



Altered neural oscillations during complex sequential movements in patients with Parkinson's disease

Marie C. McCusker^{a,b}, Alex I. Wiesman^{c,d}, Rachel K. Spooner^{a,c,e}, Pamela M. Santamaria^f, Jennifer McKune^g, Elizabeth Heinrichs-Graham^{a,c,*}, Tony W. Wilson^{a,c}

^a Institute for Human Neuroscience, Boys Town National Research Hospital, Boys Town, NE, USA

^b Interdepartmental Neuroscience Program, Yale University School of Medicine, New Haven, CT, USA

^c College of Medicine, University of Nebraska Medical Center, Omaha, NE, USA

^d The Montreal Neurological Institute, McGill University, Montreal, Canada

^e Institute of Clinical Neuroscience and Medical Psychology, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany

^f Neurology Consultants of Nebraska, Omaha, NE, USA

^g Department of Physical Therapy, Nebraska Medicine, Omaha, NE, USA

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ABSTRACT

The sequelae of Parkinson's disease (PD) includes both motor- and cognitive-related symptoms. Although traditionally considered a subcortical disease, there is increasing evidence that PD has a major impact on cortical function as well. Prior studies have reported alterations in cortical neural function in patients with PD during movement, but to date such studies have not examined whether the complexity of multicomponent movements modulate these alterations. In this study, 23 patients with PD (medication "off" state) and 27 matched healthy controls performed simple and complex finger tapping sequences during magnetoencephalography (MEG), and the resulting MEG data were imaged to identify the cortical oscillatory dynamics serving motor performance. The patients with PD were significantly slower than controls at executing the sequences overall, and both groups took longer to complete the complex sequences than the simple. In terms of neural differences, patients also exhibited weaker beta complexity-related effects in the right medial frontal gyrus and weaker complexity-related alpha activity in the right posterior and inferior parietal lobules, suggesting impaired motor sequence execution. Characterizing the cortical pathophysiology of PD could inform current and future therapeutic interventions that address both motor and cognitive symptoms.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, with a global disease burden of an estimated 6.1 million cases in 2016 (Dorsey et al., 2018). PD is most commonly characterized by progressive motor symptoms including hypo- or bradykinesia, resting tremor, postural instability, and rigidity, as well as a sequelae of fine motor impairments (Jankovic, 2008; Rodriguez-Oroz et al., 2009). In addition to these motor impairments, non-motor symptoms of PD have been increasingly recognized and include autonomic dysfunction, psychiatric disturbances, sleep changes, sensation/perception dysfunction and cognitive impairment (Garcia-Borreguero et al., 2003; Jankovic, 2008; Rodriguez-Oroz et al., 2009; Schapira et al., 2017). Patients with PD sometimes exhibit bradyphrenia, or a general slowness of cognitive

processing (Revnusuo et al., 1993; Vlagsma et al., 2016), as well as specific deficits in attention, visuo-spatial processing, and visuo-motor integration (Inzelberg et al., 2008; Lees and Smith, 1983; Rodriguez-Oroz et al., 2009). Contrary to early perspectives, recent evidence suggests that PD is a whole-brain disorder, with functional disturbances at both subcortical and cortical levels (Heinrichs-Graham et al., 2014, 2017; Melgari et al., 2014; Poewe et al., 2017; Wiesman et al., 2016; Heinrichs-Graham et al., 2014), with the latter ultimately giving rise to the cognitive impairments observed in PD.

Numerous functional neuroimaging studies have indicated aberrations in the neural systems supporting both motor planning and execution processes in patients with PD (Heinrichs-Graham et al., 2014; Heinrichs-Graham et al., 2014; Heinrichs-Graham et al., 2017; Meissner et al., 2018; Mezziane et al., 2015; Heideman et al., 2020), with

* Corresponding author at: Institute for Human Neuroscience, Boys Town National Research Hospital, 14090 Mother Teresa Ln., Boys Town, NE 68010, USA.
E-mail address: elizabeth.heinrichs-graham@boystown.org (E. Heinrichs-Graham).

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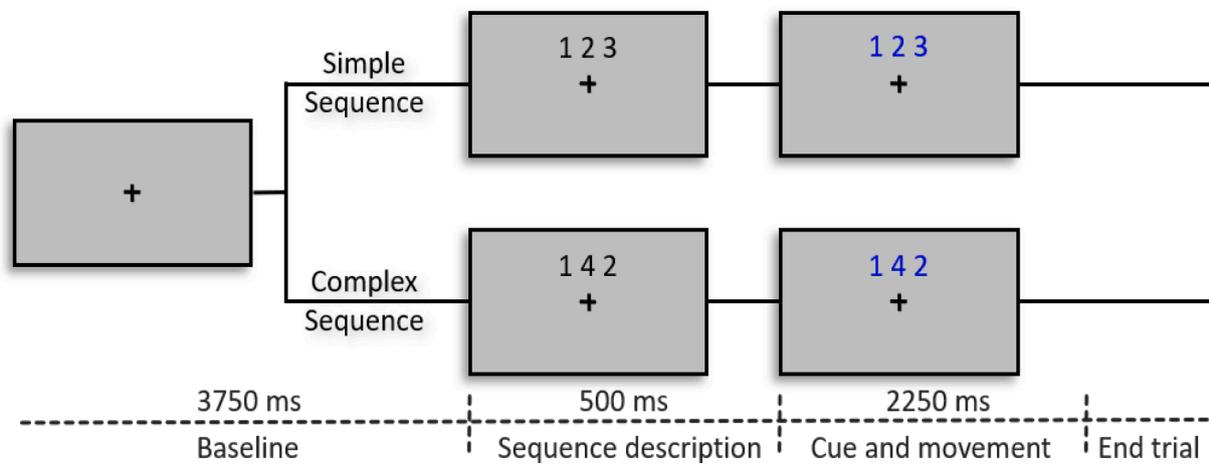


Fig. 1. Sequential Movement Paradigm. Prior to the start of each trial, participants fixated on a crosshair. After the baseline period, a series of three numbers (each corresponding to a digit on the hand) appeared on the screen in black font. The two conditions for this task correspond to different levels of motor execution complexity. After 500 ms, the numbers changed color to blue, which cued the participant to complete the sequence using the button pad. The participant had 2250 ms to complete the motor sequence and return to rest.

performance typically progressively deteriorating as movement sequences become more complex (Agostino et al., 1994; Georgiou et al., 1994; Moroney et al., 2008). Recent work examining finger tapping sequences has demonstrated that patients with PD show reduced neural responses across a distributed sensorimotor network (e.g., contralateral primary motor cortex, supplementary motor areas, ipsilateral cerebellum), concomitant with compensatory mechanisms (e.g., greater recruitment of association cortices) employed prior to movement (Martin et al., 2019). Behaviorally, many studies have reported that patients with PD have longer and more variable reaction times than healthy individuals in movement tasks (Berry et al., 1999; Doyon, 2008; Evarts et al., 1981; Fama and Sullivan, 2002; Harrington and Haaland, 1991; Heilman et al., 1976; Marinelli et al., 2010), although not all studies have found such delays (Martin et al., 2019). While these studies have broadly characterized the neural networks disrupted during complex motor performance in patients with PD, the temporal and spectral parameters of neural activity underlying this behavioral dysfunction are not well understood.

