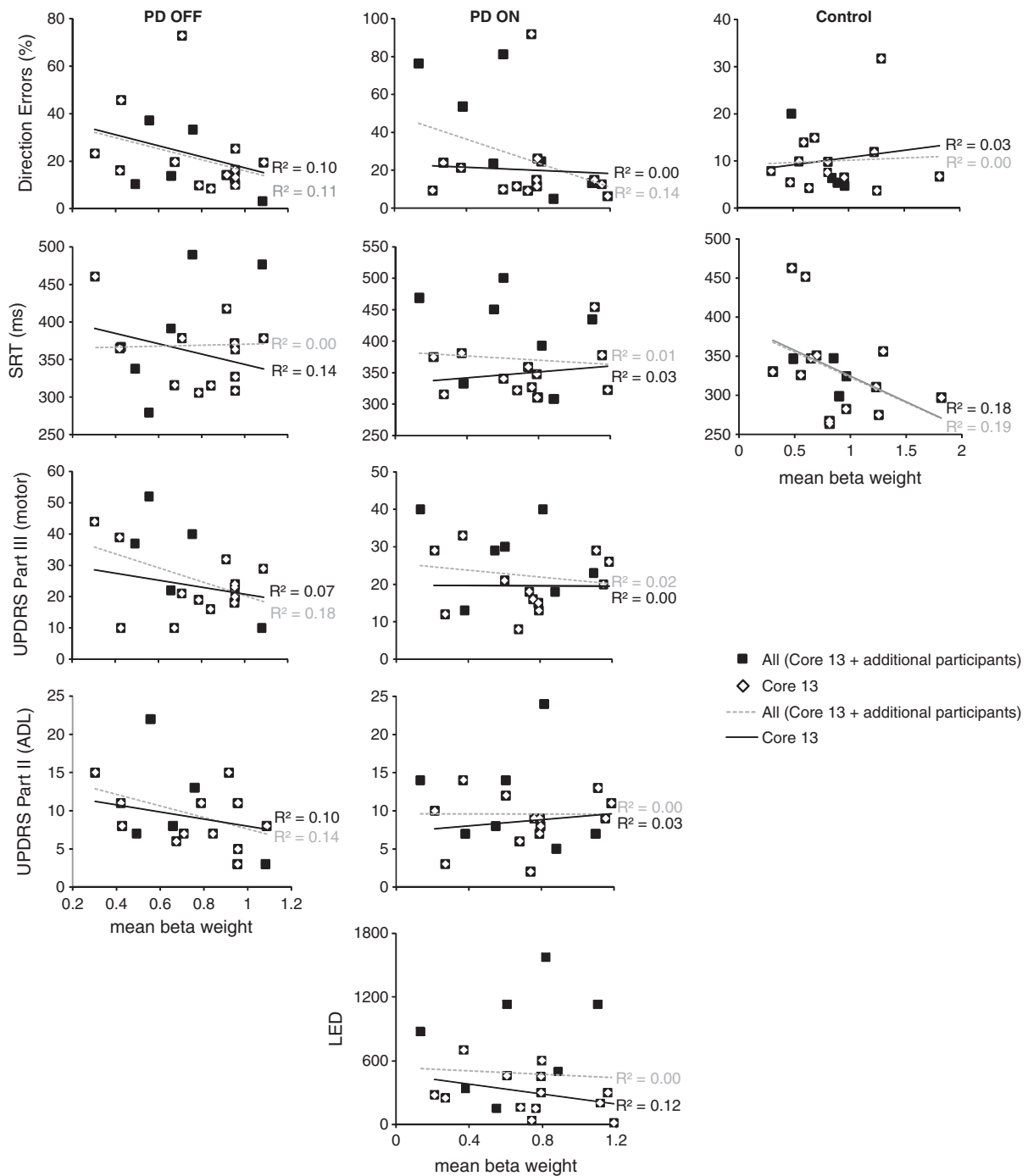
Fig. 7. Correlations of BOLD activation in FEF with antisaccade behavior (direction errors and SRT) and disease state. Mean beta weight values were extracted from time points 5 and 6 from an analysis of anti prep trials for 125 cubic voxels surrounding peak FEF activations on individual subject's antisaccade activation maps (averaged between hemispheres). 'Core 13' corresponds to the 13 participants used in the full analysis, whereas 'All' consists of the Core 13 plus additional participants (listed in Table 1) as follows: PD OFF: 15, 21, 22, 23, 24; PD ON: 16, 17, 21, 22, 23, 24, 25. Additional control subjects from our database that could be age-matched to the additional PD patients were included (N = 4). ADL, Activities of Daily Living. LED, Levodopa Equivalent Dose.

