Investigating the brain mechanisms of externally cued sit-to-stand movement in Parkinson's disease

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ABSTRACT

Background: One of the more challenging daily-life actions for a patient with Parkinson's disease is standing from a sitting position. Parkinson's patients are known to have difficulty with self-initiated movements and they benefit from external cues. However, brain processes underlying external cueing as an aid are still unknown. With mobile EEG, this can now be investigated in dynamic sit-to-stand movements.

Objective: To identify cortical correlates of the mechanisms underlying auditory cued sit-to-stand movement in Parkinson's disease.

Methods: 22 Parkinson's disease patients and 24 neurotypical participants performed self-initiated and externally cued sit-to-stand movements while cortical activity was recorded through 32-channel mobile EEG.

Results: Overall impaired integration of sensory and motor information can be seen in the Parkinson's disease patients exhibiting less modulation in the theta band during movement compared to neurotypical controls. How Parkinson's patients utilise external cueing of the sit-to-stand movements can be seen in larger high beta power over sensorimotor brain areas compared to neurotypical controls, signalling sensory integration to support the maintenance of the motor output. This appears to involve the allocation of cognitive resources to update the motor plan, reflected in frontal theta power increases in the Parkinson's patients when cued.

Conclusion: These findings provide the first neural evidence for why and how cueing improves motor function in sit-to-stand movement in Parkinson's disease. The Parkinson's patients' neural correlates indicate that cueing induces a greater activation of motor cortical areas supporting maintenance of a more stable motor output, but involves the allocation of cognitive resources to update the motor plan.

Introduction

Parkinson's disease is a degenerative disorder originating from the loss of dopaminergic projections in the substantia nigra and is characterised by both motor and non-motor symptoms [1,2]. In addition, a hallmark of Parkinson's disease is the presence of deficits in the performance of automatic behaviour[3,4]. Indeed, a large body of evidence has shown that Parkinson's disease patients have difficulties in performing internally guided movements (i.e., akinesia), and present a greater reliance on goal directed motor strategies[3-5].

The difficulty that Parkison's patients experience in initiating voluntary movements is thought to emerge from the disruption of dopaminergic connections in the basal ganglia, which underlie the control of habitual motor behaviour[3,6]. Commonly, motor symptoms of Parkinson's disease can be alleviated by the administration of dopaminergic medications, or by Deep Brain Stimulation (DBS) surgery. However, it has also been shown that pharmacological treatments are not always effective in restoring motor deficits of Parkinson's disease and may have adverse effects[7-9]. Therefore, other compensatory methods are used in the rehabilitation of Parkinson's disease to ameliorate motor dysfunctions, such as external cueing in support of goal-directed motor processes[10-14].

In clinical practice, external cueing is a strategy frequently used to prompt the generation and the execution of motor plans[6,15]. The beneficial effects of cueing on Parkinson's disease symptoms are well documented[16], with a large body of evidence demonstrating that visual, auditory and tactile cues improve motor performance and learning[12,17,18]. For example, the use of auditory and visual cues improve the speed of reaching movements towards an object[19,20], the amplitude of handwriting[21], language and semantic processing[22,23]. Similarly, external cueing has been shown to be effective in improving gait patterns[24], balance[25], gait speed, cadence and the regulation of step and stride length[11,20,26].

However, literature also suggests that not all patients benefit from cueing. The differential effect of cueing may depend on the symptomatology exhibited by the patients[16,27]. Additionally, several studies report that auditory and visual cues might impact different aspects of rehabilitation in Parkinson's disease[28-30]. For example, auditory cues can improve cadence, visual cues have a

more direct impact on stride length and gait initiation[28,30]. Although these heterogeneous findings suggest that cueing can have a positive effect in improving motor performance in Parkinson's disease, the mechanisms and targeted cognitive and motor processes underlying cueing remain poorly understood.

The sit-to-stand movement has been identified as one of the most challenging movements for Parkinon's disease patients[31,32], and has been demonstrated to be related to the risk of falls and hospitalisation[33] (for a review see[34]). Several investigations have found that both auditory and visual cued training are effective in restoring dynamic stability of Parkinson's disease patients in the sit-to-stand movement[31,35]. Despite the successful use of sit-to-stand training in rehabilitation, to the best of our knowledge, there is no research into the neural correlates of the sit-to-stand movement in cued and uncued conditions in Parkinson's disease. A number of neuroscientific studies have employed different techniques to examine cueing in Parkinson's disease, such as fMRI and deep brain recording during finger tapping movements[6,36], or functional near-infrared spectroscopy (fNRIS)[37] and electroencephalography (EEG) during walking[38-40]. Among these techniques, EEG allows the recording of brain responses to external stimuli with excellent temporal resolution, while mobile EEG[41,42] offers the advantage of recording brain activity during whole body naturalistic movements. We have previously developed the methodology to record the brain response to external events during dynamic movements such as stepping over obstacles[43], and demonstrated its utility in Parkinson's disease[44].

Notably, several studies have investigated EEG signals associated with the response to cueing in Parkinson's disease during gait[38,39], finding that external cueing facilitates the execution of movements by activating motor processes reflected in brain oscillations, particularly in the beta frequency range (13-35 Hz). Tosserams et al.[38] found that external auditory cueing during gait induced a stronger decrease in the beta frequency band over sensorimotor areas compared to uncued walking in Parkinson's disease, indicating that cueing facilitates the activation of motor processes. Likewise, Stuart et al.[39] reported an increase in high beta power over occipital areas during cued walking compared to uncued walking in Parkinson's disease, suggesting that cues induced the increase of resources allocated to visual processing. Additionally, a study of healthy participants also suggested that external cueing might modulate signals associated with cognitive control. Zhou et al.[45] reported that visual cueing during gait initiation modulated signals

associated with cognitive control processes over frontal areas in healthy participants. It is, furthermore, widely accepted that oscillations in the low frequency ranges over frontal brain areas, namely theta oscillations (4-7 Hz), index of top-down cognitive control system[46,47] and are associated with the updating of information to support behaviour[44,45,48,49].