Many studies have shown that motor control is served by multi-spectral oscillatory activity across a distributed cortical network including the primary motor cortices, superior parietal lobules, pre-motor cortices and supplementary motor areas to name a few (Grent-'t-Jong et al., 2014; Heinrichs-Graham et al., 2016; Heinrichs-Graham and Wilson, 2015; Tzagarakis et al., 2010). Specifically, decreases in activity in the alpha and beta range (i.e., event-related desynchronizations) occur prior to and during movement execution and are thought to reflect the active engagement of neuronal pools in motor planning and execution operations (Engel and Fries, 2010). These responses are at least partially distinct in both location and function. The alpha ERD typically peaks posterior to the beta ERD (Salmelin et al., 1995) and has been broadly associated with sensorimotor integration (Pineda, 2005). Conversely, the beta ERD has been shown to be related to motor planning and movement selection (Grent-'t-Jong et al., 2014; Heinrichs-Graham et al., 2016; Heinrichs-Graham and Wilson, 2015; Tzagarakis et al., 2010; Engel and Fries, 2010; Doyle et al., 2005; Heinrichs-Graham and Wilson, 2016; Kaiser et al., 2001; Kaiser et al., 2003; Park et al., 2013). Electrophysiological studies of this motor network in patients with PD have provided further insights into the cortical disturbances associated with the disease process (Heinrichs-Graham et al., 2014; Heinrichs-Graham et al., 2014; Hammond et al., 2007). For example, many studies have found reduced alpha/beta desynchronizations in patients with PD compared to healthy controls during simple movements (Heinrichs-Graham et al., 2014; Pollok et al., 2012), and some

have linked these weakened responses to impaired task performance (Hanslmayr et al., 2007; Perfetti et al., 2010; Sauseng et al., 2005; Zhang et al., 2008). Not only are alpha/beta oscillations attenuated, but patients with PD also exhibit diminished motor sequence learning compared to healthy individuals (Meissner et al., 2018). Importantly, these effects are not constrained spatially to primary motor cortices, as patients with PD have been found to exhibit differences in information processing across numerous motor, sensory, and association cortices (Mattay et al., 2002; Labyt et al., 2003; Jenkins et al., 1994; Jueptner et al., 1997; Sakai, 1998). A better understanding of the underlying pathophysiology in these regions could lead to enhanced therapeutic interventions.

In this study, we utilized a motor sequence paradigm and magnetoencephalographic (MEG) imaging to examine the effect of motor sequence complexity (i.e., simple versus complex movement sequences) on peri-movement cortical oscillations in patients with PD and demographically-matched healthy controls. We hypothesized that neural activity across an extended cortical network would exhibit interactions between group and sequence complexity.

2. Methods

2.1. Participants

This experiment enrolled 23 patients with mild-to-moderate PD (17 male, 21 right-handed) and 27 healthy adult controls (19 Male, 25 right-handed). The mean ages were 65.17 years ($SD = 6.03$, range: 53 – 80 years) for patients and 64.77 years ($SD = 6.00$, range: 54 – 75) for controls. Age information for one control was not available. All patients with PD had been prescribed a stable and regularly monitored dosage of an antiparkinsonian medication regimen for at least two months prior to study enrollment and had shown a satisfactory clinical response. All neuroimaging and behavioral tests were conducted by the patients with PD after at least a 12-hour medication washout period (i.e., the “practically-defined off state”), allowing patients to be in the medication off-state without being uncomfortable for a prolonged period due to decreased symptom suppression. The Unified Parkinson’s Disease Rating Scale (UPDRS) was administered to the patients with PD by a certified rater after consent, and both the full UPDRS score, as well as the motor subtest (UPDRS-III) were computed. Mean patient UPDRS scores (overall and UPDRS-III) were 58.78 ($SD = 20.23$, range: 32–116) and 37.61 ($SD = 11.79$, range: 15–75), respectively. Exclusionary criteria included any medical illness affecting CNS function, neurological or

psychiatric disorder (besides PD), history of head trauma, current substance abuse, and the MEG Center's standard exclusion criteria (e.g., dental braces, metal implants, battery operated implants, and/or any type of ferromagnetic implanted material). Each participant provided written informed consent and was compensated for their time and travel. The Institutional Review Board at the University of Nebraska Medical Center reviewed and approved this study, and all protocols were in accordance with the Declaration of Helsinki.

2.2. Experimental paradigm and stimuli

All participants were scheduled for MEG early in the morning (i.e., 07:30 – 08:00), and for the group with PD, a minimum of 12 h since their last dosage of antiparkinsonian medication as described above. After consent, the patients with PD were administered the UPDRS.

Next, participants were seated in a nonmagnetic chair within the magnetically shielded room. Each participant rested their right hand on a custom-made five-finger button pad while fixating on a crosshair presented centrally for 3750 ms. Following this pre-stimulus period, a series of three numbers, each corresponding to a finger on the right hand, was presented on the screen in black for 500 ms. On the button pad, the right index finger, middle finger, ring finger, and pinky finger corresponded to numbers 1, 2, 3, and 4 on the screen, respectively. After 500 ms, the numbers changed color to blue, signaling the participant to tap the fingers corresponding to the motor plan sequentially. The participant was given 2250 ms to complete the motor sequence and return to rest, after which the numbers disappeared with only the fixation crosshair remaining (Heinrichs-Graham and Wilson, 2015) (Fig. 1). Custom visual stimuli were presented electronically using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA) and back-projected onto a semi-transparent nonferromagnetic screen at an approximate distance of 1.07 m, using a Panasonic PT-D7700U-K model DLP projector with a refresh rate of 60 Hz and a contrast ratio of 4000:1.

For each trial, there were two possible conditions of varying sequence complexity. In the “simple” condition, the series of numbers presented on the screen were sequential (i.e., “1-2-3”, “2-3-4”, “4-3-2”, or “3-2-1”), resulting in the tapping of three adjacent fingers. In the “complex” condition, the numbers presented were at least one number away from the previous number in the sequence (i.e., “1-4-2”, “2-4-1”, “3-1-4”, or “4-1-3”), such that the finger to be tapped was never adjacent to the previous finger tapped. The presentation order of these conditions was pseudo-randomized to ensure there was an equal number of trials for each condition, and sequences were controlled for several variables. Specifically, the first finger tapped was controlled across conditions, ensuring that any delays related to the ease of pressing a specific button were equivalent between conditions, and thus, did not skew reaction time data. In addition, the sequences in each condition contained the same total amount of movements performed (i.e., three finger taps) and the same fingers tapped, ensuring the same neuronal populations were active in each condition and ultimately programmed the same types of movements. A total of 80 trials were completed per condition (160 trials total), making the overall MEG recording time approximately 16 min for the task.