If the BOLD signal does reflect a significant component of synaptic processes (input) as described previously, this strongly suggests that the depleted dopamine levels in PD patients off-meds does not in itself result in decreased CN BOLD activation. We suggest instead that CN activation in the PD patients off-meds may also reflect compensatory recruitment of BG processes, especially in the relatively less advanced patients, but increased DLPFC may be related to aberrant activation in more advanced patients when on medication. It has been shown that exogenous dopamine can exert beneficial, as well as detrimental

effects on behavior based on its relation to intrinsic levels in striatal areas (Cools, 2006; Cools et al., 2001, 2010), and in PFC (Seamans and Yang, 2004; Williams and Goldman-Rakic, 1995; Yang and Seamans, 1996). The fact that the LDOPA group showed greater DLPFC activation on-meds, but neither group showed greater CN activation on-meds, makes sense when one considers the following points: first, dopamine agonists are active on D2 receptors which are much more abundant in the striatal indirect pathway neurons than the PFC, and auto-regulation of dopamine levels is stronger in the striatum than in the PFC
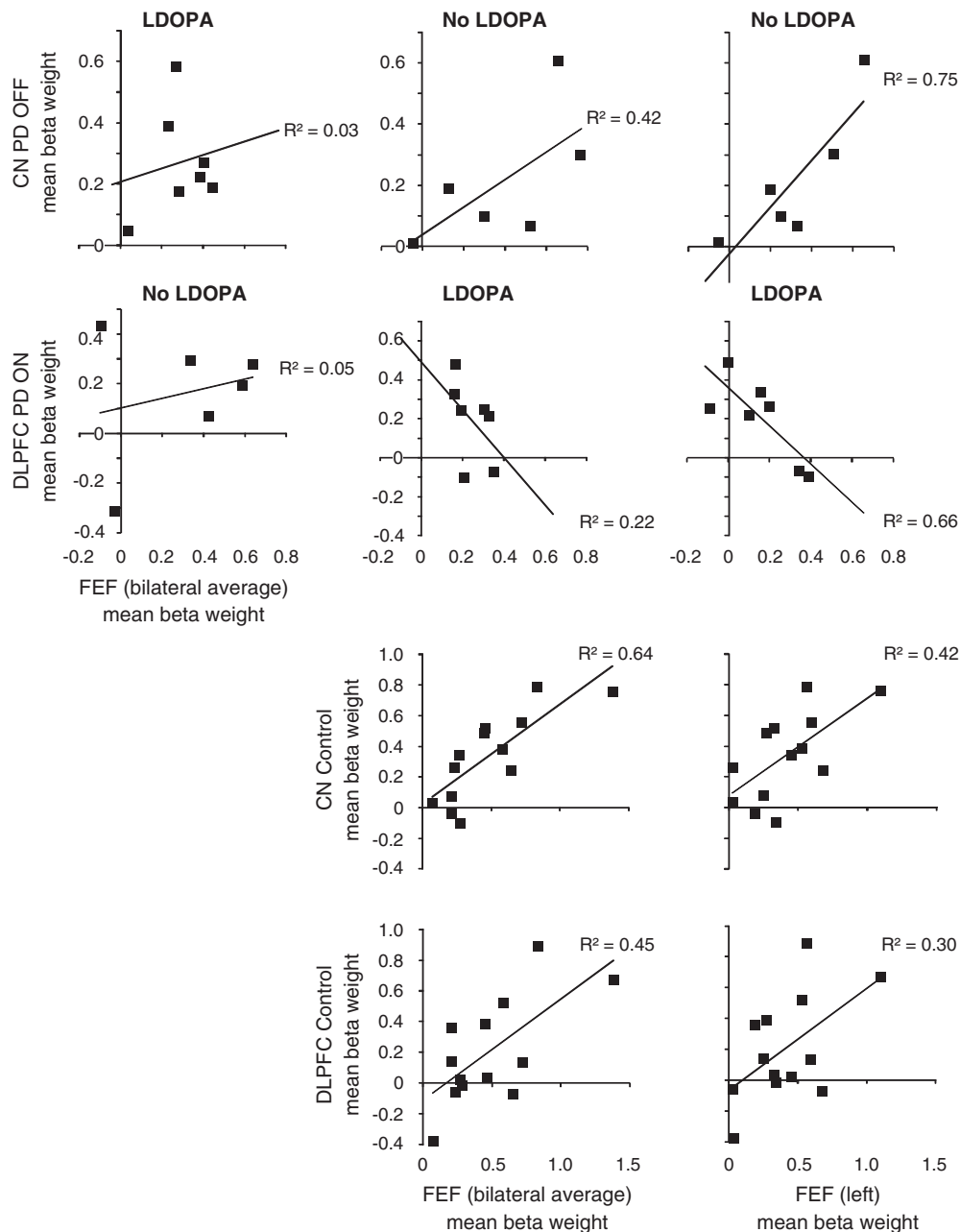
Fig. 8. Correlations of anti prep BOLD activations in FEF with CN and DLPFC. Mean beta weight values used were the same as those in Fig. 4A for right CN off-meds (separated into no-LDOPA and LDOPA groups), right DLPFC on-meds, and FEF beta values (bilateral in left and center plots, left only in right plots). These beta values derived from the random effects GLM (as in Fig. 4A) were used because DLPFC and CN peaks were not always possible to identify in contrast maps from individual subjects.