Taken together, previous findings suggest that external cueing triggers the activation of motor and cognitive processes, which are reflected in the modulation of cortical signals such as beta and theta oscillations. The aim of the present study was to explore the neural correlates of auditory-cued sit-to-stand movements in Parkinson's disease patients and healthy older adults. We recorded cortical activity using a 32-channel mobile EEG system while participants performed self-initiated and externally cued sit-to-stand movements. In particular, we targeted brain oscillations associated with sensorimotor and cognitive control processes, namely beta and theta frequency bands. As suggested by previous literature, we hypothesised that auditory cueing during the sit-to-stand movement might alter brain activity in Parkinson's disease patients compared to when they voluntarily initiate the movement, reflecting the effect that cueing has on both motor and cognitive processing.

Patients and Methods

Twenty-two PD participants were recruited from the Fresco Parkinson Center of Villa Margherita, Santo Stefano Rehabilitation (Vicenza, Italy) between May 2021 and August 2021. PD diagnoses were confirmed by clinicians and neurologists (D.V., M.P.) according to the Parkinson's Disease Society Brain Bank clinical diagnostic criteria. An aged matched group of 24 neurotypical controls (NT) took part in the experiment on a voluntary basis. There were no statistically significant differences between the PD and the NT group in terms of age ($t(40) = .833$, $p = .410$) or sex ($t(40) = 1.541$, $p = .131$). The scores of the Mini Mental State Examination (MMSE)[50] were used as an index of global cognitive functioning in both groups, using a cut-off of 24[51]. The clinical evaluation of PD participants was collected from the patients' existing medical records and were performed by clinicians and physiotherapists of the clinical institution. The onset of the disease was defined as the date of the onset of symptoms and disease severity was assessed through the Hoehn and Yahr scale (H&Y)[52]. Motor performance was determined using the United Parkinson's Disease Rating Scale (UPDRS)[53] part II (activities of daily living) and III

(motor evaluation). PD patients were tested in the ON-phase of the medication state (testing was controlled to be around 1 hour after the last assumption of medication). Table 1 summaries the demographic information for the PD patients.

TABLE 1. Participants demographics

	PD	NT
n	22	24
Age (years)	72.45 ± 8.27	68.5 ± 5.94
Sex	M = 15; F = 7	M = 12; F = 12
Education (years)	11.36 ± 4	14.08 ± 4.96
MMSE[1]	26.63 ± 6.26	29.08 ± 1.41
Disease duration	16.8 ± 8.8	-
H&Y[2]	3 ± 0.6	-
UPDRS II[3]	18.77 ± 8.42	-
UPDRS III3	31.36 ± 12.92	-
LEDD[4]	750 ± 416	-

[1] Mini Mental State Examination[50]; [2] Hoehn and Yahr scale[52]; [3] United Parkinson's Disease Rating Scale[53] ; [4] Levodopa Equivalent Daily Dose[54] at the time of testing.

All participants performed a total of 80 trials divided in two conditions (see Figure 1 for an illustration of the task). Each condition included a total of 40 trials divided into 2 experimental blocks (20 trials each). The order of conditions and blocks were randomised across participants. In the self-initiated condition (SELF), participants were asked to spontaneously stand from a sitting position using the support of armrests if needed. After reaching the standing position, they were instructed to stand still for 2 seconds, return to the sitting position and wait a few seconds before performing another trial. In the externally cued condition (CUED), participants were asked to stand from a sitting position as soon as possible after hearing an auditory cue (a tone presented for 300 ms), using the support of armrests if needed. After reaching the standing position, they were instructed to wait while standing still for 2 seconds, then to return to the sitting position and wait for the next auditory cue to repeat the movement. The cue was delivered by a trigger box connected to the EEG amplifier. The tone was delivered by the experimenter at a random interval (between 8 and 10 seconds) while the participants were sitting on the chair. For each trial, the timing of

movement ONSET was identified as the first time that participants pressed their heel on the ground (i.e., the first timestamp of pressure on the ground), recorded by the foot switches placed in their shoes, regardless of the side.

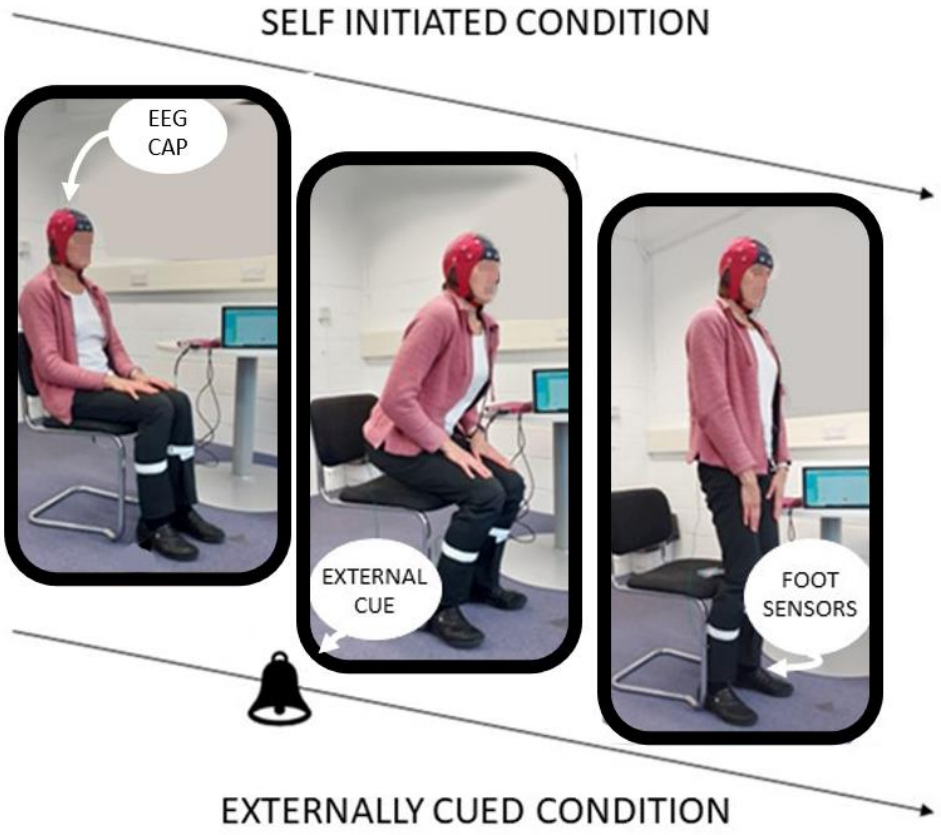

Figure 1. Representation of the experimental conditions.