2.3. MEG data acquisition, MEG coregistration and structural MRI processing

MEG data acquisition, structural coregistration, preprocessing, and sensor-/source-level analyses followed a similar pipeline as a number of previous studies (McCusker et al., 2020, 2021; Wiesman and Wilson, 2020; Spooner et al., 2019). Neuromagnetic responses were sampled continuously at 1 kHz with an acquisition bandwidth of 0.1 – 330 Hz using an Elekta/MEGIN MEG system (Helsinki, Finland) with 306 magnetic sensors, equipped with 204 planar gradiometers and 102 magnetometers. Using MaxFilter (v2.2), MEG data were individually corrected for head motion and subjected to noise reduction using the

signal space separation method with a temporal extension (Taulu et al., 2005; Taulu and Simola, 2006). Only the gradiometer data was used in further analyses.

Each participant's MEG data were coregistered with structural T1-weighted MRI data in BESA MRI (Version 2.0) prior to source-space analysis. The structural MRI data were aligned parallel to the anterior and posterior commissures and transformed into standardized space. After source analysis (i.e., beamforming), each participant's 4 mm³ functional images were also transformed into standardized space using the transform applied to the structural volume and spatially resampled.

2.4. MEG processing, time-frequency transformation and Sensor-Level statistics

Noise-reduced MEG data underwent standard data preprocessing procedures using the Brain Electrical Source Analysis (BESA) software. Cardiac and blink artifacts were removed using signal-space projection (SSP), which was accounted for during source reconstruction (Uusitalo and Ilmoniemi, 1997). The continuous magnetic time series was divided into 6400 ms epochs (-2300 ms to 4100 ms), with 0 ms defined as movement onset (i.e., first button press), and a baseline time window extending from -2250 ms to -1750 ms (i.e., before movement onset). We rejected trials having a reaction time longer than 1250 ms or taking more than 3000 ms to complete the entire motor sequence, as the latter would disrupt the baseline period. Further, epochs containing artifacts were rejected using a fixed threshold method, supplemented with visual inspection. After artifact rejection, the patients with PD had an average of 69.26 ($SD = 5.04$) trials accepted (out of 80) in the simple condition and 70.74 ($SD = 4.57$) trials (out of 80) in the complex condition. The healthy controls had an average of 70.64 ($SD = 3.60$) trials accepted in the simple condition and 70.80 ($SD = 4.76$) trials in the complex condition. Importantly, none of our statistical comparisons were biased by differences in the number of accepted trials per group, which can affect the signal-to-noise ratio, as this metric did not significantly differ across groups ($p = 0.455$) or conditions ($p = 0.446$), nor was there a significant condition-by-group interaction ($p = 0.227$).

Using complex demodulation, artifact-free epochs were transformed into the time–frequency domain (Papp and Ktonas, 1977; Kovach and Gander, 2016) (resolution: 2.0 Hz, 25 ms). Briefly, we transformed the signal into the frequency space using a Discrete Fourier Transform (DFT) with a moving time window of 25 ms. This resulted in a frequency spectrum inherently containing the same power and cross spectrum information as the original signal. The resulting spectral power estimations were averaged across trials per sensor to generate time–frequency plots of mean spectral density. The sensor-level data were normalized using the mean power during the -2250 to -1750 ms time period. The specific time–frequency windows used for source imaging were determined by a two-stage statistical analysis of the sensor-level spectrograms across both groups and conditions and the entire array of gradiometers. First, paired t -tests against baseline were conducted on each data point and the output spectrogram of t -values was thresholded at $p < 0.05$ to define time–frequency bins containing potentially significant oscillatory deviations across all participants. Next, the time–frequency bins that survived the threshold were clustered with temporally and/or spectrally neighboring bins that were also above the threshold ($p < 0.05$), and a cluster value was derived by summing all of the t -values of all data points in the cluster. Nonparametric permutation testing was then used to derive a distribution of cluster values and the significance level of the observed clusters (from stage one) was tested directly using this distribution (Ernst, 2004; Maris and Oostenveld, 2007). For each comparison, 10,000 permutations were computed to build a distribution of cluster values. The time–frequency windows that contained significant oscillatory events across all participants and conditions and were associated with motor planning or execution (see next) were subjected to a beamforming analysis. Briefly, we were particularly interested in determining the impact of movement complexity on both

Table 1
Motor sequence task behavior.

	Simple condition mean (SD)	Complex condition mean (SD)	Combined conditions mean (SD)	Group Effect (p)	Condition effect (p)	Condition × Group interaction (p)	
Reaction Time (ms)							
Controls	481.49 (144.36)	544.33 (159.32)	512.91 (137.90)	0.431	0.004	0.005	
PD	478.58 (125.48)	479.77 (137.82)	479.18 (127.47)			HC	PD
						<0.001	1.000
Movement Duration (ms)							
Controls	864.34 (127.06)	957.48 (182.64)	910.91 (145.43)	0.005	<0.001	0.662	
PD	1002.62 (124.89)	1081.91 (148.29)	1042.26 (133.21)				
Accuracy (%)							
Controls	97.30 (2.52)	97.45 (2.49)	97.37 (2.35)	0.699	0.183	0.408	
PD	96.79 (2.60)	97.43 (1.99)	97.11 (2.06)				
Overall Task Performance (ms)							
Controls	1341.56 (225.24)	1497.43 (264.62)	1419.50(244.93)	0.085	<0.001	0.046	
PD	1514.98 (265.98)	1595.84 (279.68)	1555.41 (272.83)			HC	PD
						<0.001	0.250

motor planning and motor execution responses in controls and patients with PD. Thus, we focused our analyses on the time windows representing movement planning (-500 to 0 ms, with 0 ms defined as movement onset) and movement execution (0 to 500 ms) individually. The alpha ERD and beta ERD responses within these windows were independently imaged in each participant relative to the baseline period to determine the precise brain regions generating these significant oscillatory responses.

2.5. MEG imaging and source-level analysis

MEG data were imaged using the dynamic imaging of coherent sources (Gross et al., 2001) (DICS) approach, which uses the cross-spectral densities of all combinations of MEG gradiometers averaged over the time–frequency range of interest, and the solution to the forward problem for each location on a grid specified by input voxel space. Following convention, we computed noise-normalized, source power per voxel using active (i.e., task) and passive (i.e., baseline) periods of equal duration and bandwidth (Hillebrand and Barnes, 2005; Van Veen et al., 1997). For instance, since our baseline was 500 ms, our active time periods reflecting movement planning and execution were also 500 ms. Normalized source power was computed for the selected time–frequency bands over the entire brain volume per participant and condition at $4.0 \times 4.0 \times 4.0$ mm resolution. For our ROI analysis (see next), pseudo- t values were extracted from grand-averaged clusters in the left and right primary motor cortices. We also extracted peak voxel values from regions exhibiting significant condition-by-group interactions in our whole-brain analyses, to aid in interpretation. Next, voxel time series (i.e., “virtual sensors”) were extracted from each participant’s data individually per condition and combined conditions from each of the peak coordinates for the alpha and beta bands. Briefly, virtual sensor computation was performed by applying the sensor-weighting matrix derived through the forward computation to the preprocessed signal vector, which yields a time series with the same temporal resolution as the original recording. These data were then decomposed back into time–frequency space to compute the envelope of each response per visit. Once these virtual sensor time series were extracted, we computed the vector sum of the two orientations and then the relative (i.e., baseline-corrected) and absolute (i.e., not baseline-corrected) time series envelope of each participant. The virtual sensor analyses were primarily used to estimate spontaneous alpha and beta ERD activity during the baseline to ensure there were no group differences, which could have affected the strength of peri-movement alpha and beta responses.