(Cools, 2006; Grace, 1991; Surmeier et al., 2007); second, regulation of tonic dopamine levels is thought to occur by glutamatergic inputs from prefrontal cortex to axon terminals on presynaptic dopamine cells (Grace, 1991). Thus, a correlate of increased CN activation in PD patients off-meds may relate to endogenous signals to produce more dopamine in the striatum; it, of course, may also represent increased BG drive in task-related fronto-striatal signals. We propose either of these possibilities as compensatory strategies, that become less needed on medication, but that may not bring about a behavioral benefit if there is not sufficient striatal dopamine produced (Fig. 2., Supplementary Fig. 2).

We cannot determine conclusively if the apparent decoupled relationship between DLPFC activation and FEF activation (and performance) in the DLPFC group on-meds is related to LDOPA,

because while it seems plausible that increased exogenous dopamine production might lead to aberrant activation in the less regulated PFC compared to the striatum, LDOPA has been shown to produce greater changes in striatal dopamine levels than in PFC (Cools, 2006). However, it would be expected that there should be greater PFC effects in a group of participants with likely greater striatal dopamine loss, who are taking medication to increase dopamine production (LDOPA), rather than to stimulate D2 receptors. Thus, the CN activation patterns appear to reflect increased BG recruitment when off-meds, whereas DLPFC activation patterns appear to reflect aberrant increases in activation. In any case, what appears to be most important is that the BG can operate properly at the output level to provide the necessary disinhibitory actions on thalamo-cortical signals that are important to boosting preparatory signals in FEF.