Behavioural recording and analysis

The time to execute and complete the movement (Execution Time) was recorded in both conditions, and was defined as the time between ONSET (as recorded by the foot switches) and END of the movement (i.e., when participants reached a standing position, manually defined by the experimenter). The time to plan the movement (Planning Time) could only be recorded in the CUED condition and was defined as the time between the CUE and the ONSET of the movement.

EEG acquisition and pre-processing

EEG data was recorded from 32 Ag/AgCl electrodes connected to a portable amplifier (ANT-neuro, Enschede, The Netherlands). Technical details are provided in the Supplementary Materials.

For the response-locked ERSP analysis, EEG data were segmented around the ONSET of the movement in both conditions (-3000 ms to 2000 ms). ERSPs were obtained by computing the mean difference between single-trial log spectrograms for each channel, for each participant, relative to the mean baseline spectrum from -1500 ms before to 1500 ms after movement onset. The frequency bands of interest, i.e. beta and theta, were defined by visually inspecting the single channel spectrograms across groups and conditions. Single channel plots showed prominent changes in the range of 24-35 Hz (high beta), 13-23 Hz (low beta) and 4-7 Hz (theta), which were investigated separately. Figures 3 and 4 illustrate two representative channels, Fz and Cz respectively.

In addition, we performed a cue-locked ERSP analysis focusing on the theta frequency band (4-7 Hz). The EEG data were segmented from 1000 ms before to 1000 ms after cue onset. ERSPs were obtained by computing the mean difference between single-trial log spectrograms for each channel, for each participant, relative to the mean baseline spectrum during the last 500 ms preceding cue onset.

Statistical analysis

For behavioural analysis, the difference between groups in Execution Time and Planning Time were analysed using a 2x2x2 mixed ANOVA (followed by independent sample post hoc sample t-tests) with Condition (CUED vs. SELF) as a within-subjects factor and Group (PD vs. NT) as a between-subjects factor. For the EEG analysis, single channel spectrograms and scalp maps topographies were visually inspected to identify prominent changes across participants. For the response locked analysis we investigated low and high beta power over a sensorimotor ROI, including central and parietal brain electrodes (channels C3, C4, CP1, CP2, CP5, CP6 and Cz). For the theta frequency band, by contrast, we defined two regions of interest (ROIs): frontal (channels FC1, FC2, Fz and Cz) and parietal (channels P3, P4, CP1, CP2 and Pz). To assess power modulation over time, the time window of interest was divided into consecutive 500 ms Time Bins (T1: -1500 ms to 1000 ms; T2: -1000 ms to -500 ms; T3: -500 ms to 0 ms; T4: 0 ms to 500 ms;

T5: 500 ms to 1000 ms; T6: 1000 ms to 1500 ms). To examine power modulations across groups separate mixed ANOVAs were performed, using within-subjects factors of Condition (SELF vs. CUED), Time (T1; T2; T3; T4; T5; T6) and ROIs (frontal vs. parietal for theta) and a between-subjects factor of Group (PD vs. NT). For the cue-locked analysis, theta power was computed by pooling the mean activity of frontal channels (FC1, FC2, Fz, Cz) in three different time bins after the onset of the CUE (0 to 250 ms; 250 ms to 500 ms; 500 ms to 750 ms). To examine power modulations across groups a mixed ANOVA was performed, using within-subjects factor of Time and a between-subjects factor of Group (PD vs NT).

All analyses were carried out, using SPSS (IBM SPSS Statistics for Windows, Version 21.0). The significance level for the statistical analysis was set at $p < .05$. Where the sphericity assumption was violated, the Greenhouse-Geisser method was used to correct the degrees of freedom. Post-hoc independent and paired samples *t*-tests were adjusted for multiple comparisons using Bonferroni correction.

Results

The PD group was slower than the NT group in going from sitting to standing in both conditions, due to their slower movement time rather than movement initiation (Figure 2). The mixed ANOVA on Execution Time showed a significant main effect of Group [$F(1, 40) = 26.848$, $p < .001$, $\eta_p^2 = .003$], with PD participants slower to complete the sit-to-stand movement compared to NT regardless of condition. By contrast, an independent sample t-test on (Planning Time did not reveal a difference ($p = .247$), indicating that PD participants were not significantly slower than the NT group in the time taken to initiate their movement (mean PD = 856.8 ms ±315.88 ms; mean NT = 755.4ms ± 235 ms).

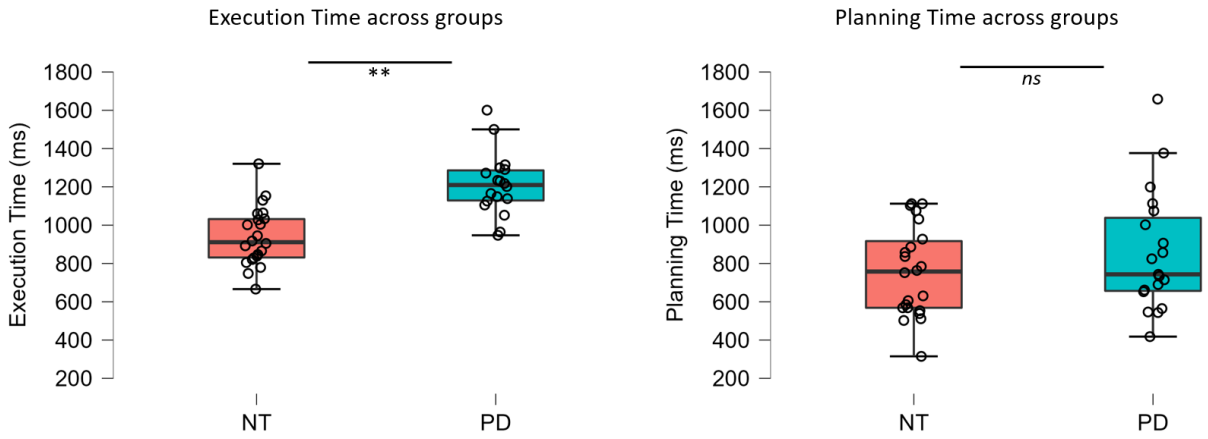

Figure 2. Left: Box plot showing the mean movement time (ms) taken to complete the movement averaged across the two conditions for each of the groups. Error bars indicate the SD for each group. The asterisks (**) indicate a significant difference at $p < .001$ between groups, showing that PD participants were slower compared to NT participants. **Right:** Box plot showing movement planning based on the mean time between the cue and initiation of the movement for each of the two groups. Error bars indicate the SD for each group.