2.6. Statistical analyses

Outliers for all of the quantitative data (e.g., task behavior, pseudo- t s

of peaks from grand-average maps and interaction maps) were identified as 3 standard deviations above or below the mean and removed from statistical analyses. For our statistical analyses, we used the statistical software JASP (version 0.12.2.0; JASP Team (2020)). Task performance measures (i.e., accuracy, movement duration, reaction time, overall performance) were statistically compared using a 2×2 repeated measures ANOVA with group (patients versus controls) as a between-subjects factor and condition (“simple” versus “complex”) as a within-subjects factor, as well as the group-by-condition interaction term. Follow-up post hoc testing was used with a correction threshold of $P_{Tukey} < 0.05$ to determine the directionality of effects.

In regard to the MEG data, we first sought to determine the effects of group and condition on primary motor cortical activity. We initially averaged the functional brain activity across groups and conditions to evaluate data quality and visualize results, and then extracted peak voxel values from the grand averaged peaks within the left precentral gyrus for each participant and condition. The effect of group, time (“planning” versus “execution”), and sequence condition (“simple” and “complex”), were then examined using these cluster peaks and $2 \times 2 \times 2$ repeated measures ANOVAs for alpha ERD and beta ERD separately.

We additionally evaluated any interactions between group and sequence complexity during movement planning and execution at the whole-brain level using a multi-stage mass univariate approach based on the general linear model. Initially, condition-subtracted (e.g., complex minus simple) whole brain images were computed, and then these difference maps were compared between groups using unpaired t -tests, which allowed us to identify condition-by-group interactions and regions generating differential oscillatory responses. A relatively strict initial alpha level of $p < 0.005$ was utilized at this stage to mitigate the risk of false positives. We chose a cluster-defining threshold (CDT) of 0.005 in this study as a balance to avoid being too liberal and overly stringent. Using Statistical Parametric Mapping software (SPM12; Wellcome Trust Centre for Neuroimaging), we performed Family-wise Error (FWE) correction on our regions of interest and compared the expected number of voxels per cluster (initial $p < 0.005$) with the cluster-level of our region(s) of interest to define a prominent cluster (FWE cluster extent for alpha, $k = 71.349$ voxels, and for beta, $k = 65.404$ voxels). Pseudo- t values corresponding to the peak voxel of each resulting cluster were extracted, tested for post-hoc effects, and used for visualization purposes.

3. Results

The majority of participants were able to successfully complete the motor sequence task. Four patients with PD and two healthy control participants were excluded from all analyses due to low task performance (i.e., <70% accuracy) or a combination of poor performance and

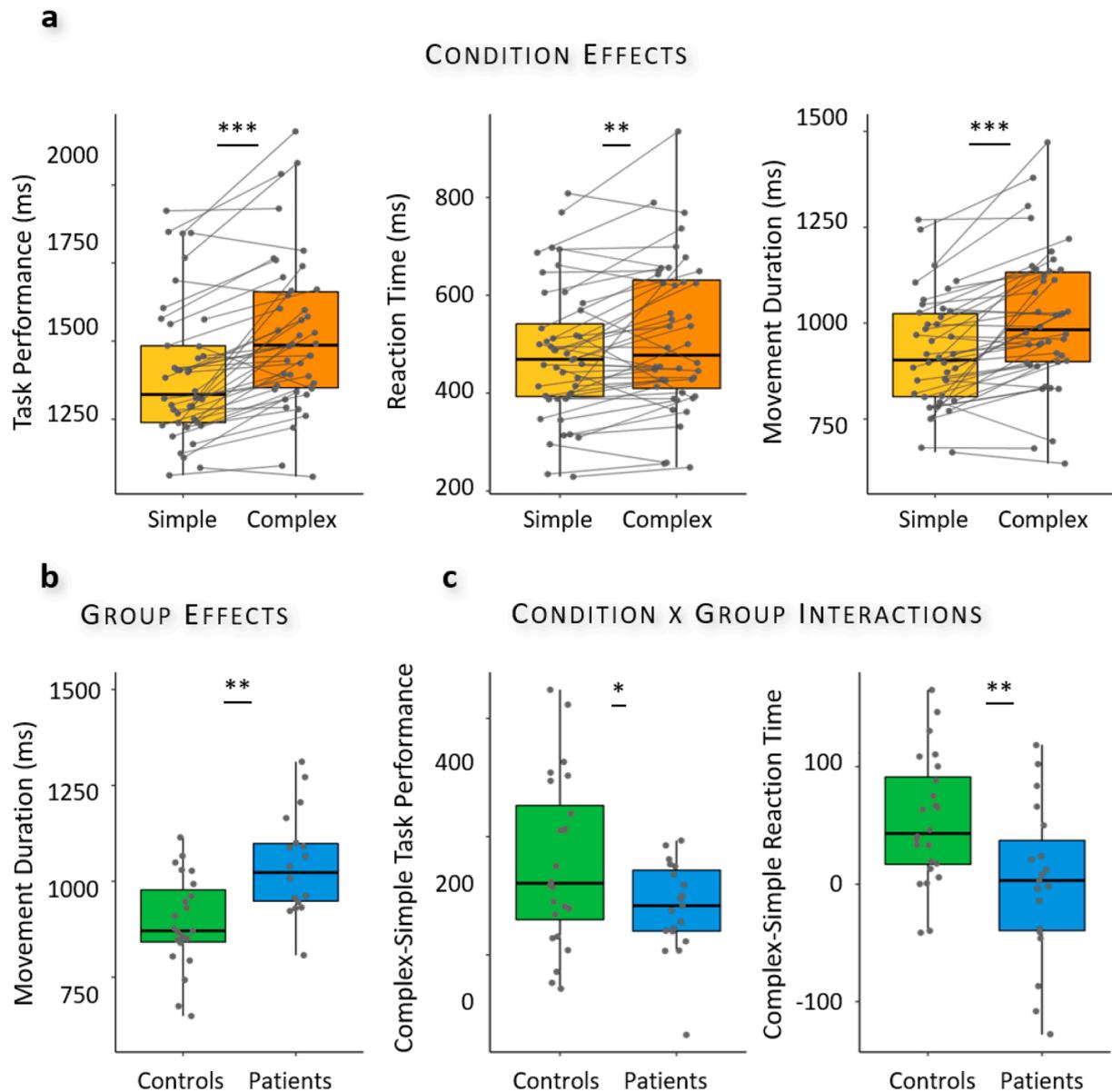


Fig. 2. Motor Sequence Complexity Task Behavioral Results. Box and whisker plots show task behavior. The y-axis denotes the behavioral measurement (reaction time, movement duration, and overall task performance (reaction time + movement duration) in ms, or complexity effect (complex – simple; in ms). Each plot includes the individual data points, median (horizontal line), first and third quartile (box), and local minima and maxima (whiskers). The lines between the individual data points display within-subject effects. Initial outliers have been removed. Only statistically significant findings are reported. (a) Condition main effects were observed for overall task performance, reaction time, and movement duration. Regardless of group, participants had longer overall task performance, slower reaction times, and longer movement duration on complex relative to simple sequences. (b) Group main effects were observed for movement duration and overall task performance. Patients with PD took longer to perform and complete the motor sequence compared to controls, irrespective of movement complexity. (c) A condition-by-group interaction was observed for overall task performance, where controls took longer to complete the complex trials compared to the simple, while the patient with PD did as well but to a lesser extent. A condition-by-group interaction was also seen for reaction time, where controls initiated movements slower during the complex sequences compared to the simple while patients with PD did not show this effect. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$.

noisy MEG data (i.e., <120 total trials accepted after excluding noisy trials and inaccurate responses).

