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Evoked midfrontal activity predicts cognitive dysfunction in Parkinson's disease

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Abstract

Objective—Cognitive dysfunction is a major feature of Parkinson's disease (PD), but the pathophysiology remains unknown. One potential mechanism is abnormal low-frequency cortical rhythms which engage cognitive functions and are deficient in PD. We tested the hypothesis that midfrontal delta/theta rhythms predict cognitive dysfunction in PD.

Methods—We recruited 100 PD patients and 49 demographically-similar control participants who completed a series of cognitive control tasks, including the Simon, oddball, and interval timing tasks. We focused on cue-evoked delta (1-4 Hz) and theta (4-7 Hz) rhythms from a single midfrontal EEG electrode (Cz) in PD patients who were either cognitively normal, with mild-cognitive impairments (PDMCI), or had dementia (PDD).

Results—We found that PD-related cognitive dysfunction was associated with increased response latencies and decreased midfrontal delta power across all tasks. Within PD patients, the first principal component of evoked EEG features from a single electrode (Cz) strongly correlated with clinical metrics such as the Montreal Cognitive Assessment (MOCA; rho=0.34) and with NIH-toolbox Executive Function scores (rho=0.46).

Conclusions—These data demonstrate that cue-evoked midfrontal delta/theta rhythms directly relate to cognition in PD. Our results provide insight into the nature of low-frequency frontal rhythms and suggest that PD-related cognitive dysfunction results from decreased delta/theta activity. These findings could facilitate the development of new biomarkers and targeted therapies for cognitive symptoms of PD.

Video Abstract

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Contributors: AS, RCC, AIE, and NSN acquired the data. AS, JRW, JFC, and NSN, conceptualized and designed the study. AS, JFC, and NSN conducted the analyses. AS, RCC, JRW, JFC, and NSN interpreted the data. AS and NSN wrote the first draft of the manuscript. AS and NSN accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder that features prominent cognitive symptoms, affecting up to 80% of patients at some point in the disease.[1] PD degrades cognitive function leading to mild cognitive impairment (PDMCI) or dementia in PD (PDD).[1] There are few reliable treatments for these aspects of PD because the mechanisms are not well understood.

Cognitive dysfunction in PD can impair executive processes such as conflict resolution, attention, and timing.[2,3] Intracranial recordings and scalp electroencephalography (EEG) have implicated prefrontal systems in these cognitive functions,[4,5] whose activity is particularly signified by low-frequency oscillations in the delta (1-4 Hz) and theta (4-7 Hz) bands located over midfrontal regions.[6] Midfrontal delta/theta rhythms are modulated by conflict, attention, and timing,[6,7] and impaired in PD.[7–11] Critically, midfrontal low-frequency rhythms engage single neurons in distributed cortical and subcortical brain networks involved in conflict resolution, response inhibition, timing, and error correction.[11–13] This line of work motivates the hypothesis that deficits in midfrontal delta/theta rhythms underlie cognitive dysfunction in PD.

We tested this idea within a large sample of PD patients across a range of cognitive functions, including mild-cognitive impairment (PDMCI) and dementia (PDD), as well as within demographically-equivalent controls. We used three well-described cognitive-control tasks that are reliably associated with impairments in midfrontal delta/theta rhythms in PD: 1) the Simon-conflict task,[10,14,15] 2) an oddball task,[9,11] and 3) an interval-timing task.[7] These tasks reliably trigger low-frequency midfrontal EEG rhythms that can be captured at a single electrode located at the cranial vertex (Cz).[6,7,9–11,16,17] Midfrontal delta/theta rhythms are proposed to signal a need for cognitive control[5,18,19] during simple responses to novelty[11] and executive functions.[7,20] We report three main results. First, response time was progressively affected by PD-related cognitive function across tasks (PD<PDMCI<PDD). Second, midfrontal delta rhythms were progressively attenuated by PD-related cognitive dysfunction. Finally, principal component analyses identified common midfrontal delta/theta variance across all tasks and strongly correlated with clinical cognitive metrics and could be used to classify PDD. These data identify frontal mechanisms of cognitive dysfunction in PD and could inform new biomarkers and treatments for neurodegenerative disease.

METHODS

Participants

We recruited a total of 100 PD patients and 49 controls to perform a variety of cognitive and motor tasks from the University of Iowa Movement Disorders Clinic between 2017 and 2021. All patients were examined by a movement-disorders physician to verify

that they met the diagnostic criteria recommended by the United Kingdom PD Society Brain Bank criteria. Control participants were recruited from the Iowa City community and similar in terms of age, sex, and education. All PD and control participants were determined to have the decisional capacity to provide informed consent in accordance with the Declaration of Helsinki and the Ethics Committee on Human Research. We obtained written informed consent from each participant. All research protocols were approved by the University of Iowa Human Subjects Review Board (IRB# 201707828). Data from some of these patients have been published previously[7,11] but did not analyze cognitive function across tasks in detail, which is our focus here. All data were collected with patients ON levodopa as usual, as previous work has reliably demonstrated that levodopa does not reliably influence midfrontal low-frequency rhythms.[7,10,21,22] In addition, we calculated the Levodopa-Equivalent Daily Dose (LEDD).[23] We used the Montreal Cognitive Assessment (MOCA) to stratify cognitive function in PD.[24,25] We defined (PDD) dementia as MOCA <22; mild-cognitive impairment (PDMCI) as MOCA 22-26; and cognitively normal as MOCA 26-30 (referred to as PD or control). All data were collected during a single 4–5-hour session with EEG. Patients also performed the full UPDRS, which includes the motor UPDRS III (mUPDRS). Executive Function tests from NIH Toolbox Cognition Battery, which included the Eriksen Flanker Test and the Dimension Change Card Sort, which were averaged and then zscored for further comparison.[26,27] Patient data was excluded for electrical noise, if they could not perform enough trials, technical issues, or fatigue. Demographics of recruited patients and control subjects are summarized in Table 1.

