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Mid-frontal theta activity is diminished during cognitive control in Parkinson's disease

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Abstract

Mid-frontal theta activity underlies cognitive control. These 4–8 Hz rhythms are modulated by cortical dopamine and can be abnormal in patients with Parkinson's disease (PD). Here, we investigated mid-frontal theta deficits in PD patients during a task explicitly involving cognitive control. We collected scalp EEG from high-performing PD patients and demographically matched controls during performance of a modified Simon reaction-time task. This task involves cognitive control to adjudicate response conflict and error-related adjustments. Task performance of PD patients was indistinguishable from controls, but PD patients had less mid-frontal theta modulations around cues and responses. Critically, PD patients had attenuated mid-frontal theta activity specifically associated with response conflict and post-error processing. These signals were unaffected by medication or motor scores. Post-error mid-frontal theta activity was correlated with disease duration. Classification of control vs. PD from these data resulted in a specificity of 69% and a sensitivity of 72%. These findings help define the scope of mid-frontal theta aberrations during cognitive control in PD, and may provide insight into the nature of PD-related cognitive dysfunction.

Keywords

EEG; theta; cognitive control; Parkinson's disease; error

1. Introduction

Parkinson's disease (PD) involves both motor and cognitive symptoms. Compared to motor symptoms, cognitive symptoms are less treatable and have greater impact on quality of life (Lawson et al., 2016; Martinez-Martin et al., 2011). There is a critical need to better understand cognitive impairments in PD. Mid-frontal theta band activity is thought to be a

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Conflict of Interest

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Supplementary materials

Supplementary materials related to this article can be found at

mechanism for cognitive control (Cavanagh and Frank, 2014), and it is diminished in PD (Parker et al., 2015a). However, it is unclear if mid-frontal theta activity is attenuated during executive demands in PD patients.

Mid-frontal theta activity (4 and 8 Hz) is particularly prevalent following novel stimuli, conflicting instructions, or after mistakes (Cavanagh and Frank, 2014; Schacter, 1977). While mid-frontal theta power has been compared to an alarm bell signaling the need for control, synchronized phasic entrainment has been advanced as a mechanism for communication and implementation of control across brain regions (Cavanagh and Frank, 2014). For instance, in both humans and rodents mid-frontal theta signals are modulated after errors during reaction-time performance, correlate with post-error adjustments, and coherent with single frontal neurons that control such adjustments (Cavanagh et al., 2011; Narayanan et al., 2013b). Furthermore, mid-frontal signals can engage and modulate subcortical processing in the subthalamic nucleus (STN) (Cavanagh et al., 2011; Herz et al., 2016; Kelley et al., 2018; Zavala et al., 2014). Activity in this band can engage single neurons involved in cognitive processing and promote cognitive control in the frontal cortex as well as in the basal ganglia. At key task moments, bursts of theta activity can synchronize activity in the ventral tegmental area, amygdala, septum, and hippocampus. Thus, theta band processes may be used to communicate this need and subsequently implement such control across disparate brain regions. Thus, mid-frontal theta is likely a key mechanism of cognitive control.

Recent work from our groups has indicated that mid-frontal theta activity depends on cortical dopaminergic input. Disrupting cortical dopamine in rodent models markedly impairs mid-frontal theta activity during interval timing (Kim et al., 2017; Parker et al., 2014; Parker et al., 2015a; Parker et al., 2015b). PD patients have attenuated mid-frontal theta activity (Chen et al., 2016; Kim et al., 2017; Parker et al., 2015a). For instance, during interval-timing tasks PD patients have less mid-frontal theta activity relative to controls (Kim et al., 2017; Parker et al., 2015a). Similarly, PD patients fail to adapt to startling and novel stimuli and have less mid-frontal theta activity associated with this adaptation (Cavanagh et al., 2017a; Chen et al., 2016). However, these tasks lack a characterization of explicit cognitive control such as conflict or errors. The preceding line of work predicts that cognitive control-related mid-frontal theta will be attenuated in PD.

We tested this hypothesis by collecting scalp EEG during performance of a modified Simon reaction-time task in PD patients and demographically-matched controls. During this task, participants must respond flexibly respond with a right or left button press as instructed by a cue. Cues could be congruent (instruction right presented on the right) or incongruent (instruction right presented on the left), and participants made occasional errors. Accordingly, this task explicitly involves cognitive control for conflict – which derives from comparisons of incongruent vs. congruent trials, and for error-processing – which derives from comparisons of error vs. correct trials, and from correct trials following error (post-error) vs. correct (post-correct) trials. Because conflict and error-related processing are associated with robust mid-frontal theta, we predicted that PD patients would have attenuated mid-frontal theta with response conflict and on post-error trials. We interpret these data in the context of cognitive deficits in PD patients.