Reaction time, movement duration, accuracy, and overall task performance (reaction time + movement duration in ms) were computed for each participant (Table 1). Both groups performed the task with high accuracy (~97% correct) with no significant effects of group, condition or condition-by-group interactions. In regard to reaction time, repeated measures ANOVAs revealed a significant main effect of condition ($F = 9.319$, $p = 0.004$) and a significant condition-by-group interaction ($F = 8.640$, $p = 0.005$). There was no significant effect of group ($p = 0.431$). Post hoc analyses of the condition effect revealed that across groups, participants were slower to respond to the complex sequences compared

to the simple ones. However, post hoc testing of the condition-by-group interaction revealed that controls were slower to respond to the complex trials compared to the simple ones, while patients with PD did not exhibit this same complexity effect. Note that p -values for post-hoc tests are provided in Table 1. For movement duration, repeated measures ANOVAs revealed significant main effects of condition ($F = 30.103$, $p < 0.001$) and group ($F = 9.007$, $p = 0.005$). Similar to our analysis of reaction time, participants in both groups took longer to complete the entire motor sequence during complex trials compared to simple ones. For the group effect, post hoc testing revealed that patients with PD took longer to complete the entire sequence than the controls, irrespective of movement complexity. There was no group-by-condition interaction.

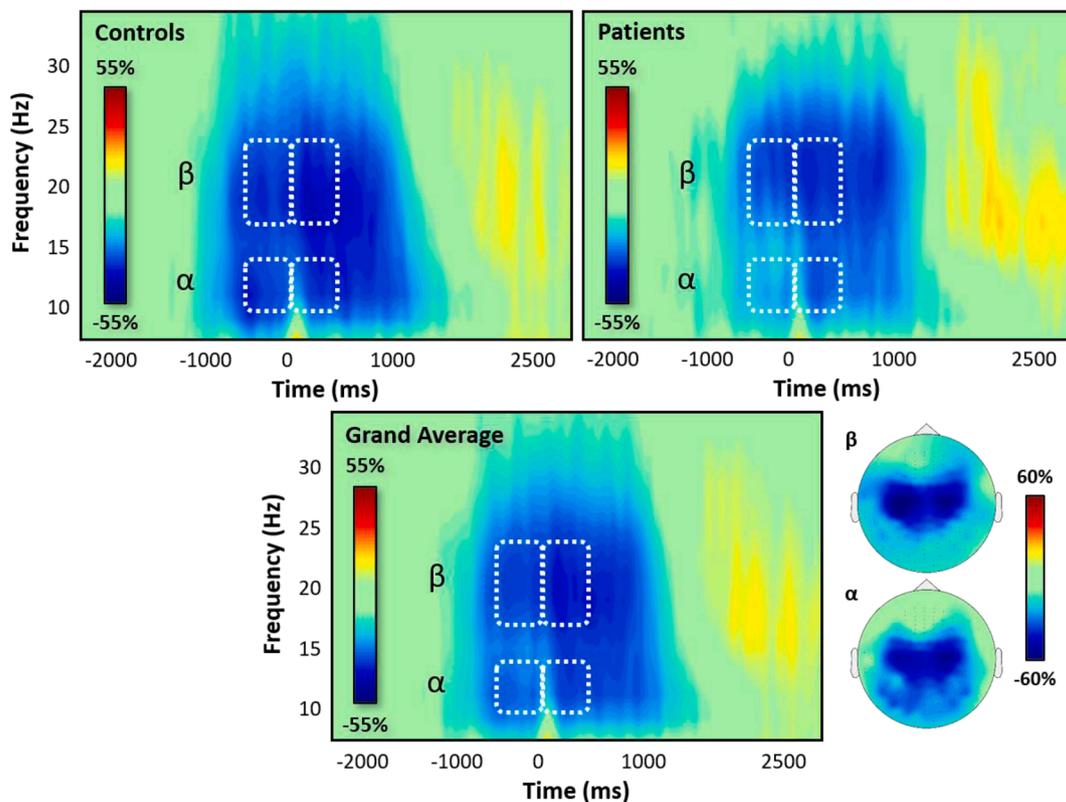


Fig. 3. Sensor-level spectrograms and topographic maps. Spectrograms from a MEG sensor near the left sensorimotor cortex (M0243) are shown for controls (left panel) and patients with PD (right panel). The top row represents each group's average spectrogram (collapsed across task conditions) and the bottom spectrogram reflects the grand average. Time (in ms) is denoted on the x-axis, with 0 ms defined as the onset of the first movement in the sequence. Frequency (in Hz) is shown on the y-axis. Signal power data is expressed as a percent difference from baseline, denoted with a color legend. The alpha and beta ERD responses corresponding to movement planning and execution that were imaged are indicated by the white, dashed boxes. Topographical maps of execution-related activity are presented to the right of the grand average spectrogram for alpha (bottom) and beta ERD (top).

Lastly, we observed a significant effect of condition on overall task performance (reaction time + movement duration in ms; $F = 42.083$, $p < 0.001$) and significant condition-by-group interaction ($F = 4.225$, $p = 0.046$). Post hoc analyses of the condition effect revealed that regardless of group, participants were slower to execute complex trials compared to the simple, and for the condition-by-group interaction, controls were slower to perform the complex trials compared to the simple ones, while the patients with PD also were to a lesser extent. All significant behavioral results are shown in Fig. 2.

3.1. MEG Sensor-Level results

Statistical analysis of sensor-level time–frequency spectrograms indicated three significant motor oscillatory responses (Fig. 3). Significant peri-movement alpha (8–14 Hz) and beta (16–24 Hz) event-related desynchronizations (ERD) were found in numerous sensors near the sensorimotor cortex ranging from about 800 ms before movement onset until about 1200 ms and 1000 ms, respectively, after movement ($p < 0.005$, corrected). Due to baseline limitations, we chose the 500 ms windows directly before and after movement onset as our movement planning (-500 to 0 ms) and execution (0 to 500 ms) windows, respectively. These four time–frequency windows (motor planning: 8 to 14 Hz and 16 to 24 Hz, -500 to 0 ms; motor execution: 8 to 14 Hz and 16 to 24 Hz, 0 to 500 ms) were subsequently imaged using beamforming. Of note, there was also a significant beta synchronization (i.e., the post-movement beta rebound [PMBR]) that extended from about 2000 ms to 3500 ms after movement onset ($p < 0.005$, corrected). However, as the PMBR is tightly linked to the termination of movement and since our task was not well-designed to balance cognitive demands across this time window, any potential group differences in the PMBR response

would potentially be confounded by performance differences. Thus, we did not analyze this response further.