Simon task: This and all subsequent tasks were presented using Psychtoolbox-3. 48 control, 47 PD, 34 PDMCI, and 18 PDD subjects were able to complete the Simon task (Figure 1A). Briefly, each stimulus was presented to the left or right side of the screen, and participants were instructed to press a left key when the stimulus was yellow or red and a right key when it was cyan or blue. These presentations were thus either spatially congruent with the screen side matching the response hand (i.e., right-sided stimulus and responding with the right hand), or incongruent, with the screen side contralateral to the response hand (i.e., right-sided stimulus and responding with the left hand) as in a standard Simon task. Stimuli consisted of four randomly assigned unique shapes. There were 120 congruent and 120 incongruent trials presented randomly in 4 blocks of 60. Data from congruent and incongruent trials were analyzed separately. Further task details are in the supplement.

Oddball task: We modified a cross-modal oddball distractor task, as described in detail previously.[11,28–30] 41 control, 44 PD, 29 PDMCI, and 17 PDD subjects were able to complete the oddball task. A white arrow appeared in the center of a black screen, and the participant was required to press the key that corresponded with the direction of the arrow (“q” for left arrow, “p” for right arrow) as quickly as possible. Participants completed four blocks of 60 trials each, for a total of 240 trials. Of the 240 trials, 80% contained the standard cues as described above, 10% contained an unexpected auditory oddball cue (non-repeating, randomly-created sine wave lasting 0.2 seconds in duration) in place of the expected tone, and 10% contained an unexpected visual oddball cue which were not analyzed. Data from standard and oddball trials were analyzed separately.

Interval-timing task: We performed a modified version of the peak-interval-timing task as described in detail previously.[7,31] 41 control, 43 PD, 31 PDMCI, and 18 PDD participants estimated the duration of an interval after reading instructions displayed as text at the center of a video screen. After the instructions were displayed for 1 second, the start of the interval was indicated by the appearance of an image of a solid box in the center of the computer screen (Figure 1C), which was displayed for the entire 18–20 seconds for 7-second intervals. Participants were instructed to press the keyboard spacebar at the start of when they judged the target interval to have elapsed (Figure 1C). All participants performed four blocks of 40 trials of randomly intermixed short and long intervals.

EEG Recordings

EEG recordings were performed according to methods described in detail previously.[32,33] Bad channels and bad epochs were identified using a combination of the Fully Automated Statistical Thresholding for EEG artifact Rejection (FASTER) algorithm that rejects artifacts with greater than +/− 3 Z-scores on key metrics[34] and the pop_rejchan function from EEGLAB. Bad channels were subsequently interpolated, except the midfrontal “Cz” channel was never interpolated. Eye blink contaminants were removed following independent component analysis (ICA).

Event-related potentials (ERPs) were low-pass-filtered at 20 Hz for analyses. We calculated average ERP for each trial type and each group (PD and control). ERPs were visually inspected, and we calculated the mean amplitude for largest deflections at electrode Cz. This included the P3 component for the Simon (0.4-0.5 seconds from cue) and oddball task (0.25-0.35 seconds), as well as the N1 for the oddball task (0.05-0.15 seconds), and the first negative wave (0.15 – 0.35 seconds) for interval timing.

Our primary interest was in midfrontal delta/theta rhythms; consequently, we utilized time-frequency analyses. We computed spectral measures 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: $e^{i2\pi tf}e^{-t\wedge 2/(2x\sigma\wedge 2)}$, where t=time and f=frequency). Wavelets increased from 1–50 Hz in 50 logarithmically-spaced steps, which defined the width of each frequency band, increasing from 3–10 cycles between 1–50 Hz and taking the inverse FFT.[35] The end result of this process was identical to time-domain signal convolution, and it resulted in estimates of instantaneous power (the squared magnitude of the analytic signal) and phase angle (the arctangent of the analytic signal). We then cut the length of each signal accordingly for each trial (−0.5-1 seconds). These short temporal epochs reflect the wavelet-weighted influence of longer time and frequency periods. Power was normalized by converting to a decibel (dB) scale ($10*\log10(power_t/power_{baseline})$), allowing us to directly compare the effects across frequency bands. The baseline for each frequency was calculated by averaging power from −0.3 to −0.2 seconds prior to cue onset.[32,33,36]

We defined delta power as 1–4 Hz and theta power as 4–7 Hz for our time-frequency regions of interest (tf-ROI). These frequency bands were extremely well-justified based on extensive prior work from our groups.[6,11,16,18,32,36] Temporal epochs were defined based on peaks in average spectral activity across all groups.[35] For the Simon task, these epochs spanned

0.4–0.75 seconds for delta/theta bands; for the Oddball task, these spanned 0.6-0.9 seconds for delta and 0.1–0.2 seconds for theta; for the Interval timing task, these spanned 0.15 – 0.45 seconds for delta and 0.1-0.3 seconds for theta. Our primarily analyses focused on how activity in these tf-ROIs changed across PD patients with cognitive dysfunction.

Statistical Analyses

All data and code is available at narayanan.lab.uiowa.edu. For response times, event-related potentials (ERP), and mid-frontal delta/theta power, we used a linear model (*lm* in R) with main effects of Group (Control/PD/PDMCI/PDD) and trial Type (Congruent vs. Incongruent, or Standard vs. Oddball) and Group*Trial type interaction. Interval timing analyses only had Group-level analyses. Post-hoc comparisons were performed via estimated marginal means (*emmeans* in R) and Tukey's post-hoc correction. Effect size was computed via eta^2 (*etaSquared* in R).[37]

The correlations between response time, ERP components, and mid-frontal delta and theta power tf-ROIs were first investigated via Spearman's rho. We then used principal component analyses (PCA) to distill shared variance across these metrics. We correlated the first principal component and clinical variables such as MOCA and Executive Function scores from the NIH-Toolbox.[27] Partial correlations (*pcor.test* in R) were used to control for mUPDRS and LEDD in comparisons of MOCA and Executive Function with principal components.

