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Dopaminergic therapy in Parkinson's disease decreases cortical beta band coherence in the resting state and increases cortical beta band power during executive control ☆

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ABSTRACT

It is not yet well understood how dopaminergic therapy improves cognitive and motor function in Parkinson's disease (PD). One possibility is that it reduces the pathological synchronization within and between the cortex and basal ganglia, thus improving neural communication. We tested this hypothesis by recording scalp electroencephalography (EEG) in PD patients when On and Off medication, during a brief resting state epoch (no task), and during performance of a stop signal task that is thought to engage two partially overlapping (or different) frontal-basal-ganglia circuits. For resting state EEG, we measured pair-wise coherence between scalp electrodes in several frequency bands. Consistent with previous studies, in the Off medication state, those patients with the greatest clinical impairment had the strongest coherence, especially in the beta band, indicating pathological over-synchronization. Dopaminergic medication reduced this coherence. For the stop signal task, On vs. Off medication increased beta band power over right frontal cortex for successful stopping and over bilateral sensorimotor cortex for going, especially for those patients who showed greater clinical improvement. Thus, medication reduced pathological coherence in beta band at rest and increased task related beta power for two potentially dissociable cortico-basal ganglia circuits. These results support the hypothesis that dopaminergic medication in PD improves neural communication both at rest and for executive and motor function.

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1. Introduction

Parkinson's disease (PD) is associated with loss of dopaminergic neurons in the midbrain and is characterized by motor symptoms such as bradykinesia, rigidity and tremor (Rodriguez-Oroz et al., 2009) and also by non-motor symptoms such as executive dysfunction, mood and sleep disorder (Chaudhuri and Schapira, 2009; Lim and Lang, 2010). While the classic 'firing rate model' in PD emphasizes excessive firing of basal ganglia output nuclei leading to excessive tonic inhibition of thalamus and cortex (Albin et al., 1989; DeLong, 1990), researchers now favor a temporal 'pattern model' which emphasizes neural oscillations. In particular, dopamine deficiency in PD apparently results in excessive oscillations and also increased inter-regional coherence especially at beta band frequencies (13–30 Hz) (Brown, 2003; DeLong and Wichmann, 2007; Weinberger et al., 2009). Such pathological beta oscillations have been recorded from the subthalamic nucleus, globus pallidus and the frontal cortex in both primate models of PD and from PD patients undergoing surgery (reviewed by Brown, 2007; Brown and Williams, 2005).

While dopamine replacement therapy is currently the gold standard treatment for improving motor function in PD the neural mechanisms of improvement are still not well understood. One hypothesis is that medication reduces the pathological oscillations and hypersynchrony within and between the cortex and the basal ganglia, particularly in the beta frequencies, thus improving communication within cortico-basal ganglia circuits (Jenkinson and Brown, 2011). Here we tested this idea by recording the scalp electroencephalogram in patients with PD while On and Off dopaminergic medication while in the resting state (no task) and also while performing a task that is suggested to engage at least two cortico-basal ganglia circuits.

For resting state EEG, the subjects sat at rest for a few minutes with their eyes open. We planned to compute pair-wise coherence between scalp electrodes in the On and Off medication state and to relate the coherence to their clinical Unified Parkinson's Disease Rating Scale (UPDRS) scores. We aimed to replicate an earlier report of excessive scalp coherence in patients Off medication, especially in the beta frequency band, and especially for those with high UPDRS scores

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(Silberstein et al., 2005). Additionally we aimed to replicate their finding that the excessive coherence was reduced by medication. In so doing, we set the stage for a novel comparison of resting and task-related EEG signatures.

We used a task that engages both going and stopping (Logan and Cowan, 1984). On each trial, subjects prepared to make a quick movement to a go signal. On a minority of trials the go signal was followed by a stop signal and the subjects tried to stop the initiated motor response. Much research shows that going relies on a premotor/basal-ganglia/primary motor network, while stopping relies on a predominantly right-lateralized prefrontal/premotor/basal-ganglia network with downstream effects on M1 (Aron et al., 2007; Chambers et al., 2009; Chikazoe, 2010; Coxon et al., 2006; Mattia et al., 2012; Mirabella et al., 2011b). EEG studies of going (movement) reveal that, during initiation, beta power is suppressed and gamma power is increased; and post-movement, there is an increased beta power over sensorimotor regions (Engel and Fries, 2010; Leuthardt et al., 2004; Levine et al., 1999; Pfurtscheller et al., 1996, 2003; Rohde et al., 2002). EEG studies of stopping, show an increase in the beta power for cortical regions such as the right inferior frontal cortex (Krämer et al., 2011; Marco-Pallarés et al., 2008; Swann et al., 2009, 2011, 2012). Of particular relevance for the current study, Swann et al. (2011) recorded scalp EEG in PD patients while they performed the stop-signal task with concurrent deep brain stimulation of the subthalamic nucleus (STN DBS). For stimulation On compared to Off, they observed faster behavioral stopping as well as increased beta band power over the right frontal cortex when the patients stopped their response. Accordingly, we focused here on a right frontal electrode cluster and beta frequency power as a marker of the integrity of a putative cortico-basal ganglia circuit for stopping action.

By performing a similar study to Swann et al. (2011), but this time using medication rather than STN DBS, we aimed to compare the treatment methods. While both treatments lead to improved clinical outcomes, they operate by different mechanisms (Zaidel et al., 2010). Dopaminergic therapy stimulates striatal activity and also exerts widespread modulation of cortical and subcortical areas (Delfs et al., 1996; Pötter-Nerger et al., 2012; Steiner and Kitai, 2001). DBS, by contrast, acts more locally, by modulating the subthalamus and thus affecting specific connected regions within the basal ganglia and the cortex (Devergnas and Wichmann, 2011; Gradinaru et al., 2009; Mcintyre et al., 2004). Notwithstanding these differences, it appears that dopaminergic therapy, like STN DBS, also reduces the pathological oscillations and hyper-synchrony within and between the basal ganglia and cortex (Hammond et al., 2007). Thus, our main aim here was to examine the effect of medication on a scalp EEG signature of a cortico-basal ganglia circuit for stopping, and to compare this with the earlier study with STN DBS (Swann et al., 2011). We also aimed to examine a scalp EEG signature of going, and to see if medication in PD would have common or different effects from stopping.