3.2. MEG imaging results

Grand average beamformer images revealed bilateral alpha and beta activity in the primary motor cortices (M1; Fig. 4). Regarding alpha in the left M1, the $2 \times 2 \times 2$ repeated-measures ANOVA (time-by-condition-by-group) revealed a significant main effect of group ($F = 7.783$, $p = 0.008$), where post hoc testing showed controls had stronger alpha ERD in the left M1 than the patients with PD irrespective of time period and condition. Note that p -values for post-hoc tests are provided in Table 2. The $2 \times 2 \times 2$ repeated measures ANOVA (time-by-condition-by-group) for beta activity in the left M1 revealed a significant main effect of time ($F = 21.063$, $p < 0.001$), a significant main effect of group ($F = 6.039$, $p = 0.019$), and a significant time-by-condition interaction ($F = 5.579$, $p = 0.024$). Post hoc analyses of the time main effect revealed that there was stronger beta ERD during the execution period than the planning period regardless of group and condition. Post hoc analyses of the group main effect showed that controls had stronger beta ERD than the patients with PD irrespective of time period and condition. Regarding the time-by-condition interaction, post hoc analyses revealed stronger beta ERD during the execution period than the planning for both conditions, irrespective of group.

In order to ensure that our oscillatory findings were not due to differences in baseline activity between groups or conditions, we performed a 2×2 repeated measures ANOVA (condition-by-group) on the absolute power during the baseline period (-2250 to -1750 ms). This analysis revealed no significant group differences during the baseline in either frequency band nor task conditions. Specifically, alpha ERD in the

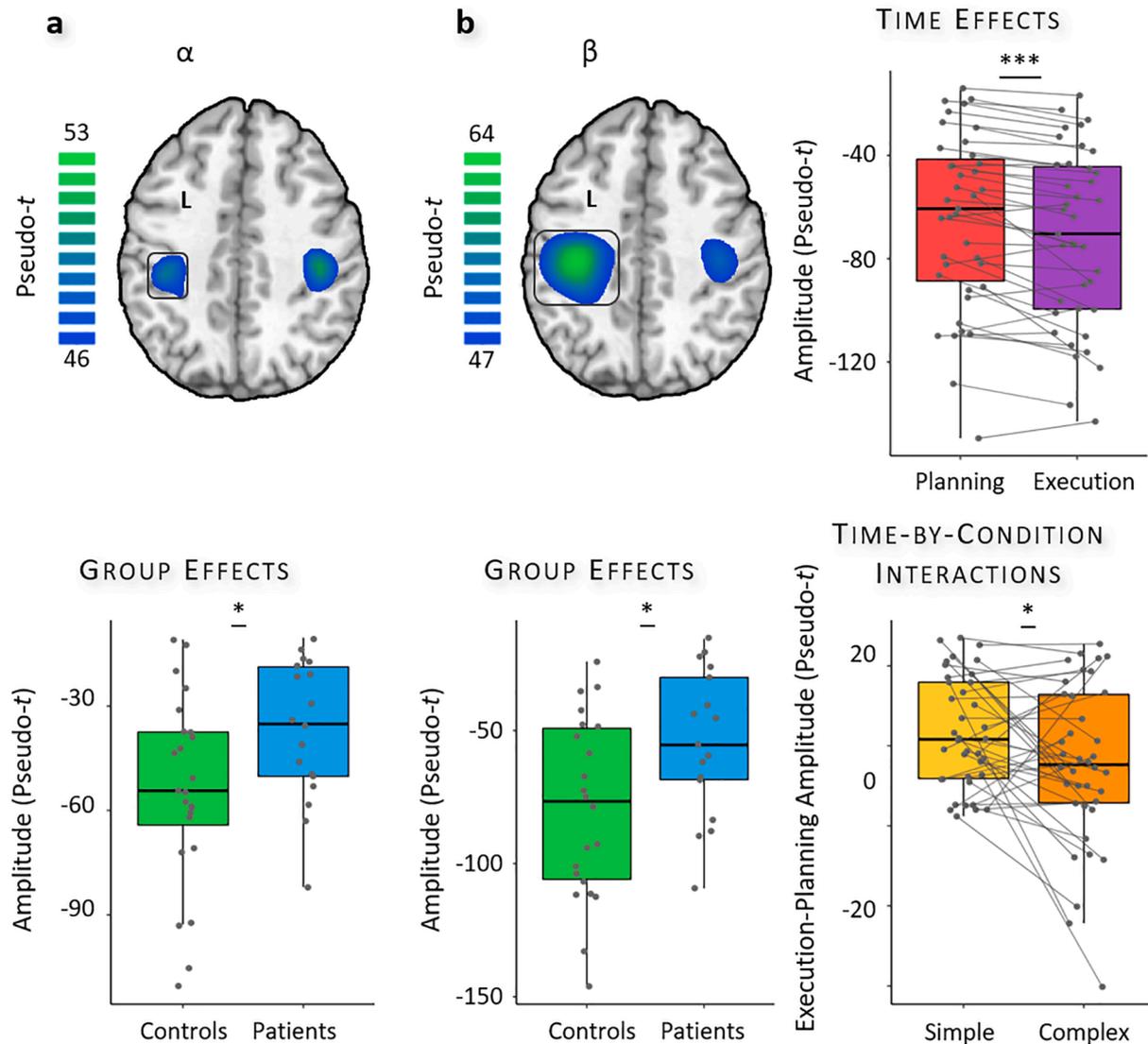


Fig. 4. Alpha and beta neural responses. Grand averaged alpha ERD and beta ERD activity are shown in the top left for each response collapsed across motor planning and execution stages are shown in the top left of (a) and (b), with the corresponding color scale bar (pseudo- t value) to the left side of each map. The box and whisker plots next to each map show amplitude (pseudo- t) extracted from the left M1 peak voxel. Each box and whisker plot includes the individual data points, median (horizontal line), first and third quartile (box), and local minima and maxima (whiskers). The lines between the individual data points display within-subject effects. Initial outliers have been removed. (a) Bottom: There was a significant main effect of group for alpha ERD activity, where controls had stronger alpha ERD responses compared to patients with PD irrespective of condition and time. (b) Top right: There was a significant main effect of time for beta ERD, where there was stronger beta ERD during the execution period than the planning period regardless of group and condition. Bottom left: There was a significant main effect of group for beta ERD, where controls had stronger beta ERD than the patients with PD irrespective of time and condition. Bottom right: There was a significant time-by-condition interaction, where post hoc analysis revealed a larger change in beta ERD amplitude from planning to execution during the complex sequences relative to the simple ones. $*p < 0.05$, $***p < 0.001$.

left and right M1 revealed no significant effects of condition (left: $p = 0.685$; right: $p = 0.495$), group (left: $p = 0.521$; right: $p = 0.198$), nor condition-by-group interaction (left: $p = 0.926$; right: $p = 0.997$). Similarly, beta ERD in the left and right M1 revealed no significant effects of condition (left: $p = 0.642$; right: $p = 0.806$), group (left: $p = 0.251$; right: $p = 0.120$), nor condition-by-group interaction (left: $p = 0.488$; right: $p = 0.354$).