Lateralization

The correlational analysis (Fig. 8), as well as the general hemispheric dominance for right side activations in DLPFC and CN throughout the main results suggests that there are lateralization factors to consider. Supplementary Fig. 1, which shows pro and antisaccade activation compared to baseline, does illustrate a right-hemisphere dominance for DLPFC. CN activations were bilateral, but were dominant in the right-hemisphere in terms of spread and magnitude. The fact that there is dominance for the right hemisphere is interesting, but we are not aware of any study that has conclusively explained why. The striatum receives cortical projections from both hemispheres (McGeorge and Faull, 1989), and we recently modeled antisaccade programming with respect to the BG as requiring ipsilateral and contralateral signals to generate a correct antisaccade (Watanabe and Munoz, 2010). However, in a previous fMRI study of the CN during a pro and antisaccade switch task, we observed greater activation of the right CN (Cameron et al., 2009), and a recent study by others observed that theta burst transcranial magnetic stimulation (TMS) over left, but not right, DLPFC impaired performance in a switching task, and correspondingly, less dopamine release was observed in the CN bilaterally (Ko et al., 2008). Together, this suggests that different task requirements may recruit differences in DLPFC-BG hemispheric recruitment, however, further studies are needed to understand this. The stronger correlations in the PD patients between RCN and left FEF, and RDLPC and left FEF is interesting, though may reflect the fact that the patients in this study were as a majority right-side affected (i.e., UPDRS motor scores were higher on the right side than left).

SEF and PEF

While our focus has been on understanding FEF activation patterns in relation to DLPFC and CN, we must address the fact that SEF and PEF showed patterns for greater activation in antisaccade preparation and generation as well, that was overall greater in the control subjects. SEF has also been shown to be important in antisaccade programming, in particular, in mediating voluntary saccade generation when alternative or conflicting responses are possible (Coe et al., 2002; Parton et al., 2007; Schlag-Rey et al., 1997). Moreover, SEF neurons show enhanced firing rates prior to antisaccade generation compared to prosaccade generation (Schlag-Rey et al., 1997), suggesting that insufficient presetting of SEF in PD may also contribute to impaired antisaccade behavior. PEF also showed greater activation in controls and PD patients on-meds compared to off-meds, suggesting that it too may be related to antisaccade deficits in PD, or at least to changes in processing in the oculomotor network. Enhanced PEF BOLD activation for antisaccade processes has been observed previously (Brown et al., 2007; Curtis and Connolly, 2008; Ford et al., 2005) and might reflect modulation of attention in fronto-parietal networks (Bisley and Goldberg, 2010; Curtis et al., 2005; Desimone and Duncan, 1995; Miller and Cohen, 2001) important to generating a saccade away from a peripheral stimulus. Tasks that require 'top-down' attentional deployment typically result in decreased cortical activation in PD (Dagher and Nagano-Saito, 2007), and frontal–parietal networks have been implicated as being important to executive function, attention, and spatial working memory (Leh et al., 2010). Thus, it is likely that SEF and PEF also play a role in a network related to antisaccade preparation, which as we suggest, is dependent on proper task set configuration in cortical regions important to voluntary motor output.

Future directions and conclusion

What might these results mean in a broad context beyond saccade control? Decreased frontal cortical fMRI activations in PD have been described previously, especially in relation to BG signaling and impaired task performance (Leh et al., 2010). However, as with this study, it is not clear what *increased* activation means in PFC and the BG. If behavior is improved, then 'abnormal' (relative to control subjects) increases in activation are interpreted as compensatory mechanisms. However, if behavior is not improved, it suggests an 'overdosing' effect of medication, failed compensation, or aberrant activations associated with worse performance. We cannot address these issues with this study, however, what we have shown more broadly, is that it is important to look at executive deficits at a motor output stage where activation patterns are more interpretable with behavioral production: this is more difficult to do in areas such as primary motor cortex, where there has not been, to our knowledge, characterization of neuronal signatures related to specifically to task set. It can be concluded from this study, using the oculomotor system, that the degree to which motor areas can be properly configured prior to response initiation dictates subsequent performance, and might be the major reason why PD patients display deficits in the voluntary behavioral control. Future research studies, and treatments, of PD might therefore benefit from assessing how signals related to cognitive mechanisms such as task set preparation, decision making, and general executive control are modulated in motor regions.

Supplementary materials related to this article can be found online at doi:10.1016/j.neuroimage.2012.01.057.

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