Response-locked analysis

Low Beta. The mixed ANOVA revealed a main effect of Time [$F(1, 1.5) = 8.522$, $p < .001$, $\eta_p^2 = .122$], showing a stronger relative increase of low beta power in time window 4, i.e., just after the participants pressed their heel to the ground [T4 vs. T2: $t(39) = 3.423$, $p < .011$; T4 vs. T3: $t(39) = 3.107$, $p < .032$; T4 vs. T5: $t(39) = 4.753$, $p < .001$; T4 vs. T6: $t(39) = 4.916$, $p < .001$]. Moreover, there was a significant 2-way interaction between Condition and Time [$F(1, 2.75) = 5.987$, $p < .001$, $\eta_p^2 = .024$]; post hoc t-tests revealed a stronger relative increase of low beta power in the CUED condition compared to SELF in T1 [$t(39) = 2.640$, $p = .050$]. There were no other significant main effects or interactions ($p > .05$).

High Beta. The analysis of the EEG data suggested that the external cueing condition modulated cortical activity in the high beta frequency band. In particular, as shown in Figure 3, external cueing induced prominent changes in the high beta range in PD, compared to the self initiated condition but also compared to the NT group. The mixed ANOVA revealed a main effect of Time [$F(1, 1.70) = 30.365$, $p < .001$, $\eta_p^2 = .319$], with a stronger relative increase of high beta power occurring just before (T3) and after (T4) the participants pressed their heel to the ground [T3 vs T1: $t(39) = 4.065$, $p < .001$; T3 vs T2: $t(39) = 4.234$, $p < .001$; T3 vs T4: $t(39) = 6.288$, $p < .001$; T4 vs T1: $t(39) =$

10.353, p < .001; T4 vs T2: t(39) = 10.523, p < .001; T4 vs T5: t(39) = 7.258, p < .001; T4 vs T6: t(39) = 8.668, p < .001].

There was a significant 2-way interaction between Condition and Group [F(1, 40) = 11.107, p = .002, η_p^2 = .006, see Figure 3]. Post hoc paired sample t-tests revealed a stronger relative increase of high beta power for the PD group compared to the NT group in the CUED condition [t(39) = 2.895, p =.031], but no difference between groups in the SELF condition (p = 0.772). Importantly, the between-conditions modulation of high beta power followed opposite patterns in the two groups (Figure 3). Therefore, the interaction between Condition and Group was further investigated by looking separately at each group with post hoc paired sample t-tests. In the NT group a stronger relative increase of high beta power occurred in the SELF condition compared to the CUED condition [t(22) = 2.252, p = .035]. Conversely, in the PD group, a significant main effect of Condition [t(18) = 2.666, p = .015] showed that a stronger relative increase of high beta power occurred in the CUED condition compared to the SELF condition.

As revealed by the ANOVA, there was furthermore a significant 3-way interaction between Condition, Time and Group [F(1, 2.08) = 4.413, p = .014, η_p^2 = .014], which was further investigated by looking separately at the interactions between Condition and Group in each Time. A significant interaction between Condition and Group, showed that a stronger increase of high beta power in the PD group compared to NC, was most pronounced in the CUED condition at time bin(s) T3 [F(1, 39) = 5.032, p = .027, η_p^2 = .041; t(39) = 2.090, p = .043] and T4 [F(1, 39) = 6.436, p = .015, η_p^2 = .029; t(39) = 2.321, p = .025], as can also be seen in Figure 3. This shows that the relative increase in high beta in the cued condition is particularly pronounced in the Parkinson's patients when they pressed their heel to the ground and during the movement, when they were reaching the standing position.