2. Materials and methods

2.1. Experimental Design

The University of New Mexico Office of the Institutional Review Board approved the study and all participants provided written informed consent. Participants were paid \$20/hr for participation. Participants included 28 individuals with PD who were recruited from the Albuquerque, New Mexico community and an equal number of sex and age matched controls. We have previously reported data from this cohort of participants before, including separate EEG tasks and behavior from this modified Simon task, where major findings were related to the years since diagnosis (Cavanagh et al., 2017a; Cavanagh et al., 2017b). This is the first report on the control-specific EEG from this cohort. The PD group visited the lab twice, seven days apart: once on medication (ON) and once after a 15-hour overnight washout from their individual prescriptions of dopaminergic medication used to treat PD (OFF). Table S1 demonstrates the doses of antiparkinsonian medication for each patient at the time of the on-medication experiments.

All patient and control sessions were run at 9 AM; 14 patients were ON in their first session, 14 were OFF. The PD group completed neuropsychological and questionnaire assessments in their ON state (see Table 1). United Parkinson's disease Rating Scale (UPDRS) motor scores were videotaped in each patient session and were scored by a movement disorders specialist. All participants had Mini Mental State Exam (MMSE) scores above 26. PD and control participants did not differ on any measurements of education or premorbid intelligence (see Table 1). We first gathered resting EEG data (1 min eyes open, 1 min eyes closed; one participant had missing resting data in their ON state) from participants, then task-related EEG reported below.

2.2. Conflict Task

This utilized a Simon (spatial conflict) task that was modified to examine the influence of response conflict on reinforcement learning (Cavanagh and Frank, 2014; Cavanagh et al., 2017b). In this report, we are interested in testing the hypotheses of altered EEG and performance during conflict monitoring, which took place during the training phase described below. In each training phase, a modified Simon task was utilized to elicit response conflict during the presentation of four unique stimuli (Fig. 1A). Each stimulus was presented to the left or right side of the screen. Participants were instructed to press the left gamepad button when the stimulus was yellow and the right button when it was blue. These presentations were thus either spatially congruent (screen side = response hand) or incongruent (screen side ≠ response hand) as in a standard Simon task. Stimuli consisted of four randomly assigned unique shapes. Following an accurate response, participants could gain points (rewarded trial; green +1) or not (punishing trial; red 0) according to a probabilistic schedule (Cavanagh et al., 2017b). Although this Simon task had a modification of feedback presentation, this manipulation was the focus of a separate hypothesis test (Cavanagh et al., 2017b) and our current hypotheses focus specifically on conflict and error-related alterations. We expect these findings will be robust to the exact nature of cognitive task (e.g. Simon, flanker, Stroop, etc) and will generalize to other

findings of frontal midline theta alterations during cognitive demand (Cohen, 2016; Cohen et al., 2008; van Steenbergen et al., 2012).

There were 20 occurrences of each stimulus per training block and four blocks total. The inter-trial interval consisted of a fixation cross for 1000 ms. If participants did not respond by the response time (RT) deadline (750 ms) or if they made an error, they received informative feedback ('No Response' or 'ERROR!', respectively) and the same trial was added to the end of the block. We anticipated that the 750 ms response deadline may be too fast for some patients, so following practice we allowed it to double (1500 ms) if needed. There were four PD and one control participant who used the doubled RT deadline; PD patients all had the same RT deadline for their ON and OFF sessions.

2.3. EEG Recording and Preprocessing

EEG was recorded continuously from sintered Ag/AgCl electrodes across 0.1 to 100 Hz with a sampling rate 500 Hz, an online CPz reference, and a ground at AFz on a 64 channel Brain Vision system. The vertical electrooculogram (VEOG) was recorded from bipolar auxiliary inputs. First, very ventral temporal sites (FT9, FT10, TP9, and TP10) were removed, as they tend to be unreliable, leaving 60 electrodes. Data were epoched around the stimulus onset (−2000 to 2000 ms), from which the associated stimulus responses were isolated. Activity at the reference electrode CPz was re-created and bad channels and bad epochs were identified using a conjunction of the FASTER algorithm (Nolan et al., 2010) and pop_rejchan from EEGLab and were subsequently interpolated and rejected respectively. Eye blinks were removed following ICA. Data were then re-referenced to an average reference.

All analyses in this report are from the Cz vertex electrode. ERPs were filtered from 0.1 to 20 Hz. Quantification of ERP differences was focused on canonical events of negative or positive deflections in voltage. These were analyzed as the peak-to-trough difference in the dominant canonical cue- or response-locked morphological feature (e.g. P2 and N2 for cue, pre-response peak and ERN for response). Topographic maps are shown to detail the sensitivity of mid-frontal areas to PD-related differences, although a wider range of findings suggest that a variety of non-specific brain alterations are non-specifically related to PD (Seer et al., 2016).