2. Materials and methods

2.1. Participants

Sixteen PD patients (eight females, mean age 62.6 ± 8.3 years) and sixteen matched controls (nine females, 63.5 ± 9.6 years) participated. All participants were right handed. The PD patients were clinically typical, responsive to dopaminergic therapy. All had mild to moderate PD (between stages II and III on the Hoehn and Yahr scale (Hoehn and Yahr, 1967)). Clinical characteristics of the patients, including medications and dosages, are presented in Tables 1 and 2. The patients were well matched with controls on age, gender and handedness, as well as on the Mini-Mental Status Exam (MMSE) and the North American Reading Test (NAART) (Ps > 0.2) (Table 2). However, the patients did score higher on the Beck Depression Inventory (BDI) both On and Off medication compared to controls ($t_{30} = 4.25$, $P < 0.005$ and $t_{27} = 3.05$, $P < 0.01$ respectively), with their scores being consistent with a sub-clinical level of depression as is commonly seen in PD (Table 2). Dopaminergic medication significantly improved motor symptoms, as measured by the motor section of the United Parkinson's Disease Rating Scale (UPDRS III) ($t_{15} = 4.00$, $P < 0.005$) (Table 2) (henceforth, referred to as UPDRS).

The patients were recruited from Scripps Clinic in La Jolla, California and controls were recruited from the local community or were spouses of the patients. All the participants provided written informed consent according to an Institutional Review Board Protocol at the University of California, San Diego.

One PD patient was excluded from the EEG analysis due to facial dyskinesia during the On medication session.

2.2. Procedure

Each patient visited the laboratory for two sessions, On and Off medication. The order of the visits was counter-balanced between patients. For the Off session, the time between the last dose of dopaminergic medication and the visit was 12 h or more, and for the On session, the patients took their usual morning dose before coming for the session. Clinical evaluations and rating scales were performed in the following order for the sessions/days: Session 1 — handedness test (Oldfield, 1971), BDI, UPDRS, MMSE and NAART; Session 2 — BDI and UPDRS.

Controls visited the laboratory once and clinical evaluations and rating scales were performed in the following order: handedness test, BDI, MMSE and NAART.

Following these evaluations, the EEG setup and recordings began, with the stop-signal task followed by the resting state.

2.3. Experiments

Experimental stimuli were presented on a 24 in. LCD monitor. Two button boxes were used to collect left and right index finger responses. Experiments were designed using MATLAB and the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997).

2.3.1. Resting state

EEG data were recorded for 3 min. The subjects were instructed to relax, keep their eyes open and maintain fixation on a white cross at the center of the screen.

2.3.2. Stop-signal task

The stop-signal task (Fig. 1) was identical to an earlier study we conducted with PD patients undergoing STN DBS (Swann et al., 2011). Briefly, every trial consisted of a fixation at the center of the screen for 500 ms. A Go-trial (67% of trials) consisted of a Go signal, indicated by a white square, appearing to the left or to the right of the fixation. Subjects had to make a response within 1500 ms (hold time) using their left and right index fingers. A Stop-trial (33% of trials) consisted of a Go signal (white square) appearing to the left or right as before, which turned red after a variable delay, the stop signal delay (SSD). The SSD was dynamically varied using four independently tracking staircases (two staircases for stop trials with a leftward pointing Go stimulus and two staircases for stop trials with a rightward pointing Go stimulus) to achieve a successful stopping probability of approximately 50% (Aron and Poldrack, 2006). Two staircases were selected per hand to ensure subjects do not predict when a stop signal would occur. The initial SSDs were 150 ms and adjusted in steps of 50 ms, reducing for failed stop trials and increasing for successful stop trials. Subjects were instructed to be as quick and accurate as possible and to do their best to stop when a stop signal occurred (even though this would not always be possible). There was a blank screen in the inter trial interval, which was jittered between 1 and 1.4 s.

Table 1
Patient clinical characteristics.

Patient ID	Age/gender/ handedness	Disease duration (years)	Medications	Dose (mg)	Frequency (times/day)	Hours since medication (On)	Hours since medication (Off)	UPDRS III[a] (On)	UPDRS III[a] (Off)
1	52/f/r	9	Lev	25/100	3	1.75	12.5	33	43
			LevR	25/100 or	1	1.75	12.5		
			Rop	4	1	1.75	12.5		
			Am	100	2	1.75	12.5		
			Ras	1	1	1.75	12.5		
2	67/f/r	2	Lev	25/100	3	4	13	22	28
			Ras	1	1	4	13		
3	55/f/r	12	Lev	25/100	2.5	3.5	13	16	32
			Ras	1	1	1.5	13		
4	62/f/r	8	Lev	25/100	1–3	3	12	34	40
5	74/m/r	1	Lev	25/100	4–6	1.5	15	44	47
			Ras	1	1	1.5	15		
			Rop	8	4	1.5	15		
6	71/f/r	1	Lev	25/100	3	3	14	20	20
			Ras	1	1	11.5	13		
7	62/m/r	2	Lev	25/100	3	2.75	13.5	54	49
			Ras	1	1	2.75	13.5		
			Pr	1	1	2.75	13.5		
8	63/m/r	2	Ras	1	1	5	24	31	38
			RopXL	8	1	4	24		
9	53/m/r	11	Lev	25/100	8	2.5	16	49	75
			LevR	25/100	4	2.5	16		
			Rop	2	12	2.5	16		
			Sel	1	1	2.5	16		
			Am	100	2	2.5	16		
10	74/m/r	2	Lev	100	3	2.5	17	27	32
			Ras	1	1	2.5	17		
11	55/m/r	2	Lev	25/100	3	2.5	16	30	30
			Rop	12	1	2.5	25.5		
			Ras	1	1	2.5	25.5		
12	69/f/r	6	Sel	5	2	2.5	13	30	38
			Pr	1.5	3	2.5	13		
13	47/m/r	6	Sel	1	1	3.25	13	42	58
			RopXL	12	1	3.25	25		
14	66/f/r	3	Lev	25/100	3	2	12.5	36	44
			Ras	1	1	2	12.5		
			Pr	1	1	2	12.5		
15	71/f/r	3	Lev	25/100	4	2.75	13	25	42
			Ras	1	1	2.75	13		
16	61/m/r	9	Lev	25/100	6	3	16	46	48
			LevR	25/100	1	3	27		
			RopXL	8 & 12	1 & 1	3	27		
			Ras	1	1	3	27		
			Ent	200	6	3	27		

Note: Medication names: Am — Amantadine, Ent — Entacapone, Lev — Carbidopa/levodopa (regular formulation), LevR — Carbidopa/levodopa (sustained release), Pr — Pramipexole, Ras — Rasagiline, Rop — Ropinirole, RopXL — Ropinirole (extended release), Sel — Selegiline.
[a] UPDRS III score range is 0–108. Higher scores reflect greater impairment.