Pattern classification was performed using support vector machines (SVM; *fitcsvm.m* in MATLAB) with 500 iterations of 5X, 10X, and leave-one-out (LOO) cross-validation. Feature selection leveraged the first 3 principal components (exploratory analysis suggested more components did not add more information). Predictions were computed based on an SVM model using *predict.m* in MATLAB. ROC curves were computed using *perfcurve*.m. Classification was done for 1) PD (n=40) vs. PDD (n=16), 2) PD vs PDMCI (n=43), and 3) PDMCI vs. PDD, and 4) between group shuffled data derived from the PD vs. PDD group. Statistical significance was assessed using an empirically-derived p-value obtained by 1000 repetitions of classification of group-shuffled data.

RESULTS

We investigated how cognition in PD affected cognitive control. First, we examined response times (RT) during the Simon, oddball, and interval timing tasks (Figure 1). For the Simon task, there was a main effect of Group (Control, PD, PDMCI, and PDD; F=6.6, p=0.002, eta^2=0.06; see table 2 for RTs for all tasks) as well as trial Type (congruent vs. incongruent; F=5.7, p=0.02, eta^2=0.03), but no interaction. Accordingly, there was no main effect of Group on response slowing on incongruent vs. congruent trials (Supplementary Figure 1). This pattern was similar in the oddball task, with a main effect of Group (F=9.3, p=0.0001, eta^2=0.09) and a marginally significant effect of trial Type (oddball vs. standard; F=3.2, p=0.07, eta^2=0.02). As in the Simon task, there was no interaction (post-hoc comparisons for PD vs. PDD were marginally significant for oddball p=0.07 and significant for standard p=0.04) and no main effect of Group in oddball-related slowing (Supplementary Figure 1). These findings indicate that PD-related cognitive dysfunction does not reliably affect

behavioral indicators of control adaptation during incongruent Simon trials or novelty during Oddball trials. Finally, there was a significant effect of Group in the interval timing task ($F=4.2$, $p=0.02$, $eta^2=0.09$; post-hoc comparisons were significant between PD and PDD $p=0.05$ and between PDMCI and PDD $p=0.02$).

We next turned to EEG, which captures cortical neurophysiology with fine temporal resolution, to explore the neural bases of these PD-related changes to behavior. Selected ERP components from the midfrontal electrode Cz did not reveal main effects of Group in Simon or timing tasks (Supplementary Figure 2). However, for oddball-related activity between 0.25-0.35 seconds (Supplementary Figure 2D–F), we found main effects of Group ($F=5.6$, $p=0.005$, $eta^2=0.05$) as well as Type (oddball vs. standard; $F=36.2$, $p=1x10^{-8}$, $eta^2=0.16$), and a marginally significant interaction ($F=2.6$, $p=0.08$; post-hoc comparisons between PD and PDD for oddball $p=0.002$). This was also true for the earlier N1 peak (0.05 – 0.15 seconds; Supplementary Figure 3): Group ($F=4.4$, $p=0.01$, $eta^2=0.05$) and Type ($F=4.3$, $p=0.04$, $eta^2=0.02$), but without an interaction. These data suggest that oddball-related ERPs could independently discriminate cognitive dysfunction in PD.[9,17]

Our past work has suggested that spectral analyses of midfrontal EEG can predict cognitive dysfunction in PD.[8,32,36] We tested this idea by applying time-frequency analyses to midfrontal activity during the Simon, oddball, and interval timing tasks. We focused on midfrontal EEG electrode Cz which past work has established as the focus of cognitive control.[11,16,18,32,36] We noticed that across tasks, there was a consistent pattern of decreased cue-evoked midfrontal delta/theta power that decreased with cognitive dysfunction in PD (Figure 2).

To quantify this finding, we selected midfrontal tf-ROIs. We focused on delta (1–4 Hz) and theta (4-7 Hz) bands that are extraordinarily well-justified from our prior work.[6,11,16,18,32,36] Temporal epochs for tf-ROIs were based on maximal spectral activity on average across all patients (Figure 3A,3D, and 3G). Here we focused on how activity in these EEG tf-ROIs covaried with cognitive dysfunction in PD. For the Simon task, there were main effects of Group on delta power (1-4 Hz; 0.4-0.7 seconds; $F=13.6$, $p=3x10^{-6}$, $eta^2=0.12$; post-hoc comparisons between PD vs. PDD were significant for congruent $p=0.01$ and incongruent $p=0.005$) and theta power (4-7 Hz; 0.4-0.7 seconds; $F=6.2$, $p=0.003$, $eta^2=0.06$), but no effects of trial Type or higher interactions. We observed a similar pattern for the oddball delta power (Figure 3D) with main effects for Group (1-4 Hz; 0.6-0.9 seconds; $F_{=}8.5$, $p=0.003$, $eta^2=0.09$; post-hoc comparisons for PD vs. PDD for oddball trials $p=0.02$; Figure 3E) but no effect of Type or higher interactions. However, for theta ROIs (4-7 Hz; 0.1-0.2 seconds; Figure 3F), there was a main effect of Type, Group or higher interactions. Finally, for Interval Timing (Figure 3G), there were main effects of Group on delta power (1-4 Hz; 0.15 – 0.45 seconds; $F=4.2$, $p=0.02$, $eta^2=0.09$; Figure 3H; post-hoc comparisons between PD vs PDD were significant $p=0.01$) but no reliable effects on theta power (4-7 Hz, 0.1-0.3 seconds; Figure 3I). There were few reliable effects of PD-related cognition on beta power (Supplementary Figure 4). Across tasks, these data provide convergent evidence that PD-related cognitive disturbance is consistently associated with diminished delta–band power ($eta^2=0.09$-0.12). Surprisingly, there was no reliable evidence of control-related effects for congruent vs. incongruent or standard vs. oddball contrasts (Supplementary Figure 5).

We examined the relationship between these metrics across tasks and patients. There were 35 control participants, 40 PD patients, 27 PDMCI patients, and 17 PDD patients that completed all tasks. Correlation values between these variables are shown in Figure 4A, only including values with a corrected FDR $p<0.05$. We used a data-driven principal component analysis to capture patterns across task.[38] PC1 loaded highly on delta and theta activity across tasks (Figure 4B). Strikingly, we found that PC1 effectively captured differences in cognition in PD (Main effect of Group on PC1 Score: ($F=5.2$, $p=0.008$, $eta^2=0.11$; post-hoc differences between PD and PDD $p=0.007$; Figure 4B) and explained 30% of variance in our data across all tasks.