Time-Frequency measures were computed by multiplying the fast Fourier transformed (FFT) power spectrum of single trial EEG data with the FFT power spectrum of a set of complex Morlet wavelets (defined as a Gaussian-windowed complex sine wave: $e^{i2\pi ft}e^{-t^2/(2\sigma^2)}$, where t is time, f is frequency (which increase from 1–50Hz in 50 logarithmically spaced steps), and defines the width (or 'cycles') of each frequency band increasing from 3 to 8 cycles between 1 and 50 Hz and taking the inverse FFT. The end result of this process is identical to time-domain signal convolution, and it resulted in estimates of instantaneous power (the magnitude of the analytic signal) and phase angle (the arctangent of the analytic signal). Each epoch was then cut in length (−500 to +1000 ms).

Power was normalized by conversion to a decibel (dB) scale ($10*\log_{10}(\text{power}/\text{power}_{\text{baseline}})$), allowing a direct comparison of effects across frequency bands. The baseline

for each frequency consisted of the average power from -300 to -200 ms prior to the onset of the imperative stimuli, which is common in the field since a small time sample reflects the wavelet-weighted influence of longer time and frequency periods. Our primary hypotheses pertained to theta activity (4–8 Hz) modulated after cues and with responses. This time-frequency Region of Interest (tf-ROI) derives from extensive past work (Cavanagh et al., 2017a; Cavanagh et al., 2017b; Chen et al., 2016; Kelley et al., 2018; Kim et al., 2017; Parker et al., 2015a), and was constrained to 4–8 Hz 400–500 ms after cues and 200 ms before to 50 ms after response, that was denoted by blue box in all figures. In addition to this well-motivated *a priori* tf-ROI, we utilized cluster-based permutation correction on the full time-frequency plots in order to reveal any other reliable differences between groups. Note that this time epoch was motivated by our past work and thus distinct from the ERP analysis above. We restrict our analyses to electrode Cz and *a-priori* ROIs to be consistent with our prior work.

This procedure thresholded the size of the statistical cluster against 1000 permutations of group labels and taking the one-dimensional cluster mass at the 95th percentile as the threshold for chance occurrence. For binary comparisons between control and PD, we used two-tailed t-tests with an alpha level of 0.05. Analysis of behavior, ERP, and spectral power in targeted ROIs was conducted by analyses-of-variance (ANOVA). Subject groups (PD and control), visit number (i.e., 1 for controls and PD patients ON first, 2 for PD patients OFF first), conflicts (congruent and incongruent) or responses (correct and error) or post-responses (post-correct and post-error) factors were used for ANOVAs. Effect size was shown by partial Eta squared (η^2) and calculated from ANOVA sums of squares (SS) using the formula: $SS_{\text{effects}} / (SS_{\text{effects}} + SS_{\text{error}})$.

2.4. Classification

Pattern classification was performed to distinguish the PD ON medication from the CTL group using features from the theta-band tf-ROI values from the four major contrasts reported in Figures 3–Figures 6 as well as relative resting alpha band power from Figure 2. Theta-band tf-ROIs used the difference between the conflict/error and congruent/correct contrasts, highlighting individual differences in conflict-specific variance. Resting alpha power was quantified as the relative 8–12 Hz power compared to the power over 1–50 Hz. For the one participant with missing ON state resting EEG, we used the data from their OFF session.

We report on the average of 500 leave-one-out (LOO) cross validation tests using randomized PD and CTL group test-set holdouts. Training sets (N=27 for each group) were z-score normalized based on the combined mean and standard deviation, and test set holdouts (N=1 for each group) were normalized to the training set mean and standard deviation. Classification of the training set was performed with a linear support vector machine (SVM) (fitsvm.m); out of sample prediction of the training weights on the test sample holdouts was then performed (predict.m).

The findings reported here were robust across multiple classification algorithms (LASSO and SVM), four cross validation methods (5-times, 10-times, LOO and a matched LOO procedure where each single individual from the PD group was held out of the training set

along with their age- and sex-matched individual from the CTL group), medication status (ON vs. CTL and OFF vs. CTL), and feature variations (conflict condition only vs. condition differences, raw alpha power vs. relative alpha power), see Fig. S2A–C. All scripts and datasets are available on PRED+CT (www.predictsite.com) (Cavanagh et al., 2017c).

3. Results

3.1. Behavioral Performance

Our aim was to explore the scope of cognitive control in PD. Twenty-eight PD patients and 28 demographically-matched controls performed a modified Simon reaction-time task (Fig. 1A). This task requires participants to flexibly respond with a right or left button press as instructed by a cue. Cues could be congruent (instruction right presented on the right) or incongruent (instruction right presented on the left). This task explicitly involves cognitive control for *conflict* – which derives from comparisons of incongruent vs. congruent trials, and for *error-processing*; which derives from comparisons of error vs. correct trials, and from correct trials following error (post-error) vs. correct (post-correct) trials. Both control and PD patients had slower responses on incongruent trials (Fig. 1B), but there was no consistent difference between control and PD patients. A 2×2 ANOVA revealed that there was a main effect of conflict ($F_{(1, 54)}=110.8$, $p=0.0001$, $\eta^2=0.7$) but no effect of group (i.e., control vs. PD) or higher interactions. Error rates were similar between control and PD ($5.6\pm0.5\%$ for control vs $6.3\pm0.8\%$ for PD; $t_{(54)}=-0.8$, $p=0.4$; Fig. 1C). Finally, after errors both control and PD patients had slower reaction times (ANOVA: main effect of post-error: $F_{(1, 54)}=70.7$, $p=0.0001$, $\eta^2=0.6$) but there was no effect of group or higher interactions. There was no effect of prior trial congruency on the current trial RT (the “Gratton Effect”: interactions with PD $F<1$). In sum, PD participant performance was indistinguishable from controls during all aspects of the Simon reaction-time task.

