Title page

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

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Neural markers of cueing in Parkinson's disease

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ABSTRACT

Background: One of the more challenging daily-life actions for Parkinson's disease patients is starting to stand from a sitting position. Parkinson's patients are known to have difficulty with self-initiated movements and benefit from external cues. However, the brain processes underlying external cueing as an aid remain unknown. The advent of mobile EEG now enables the investigation of these processes 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 healthy age-matched 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 patients exhibiting less modulation in the theta band during movement compared to healthy age-matched controls. How Parkinson's patients utilize external cueing of sit-to-stand movements can be seen in larger high beta power over sensorimotor brain areas compared to healthy controls, signaling sensory integration supporting the maintenance of motor output. This appears to require changes in cognitive processing to update the motor plan, reflected in frontal theta power increases in 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 greater activation of motor cortical areas supporting the maintenance of a more stable motor output, but involves the use of cognitive resources to update the motor plan.

Key words: movement cueing; Parkinson's disease; EEG; activities of daily living; neuro-rehabilitation

Introduction

Parkinson's disease is a degenerative disorder originating from the loss of dopaminergic projections in the substantia nigra and is characterized by both motor and non-motor symptoms [1,2]. Parkinson's disease is characterized by deficits in automatic behavior[3,4], difficulties in performing internally guided movements (i.e., akinesia), and a greater reliance on goal directed motor strategies[3-5].

The difficulty that Parkison's patients experience in initiating voluntary movements is thought to arise from the disruption of dopaminergic connections in the basal ganglia[3,6]. Commonly, motor symptoms of Parkinson's disease can be alleviated by the administration of dopaminergic medications, or through deep brain stimulation surgery. However, it has also been shown that pharmacological treatments are not always effective and may even have adverse effects[7-9]. Therefore, other compensatory methods are employed in the rehabilitation of Parkinson's disease to ameliorate motor dysfunctions, such as external cueing to support goal-directed behavior[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, similarly to pharmacological treatment, the literature also suggests that not all patients benefit from cueing. Therefore, to better understand the largely positive but equally heterogeneous effects of cueing in improving motor performance in Parkinson's disease, we need to examine the brain mechanisms underlying cueing. Such understanding could explain, for example, why Parkinson's patients with certain symptomatology may benefit less [16,27], or why auditory and visual cues might impact different aspects of rehabilitation in Parkinson's disease[28-30]. Currently, the mechanisms and targeted cognitive and motor processes underlying cueing remain poorly understood.

The sit-to-stand movement has been identified as a challenging movement for Parkinson's disease patients[31,32], and is related to the high risk of falls and hospitalization[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];

however, to the best of our knowledge, there is no research into the neural correlates of externally cued sit-to-stand movements in Parkinson's disease. A number of neurophysiological studies have employed different techniques to examine neural markers of 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, mobile EEG[41,42] allows the recording of brain activity during whole body naturalistic movements with excellent temporal resolution. We have previously developed the methodology to record brain responses 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, 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). For example, Tosserams et al.[38] found that external auditory cueing during gait induced a stronger decrease in beta power over sensorimotor areas compared to uncued walking in Parkinson's disease, indicating that cueing facilitates the activation of motor processes. Furthermore, power increases in the theta low frequency range (4-7 Hz), regarded as indices of top-down cognitive control[45,46] and updating of information to support behavior[47,48] are significantly attenuated in Parkinsons' disease[49], indicating the presence of cognitive dysfunction. Indeed, a significant reduction in the modulation of theta frequency bands, has been observed during the performance cognitive control tasks in Parkinson's disease patients with cognitive

impairments and dementia, compared to controls and with Parkinson's disease without cognitive deficits[50].

Taken together, previous findings suggest that external cueing triggers the activation of motor and cognitive processes, reflected in the modulation of cortical signals such as beta and theta oscillations. Therefore, the present study aims to explore the neural correlates of auditory-cued sit-to-stand movements in Parkinson's disease patients relative to 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. Based on the previous literature, we hypothesized that auditory cueing during 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.