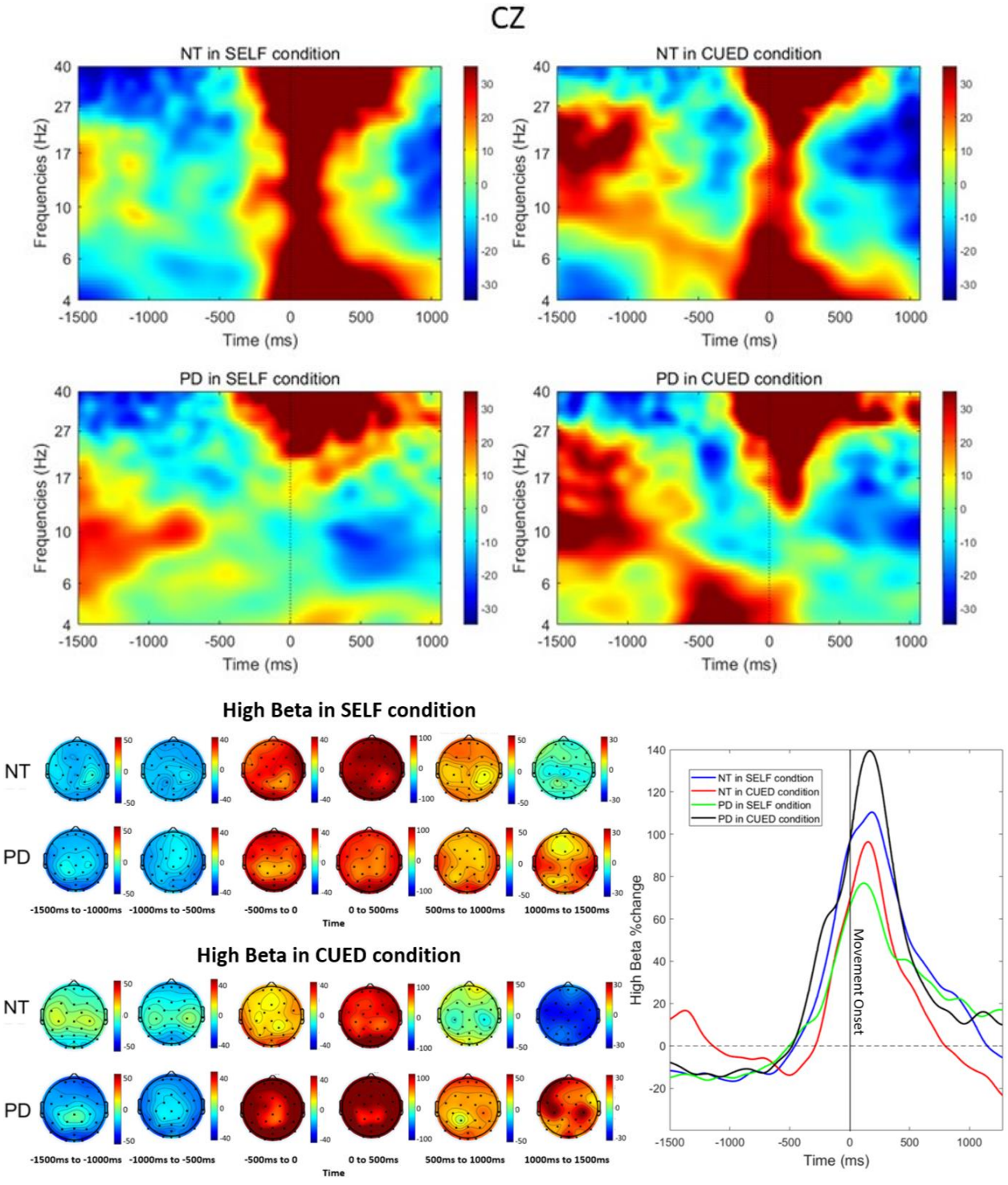

Figure 3. Top: Spectrograms of a representative central channel (Cz) per condition and group. Dashed lines (time 0) indicate the onset of the movement. **Bottom left:** Scalp maps of high beta activity per group and conditions in the different time bins. **Bottom right:** Graph of % change in high beta activity per condition in the two groups over time.

Theta. The mixed ANOVA revealed a main effect of Condition [$F(1, 39) = 10.083$, $p = .003$, $\eta_p^2 = .001$] reflecting higher theta power e in the CUED condition compared to the SELF condition. A significant 2-way interaction between Condition and Time [$F(1, 3.21) = 4.687$, $p = .003$, $\eta_p^2 = .015$] revealed a larger increase of relative theta power in the CUED condition compared to the SELF condition just before the onset of the movement [T3: $t(40) = 3.604$, $p < .018$]. A main effect of Time [$F(1, 40) = 8.059$, $p < .001$, $\eta_p^2 = .112$] indicated a stronger relative increase of theta power when participants started to stand from the sitting position, corresponding to the first press of the heel to the ground, compared to the other time bins [T4 vs T1: $t(40) = 5.314$, $p < .001$; T4 vs T2: $t(40) = 4.609$, $p < .001$; T4 vs T3: $t(40) = 3.610$, $p = .005$; T4 vs T5: $t(40) = 2.999$, $p = .034$; T4 vs T6: $t(40) = 5.297$, $p < .001$]. Additionally, theta power increase was prominent around the time of the movement onset, but was attenuated in the PD group compared to the NT group (Figure 4). Indeed, the significant 2-way interaction between Time and Group [$F(1, 40) = 6.587$, $p = .003$, $\eta_p^2 = .092$, see Figure 4] showed a stronger relative increase of theta power in the NT group compared to the PD group when participants started to stand (T4), as shown by a post hoc independent samples t-tests [$t(40) = 3.709$, $p < .017$], with no reliable differences in the other Time Bins ($p > .05$). The mixed ANOVA did not indicate any other significant main effects or interactions ($p > .05$).