3.2. EEG at Rest

Prior to task-related-analyses, we examined resting-state data to investigate whether PD patients had altered low-frequency power at mid-frontal leads in a task-unrelated state (Caviness et al., 2016). This is both theoretically valuable and methodologically important as an altered baseline could influence post-event power estimates that have been decibel converted from a presumably benign baseline, as is common in the field. We used a short-window FFT to capture the power-spectral density estimate. Crucially for our analyses, there was no difference in theta activity (4–8 Hz) at electrode Cz at rest ($t_{(54)}=-1.2$, $p=0.24$). We also compared activity during the task in the 500 ms “baseline” prior to cue onset and found no differences in task-related baseline theta activity at electrode Cz (theta: $t_{(54)}=-0.73$, $p=0.46$; Fig. 2B). However, in both resting data and in task-related baseline data we found differences in alpha activity (9–12 Hz; resting: $t_{(54)}=-1.97$, $p=0.05$; task-related baseline: $t_{(54)}=-1.99$, $p=0.05$; Fig. 2A and B). These data are in line with past studies describing differences in resting-state PD-related EEG (Caviness et al., 2015; Klassen et al., 2011), and suggest that differences in mid-frontal theta bands between control and PD are not driven by differences in tonic activity or task-related baselines.

3.3. Cue-related EEG activity

Next, we explored how mid-frontal activity related to preparing responses was changed in PD. Cue-locked event-related potential (ERP) features were similar in control vs. PD (difference between P2 at 195 ms and N2 at 315 ms: main effect of conflict: $F_{(1, 54)}=1.35$, $p=0.25$, $\eta^2=0.03$; main-effect of group: $F_{(1, 54)}=0.8$, $p=0.4$, $\eta^2=0.2$; interaction: $F_{(1, 54)}=0.23$, $p=0.63$, $\eta^2=0.004$; Fig. 3A–C). We examined the spectral properties of these signals using wavelet-based time-frequency analysis. PD patients had significantly attenuated cue-triggered theta and alpha activity (Fig. 3D–F), yet both groups had reliable conflict-related theta activity (Fig. 3G–I). The tf-ROI cue-related activity was attenuated on both congruent and incongruent trials for PD patients (blue box in Fig. 3I; main effect of conflict: $F_{(1, 54)}=49.6$, $p=0.001$, $\eta^2=0.5$; main-effect of group: $F_{(1, 54)}=3.8$, $p=0.05$, $\eta^2=0.5$; no interaction; Fig. 3J). Cue-related activity had similar scalp topography with a few differences over para-median leads (Fig. 3K–M). Despite reliably altered neural activity between groups, we did not find differences in mid-frontal theta activity specific to cue-related conflict in PD.

3.4. Response-related EEG

Conflict-related activity can also be observed phase-locked to responses. As with cues, ERPs for response were similar between control and PD (difference between pre-response peak at –55 ms and post-response trough at 15 ms; main effect of conflict: $F_{(1, 54)}=4$, $p=0.051$, $\eta^2=0.07$; main-effect of group: $F_{(1, 54)}=0.4$, $p=0.6$, $\eta^2=0.06$; interaction: $F_{(1, 54)}=0.01$, $p=0.9$, $\eta^2=0.0002$; Fig. 4A–C). PD patients had attenuated response-related theta and alpha band power (Fig. 4D–F). Only the control group had significant conflict-specific activity, but the difference between groups did not reach cluster-corrected significance (Fig. 4G–I). However, an ANOVA of response-related spectral power in our *a priori* tf-ROI (blue box in 4I) revealed a main effect of conflict ($F_{(1, 54)}=44.8$, $p=0.001$, $\eta^2=0.45$), a main effect of group: $F_{(1, 54)}=5.7$, $p=0.02$, $\eta^2=0.6$), and a significant interaction of response conflict with PD ($F_{(1, 54)}=5.03$, $p=0.03$, $\eta^2=0.08$; Fig. 4J). This activity had similar mid-frontal topography in control and PD patients, albeit more constrained in PD (Fig. 4K and L). Notably, PD patients had slightly right-lateralized centro-frontal differences in theta activity as a result of conflict that could be consistent with a motor cortical source. These data indicate that PD patients had attenuated mid-frontal theta specific to response-conflict.