Shared midfrontal variance as captured by PC1 was strongly linked with clinical metrics of cognitive function in PD patients. Specifically, PC1 was correlated with cognitive function as measured by the MOCA (Spearman rho=0.34, $p=0.002$; Figure 5A) and Executive Function from the NIH Toolbox (Spearman rho=0.46, $p=0.00003$; Figure 5B). Of note, there was a significant negative correlation between PC1 and the mUPDRS (Spearman rho=−0.25, $p=0.02$). However, the correlation between MOCA and PC1 was significant when controlling for mUPDRS (MOCA vs PC1 (Spearman rho=0.30, $p=0.006$), and the correlation between Executive Function and PC1 was also significant when controlling for mUPDRS (Spearman rho=0.40, $p=0.0003$). Although there was no reliable correlation between PC1 and LEDD (Spearman's rho=0.16, $p=0.14$), correlations between MOCA/EF and PC1 was significant when controlling for LEDD (MOCA: Spearman rho=0.32, $p=0.004$; EF: Spearman rho=0.44, $p=0.00008$). No significant correlations were found between PC1 score and MOCA and Flanker activity for controls (Supplementary Figure 6).

Finally, we used SVM-based pattern classification to examine if we could predict dementia in PD from these first 3 principal components. Critically, all classification was binary and performed within PD patients. We found that SVMs could accurately distinguish PDD (16 patients) from PD patients (40 patients; AUC=0.75; Figure 5C). This was significantly higher than AUCs in shuffled data (shuffled AUC=0.50; $p<0.001$) and higher than AUCs for detection of PDMCI from PD (AUC=0.66) and from PD (AUC=0.47). These findings provide insight into the nature of midfrontal delta/theta rhythms and suggest that evoked midfrontal activity predicts cognitive dysfunction within PD patients.

DISCUSSION

We tested the hypothesis that diminished midfrontal delta/theta rhythms are associated with cognitive dysfunction in PD. Across three cognitive tasks in 100 PD patients, common features of midfrontal delta rhythms were decreased with PD-related cognitive dysfunction. Shared midfrontal variance was captured by PCA and predicted executive function. These results are remarkable when considering that they relied only upon a single midfrontal scalp EEG electrode at Cz. Our findings indicate that cue-evoked midfrontal delta/theta rhythms predict cognitive dysfunction in PD.

Our work is in line with prior studies from our group and others documenting reliable PD-related decreases in midfrontal delta/theta rhythms.[8,9,22,32,36,39] We extend this work to demonstrate that PD patients with cognitive dysfunction have progressive deficits in

these cortical rhythms, with PDD patients having most attenuated midfrontal delta/theta activity. These deficits are not readily explained by motor deficits as correlations between PC1 MOCA/Executive Function persisted even when controlling for motor function as measured by the mUPDRS. Prior quantitative EEG studies (qEEG) have noted increased resting-state theta rhythms with cognitive dysfunction in PD; by contrast, we find decreased cue-evoked delta and theta activity when compared to a pre-trial baseline during a cognitive task.[7,10,40,41] An advantage of our task-based approach is that arousal and behavioral control are less variable and facilitate insight into behavioral operations. Our findings have mechanistic significance because midfrontal delta/theta activity signals need for cognitive control in response to novelty, errors, timing, or conflict across species.[6,16,32]

Low-frequency delta/theta bursts can powerfully engage cortical and subcortical brain networks,[5,12,13] and synchronize single neurons in local and distant brain regions[11] involved in the details of cognitive processing. Our work suggests that cognition is dysfunctional in PD patients because they fail to modulate cue-evoked midfrontal delta/theta rhythms to engage in cognitive operations, resulting in cognitive dysfunction and ultimately contributing to MCI and dementia. Supporting this idea is evidence that prefrontal ~4 Hz stimulation can boost cognitive performance in PD and in PD rodent models,[13] although much work remains to develop this idea into viable therapy for PD patients.

Cognitive control is required during the Simon task on congruent vs. incongruent trials and in the oddball task on oddball vs. standard trials[6,10,11,14,29] and is indicated by slower reaction times on incongruent/oddball trials,[11,36] as well as by greater midfrontal delta/theta power.[6] While we observed control-related effects, these were not reliably affected by cognition in PD as noted by unreliable Group effects for both response times and EEG metrics. These data indicate that non-specific low-frequency cortical deficits may reflect generic orienting or engagement signals rather than control-related processes *per se.*[22] While levodopa can powerfully affect attention,[42] our prior work showed that levodopa does not reliably affect response times or delta/theta rhythms during the Simon task[36] or the interval-timing task.[7]

In addition, our results advance the idea of midfrontal delta/theta activity as a candidate biomarker for cognitive deficits in PD. The lack of strong control-related effects suggest that even a low-salience imperative cue requiring a response might trigger midfrontal delta/theta activity and be attenuated in PD.[39] We note that our tasks are simple and time-efficient, and can performed by PD patients with marked cognitive dysfunction as well as in the operating room.[11,13] Fascinatingly, response-time effects are primarily observed in PDMCI/PDD, which may underlie classic behavioral studies in PD that simply describe behavioral slowing.[43] Our behavioral data imply that PD patients with cognitive dysfunction have the most pronounced behavioral slowing.

We demonstrated that PD-related cognitive function affects behavior and midfrontal delta/theta activity, and some event-related potentials (i.e., the oddball P3). We did not observe other consistent effects of traditional time-averaged EEG event-related potentials. Analyzing these potentials requires averaging across repeated trials and they are only sensitive to discrete temporal changes in canonical peaks and troughs, only capturing a small fraction

of all EEG activities.[44] By contrast, spectral approaches capture all cue-related activities and may be more sensitive to higher-order cortical changes in PD.[35] Our data demonstrate reliable behavioral changes with PD as well as robust spectral changes, making them ideal for the development of future biomarkers for PD.[9,28]

Our study is limited by the number of tasks and assays we performed, although we were constrained by patient-related fatigue, particularly in groups with PDMCI/PDD. Because we did not investigate other patient populations such as Alzheimer's disease, Dementia with Lewy Bodies, and other neurodegenerative diseases, the changes we report here may not be specific to PD might be common in other diseases impacting memory and attention. Furthermore, EEG has limited spatial resolution but its temporal resolution permits detailed time-frequency analysis.