Table 2
Demographic and rating scale measures.

	PD patients N = 16	Controls N = 16
Age (years)	62.62 (8.32)	63.50 (9.66)
Sex	8f	9f
Handedness	All R	All R
MMSE	28.94 (1)	29.19 (1.10)
NAART	46 (6.27)	49.12 (7.14)
BDI [a]		3.27 (3.20)
Off medication	9.44 (5.07)	
On medication	7.76 (5.05)	
UPDRS III [b]		N/A
Off medication	41.5 (12.95)	
On medication	33.68 (10.86)	

Note: All values are given as mean (standard deviation).
MMSE, Mini-Mental Status Exam; NAART, North American Adult Reading Test; BDI, Beck Depression Inventory, UPDRS, Unified Parkinson's Disease Rating Scale.
[a] BDI Patients Off and On versus controls, $t_{27} = 3.05$, $P < 0.01$ and $t_{30} = 4.25$, $P < 0.005$ respectively.
[b] UPDRS III Patients Off versus On, $t_{15} = 4.00$, $P < 0.005$.

The task consisted of 8 blocks of 96 trials each, with end-of-block feedback given. Prior to EEG recording, subjects were trained on a short block of 40 trials.

2.4. EEG recordings

EEG was recorded using a 32 channel ActiveTwo (Biosemi Instrumentation system) using a sampling frequency of 512 Hz. Two extra electrodes were placed over left and right mastoids, used for reference and two electrodes were placed lateral and below the left eye for vertical and horizontal electro-oculogram.

2.5. Analysis

2.5.1. Behavior for the stop-signal task

The following behavioral indices were estimated: correct go RT (reaction time on correct Go trials), failed stop RT (reaction time on stop trials when the subject failed to stop), percent go discrimination errors (percentage of trials where the subject pressed the button box on the wrong side), percent go omission errors (percentage of trials where the subject failed to respond on Go trials), probability of stopping

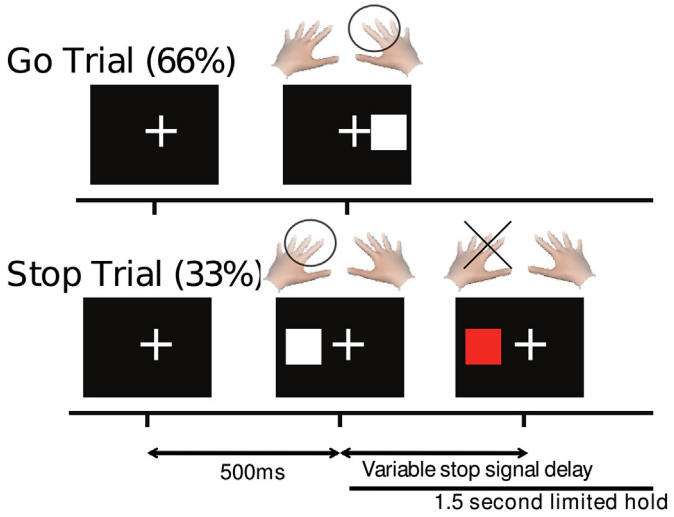

Fig. 1. Stop-signal task: Each trial began with a fixation cross, followed 500 ms later by the appearance of a white square (Go signal). The square appeared to either the left or the right of the fixation cross requiring a response from the corresponding hand. Stop trials were identical to Go trials, except they were less likely (33% of trials) and the white square turned red after a variable delay (stop signal delay).

overall (percentage of stop trials where subject was successful in stopping), overall SSD (mean SSD from the four staircases), and integration SSRT (Stop Signal Reaction Time using the integration method (Logan and Cowan, 1984; Verbruggen et al., 2013)).

2.5.2. EEG preprocessing

This was highly similar to our previous study (see Swann et al. (2011)) and was performed using a combination of custom MATLAB scripts and EEGLAB (Delorme and Makeig, 2004). It consisted of referencing to mastoids, filtering between 0.05 and 50 Hz, performing independent component analysis denoising to remove eye and muscle artifacts and visual inspection to ensure clean data. For the resting state EEG data, to reduce the spurious effects of volume conduction on pairwise coherence between electrodes (Greenblatt et al., 2012; Winter et al., 2007), current source density estimates were evaluated using a spherical spline algorithm (Perrin et al., 1989) implemented in the MATLAB 'CSD toolbox' (Kayser and Tenke, 2006).

2.5.3. EEG analysis, resting state

Three minutes of EEG data were epoched into windows of 5 s each. Power spectrum estimates of these epochs were evaluated using the Fast Fourier Transform, after multiplying by a Hamming window. Mean power was estimated in the frequency bands delta (0–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (30–50 Hz).

Coherence analysis was performed using complex Gaussian filters with center frequencies between 0 and 50 Hz. 32 such filters were selected with varying time and frequency bandwidths, consistent with prior studies (Canolty et al., 2007; Swann et al., 2011) and also with the approach taken for event-related time-frequency analysis of the stop-signal task (see below). Absolute values of coherence 'Coh' were evaluated using the expression $\mathrm{Coh}(t,f)=\frac{|W_{xy}(t,f)|}{\sqrt{W_{xx}(t,f)}\sqrt{W_{yy}(t,f)}}$ where $W_{xy}(t,f)=\frac{1}{N}\sum_{k=1}^{N} W_x(t,f)\cdot W_y^*(t,f)$ is the analytical signal of channel x after filtering, $W^*_x(t,f)$ is its complex conjugate, $W_{xx}(t,f)$ is the auto-spectra of channel x, $W_{xy}(t,f)$ is the cross-spectra of channels x and y, and N is the number of epochs. These coherence values were then normalized using Fisher's z-transform. The final coherence values were averaged over the entire time duration (except for epochs affected by artifacts) to obtain one coherence value per channel pair for each Gaussian filter for each subject (i.e. $\mathrm{Coh}^f_{n1,n2}$ where n1 and n2 are the channel numbers and f is the center frequency of the Gaussian filter). This was performed for all pair-wise combinations of the 32 channels.

The relationship between a patient's coherence values in these frequency bands ($\mathrm{Coh}^f_{n1,n2}$) and clinical state (obtained from UPDRS) was evaluated using Pearson's correlation coefficient (r). The total number of these significant pairs (out of the 32 channel combinations) was used to deduce which frequency bands were most associated with clinical impairment or improvement.