3.5. Error-related EEG

Cognitive control is also required after errors which can involve prominent modulations in mid-frontal theta rhythms. Response-related ERPs revealed effects of error-related processing in both control and PD patients (difference between pre-response peak at –55 ms and post-response trough at 25 ms; main effect of errors: $F_{(1, 54)}=17.5$, $p=0.001$, $\eta^2=0.24$; Fig. 5A–C). Similar to , PD patients had less theta and alpha power after both error and correct responses (Fig. 5D and E), but the error-specific contrasts did not reach significance after multiple comparisons correction. An ANOVA of error-related spectral power at the *a priori* tf-ROI (blue box in Fig. 5G) revealed main effects of errors and group (errors: $F_{(1, 54)}=11.5$, $p=0.001$, $\eta^2=0.2$; group: $F_{(1, 54)}=5.02$, $p=0.03$, $\eta^2=0.4$; Fig. 5F) but no higher interactions. These data indicate that the PD group had diminished overall activity

(similar to cue conflict). Unlike response-conflict, there were no significant differences between control and PD groups for error-specific processing.

3.6. Post-error EEG

Cognitive control is required to slow responses on trials following error-trials (post-error trials; Fig. 1D). Analyses of ERPs on post-error trials revealed a significant main effect on post-error trials compared with post-correct trials but no effect of group or interaction (difference of between pre-response peak at -55 ms and post-response trough at 15 ms; $F(1, 54)=7.6$, $p=0.008$, $\eta^2=0.12$; Fig. 6A–C). We investigated if post-error mid-frontal theta activity was affected by PD (tf-ROI: blue box in Fig. 6D). An ANOVA revealed a main-effect of post-error trials ($F(1, 54)=6.37$, $p=0.01$, $\eta^2=0.1$), a main effect of group ($F(1, 54)=7.3$, $p=0.01$, $\eta^2=0.5$), and a significant interaction ($F(1, 54)=6.1$, $p=0.02$, $\eta^2=0.1$; Fig. 6E and F). These differences in post-error theta power were significantly correlated with disease duration for patients with PD patients (Fig. 6G: $\rho=0.4$, $p<0.03$). These data indicate that PD patients had attenuated mid-frontal theta for post-error related processes. When combined with the impairments in mid-frontal PD for response-conflict in PD, these data help define the scope of cognitive control deficits in PD (Fujisawa and Buzsáki, 2011).

3.7. Boundary Conditions

All findings reported here ON medication were highly similar OFF medication (Fig. 7), and there were no ON vs. OFF differences (Fig. 8) with the exception that post-error effects appeared to be specific to ON medication. The correlation between post-error theta and disease duration did not hold OFF medication, but the difference between ON and OFF theta power was still significant (see Fig 7–Fig 8). We did not find correlations with UPDRS or other relevant symptom variables. This specificity to years diagnosed is similar to major behavioral and EEG effects observed in other investigations with this same cohort (Cavanagh et al., 2017a; Cavanagh et al., 2017b). We also tested if these group differences extended to inter-trial phase consistency; there were no significant interactions but some findings of reduced phase consistency to responses in PD patients (Fig. S1). Finally, all control patients had one visit, whereas PD patients could be ON first, or OFF first. We included the visit number as a factor in all ANOVAs; there were no significant main or interaction effects in any case. These data indicate that PD patients have attenuated mid-frontal theta power associated with critical task events such as instructional cues and responses, and attenuated mid-frontal theta specifically associated with error-related and conflict-related cognitive control.

3.8. Pattern Classification

Figure 9 shows the results of the pattern classification procedure. While error-specific theta power was at chance, the other three task conditions had near-chance sensitivity but reasonable specificity (72–77%). Resting alpha power had impressive sensitivity (85%) but poor specificity (22%). The combination of all variables yielded a balanced 69% sensitivity and 72% specificity. While these outcomes are modest, they are highly stable across algorithm, cross-validation procedure, medication status and feature details (Fig. S2). While these features only represent a small fraction of available data in the EEG, they were all *a priori*-motivated and they suggest that a larger-scaled study could benefit from this prior

knowledge that resting and task-based EEG activities contribute unique variance towards reliable group dissociation.

4. Discussion

We tested the hypothesis that PD patients had attenuated mid-frontal theta rhythms involved in cognitive control using a modified Simon reaction-time task. PD patients had lower mid-frontal theta power around key task events such as cues and responses. In support of our hypothesis, we found that PD patients had attenuated mid-frontal theta activity related to response conflict and post-error processing. By contrast, we did not find consistent evidence of differences in PD patients for cue-related conflict or errors. We found that post-error mid-frontal theta was related to disease duration, and that these variables could be used to classify control vs. PD with high specificity, whereas alpha rhythms had high sensitivity. Our results here help define the scope of mid-frontal theta activity during cognitive control in PD.