Methods

Participants

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. A total of 22 PD participants and an age-matched

group of 24 healthy age-matched controls (HC) participated on a voluntary basis. There were no statistically significant differences between the PD and the HC group in terms of age ($t(44) = 1.481$, $p = .146$) or sex ($X^2(1) = 1.565$, $p = .211$). The scores of the Mini Mental State Examination (MMSE)[51] were used as an index of global cognitive functioning in both groups, using a cut-off of 24[52]. There were no statistically significant differences between the PD and the HC group in the MMSE scores ($t(44) = 1.585$, $p = .120$). 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)[53]. Motor performance of PD patients was determined using the United Parkinson's Disease Rating Scale (UPDRS)[54] part II (activities of daily living) and III (motor evaluation) while in the ON-phase of medication. PD patients were tested in the ON-phase of the medication state (around 1 hour after the last assumption of medication). Detailed clinical data are presented in Table 1 in the Supplementary Material.

Study Design

All participants performed a total of 80 trials divided equally in two conditions (Figure 1). Each condition was divided into 2 experimental blocks (20 trials each). The order of conditions and blocks were counterbalanced across participants. In the self-initiated condition (SELF), participants were asked to spontaneously stand from a sitting position, whereas in the externally cued condition (CUED) they were asked to stand immediately after hearing a 300ms auditory cue, delivered by the experiment at an 8-10 seconds random interval. 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 (SELF condition) or to wait until the next auditory cue (CUED condition). In both conditions the participants were free to use the support of armrests if needed. 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), recorded by the foot switches placed in their shoes, regardless of the side.

[FIGURE 1 ABOUT HERE]

Data Acquisition and Preprocessing

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

EEG data was recorded from 32 Ag/AgCl electrodes connected to a portable amplifier (ANT-neuro, Enschede, The Netherlands). Technical details of the preprocessing are provided in the Supplementary Materials S1.

Response-locked analysis: EEG data were segmented from 3000ms before to 2000ms after movement ONSET. Event Related Spectral Perturbations (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 1500ms before to 1500ms after movement onset. Frequency bands of interest were defined by visually inspecting single channel spectrograms across groups and conditions. Single channel plots showed significant ~~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).

The Cue-locked analysis: it was focused on the theta power band (4-7 Hz) dynamics. The EEG data were segmented from 1000ms before to 1000ms 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 500ms preceding cue onset.

Statistical analysis

All statistics were performed in SPSS (IBM SPSS Statistics, v21.0). Differences between groups in ET and PT were analyzed 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. HC) as a between-subjects factor. For EEG analysis, single channel spectrograms and scalp map topographies were visually inspected to identify region of interests (ROIs).

For response locked analysis, low and high beta power was assessed in a sensorimotor ROI (C3, C4, CP1, CP2, CP5, CP6 and Cz), whereas theta power in frontal (FC1, FC2, Fz and Cz) and parietal (P3, P4, CP1, CP2 and Pz) ROIs. The time window of interest was divided into 500 ms Time Bins (T1: [-1500, -1000ms]; T2: [-1000, -500ms]; T3: [-500, 0ms]; T4: [0, 500ms]; T5: [500,

1000ms]; T6: [1000, 1500ms]). 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 ROI for theta (frontal vs. parietal) and a between-subjects factor of Group (PD vs. HC). For the sake of brevity, low beta analysis is reported in Supplementary Material S2.

For 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, 250ms]; [250, 500ms]; [500, 750ms]), And investigated via a mixed 2x2 ANOVA, using within-subjects factor of Time and a between-subjects factor of Group (PD vs HC)[1].

Significance level was set at p =.05 and the Greenhouse-Geisser correction was used where the sphericity assumption was violated. Post-hoc independent and paired samples *t*-tests were adjusted for multiple comparisons using Bonferroni correction.

Results

The mixed ANOVA on Execution Time showed a significant main effect of Group [F(1, 40) = 26.848, p <.001, η_p^2 = .003], with PD participants slower to complete sit-to-stand movements

[1] In addition to the main analysis, we also examined the differences within the PD group between tremor dominant (n = 10) and non-tremor (n = 9) PD participants. A mixed ANOVA, using within-subjects factors of Condition (SELF vs. CUED), Time (T1; T2; T3; T4; T5; T6) and ROI (frontal vs. parietal) for beta and theta frequency bands separately, and including as between-subjects factor the PD groups (tremor dominant vs. non-tremor). The mixed ANOVAs did not reveal any significant main effect or interactions with group (p > .05), therefore no differences between tremor and non-tremor patient groups were found.

compared to HC regardless of condition. By contrast, an independent sample t-test revealed no differences in Planning time (p =.247), indicating that PD participants were not significantly slower than the HC group in initiating their movements (mean PD = 856.8 ± 315.88ms; mean NT = 755.4 ± 235ms).