2.5.4. EEG analysis, stop-signal task

Time-frequency analysis was performed using the same Gaussian filters used in the coherence analysis for the resting state EEG. The analysis was similar to prior studies (Canolty et al., 2007; Swann et al., 2011). In brief, the EEG data were time-locked to events corresponding to all stop trials (successful and failed combined); this was performed to increase statistical power of our analysis (although see below for a key analysis which analyzed successful and failed stop trials separately). The data were then filtered using the Gaussians to obtain the analytic signal, the absolute value of which was taken at each timepoint for each of the 32 center frequencies. These were then corrected to a baseline which consisted of 500 ms in the inter trial interval. The data were then averaged over trials for each condition (e.g. all stop trials) to create an averaged event-related time-frequency map for that condition for each channel. Based on other EEG results with the stop signal task (Schmajuk et al., 2006; Swann et al., 2011), time-frequency maps were averaged over a right frontal electrode cluster (F8, FC6) for each subject. For evaluating the significance for each condition within each group; one sample t-tests were used at each time-frequency point. For testing between group differences, paired sample t-tests were used between patients' On and Off sessions and unpaired sample t-tests between the high and low improvement groups. The normality of these baseline-corrected time-frequency points was evaluated using the Shapiro Wilk test.

3. Results

3.1. Resting state EEG

Earlier studies have shown that coherence is greater in the Off vs. On medication state, and in particular, that this effect is greatest for those patients who have higher (worse) UPDRS scores (Silberstein et al., 2005). Accordingly, for each pair of electrodes, and in each frequency band, we analyzed the correlation of the mean coherence ($\mathrm{Coh}^f_{n1,n2}$) with the subject's UPDRS score (Silberstein et al., 2005; Stoffers et al., 2008). A sample estimation of this correlation for one of the Gaussian filters for patients Off medication is shown in Fig. 2A. This correlation is evaluated similarly for all possible pairs of the 32 electrodes (496 pairs) (Fig. 2B) and the number of positively correlated significant pairs was selected (Fig. 2C). This number was expressed as a percentage and this estimation was repeated for each of the Gaussian filters (Fig. 2D).

For patients Off medication, this analysis revealed positive correlations in the higher frequencies, with the beta frequency band in particular having the largest number of significant pairs (Fig. 2D/E Off condition). Thus, increases in coherence correlated with disease severity. For patients On medication, this cortical coherence was reduced (Fig. 2E On condition). Further, the reduction was greatest in those patients who improved the most on the UPDRS. We tested this by correlating the medication-related difference in pairwise coherence ($\mathrm{Coh}^f_{n1,n2}$ Off–On) with the medication-related change in UPDRS scores (UPDRS Off–On) for each subject in each frequency band. We observed that more pairs were positively correlated at the higher frequencies (including beta) signifying greater reductions in coherence in proportion with clinical improvement (Fig. 2E Off–On condition). This shows that medication reduces the pathological 'locking' at the cortex, especially in the beta and gamma bands.

For completeness, we examined power spectrum effects. There were increases in power in the lower frequencies, also commonly referred to

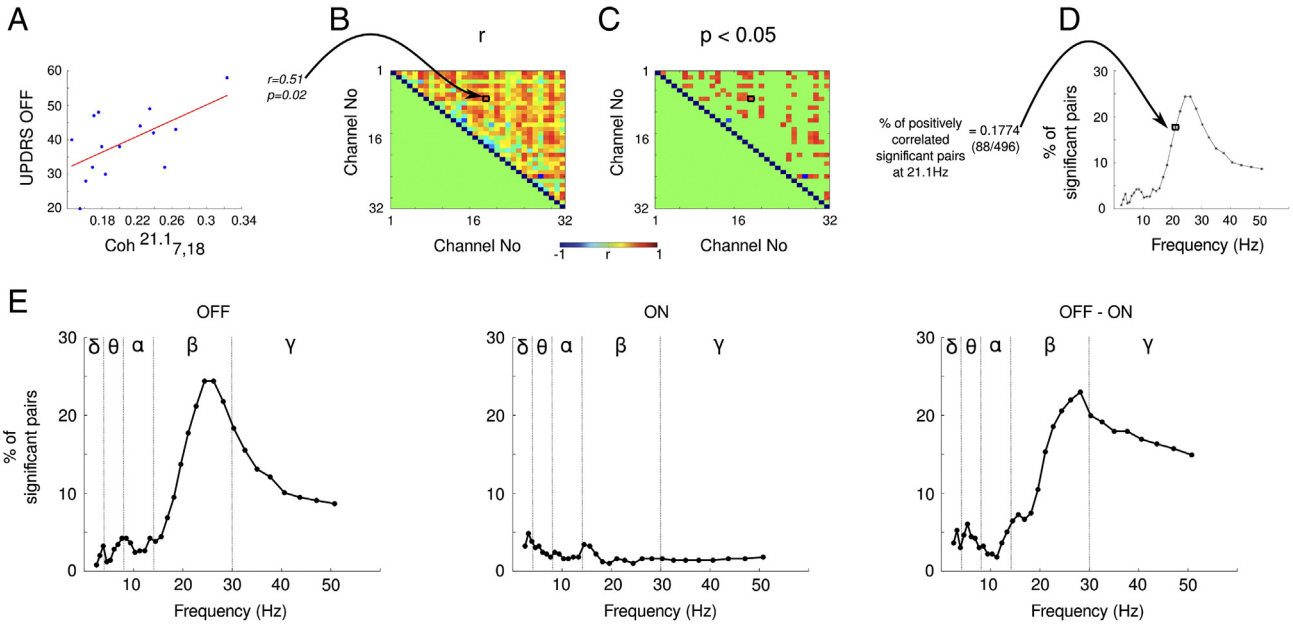

Fig. 2. Correlation between scalp-level coherence and UPDRS scores. A. An example plot of coherence values at f = 21.1 Hz (beta) Gaussian frequency filter for channels 7 and 18 ($Coh^{21.1}_{7,18}$) plotted vs UPDRS for each subject (15 subjects) in the Off medication condition resulting in a Pearson correlation coefficient, r = 0.51 and significance, P = 0.02. B. Grid for 32 channels in beta band (f = 21.1 Hz) showing correlation (r) of pair-wise coherence with UPDRS per subject, red indicating positive correlation and blue indicating negative correction. C. Grid for 32 channels in beta band (f = 21.1 Hz) showing significant correlation pairs at P < 0.05. D. The total number of significant positively correlated pairs in the Off medication state computed at each of the individual Gaussian frequency filters (where e.g. 18% significant pairs at 30 Hz means that 18% of all the 496 possible pairs showed a significant correlation, across subjects, between coherence and UPDRS score). E. The total number of significant positively correlated pairs computed at each of the individual Gaussian frequency filters of Off Medication state (left lower panel; same as Panel D), On medication state (middle lower panel) and the Off–On difference (right lower panel). Those patients with greater clinical impairment had stronger coherence in the Off state, with more pairs positively correlated in the beta band. The correlation between coherence values and UPDRS scores for patients is weaker On medication. The reduction in coherence in beta and gamma bands with medication is strongest in those patients who show the greatest clinical improvement, where positive correlations indicate that greater reductions in coherence correspond to greater clinical improvement as indicated by the UPDRS scores. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