We have previously observed diminished mid-frontal theta in PD. For instance, cue-related mid-frontal theta activity was attenuated in PD patients during timing and novelty response tasks (Cavanagh et al., 2017a; Chen et al., 2016; Kim et al., 2017; Parker et al., 2015a). Here we found similar decreases in mid-frontal signals around task events, but we extend these findings to the execution of cognitive control. We observed attenuated mid-frontal theta activity specific to some aspects of cognitive control – such response conflict and post-error slowing – yet not to cue conflict or error commission. Response-conflict and post-error processing are involved in actively slowing responses (Botvinick et al., 2004; Miller, 2000), whereas cue-related and error-related signals may be dominated by earlier orienting processes. While this taxonomy of processing offers novel testable hypotheses for control-specific differentiation in PD patients, these diverse functions may share medial frontal source yet may make invoke diverse downstream networks. Future work recording directly from medial cortex or in animal models may help resolve these issues (Carter et al., 1998; Carter et al., 2001; Devinsky et al., 1995).

We studied rather high-performing PD patients; consequently we did not get strong behavioral deficits. Prior study of Simon reaction-time performance have revealed mild performance effects in PD (Wylie et al., 2010). This suggests that if we studied more poorly performing PD patients or increased task difficulty, it might increase the likelihood of finding cognitive-control deficits in PD patients. However, the EEG differences we observe here could not be accounted for by behavioral differences in task performance.

Indeed, past work has found that N2 and ERN amplitudes are diminished in non-demented PD patients, analogous to this study (Seer et al., 2016; Seer et al., 2017), as are P3a amplitudes (Polich, 2007; Solis-Vivanco et al., 2015; Tsuchiya et al., 2000; Zeng et al., 2002). Taken together, these findings suggest a common deficit in the mid-frontal mechanisms that signal the need for cognitive control.

Our working model is that mid-frontal theta signals are a mechanism of cognitive control (Cavanagh and Frank, 2014). The putative source for these signals is in medial frontal cortex

(see reviews by (Cavanagh and Shackman, 2015; Holroyd and Coles, 2002)). In animal models bursts of theta activity engage medial frontal single neurons involved in cognitive control, such as errors and guiding responses (Narayanan et al., 2013a; Parker et al., 2015a). In humans mid-frontal theta signals can engage and respond to processing in downstream brain regions such as the STN (Cavanagh et al., 2011; Kelley et al., 2018; Zavala et al., 2013; Zavala et al., 2014). Moreover, medial frontal 4 Hz rhythms can be coherent across a wide range of brain areas in service of adaptive behavior, including hippocampus and midbrain (Fujisawa and Buzsáki, 2011). These cortical rhythms can provide a window into mechanistic cognitive control processes from medial frontal circuits such as anterior cingulate cortex.

We also observed signals beyond theta rhythms. One of our most prominent findings was in the alpha band, which was also different at rest and in the pre-task baseline (Caviness et al., 2015; Caviness et al., 2016; Klassen et al., 2011). Theta and delta bands were similar at rest, suggesting that the task events and ERP effects noted here are not contaminated by tonic brain-state differences and are truly due to differences in the exertion of control. Frontal alpha rhythms and synchrony have been associated with motor preparation and planning in PD (Babiloni et al., 1999; Klimesch, 1999), which may explain differences in alpha power around responses and cues. This may also account for motor cortically-lateralized effects in Figure 5; these suggest promising avenues for future research.

It is notable that we did not find any effects of levodopa in mid-frontal theta dynamics. However, the lack of medication effects in this study does not preclude a role for cortical dopamine in mid-frontal theta rhythms. First, dopamine is necessary for mid-frontal theta activity in rats (Kim et al., 2017; Parker et al., 2015b) and it can alter related signals via pharmacological challenge in humans (Jocham and Ullsperger, 2009), it remains unclear if dopamine is necessary and sufficient for human mid-frontal theta activity. Second, it is unknown if mid-frontal theta is only sensitive to cortical dopamine, or if there is an influence of striatal or midbrain projections. Levodopa primarily acts at striatal receptors (Rakshi et al., 1999), and dopamine has a complex influence over cortical function due to non-linear 'U-shaped' dynamics (Cools and D'Esposito, 2011; Cools et al., 2010). Third, PD is a heterogeneous and complex disease involving multiple neurotransmitter systems as well as alpha-synuclein aggregates (Alberico et al., 2015; Narayanan et al., 2013b). It is possible that diminished mid-frontal theta is primarily due to neurodegeneration, or a complex mix of adaptation to diminished neurotransmitter tone in highly vulnerable cortical areas.

These uncertainties are all testable, and their discovery will have clear clinical benefits. Future studies may be able to account for inverted-U dynamics by assessing individual polymorphisms associated with frontal dopamine (such as catechol-o-methyl transferase) or via more selective pharmacological agents (Hoogland et al., 2010). When combined with longitudinal observations, the causal determinants of mid-frontal theta (and Parkinson's-related deficits therein) may be narrowed down. Future studies should also combine targeted animal work with intracranial recordings in human and/or non-human primates to resolve the role of medial frontal dopamine on delta/theta activity.