In summary, our data demonstrate that midfrontal delta signals were reliably attenuated in PD-related cognition, and could be used to diagnose cognitive dysfunction in PD. These findings imply that PD-patients have cognitive deficits because they fail to engage basic orienting processes. This mechanistic insight could inspire future work on fundamental processes that fail in PD patients, and could inspire new biomarkers as well as novel rehabilitation and neuromodulation strategies targeting cognition in PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key messages

Parkinson's patients can have cognitive dysfunction but the mechanism is unknown. This study links cognitive dysfunction in PD to midfrontal delta/theta rhythms that are measurable via scalp EEG. Our work provides insight into fundamental mechanisms of PD-related cognitive dysfunction and could lead to novel targeted therapies and neurophysiological biomarkers for cognitive symptoms of PD.

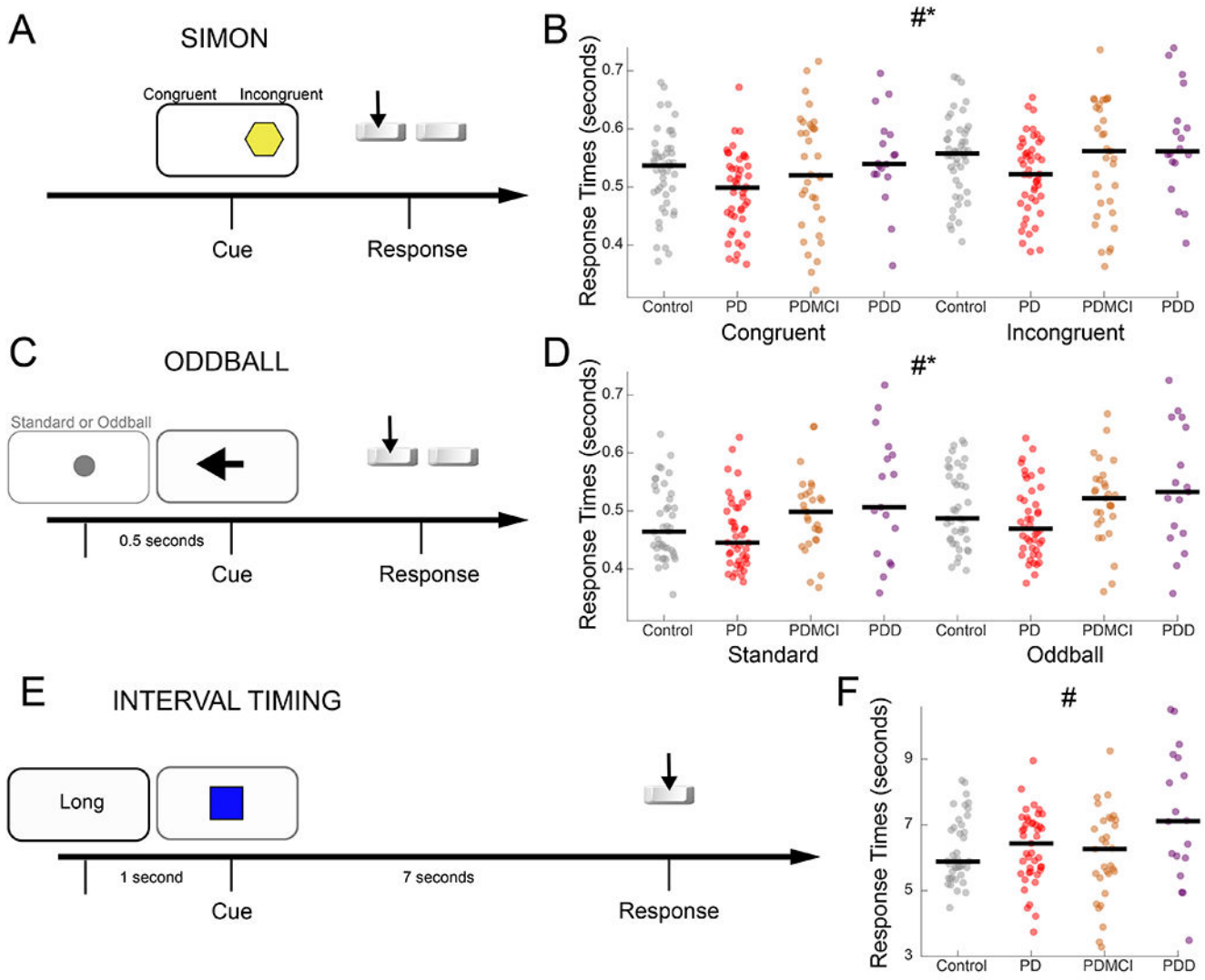

Figure 1: Responses during cognitive control tasks are slowed with cognition in PD.

A) Simon task, in which patients are presented cues on the left or the right of the screen which indicates a left or right response. Congruent trials involve a cue on the same side (i.e., left cue on the left) and incongruent trials involve cues on opposite side (left cue on the right). B) Response times for congruent and incongruent trials for 48 control (gray), 47 PD (red), 34 PDMCI (orange), and 18 PDD (plum) patients; the black bar is the median. C) Oddball task, in which standard stimuli (80% of trials) and novel auditory cues (10% of trials) precede a left or right response as cued by an arrow. 10% of trials included a novel visual cue; these were not analyzed. D) Response times for standard and oddball trials for 41 control, 44 PD, 29 PDMCI, and 17 PDD patients; the black bar is the median. E) Interval timing task in which participants must estimate an interval of 7 seconds with a keypress. F) Response times for 41 control, 43 PD, 31 PDMCI, and 18 PDD patients; the black bar is the median. *=main effect of trial Type; #=main effect of Group.