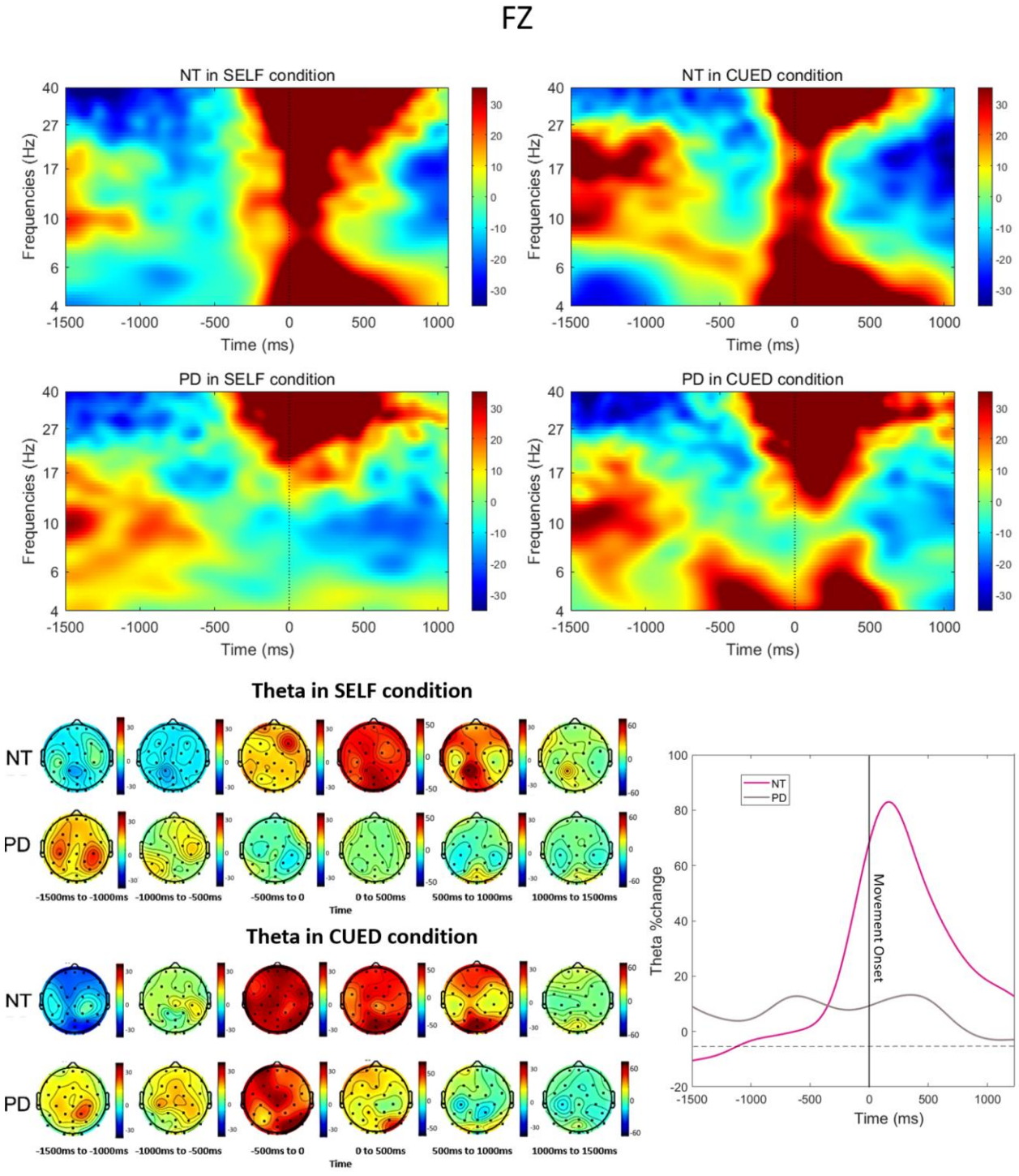

Figure 4. Top: Spectrograms of a representative frontal channel (Fz) per condition and per group. Dashed lines (time 0) indicate the onset of the movement. **Bottom left:** Scalp maps of theta activity per group and condition in the different time bins. **Bottom right:** Line graph of theta activity averaged across all analysed electrodes and across conditions for each of the two groups.

Cue locked analysis

Theta. Separate analysis was performed for cue-locked brain responses (i.e. in the CUED condition only), examining the factors of Time and Group. The mixed ANOVA revealed a 2-way interaction between Time and Group [F(1, 1.3) = 5.968, p < .019, η_p^2 = .053] as the relative increase of theta spectral power was enlarged in the PD group compared to the NT group immediately after the cue in the CUED condition (0 to 250 ms = t(40) = 3.059, p = .004, see Figure 5) but no difference in the other Time Bins (p > .05). There were no other effects.

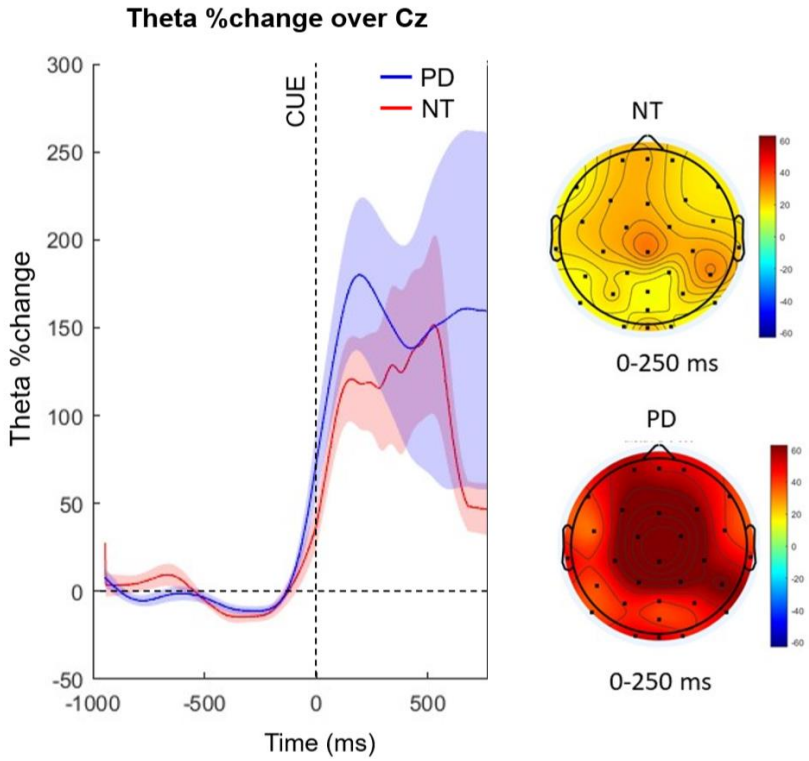

Figure 5. Left: Cue-locked averaged theta activity over a representative central channel (Cz) in the two groups in the CUED condition. Dashed lines (time 0) indicate the onset of the cue. As we can see, PD participants (blue line) presented an enlarged theta response to the cue compared to NT participants (red line). **Right:** Scalp maps of theta activity in NT (top topography) and PD group (bottom topography) in the time bin immediately after the cue (0 to 250 ms).

Discussion

In the present study, we investigated the neural response of Parkinson's patients making self initiated or externally cued sit-to-stand movements, in comparison to age-matched neurotypical

controls. The results revealed that external cueing induced a larger increase in the high beta (24-35 Hz) frequency band over sensorimotor brain locations, compared to self initiated movements in Parkinson's disease patients only. This specific response to cueing seen in Parkinson's patients inducing greater activation of motor cortical areas, we infer, shows how cueing supports the maintenance of a more stable motor output, compared to self initiated movements in Parkinson's disease. Moreover, the processing of the auditory cue was associated with a larger response in the theta (4-7 Hz) frequency band in the Parkinson's disease group, compared to healthy neurotypical participants, suggesting the allocation of additional cognitive resources dedicated to movement initiation. This neural evidence provides new insights for the understanding of the effect of external cueing strategies in Parkinson's patients, who generally struggle with initiating sit-to-stand movements. Below we will discuss the analysis of the brain response to the cue and during movement.