One limitation arising from our OFF/ON studies is that PD patients had two visits while controls only had one. However, because this was counterbalanced, and controls and PD patients rapidly learned this task, and past work from our has found similar differences between PD and control patients in a single session, the effect of exposure is likely restricted (Chen et al., 2016; Kim et al., 2017; Parker et al., 2015a). Another limitation is that we were focused on our *a priori* hypothesis of mid-frontal theta. Exploratory analyses of this dataset may generate hypotheses about differences between control and PD patients at other electrodes using other analytical frameworks. Our release of this dataset might facilitate these analyses. Future studies might combine targeted animal work or intracranial recordings in human and/or non-human primates to resolve the role of medial frontal dopamine on delta/theta activity.

5. Conclusions

Some of the most debilitating aspects of PD include cognitive and mood disturbances. While it is widely appreciated that cell death in PD somehow contributes to deficits in higher cognitive functioning, the mechanisms underlying these deficits remain unclear. Compared to motor symptoms, neurobehavioral symptoms are not only less treatable but they are stronger decrements on quality of life (Lawson et al., 2016; Martinez-Martin et al., 2011). In this investigation, we tested a novel hypothesis generated from our prior work on the mechanisms of cognitive control and deficits in these same mechanisms in PD patients. The findings reported here suggest the deficient mid-frontal theta may be a novel candidate biomarker for cognitive dysfunction in PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Cognitive control involves mid-frontal theta activity.
- We investigated mid-frontal theta in PD patients using a task that explicitly measures cognitive control.
- Mid-frontal theta activity related to conflict and error-related cognitive control is attenuated in PD.
- These data help define the scope of cognitive deficits in PD.

Fig. 1. A modified Simon reaction-time task to measure cognitive control.

A) In this task, a cue instructs left vs. right button-presses. Congruent trials involve a cue presented on the right instructing a response on the right; incongruent trials involve a cue presented on the left instructing responses on the left. After button-presses, feedback is given. *Conflict* is measured by comparing incongruent vs. congruent trials; *Error processing* is measured by comparing error vs. correct trials, or correct trials after errors (post-error) vs. correct trials after correct trials (post-correct). B) For both control (blue) and PD patients (red), responses are slower on incongruent vs. congruent trials, reflecting cognitive control. An ANOVA revealed a highly significant effect of conflict ($p<0.001$; ANOVA results in black text) but no main effect or interaction with group. C) Error-rates were similar between groups. D) An ANOVA revealed that there was a main-effect of post-error slowing without effects of PD or interactions (black text). η^2 = effect size; $^{**}p<0.01$.

Fig. 2. Baseline differences in EEG activity between PD patients and controls.

A) During 2 minutes of resting-state activity, there were no differences in theta activity but significant increases in alpha activity in the PD group. B) During task performance prior to instructional cue, we observed no consistent differences in theta activity but again found differences in alpha-related activity. These findings suggest that task-related evoked theta activities should remain unaffected by these background spectral differences. $*=p < 0.05$ for each frequency; Topographic electrodes with significantly different power are indicated with a diamond.

Fig. 3. Cue-related activity is attenuated in PD.

Event-related potentials (ERPs) for A) controls on congruent (solid blue) and incongruent (light blue) trials, and for B) PD patients on congruent (solid red) and incongruent (light red) trials. C) Event-related potential analyses revealed elevated response to cues in PD, quantified as the difference between the P2 (195 ms) and the N2 (315 ms) components (black lines in A and B). Time-frequency spectrograms around all cues (average of both congruent and incongruent) for D) control and E) PD patients. F) PD patients had attenuated cue-triggered theta rhythms (4–8 Hz) and alpha rhythms (9–12 Hz). Conflict-related theta activity was higher on incongruent vs. congruent trials for both (G) control and (H) PD patients. (I) there was no significant difference between control and PD patients in cue-related conflict activity. J) The ROI in I (blue box: 400–500 ms after cue, 4–8 Hz) did not reveal a conflict-specific interaction. Scalp topography of this ROI for (K) control and (L) PD patients; there were few differences for conflict (M). J: $*=p < 0.05$, $**p < 0.01$. D-I: Permutation-corrected statistical significance $p < 0.05$ outlined in bold lines; K-M: Statistically significant electrodes $p < 0.05$ indicated by diamonds. **Effect size was denoted by partial eta-squared (η^2).** C or Cong = Congruent; I or Incong = Incongruent.

Fig. 4. Response conflict is attenuated in PD.