as EEG slowing (Stoffers et al., 2007), where patients On medication had more theta compared to controls at occipital electrodes (see Inline Supplementary Fig. S1). We also observed a decrease in beta and gamma power particularly at the frontal channels, although this effect was not significant. We did not observe any significant differences between patients On and Off their medication in any particular frequency band (see Inline Supplementary Fig. S1).

Inline Supplementary Fig. S1 can be found online at http://dx.doi.org/10.1016/j.nicl.2013.07.013.

Thus, consistent with prior research (Silberstein et al., 2005; Stoffers et al., 2008) our results show that while dopaminergic medication has little effect on modulating power at the cortex, it does successfully modulate intra-cortical coherence.

3.2. Stop-signal task

3.2.1. Behavioral results

The patients took significantly longer to stop their responses than controls as SSRT was longer (On vs. controls: $t_{30} = 2.07$, $P < 0.05$; Off vs. controls: $t_{30} = 2.47$, $P < 0.05$). However, there was no difference in SSRT for On vs. Off ($P > 0.6$) (Table 3; Fig. 3B). Thus, dopaminergic treatment did not improve the patients' stopping ability.

On other indices, performance between the groups was similar, with no significant differences for correct Go RTs (Fig. 3A), except for the discrimination accuracy on Go trials (i.e. making the correct response), where patients On medication made more errors than controls ($t_{30} = 2.86$, $P < 0.01$) and more errors than patients Off medication ($t_{15} = 2.46$, $P < 0.05$).

3.2.2. EEG time-frequency results

These were analyzed for the right frontal cluster (electrodes F8 and FC6), time-locked to the stop signal. As predicted from our prior findings (Swann et al., 2011), there was a relative increase in beta (although higher beta (>20 Hz) in this study) at the time of stopping in the On group and the Off group and also in controls; however, this increase did not reach significance relative to the inter trial interval baseline in any group (see Inline Supplementary Fig. S2). Although the weak effect in controls was surprising (see Discussion below) we note that the main objective of this study was to examine the effect of medication. Consequently we focus on the patients henceforth.

Inline Supplementary Fig. S2 can be found online at http://dx.doi.org/10.1016/j.nicl.2013.07.013.

Table 3
Stop-signal task behavioral performance.

	Controls	Patients	
		On medication	Off medication
Go RT (ms)	518.77 (108.79)	528.41 (98.97)	523.09 (98.04)
Failed Stop RT (ms) [a]	459.94 (94.66)	462.78 (81.95)	453.89 (73.48)
Go discrimination error (%) [b]	0.37 (0.41)	1.17 (1.02)	0.49 (0.53)
Go omission error (%)	0.12 (0.20)	0.97 (2.02)	0.23 (0.44)
Prob. stopping overall (%)	50.36 (2.86)	49.08 (5.69)	51.93 (3.99)
Overall SSD (ms)	264.80 (109.87)	242.83 (102.32)	236.02 (84.43)
Integration SSRT (ms) [c]	246.04 (25.78)	267.90 (43.32)	269.78 (35.43)

Note: All values are given as mean (standard deviation). Go RT, reaction time on correct Go trials; failed stop RT, reaction time on stop trials when the subject failed to stop; percent go discrimination errors, percentage of trials where the subject pressed the button box on the wrong side; percent go omission errors, percentage of trials where the subject failed to respond on Go trials; Probability of stopping overall, percentage of stop trials where subject was successful in stopping; overall SSD, mean SSD from the four staircases, and integration SSRT.

[a] For each group, failed stop RT is faster than Go RT, consistent with a valid context dependent horse-race model.

[b] Go discrimination error controls vs PD On, $t_{30} = 3.86$, $P < 0.01$; Go discrimination error PD On vs PD Off, $t_{15} = 2.46$, $P < 0.05$.

[c] Integration SSRT controls vs PD On, $t_{30} = 2.07$, $P < 0.05$; Integration SSRT controls v PD Off, $t_{30} = 2.47$, $P < 0.05$.

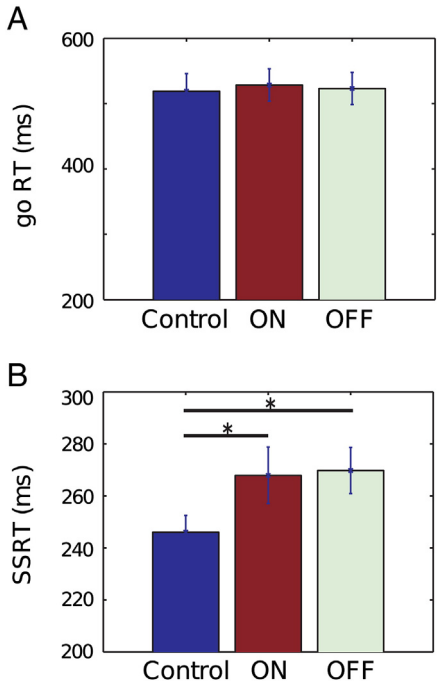

Fig. 3. Stop signal task results A. Mean Go RTs for controls and patients On and Off medication. There is no significant difference between the groups. B. Mean SSRTs for controls and patients On and Off medication. There are significant differences between the controls and patients On medication ($t_{30} = 2.07$, $P < 0.05$); as well as between the controls and patients Off medication sessions ($t_{30} = 2.47$, $P < 0.05$).

Given that reductions in coherence during the resting condition correlated with the individual patient's clinical improvement (measured by the UPDRS) (Fig. 2), the stopping-related data were further examined by dividing the patients into two groups based on a median split of clinical improvement indicated by the difference in UPDRS scores (Off–On). Eight patients formed a 'high-improvement' group and seven a 'low-improvement' group.