Regarding our whole-brain analysis of condition-by-group interaction effects, there were no significant interactions during the planning period for either the alpha ERD or beta ERD. Conversely, we found significant interactions for the alpha ERD execution response in the right posterior parietal cortex (rPPC) and right inferior parietal lobule (rIPL) and for the beta ERD execution response in the right medial frontal gyrus (Fig. 5). All of these significant effects were based on an initial alpha level $p < 0.005$. Post hoc testing of peak clusters revealed that controls

had significantly stronger alpha ERD responses in the rPPC during the complex sequence execution than the simple, while patients with PD did not display any differences as a function of sequence complexity. Additionally, there was a significant difference in the complex condition between groups, where controls had significantly stronger alpha ERD responses in the rPPC compared to patients with PD, while there was no group difference in the simple condition. For the rIPL, controls had significantly stronger alpha ERD responses during the complex compared to the simple sequences, while patients with PD demonstrated stronger alpha ERD during the simple compared to complex sequences. In regard to movement-related beta activity, controls had significantly stronger beta ERD responses during the complex compared to simple sequences in the right medial frontal gyrus, while patients with PD did not show a difference as a function of task condition. Note that p -values for post-hoc tests are provided in Table 2. Regarding FWE correction,

Table 2
MEG results.

Grand Average Maps				
	Condition Effect (<i>p</i>)	Group Effect (<i>p</i>)	Time Effect (<i>p</i>)	Time × Condition Interaction (<i>p</i>)
α ERD Left M1	0.389	0.008	0.072	0.188
β ERD Left M1	0.520	0.019	<0.001	0.024
				Simple Complex
				0.028 <0.001
Whole-Brain Interaction Maps				
	Condition Effect (<i>p</i>)	Group Effect (<i>p</i>)	Condition × Group Interaction (<i>p</i>)	
α ERD rPPC	0.042	0.040	<0.001	Condition
				HC PD
			<0.001	0.716
				Group
			Simple	Complex
			0.975	0.006
α ERD rIPL	0.762	0.553	<0.001	Condition
				HC PD
			0.003	0.042
β ERD r meFG	0.451	0.250	0.004	Condition
				HC PD
			0.029	0.443

α, alpha; β, beta; ERD, event-related desynchronization; M1, primary motor cortex; *p*, *p*-value; rPPC, right posterior parietal cortex; rIPL, right inferior parietal lobule; r meFG, right medial frontal gyrus; HC, healthy controls; PD, patients with Parkinson's disease

alpha ERD activity in the rPPC (including the rIPL peak) had a $k = 144$, which survived our expected threshold of $k = 71.349$ voxels per cluster. However, beta ERD effects in the right medial frontal gyrus only had a cluster level of $k = 5$, which did not fit this threshold cluster definition ($k = 65.404$ voxels per cluster). Thus, the latter beta ERD results should be interpreted with caution.

4. Discussion

In this study, we used a sequential finger tapping paradigm to study the effects of movement complexity on the neural dynamics serving successful sequence planning and execution in patients with PD and healthy controls. When comparing performance on the MEG motor task, we found patients with PD were significantly slower in completing the set of sequential movements compared to controls, and in general had smaller complexity effects. In regard to the brain activity, grand averaged alpha and beta ERD responses during motor execution emerged across the bilateral M1, with controls exhibiting stronger alpha and beta ERDs compared to patients with PD regardless of sequence complexity. We also found that, compared to the healthy controls, patients with PD exhibited distinct complexity-related patterns of oscillatory activity in the alpha range in the right parietal cortices during the execution of more complex motor sequences related to simple ones. The implications of these findings are discussed below.

First, our behavioral results reflect impaired motor plan integration and coordination in PD. For instance, in healthy young and older adults, a large difference in behavioral outcomes (e.g., reaction times, movement durations) between complex and simple movement sequences is expected, such that complex sequences take longer to initiate and fully execute (Heinrichs-Graham and Wilson, 2015). However, patients with PD exhibited no such effect and instead took significantly longer than controls to complete the motor sequences, regardless of complexity. This suggests that patients with PD did not effectively integrate motor planning information in the early portion of the trials and instead

attempted to do so while actively executing the motor sequence, resulting in slower task performance. This data complements an earlier study that showed that patients with PD exhibit more reactive movement-related oscillatory patterns rather than proactive patterns (Grent-t-Jong et al., 2014). An alternative to the deficits in motor planning argument would be that the patients with PD had longer movement times because they were just more bradykinetic, and thus have slower movement execution in general. This interesting interpretation should be more directly tested in further studies, especially to examine whether beta ERD responses could adequately distinguish bradykinesia from other symptoms of PD (Boon et al., 2020; Lofredi et al., 2019). Nonetheless, this strategy did not equate to reduced accuracy on the task, as the patients with PD performed equivalently to controls regardless of movement complexity. This is not surprising, as previous studies have found preserved task accuracy in patients with PD (Seidler et al., 2007; Ruitenberg et al., 2015). Overall, our data suggest that individuals with PD struggled to integrate and execute motor plans during our task.

Interestingly, we also observed complexity-by-group interactions in the rIPL and rPPC in the alpha band and in the right medial frontal in the beta range. When performing complex sequences, healthy controls showed stronger alpha ERD responses in the rPPC than patients with PD, while no such difference was present during the execution of simple sequences. Also, the patients with PD displayed the opposite alpha ERD trajectory in the rIPL than the controls, where they had increased alpha ERD in the simple sequences than the complex ones. In conjunction, these suggest that patients with PD have altered neural oscillations especially during more complex movements. One potential explanation for this is that there may be a neural resource limit in patients with PD that prevents them from recruiting sufficient neural resources to execute complex motor sequences more efficiently. They may compensate for this shortage by recruiting other brain areas, as seen in motor planning and learning (Mentis et al., 2003; Nakamura et al., 2001).

Importantly, we did not observe any significant neural differences in the primary somatosensory or motor cortices for the complexity-by-group interactions, which makes sense given that the actual motor commands were closely balanced between the two conditions. Indeed, an earlier study of healthy younger adults using this task found no significant condition effects in the primary motor cortices, and instead found elevated beta execution-related activity in frontal and parietal regions (Heinrichs-Graham and Wilson, 2016). Additionally, the virtual sensors time series data support that these findings are not due to differences in spontaneous activity, nor a continuation of the PMBR response, and are instead likely due to actual differences in ERD activity during the task. These results, concomitant with our condition-by-group interactions observed outside the motor system, align well with recent work which emphasize the notion that PD pathophysiology is whole-brain in nature, and furthermore, that the neural aberrancies found in the rIPL and rPPC in the alpha range are likely related to higher order processing (Heinrichs-Graham and Wilson, 2015).