The analysis of brain activity during the sit-to-stand movement revealed that oscillations in the high beta range over sensorimotor EEG electrodes were distinctly differently modulated in Parkinson's disease compared to age-matched controls. The Parkinson's patients exhibited enlarged high beta power, specifically in the externally cued sit-to-stand compared to when the movement was self initiated. Indeed, while the Parkinson's patients exhibited a similar increase in beta power to neurotypical participants when the movement was self-initiated, the patients exhibited a larger increase when they performed the movement in response to the cue, compared to healthy individuals. This was evident in a dissociating pattern of modulation in the high beta range in the two groups of participants. Neurotypical participants showed more activity in high beta range when the movement was self-initiated compared to when it was externally triggered, whereas Parkinson's disease patients exhibited a larger increase of power in the high beta range in response to the auditory cue, compared to when they had to voluntarily initiate the movement. This finding suggests that cueing has a specific effect on sensorimotor brain processes during movement in Parkinson's disease patients, reflected in enlarged modulation of high beta oscillations.

Notably, Tan and colleagues[55] argue that beta power increases over sensorimotor areas might represent the interplay between both sensory processing and transfer of information, but also the estimation of uncertainty of feedforward models, in order to maintain the motor state. As sustained by a large body of computational works[56-58], motor behaviour relies on the estimation of the

mismatch between feedforward internal models and actual motor output, which are updated depending on the incoming sensory information. In addition, according to Tan et al.[55], the motor system weighs the confidence of the estimations, by increasing the reliance of the sensory feedback in situations of uncertainty. Within this framework, beta power increases over the sensorimotor cortex signal higher confidence in the feedforward estimation, promoting the updating and the maintenance of the motor plan[55]. Therefore, our results showing a larger beta power increase in Parkinson's disease patients when the movement was externally cued compared to when it was self initiated, suggests that cueing promotes the integration of sensory information[59-61] and the maintenance of the motor state, reducing the uncertainty on the feedforward estimation[55].

It is important to note that this account is supported also by evidence from animal research, which has shown that beta oscillations might be related to cue utilisation in behavioural output. Leventhal et al.[62] reported beta power increases both in the basal ganglia and in the cortex around the time of the rodent's movement onset in response to a go cue. Additionally, they investigated beta modulation in relation to stop cues, in order to differentiate between different behavioural outcomes in response to a cue. Similarly to the go cue, they observed an increase of beta power only for successful stop trials, but not during unsuccessful ones, suggesting that beta increase of power might be related to the actual utilisation of the cue in the generation of the behavioural response. Taken together, this evidence opens new routes to the investigations of how cueing supports motor behaviour in neurodegenerative disease. Our work represents the first attempt in the understanding of the cortical response of the brain to cueing in Parkinson's disease, which needs further investigations to promote the development of targeted strategies in rehabilitation settings.

Evidence for a specific brain response to external cueing in Parkinson's disease patients was further demonstrated through the cue-locked analysis, which revealed a larger frontal theta increase immediately after the onset of the cue in the patients group, compared to neurotypical participants. It is widely accepted that frontal theta oscillations provide an index of cognitive control mechanisms that play a key role in allocating cognitive resources and organising activities across cortical areas[46,63]. Mid-frontal theta activity is thought to be associated with processes underlying a top-down cross-modal multisensory control system[46,47]. In our previous works[43,44], we observed a prominent theta power increase when participants had to step over unexpected obstacles

while walking, providing supporting evidence for the involvement of theta oscillations in the continuous updating of information[48,49]. The present results indicate that Parkinson's disease patients recruited more cognitive resources compared to neurotypical participants when responding to the auditory cue. Viewed in this way, the present findings also provide further support for the idea that the most relevant benefit of external cueing in the rehabilitation of Parkinson's disease is to promote an effective allocation of cognitive resources during task performance[12,29].

Regardless of whether the movement was cued or not, the data furthermore demonstrated between group effects in the response locked analysis, revealing that Parkinson's disease patients exhibited attenuated modulation in the theta frequency range compared to neurotypical participants when they started to stand from the sitting position. Consistent with the hypothesised role of theta activity in allocating cognitive resources to the task at hand, this shows that Parkinson's disease patients have fewer cognitive resources available when initiating the movement and standing from a sitting position compared to neurotypical controls. The neural correlates of sit-to-stand movements have not previously been reported, but attenuation of theta rhythm in Parkinson's disease patients was previously found in motor tasks involving lower limbs, such as pedalling[64] or during obstacle avoidance[44]. Furthermore, the difference in theta modulation that we found was independent of electrode position, indicating that theta oscillations were similarly reduced in the Parkinson's disease group over both frontal and parietal brain areas, compared to neurotypical participants. Theta oscillations over the frontoparietal network have been suggested to support cognitive control functions through the integration of sensory and motor information[65,66]. Additionally, theta increase over the frontoparietal network has also been related to the assessment of relevant information preceding behavioural decisions[67,68]. Therefore, our results suggest that the reduction in theta power observed when Parkinson's disease patients started to stand from the sitting position, compared to healthy participants, most likely indicates general impaired integration of sensory and motor information to perform the movement[65,66], or difficulty in monitoring the action plan at the moment of behavioural decision[67,68].

Overall, the results of the present study showed that auditory cueing of the sit-to-stand movement in Parkinson's disease activates both motor and cognitive processes indexed by beta and theta oscillations. The neural marker of Parkinson's patients' response to the cue indexed by a specific pattern in high-beta, as well as the markers on cognitive resource allocation indexed by

theta, are important for potential innovation in the design and improvement of compensatory strategies used in rehabilitation of Parkinson's disease. For example, a possible development could be the application of external cueing in combination with neurofeedback based approach [69]. While this data provides new insight into the understanding of the beneficial effects of cueing, further investigations are needed in particular to examine the links between brain oscillations and behavioural responses. In the present study we did not employ sensitive behavioural indexes, which would be helpful to evaluate movements parameters, such as kinematic measurements. Additionally, it would also be relevant to assess and compare the cortical activity underlying different cueing modalities across different symptomatology of Parkinson's disease, in order to provide suggestions for the design of the most effective personalised approach for each patient. Lastly, but importantly, it is necessary to understand whether external cueing might be modulated by pharmacological medication. In the present study, Parkinson's disease patients were tested only after the administration of levodopa medication, nonetheless, the present data show a specific brain response to auditory cueing in the Parkinson's patients, even on a stable pharmacological regimen. Whilst further experiments targeting this issue are required, the present findings suggest that external cueing and levodopa assumption might have independent effects on cognitive and cortical processes in Parkinson's disease.