First, we examined behavior by using a mixed model repeated measures ANOVA to test the effect of medication On vs Off for high vs low improvement groups. Surprisingly, this did not reveal any significant main effects of group or interactions between group and medication (see Inline Supplementary Table S1). Nevertheless, there was a notable group difference in the EEG. We observed a stopping-related increase in beta and gamma band power in the right frontal cluster in the high-improvement group (especially when On medication), but less for the low-improvement group (Fig. 4A, B). Within the high improvement group, there was strongly elevated stopping-related beta and gamma for On vs. Off; however, this was not the case in the low improvement group (Fig. 4C). Finally, the interaction 'high vs low' improvement and 'On vs Off' medication was significant ($P < 0.05$) (Fig. 5) (This was estimated by performing an unpaired sample t-test of the On minus Off time-frequency maps of high and low improvement groups). Notably, this increase was not only for all stop trials taken together but also for the subset of successful stop trials, thus obviating the concern that it could have been driven by relative differences in desynchronization on failed stop trials or an effect of the movement itself. In addition, we compare this result for the successful stop trials for the right frontal cluster with the equivalent left frontal cluster (F7, FC5) (Inline Supplementary Fig. S3). We observed a greater increase in beta in the right frontal cluster compared to the left cluster around the time of stopping.

Inline Supplementary Table S1 and Fig. S3 can be found online at http://dx.doi.org/10.1016/j.nicl.2013.07.013.

To map the spatial extent of this effect, we inspected the mean beta frequency t-score values of this interaction ('high vs low' improvement and 'On vs Off' medication) as a topography map (Fig. 6A); averaged in time segments of 200 ms. There was an increase in beta in a right frontal cortical locus and at a time range (around SSRT) consistent with our earlier study for patients On vs Off STN DBS (Swann et al., 2011). As a comparison, we also inspected the same beta frequency interaction for successful Go trials time-locked to the button press (Fig. 6B) (Also see Inline Supplementary Fig. S4). There was an increase around the time of the button press and extending post-movement, but this increase was concentrated in the sensorimotor rather than frontal regions.

Inline Supplementary Fig. S4 can be found online at http://dx.doi.org/10.1016/j.nicl.2013.07.013.

4. Discussion

We studied PD patients who were On and Off dopaminergic therapy using both resting state EEG and an executive control task with EEG. For the resting state EEG, when patients were Off medication, there was strong pair-wise scalp coherence in the beta band, especially for the patients with greater clinical impairment. Dopaminergic therapy reduced this pathological synchronization, in proportion with clinically relevant improvement (UPDRS scores), especially in the beta and gamma bands. For the stop-signal task, the patients were behaviorally impaired in stopping compared to controls, but medication did not remediate this. Based on the resting state EEG results, we split the patients into those with higher and lower clinical improvement (UPDRS) for On vs. Off medication. EEG analysis showed a frontal beta band increase at the time of stopping for the high improvement group when On vs. Off medication, and this medication induced task-related increase was significantly greater than for the low improvement group. Notably, for Go trials there was also a beta band increase, but it was more over sensorimotor than frontal regions, possibly pointing to dissociable effects on different fronto-basal-ganglia circuits for stopping and going. Taken together, the main results show that for the patients who benefited the most from medication, there was a reduced pathological cortical synchronization in the beta band in the resting state and also increased task-related beta band power for stopping at a right frontal focus and for going over sensorimotor cortex.

4.1. Dopaminergic medication reduces pathological coherence at the scalp

With resting state EEG, we showed that those patients with the greatest clinical impairment had the strongest beta band coherence between cortical areas when Off medication, and also that those patients who benefited the most from medication (evaluated with UPDRS) showed the greatest reduction in this coherence. This is consistent with Silberstein et al. (2005) who also observed that medication-induced changes in beta band coherence correlated with clinical improvement. The opposite effect was observed in an MEG study (Stoffers et al., 2008), although in a further analysis, a subset of patients did show decreases in beta coherence with medication (Stam, 2010; Stoffers et al., 2008).

Our results point to the efficacy of dopaminergic medication in reducing the pathological 'locking' at the cortex at frequencies such as beta and gamma when patients are at rest. It is important to note that this change in coherence occurred despite the fact that there were no significant differences in power in these frequency bands for On vs. Off medication. This is consistent with prior reports of medication-related coherence change without changes in power (Brown, 2007; Stam, 2010; Stoffers et al., 2008). One aspect of the finding is counter-intuitive, namely, medication also reduced coherence in the gamma band. This is puzzling because gamma has been considered pro-kinetic in PD, whereas beta is antikinetic (Brown, 2003), and thus we would expect an increase rather than a decrease in coherence in the gamma band when On medication. However, Silberstein et al. (2005) also reported a reduction in resting state gamma band cortical coherence On dopaminergic medication (but no reduction following STN DBS). It remains to be determined how dopaminergic drugs and deep brain stimulation differ in this regard.