Before closing, it is important to acknowledge the limitations of this study. First, the condition-by-group patterns of oscillatory activity observed in the current study were uniquely informative when it comes to the impact of increasingly complex movements in those with PD, however our task focused on finger tapping and generalizations to other movement patterns such as gait will require additional studies. Second, although it has been found to be an important moderator of neural motor effects in patients with PD (Heinrichs-Graham et al., 2017), we did not have a large enough sample to effectively analyze the impact of affected side on motor sequence complexity, and this should be a focus of future studies. Another limitation is that we used a cluster-defining threshold (CDT) of 0.005. According to Eklund et al. (2016), a more stringent threshold (e.g., $CDT < 0.001$) that further reduces the risk of false positives is often most appropriate, though this analysis was focused on fMRI data rather than MEG data and the inter-modality differences in smoothness would affect this. Thus, these results should

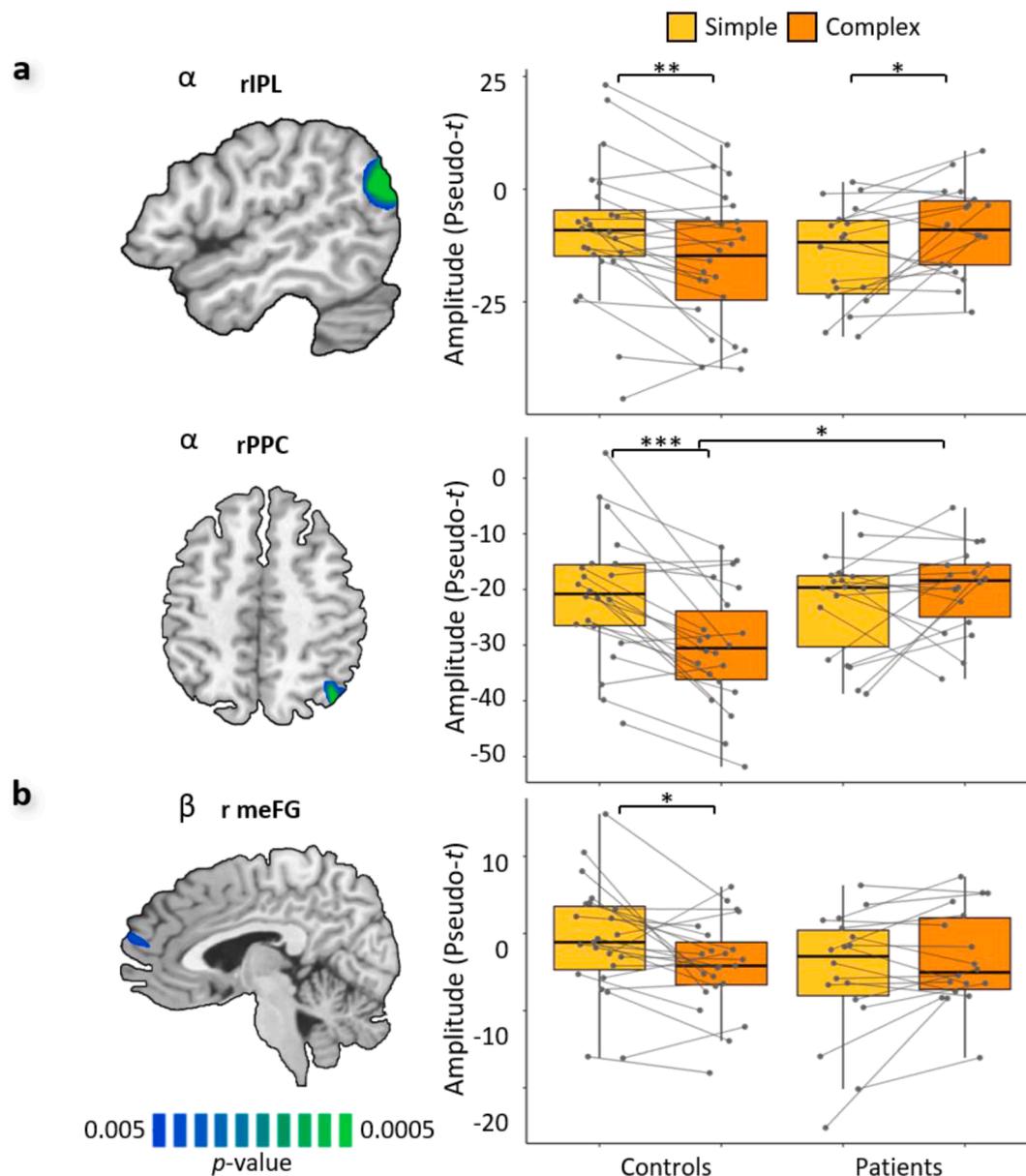


Fig. 5. Interactions between group and movement complexity on alpha and beta neural oscillatory responses. Statistical maps of significant condition-by-group interactions for the alpha ERD response (a) in the right inferior parietal lobule (rIPL; top row) and right posterior parietal cortex (rPPC; middle row), and for the beta ERD response (b) in the right medial superior frontal gyrus (r meFG; bottom row) during the movement execution stage are to the left, with their corresponding p -values scale bar at the bottom. The box and whisker plots next to each map show the peak amplitude for each significant region (pseudo- t). The box and whisker plots include the individual data points, median (horizontal line), first and third quartile (box), and local minima and maxima (whiskers). The lines between the individual data points display within-subject effects. Initial outliers have been removed. (top row) Controls had significantly increased alpha ERD responses in the rIPL during complex sequences compared to simple, while patients showed the opposite trajectory. (middle row) Controls had significantly stronger alpha ERD responses in the rPPC during complex sequences than simple, while patients did not. There was a significant difference in only the complex condition between groups, where controls showed increased alpha ERD in rPPC than patients. (bottom row) Controls had significantly stronger beta ERD during complex sequences compared to the simple, while patients showed no difference. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$.

be interpreted with caution and future studies should empirically test whether MEG beamformer maps are susceptible to the same issues with cluster defining thresholds given their distinct spatial smoothness. Despite these limitations, these findings provide clear neural and behavioral evidence that patients with PD exhibit altered neural oscillations during the performance of complex motor sequences. More broadly, our study was the first to characterize the multispectral oscillatory dynamics serving the performance of simple and complex sequences in patients with PD. These data provide critical new insight into the pathophysiology of PD, especially in the context of the cortical oscillations underlying impaired motor function.

CRediT authorship contribution statement

Marie C. McCusker: Formal analysis, Visualization, Writing – original draft. **Alex I. Wiesman:** Funding acquisition, Supervision, Visualization, Writing – review & editing. **Rachel K. Spooner:** Visualization, Writing – review & editing. **Pamela M. Santamaria:** Investigation. **Jennifer McKune:** Investigation. **Elizabeth Heinrichs-Graham:** Conceptualization, Investigation, Supervision, Writing – review & editing. **Tony W. Wilson:** Conceptualization, Funding acquisition, Investigation, Supervision, Visualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author, Dr. Elizabeth Heinrichs-Graham, upon reasonable request.

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