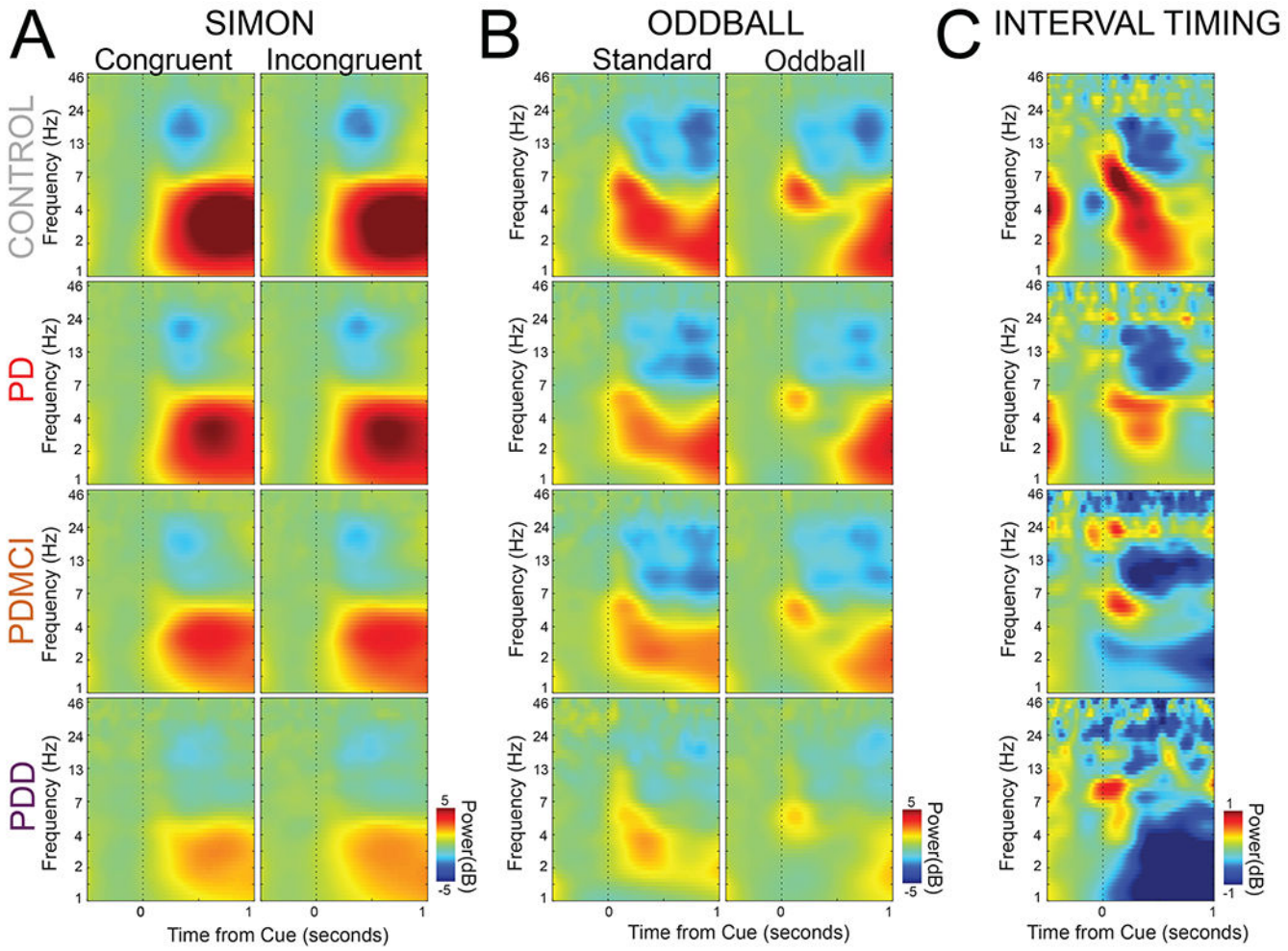

Figure 2: Midfrontal delta/theta rhythms in Simon, Oddball, and Interval timing tasks.

A) Cue-evoked time-frequency spectrograms from EEG electrode Cz during the Simon task on congruent and incongruent trials for 48 control, 47 PD, 34 PDMCI, and 18 PDD patients. B) Cue-evoked time-frequency spectrograms from EEG electrode Cz during the Oddball task on Standard and Oddball trials for 41 control, 44 PD, 29 PDMCI, and 17 PDD patients. C) Cue-evoked time-frequency spectrograms from EEG electrode Cz during the Interval Timing task for 41 control, 43 PD, 31 PDMCI, and 18 PDD patients. Across tasks, there was a consistent pattern of decreased midfrontal cue-evoked delta/theta power.