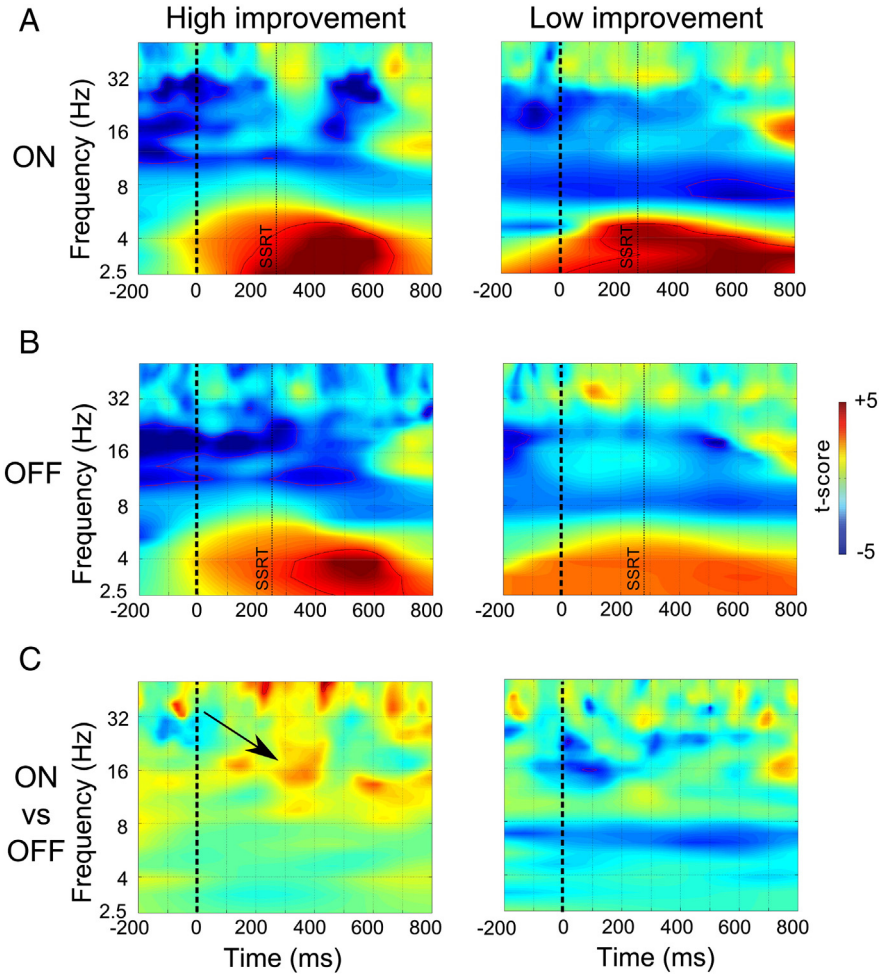

Fig. 4. Beta and gamma band power of right frontal cortex is increased for stop trials in the high improvement group. A. All stop trials (successful and failed combined) for the On medication condition for high and low improvement groups. B. All stop trials for the Off medication condition for high and low improvement groups. C. All stop trials for the On vs Off between-session comparison for high and low improvement groups. Time-frequency results are shown for the right frontal cluster (F8, FC6). Plots are generated from trials time-locked to the stop signal, here corresponding to 0 ms. T-score significance values are displayed as color; t-score values reach significance at $t_7 = 2.36$ (high improvement group) and $t_6 = 2.44$ (low improvement group). Significance at $P < 0.05$ is outlined in black indicating positive direction and red indicating negative direction. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4.2. Dopaminergic medication increases task-related power at the scalp

The observation above that medication reduced cortical coherence in the beta band, especially in those patients who showed the greatest clinical improvement, raises the possibility that medication had its effects by ameliorating impaired cortico-basal-ganglia neural communication. Our analysis of the stop-signal task EEG data allowed us to test this possibility. Based on our prior studies, we focused on a right frontal

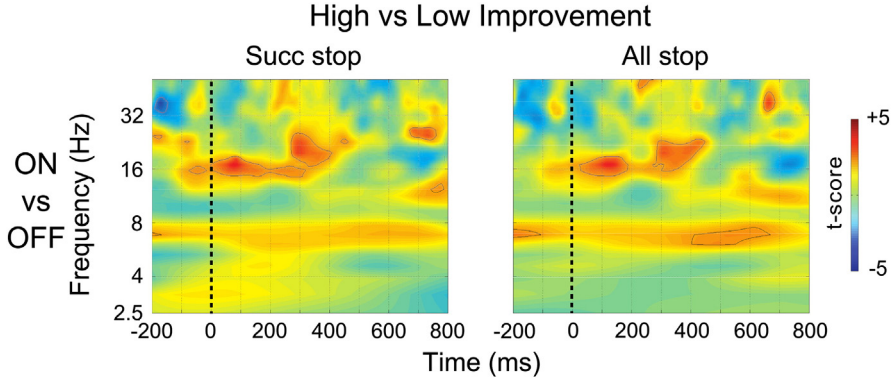

Fig. 5. Medication increases right frontal beta band power for stopping more in the high than low improvement group. Successful stop and all stop (successful and failed combined) trials for On vs Off medication for the high vs low improvement group comparison. There is a significant increase in beta power starting from the time of the stop signal and peaking around the time of SSRT. Time-frequency results are shown for the right frontal cluster (F8, FC6). Plots are generated from trials time-locked to the stop signal, corresponding to 0 ms here. T-score significance values are displayed as color. T-score significance values are displayed as color; t-score values reach significance at $t_{13} = 2.16$ (high vs low and On vs Off comparison). Significance at $P < 0.05$ is outlined in black indicating positive direction and red indicating negative direction. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

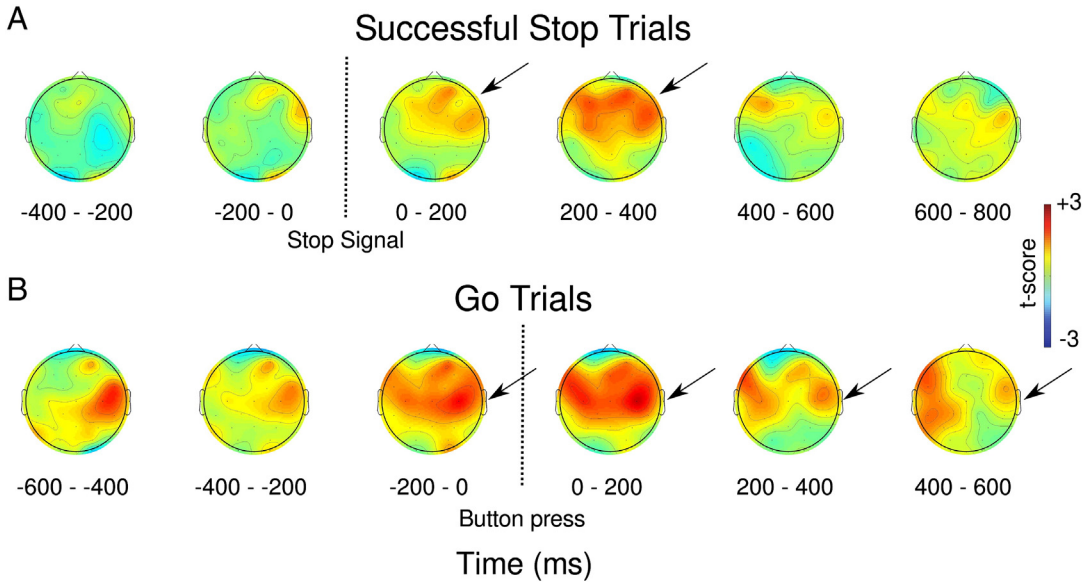

Fig. 6. Time and frequency averaged beta frequency t-score values for On vs Off medication for the high vs low improvement group comparison displayed as a topography map. A. Successful stop trials where 0 ms corresponds to the time of the stop signal. B. Successful Go trials where 0 ms corresponds to the time of the button press. Trials include Go stimulus that appeared on both left and right. T-score significance values are displayed as color; t-score values reach significance at $t_{13} = 2.16$ (high vs low and On vs Off comparison). Arrows point to critical regions of increase; the increase in beta for stopping begins and is concentrated more at the right frontal regions, in the time associated with stopping (0–400 ms). The increase in beta while going and post movement is concentrated more at the sensorimotor regions.

cluster that showed an increase in beta power at the time of stopping (Swann et al., 2011). We hypothesized that communication within this stopping network, observed from the scalp oscillations in the beta band, would be stronger when patients were On compared to Off dopaminergic medication. Although this prediction was not born out when comparing all patients On with all patients Off, it did emerge when splitting the patients into high vs. low improvement groups, based on the change in UPDRS scores with medication (and motivated by the resting state EEG findings). Specifically, there was a significant increase in right frontal beta band power for the On–Off comparison between the high and low improvement groups in a time range consistent with the stopping process.