Response-related ERPs for A) controls on congruent (solid blue) and incongruent (light blue) trials, and for B) PD patients on congruent (solid red) and incongruent (light red) trials. C) ANOVA (difference between -55 ms and 15 ms; black lines in A and B) revealed a main effect of conflict without a main effect of group or higher interaction. Time-frequency spectrograms for all correct responses (including both congruent and incongruent trials) for D) control and E) PD patients revealed significantly more theta and alpha power for control relative to PD (F). Conflict-related theta activity was higher for incongruent vs. congruent trials for control patients (G) but not for (H) PD patients. I) Difference of Control and PD. J) There was significant difference in conflict tasks and between control and PD patients as well as an interaction (-200–50 ms, 4–8 Hz; blue box in I). K-M: Scalp topography of activity from the tf-ROI in I; there were differences for theta activity over midline and R lateralized electrodes as a result of conflict in (M). C&J: $*=p<0.05$, $**p<0.01$ D-I: Permutation-corrected statistical significance $p<0.05$ outlined in bold lines; K-M: Statistically significant electrodes $p<0.05$ indicated by diamonds. **Effect size was denoted by partial eta-squared (η^2).** C or Cong = Congruent; I or Incong = Incongruent.

Fig. 5. Response-related activity is attenuated in PD.

Event-related potentials for correct and error trials for (A) controls (correct: blue; error: light-blue) and B) for PD (correct: red; error: light-red). C) ANOVA of response-related ERPs (difference between -55 ms and 25 ms) revealed a main effect of errors only. D) Time-frequency analyses reveal that PD patients have attenuated theta signals for all responses on both correct and error trials, but E) control and PD patients did not have consistent differences on correct vs. error trials. F) There was a main effect of errors and group but no significant interaction (-200 – 50 ms, 4 – 8 Hz; blue box in E). G) Scalp topography of activity from the tf-ROI in E; there were few consistent differences between control and PD patients. C&F: $*=p<0.05$, $**p<0.01$. D-E: Permutation-corrected statistical significance $p<0.05$ outlined in bold lines. **Effect size was denoted by partial eta-squared (η^2).**

Fig. 6. PD patients have impaired post-error activity.

Event-related potentials for controls (A) on correct responses (blue) and following errors (light blue) for controls and for B) PD patients (post-correct: red; post-error: light red). C) ANOVAs of response-related ERPs (difference P-25 – N25) reveal a main effect of errors only. D) Comparisons of mid-frontal spectral activity between control and PD patients on post-error vs. post-correct trials. E) In response tf-ROIs (–200–50 ms, 4–8 Hz) there was a main effect of post-error trials, a main effect of group, and a significant interaction. F) Scalp topography revealed that this activity had central topography; statistically significant electrodes $p < 0.05$ indicated by diamonds G) Correlation of disease duration with post-error-related mid-frontal theta in PD. C&E: $^* = p < 0.05$, $^{**} = p < 0.01$. **Effect size was denoted by partial eta-squared (η^2).** PC = post-correct; PE = post-error.

Fig. 7. PD patients OFF medication vs. control subjects.

A-D) In all conditions except post-error trials, there was significant main effect for condition; all contrasts had a main effect for group. Significant interactions were only observed in cue- and response-related conflict tasks. A-D: $*=p<0.05$, $**p<0.01$; C or Cong = Congruent; I or Incong = Incongruent; PC = post-correct; PE = post-error. Effect size was denoted by partial eta-squared (η^2).

Fig. 8. OFF vs. ON states in PD patients

A-B) Cue- and response-related conflict tasks had significant effects for condition only. C) There were no main effects or interaction effects for the error contrast. D) Post-error theta power was specifically diminished in patients ON medication. A-D: $*=p<0.05$, $**p<0.01$; C or Cong = Congruent; I or Incong = Incongruent; PC = post-correct; PE = post-error. Effect size was denoted by partial eta-squared (η^2).

Fig. 9. Classification of PD vs. control based on theta-band tf-ROI values and resting alpha power.

A receiver operating characteristic plot shows the true vs. false positive rates of PD vs. control discrimination for each condition separately, as well as the combination of all variables. Total accuracy (average of sensitivity and specificity) is also displayed for each condition.

Table 1.Patient and control participant demographics (mean $\pm$ SD).

	PD	Control	Statistic
Sex	17 M, 11 F	17 M, 11 F	
Age	69.8 (8.59)	69.2 (9.2)	t(54)=-0.2, p=.82
Years of Education	17.3 (3.24)	16.6 (3.1)	t(54)=-0.7, p=.47
Parent's Years Ed	12.5 (3.82)	12.4 (3.4)	t(54)=-0.2, p=.82
MMSE	28.6 (1.06)	28.8 (1.0)	t(54)=0.6, p=.52
NAART	45.0 (10.20)	47.0 (7.4)	t(54)=.08, p=.41
BDI	7.7 (5.23)	4.9 (4.7)	t(54)=-2.05, p=.05
UPDRS ON	22.1 (10.15)		
UPDRS OFF	23.8 (8.71)		
LED	703 (440)		
Years since Diagnosis	5.6 (4.18)		

All controls were age and sex matched to a patient. Only BDI differed between groups. BDI = Beck Depression Inventory, MMSE = Mini Mental State Exam, NAART = North American Adult Reading Test, UPDRS = United Parkinson's Disease Rating Scale (motor), LED = L-Dopa equivalence dose in mg.