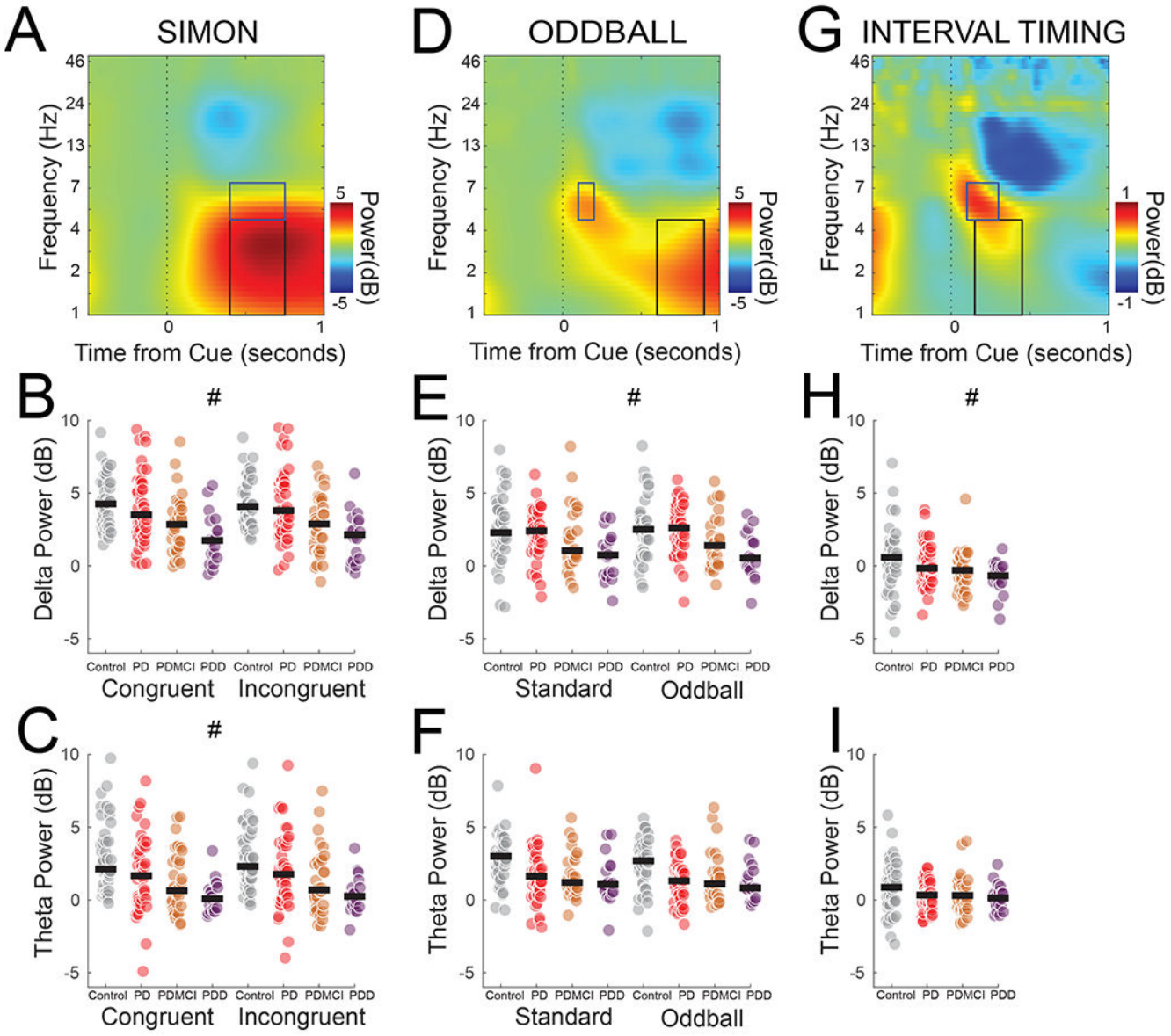

Figure 3: Cue-triggered midfrontal delta activity is decreased with cognitive dysfunction in PD.

We performed time-frequency analyses of activity from midfrontal electrode Cz. During the A) Simon task across all participants, we found prominent cue-triggered low-frequency rhythms <7 Hz. We identified time-frequency regions of interest (tf-ROIs; outlined in black) for theta (4-7 Hz) and delta (1-4 Hz) bands from 0.4–0.75 seconds; 48 control (grey), 47 PD (red), 34 PDMCI (orange), and 18 PDD patients (plum). Power for delta (B) and theta (C) bands during the Simon task. D) Oddball task time-frequency analyses for E) delta bands from 0.6-0.9 seconds and F) theta bands from 0.1-0.2 seconds; 41 control, 44 PD, 29 PDMCI, and 17 PDD patients. G) Interval-timing time-frequency analyses revealed that (H) delta bands from 0.1-0.3 seconds and I) theta bands from 0.15-0.45 seconds; 41 control, 43 PD, 31 PDMCI, and 18 PDD patients; the black bar is the median. #=main effect of Group.