In addition to the right inferior frontal cortex, studies have shown the involvement of motor cortices (M1 and PMc) in canceling initiated limb movements (Coxon et al., 2006; Mattia et al., 2012; Mirabella et al., 2011b). In particular, it has been thought that these regions act as the final target of the inhibition commands generated by the putative frontal-basal ganglia network (Mattia et al., 2012). It is difficult to make specific conclusions with respect to the regions given the limited spatial resolution of scalp EEG, however, the topography maps of this beta increase show frontal as well as motor regions (M1). Moreover, this significant increase was also observed for successful stop trials and not just for all stop trials. Although we observed an increase in beta for unsuccessful stop trials too, this increase was much smaller than for successful stop trials.

Overall, these results provide further evidence for the importance of the beta band for stopping within a putative fronto-basal-ganglia network (Krämer et al., 2011; Marco-Pallarés et al., 2008; Swann et al., 2011, 2012). Though we did not observe any differences in SSRT between patients On and Off dopaminergic medication, we did observe changes in the EEG that were modulated by medication especially in the patients with the greatest clinical improvement, and in a way that was very similar to STN DBS. Taken together with our STN DBS report (Swann et al., 2011) our results suggest that dopamine therapy also modulates communication in a putative frontal-basal-ganglia circuit that is important for stopping action, especially for the group of patients who had the best response to medication.

We also show that beta-frequency is affected by medication during and after movement (going), although this was more over sensorimotor than frontal regions. In particular, such beta-frequency effects have been observed in sensorimotor regions for imagined or self-paced movement — something that is also modulated by dopaminergic medication (Devos and Defebvre, 2006; Devos et al., 2003; Labyt et al., 2005; Priori et al., 2002). These results suggest that dopaminergic medication affects functionally distinct basal ganglia loops (a prefrontal/premotor-basal-ganglia executive loop for stopping versus a premotor/primary motor/basal-ganglia loop for going/movement). The results also highlight the utility of using EEG in conjunction with behavioral approaches to look at medication effects.

4.3. Limitations

The study was subject to several limitations. Firstly, for the resting state EEG analysis, the correlation between the number of coherence pairs and UPDRS was not significant when corrected for multiple comparisons. However, our results, for beta frequency specifically, are a replication of Silberstein et al. (2005). Second, while Swann et al. (2011) showed that STN DBS improved stopping behavior (faster SSRT for On vs. Off stimulation) (and also see Mirabella et al., 2012; van den Wildenberg et al., 2006) that was not the case here: SSRT was very similar for On vs. Off medication, although both were impaired (longer SSRT) compared to controls. Notably, other stop signal studies in PD patients testing the effect of medication also reported no differences in SSRT for On vs Off (Alegre et al., 2012; Obeso et al., 2011). Furthermore, in our study even when we compared the high and low improvement groups, there was still no difference in SSRT for On vs Off in either group. This lack of medication effect on behavioral stopping is at odds with our EEG findings that beta band power was strongly increased over right frontal cortex when stopping in the high improvement group and especially when On medication. This discrepancy could be explained by differential sensitivity of behavior vs. electrophysiology to the effects of medication. Further research is required to establish if the observed beta band response in the task is causally important for stopping, and whether medication would affect behavioral stopping in a larger sample or in patients with a more uniform clinical and medication picture. Third, an anomalous aspect of this study was that the control subjects did not have a significant increase in beta-frequency at the time of stopping (although there was a numerical increase in the high

beta band). We attribute this to advanced age (a mean of 64 years) and/or to baseline levels of beta power that could have weakened the observed stopping-related response. Importantly, the main conclusions of this report do not rely on a comparison of electrophysiological responses between patients and controls. Fourth, while the main EEG result of a right frontal beta band increase around the time of stopping for the high versus low improvement group and especially for On medication was significant at the individual time-frequency point level, it was not when correcting for all possible comparisons. However, the frequency band and timing of this effect are highly consistent with prior studies (Krämer et al., 2011; Marco-Pallarés et al., 2008; Swann et al., 2011, 2012). In addition, the beta frequency behavior for the high and low improvement groups that we observe during stopping, that is a decrease followed by an increase, is also similar to that seen in the STN while performing a similar task (Alegre et al., 2012; Ray et al., 2012); though interpretations of this beta vary between differences in going for successful stop trials, an active inhibitory process, or a mixture of both. Fifthly, in this study we filtered the data to 50 Hz and thus restricted our analysis till the lower gamma range (30–50 Hz). It may be possible for further studies to study the effects of medication at higher gamma both for rest and for task related EEG. Finally, in this study, the stop signal task was always followed by the resting state. During a pilot study with older controls, we observed that having the resting state EEG first introduced some tiredness, though the duration was only 3 min, and hence these tasks were not counterbalanced.

5. Conclusion

Dopaminergic medication reduced resting state EEG beta coherence and increased task-related beta power for PD patients who had the greatest clinical improvement. This bolsters earlier reports of the importance of the beta band for communication within a putative fronto-basal ganglia circuit for inhibitory control. It is also consistent with an earlier report showing that STN DBS On vs. Off also modulated right frontal beta band power in the same way. However, although STN DBS did improve stopping behavior, dopaminergic medication did not. Additionally we observed a change in beta over sensorimotor regions for going which was also modulated by medication. The results argue for the importance of electrophysiology over and above pure behavior for testing hypotheses about the effect of dopaminergic medication on higher cognitive functions. Overall, the results advance the understanding of the clinical pathophysiology of PD, the effects of dopaminergic drugs on cortical oscillations and on the implementation of inhibitory control. Specifically, we interpret the findings as showing that medication reduces pathological 'locking' at the cortex, thus enabling improved information transfer in cortico-basal ganglia circuits.

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