Conclusion

To the best of our knowledge, this is the first attempt to investigate the cortical correlates of auditory cued sit-to-stand movement in Parkinson's disease patients. The results suggest that cueing modulates motor and cognitive related brain activity in Parkinson's disease patients, reflected in beta and theta oscillations respectively. Increase of power in the beta frequency band support the maintenance of the motor state, most likely reflecting both the greater effort in sensory integration and more confidence in the estimation of motor output, whereas enlarged theta power immediately after the cue in Parkinson's disease patients signals the involvement of cognitive processes related to the updating of motor plans. These neural markers of externally cued daily life activities such as the sit-to-stand movement, might be used as targets to improve rehabilitation strategies, combining for example cueing with neurofeedback.

Data Sharing

The anonymized data of the present study are available upon request from the corresponding author (MM).

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Author Roles

MM, MI, DK, DV, MP, EP contributed to the design and conception of the project: MM contributed to the organisation and the execution of the project, statistical analysis of the data, wrote the first draft and reviewed the final version of the manuscript; MM, DK, SL contributed to the analysis of the data; MM, MI, DK, SL, MGE, DID contributed to the review and the interpretation of the results; MM, MI, DK, SL, DV, MP, EP, MGE, DID reviewed and edited the final version of the manuscript.

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Supplementary Materials

1. Technical details of EEG acquisition and pre-processing

Electrodes were positioned according to the International 10-20 system (FP1, FPz, FP2, F7, F3, Fz, F4, F8, FC5, FC1, FC2, FC6, M1, T7, C3, Cz, C4, T8, M2, CP5, CP1, CP2, CP6, P7, P3, Pz,

P4, P8, POz, O1, Oz, O2) with AFz electrode used as ground and CPz electrode used as reference. The electrode impedances were reduced below 5 kΩ before recording. During recording, EEG data were sampled at 500 Hz and bandpass filtered at 0.01-250 Hz. EEG data analyses were performed using custom scripts written in MATLAB 2019a (The MathWorks) incorporating EEGLAB toolbox[1] (Delorme and Makeig, 2004). Data from the mastoid channels (M1 and M2) were removed from the analysis, and all remaining EEG data was filtered using a 0.1 Hz to 40 Hz bandpass filter. EEG channels with prominent artifacts were automatically selected (kurtosis > 5 SDs) and interpolated, and all channels were then re-referenced to the average of all electrodes. Data were down sampled to 250 Hz and an extended infomax Independent Component Analysis (ICA)[2], Makeig et al., 1996) was performed to identify and remove non-brain signals. Brain-related-ICs were identified using the IClabel plugin[3] (Pion-Tonachini et al., 2019). Components exceeding a 90% probability of being eye, muscle, heart, line noise, and channel noise were rejected. Only brain ICs with dipoles located inside the head and a residual variance lower than 15% were kept, resulting in 21% of components retained per condition for the subsequent analysis. After the noisy components' rejection, two distinct segmentations and two different analyses of Event Related Spectral Perturbations (ERSPs) were performed.

2. Supplementary analysis: Targeted analysis on response locked theta activity

Although the mixed ANOVA did not show any broad statistical differences in theta modulation across conditions in the PD group, visual examination of the spectrogram of the FZ channel displayed in Figure 4 suggests that theta activity might be differently modulated across conditions in the PD group. In particular, the spectrograms suggest that the main difference might only emerge at a specific time, i.e., around the onset of the movement. To examine this effect, we conducted two additional targeted repeated measure ANOVAs on theta activity separately for each group, including as within factors the condition (SELF vs CUED), midline channels (FZ, CZ, PZ) and the time bins around the movements (from -500 ms to 0 and 0 to 500 ms).

In the NT group, a main effect of Time [F(1, 21) = 5.481, p = .029, η_p^2 = .113] showed that a stronger increase of relative theta power occurred just after time 0, when the movement had started. Moreover, a two-way interaction between Time and Electrodes [F(1, 21) = 4.001, p = .029, η_p^2 =

.007] showed a difference in theta modulation across electrodes, as after time 0 there was a stronger increase of theta power in PZ compared to CZ (t(21) = 3.516, p = .011, see right panel of Figure 5). In the PD group, a main effect of Condition [F(1, 18) = 4.554, p = .047, η_p^2 = .062] revealed a stronger increase of theta power in the CUED conduction compared to the SELF (displayed in the left panel of Figure 5).

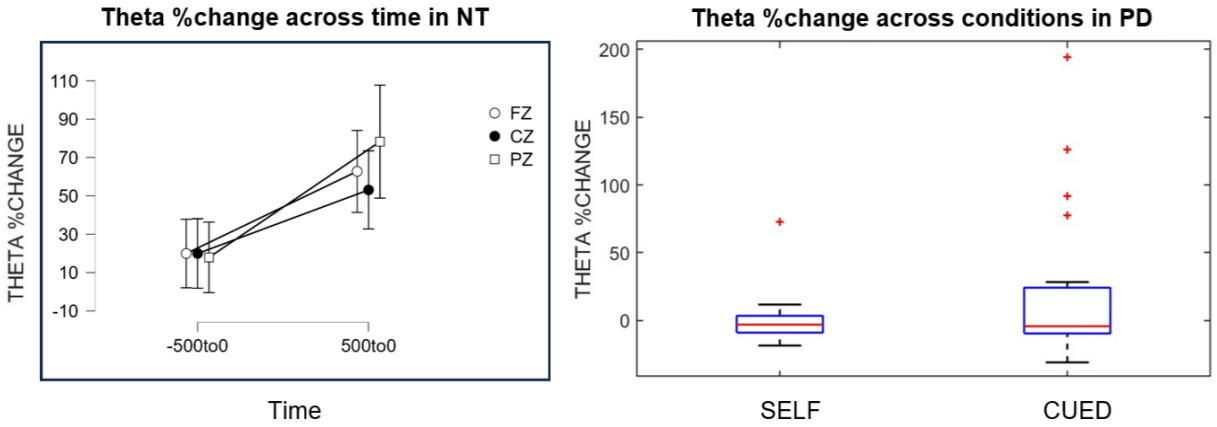

Figure 5. Left: Line graph of theta activity averaged across electrodes and time for the NT group. Vertical lines indicate the standard error**. Right:** Boxplot of theta activity averaged across conditions in the PD group.

Supplementary Materials References

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