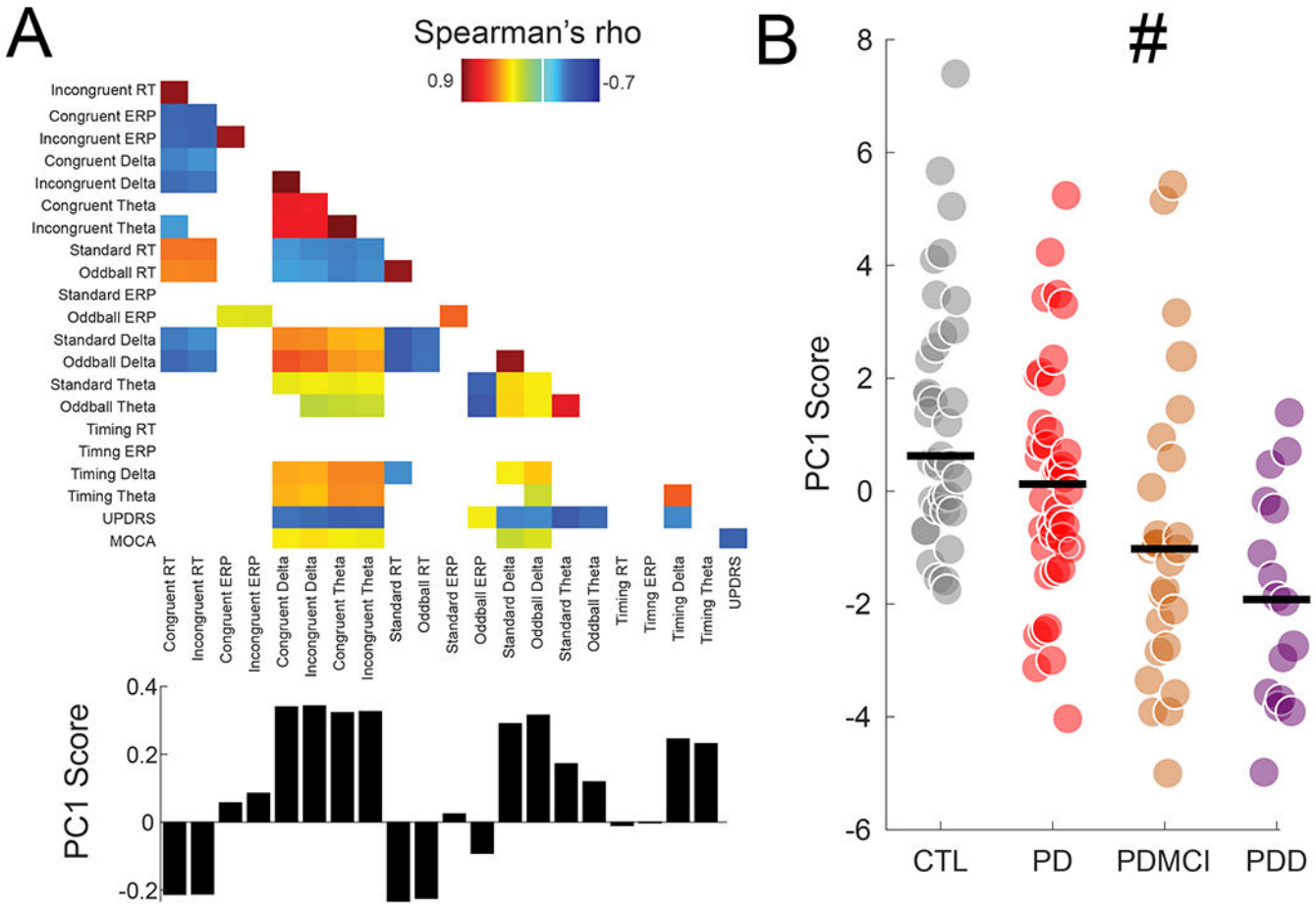

Figure 4: Principal components identify shared variance across tasks.

Data from 35 control participants (grey), 40 PD (red), 27 PDMCI (orange), and 16 PDD participants (plum) who completed all tasks. A) Correlation matrix of response-times and delta/theta activity from Simon, Oddball, and interval timing tasks. Below, the first component from principal component analysis (PC1) loaded highly on delta/theta activity, and inversely on response time. B) PC1 was strongly affected by cognition in PD and PC1 explained 30% of variance in A. #=main effect of Group.

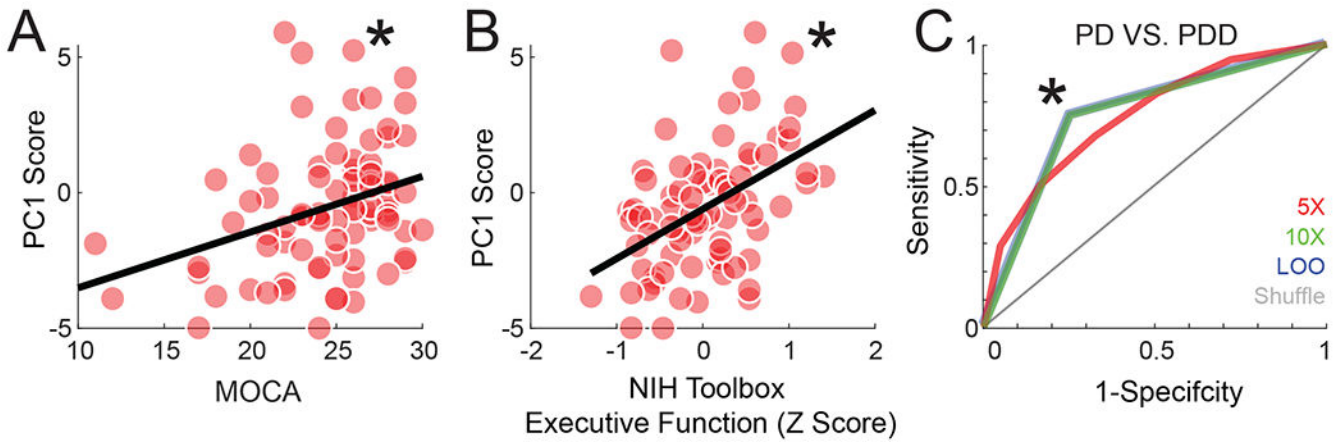

Figure 5: Shared midfrontal variance predicts cognitive dysfunction in PD.

A) PC1 correlated with cognitive function, as identified by the Montreal Cognitive Assessment (rho=0.34) and by B) NIH Toolbox executive dysfunction (rho=0.46). No reliable correlation was observed in control participants. *=p<0.05. C) Pattern classification techniques could accurately identify PD patients without cognitive dysfunction (PD; 40 participants), or PD patients with cognitive dysfunction (PDD; 16 participants). 5x cross-validation in red, 10x cross-validation in green, leave-one-out cross-validation in blue, and shuffled data in grey. *=p<0.001 vs. shuffled data.

Table 1:

Demographic, disease, non-motor, motor, and cognitive characteristics

	Control (N=49)	PD (N=47)	PDMCI (N=34)	PDD (N=19)
Demographics and Disease				
Gender, M/F	26/23	27/20	25/9	16/3
Age, years	70.9 (1.1)	66.0 (1.1)	71.2 (1.4)	70.2 (1.9)
Disease duration, years	-	4.8 (0.6)	4.4 (0.5)	4.8 (1.0)
LEDD, mg/day	-	758.8 (54.9)	750.3 (75.3)	1065.8 (130.5)
Cognition Characteristics				
MOCA (0-30)	26.7 (0.3)	27.4 (0.2)	23.7 (0.2)	17.8 (0.8)
Motor Characteristics				
mUPDRS (0-56)	-	11.2 (1.0)	11.9 (1.1)	16.5 (1.9)

Values are expressed as mean (standard error of the mean).

Abbreviations: Male, M; Female, F; Levodopa Equivalent Daily Dose, LEDD; Montreal Cognitive Assessment, MOCA; motor Unified Parkinson's Disease Rating Scale or UPDRS III, mUPDRS.

Table 2:

Response times across tasks (in milliseconds)

	SIMON					
	Congruent			Incongruent		
	Median	***Q1***	***Q3***	***Median***	***Q1***	***Q3***
Control	537	490	561	558	509	592
PD	499	451	536	522	479	567
PDMCI	520	450	602	562	473	641
PDD	540	522	586	561	542	611
	ODDBALL					
	Standard			Oddball		
	Median	***Q1***	***Q3***	***Median***	***Q1***	***Q3***
Control	464	432	530	487	451	560
PD	445	412	505	469	435	525
PDMCI	498	451	528	522	484	553
PDD	506	426	596	533	461	644
	INTERVAL TIMING					
	Median	***Q1***	***Q3***			
Control	5889	5476	6918			
PD	6437	5597	7054			
PDMCI	6269	5455	7140			
PDD	7118	6011	8911			