[FIGURE 2 ABOUT HERE]

Response-locked analysis

High Beta. As shown in Figure 3, external cueing induced significant ~~prominent~~ changes in high beta power in PD, compared to the self-initiated condition and also compared to the HC group. The analysis revealed a main effect of Time [F(1, 1.70) = 30.365, p <.001, η_p^2 = .319], with a stronger relative increase of high beta power occurring just before (T3) and after (T4) heel press [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].

A significant Condition x Group interaction [F(1, 40) = 11.107, p =.002, η_p^2 = .006, see Figure 3] was investigated via post hoc paired samples t-tests, revealing a stronger relative increase of high beta for PD participants in the CUED condition [t(39) = 2.895, p =.031], but no difference between groups in the SELF condition (p =.772). Notably, the direction of high beta power modulation differed between groups (Figure 3). In the HC 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 stronger relative increase of high beta power occurred in the CUED condition compared to the SELF condition [t(18) = 2.666, p =.015].

A significant 3-way interaction between Condition, Time and Group [F(1, 2.08) = 4.413, p =.014, η_p^2 = .014] was further investigated by separately examining the Condition x Group in each Time bin. The analysis showed that a stronger increase of high beta in the PD group compared to HC, was most pronounced in the CUED condition at time bins 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] (Figure 3), which correspond the participants' heel press to the ground and the early phase of the sit-to-stand movement.

[FIGURE 3 ABOUT HERE]

Theta. The analysis revealed a main effect of Condition [F(1, 39) = 10.083, p =.003, η_p^2 = .001] reflecting higher theta power in the CUED condition compared to the SELF condition. A significant Condition x Time interaction [F(1, 3.21) = 4.687, p =.003, η_p^2 = .015] revealed a larger increase of relative theta power in the CUED condition just before movement onset [T3: t(40) = 3.604, p <.018]. A main effect of Time [F(1, 40) = 8.059, p <.001, η_p^2 = .112] indicated a stronger relative increase of theta when participants first pressed their 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]. Notably, theta power increase was prominent around movement onset, but was attenuated in the PD group compared to the HC

group (Figure 4). Indeed, the further investigation of the significant Time x Group interaction between Time and Group [$F(1, 40) = 6.587$, $p = .003$, $\eta_p^2 = .092$, see Figure 4] via post hoc independent samples t-tests showed a stronger theta power increase in the HC group compared to the PD group when participants started to stand (T4), [$t(40) = 3.709$, $p < .017$], 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 ABOUT HERE]

Cue-locked analysis

Theta. The analysis revealed only a significant Time x Group interaction [$F(1, 1.3) = 5.968$, $p < .019$, $\eta_p^2 = .053$]. Post-hoc t-tests showed increased theta power in the PD group compared to the HC group immediately after cue onset (0 to 250ms = $t(40) = 3.059$, $p = .004$, see Figure 5) but no other differences or effects ($p > .05$).

[FIGURE 5 ABOUT HERE]

Discussion

We investigated the neural response of Parkinson's patients making self-initiated or externally cued sit-to-stand movements, in comparison to age-matched healthy age-matched controls. We found that external cueing enlarged high beta power over sensorimotor areas in Parkinson's disease participants at the early phases of their movement, compared to healthy controls and compared to

self-initiated movements. This specific response of sensorimotor areas to cueing, 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 an enlarged theta power in the Parkinsonian group, presumably reflecting cognitive processing 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 movement.

The analysis of brain activity during the sit-to-stand movement revealed that high-beta oscillations over sensorimotor areas were differently modulated in Parkinson's disease compared to age-matched controls. Opposite to the modulation in healthy participants, Parkinson's disease patients exhibited a larger power increase 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, which might indicate the integration of sensory information in support of movement initiation in Parkinson's disease patients. In line with this account, Tan and colleagues[55] argue that beta power increases over sensorimotor areas might represent the interplay between both sensory processing and transfer of information, and also the estimation of uncertainty of feedforward models, in order to maintain the motor state. As supported by a large body of computational work[56-58], motor behavior 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. This is further supported by animal research, which has shown that beta oscillations might be related to cue utilization in behavioral output. Leventhal et al.[59] 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. 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]. Accordingly in our study, the enlarged sensorimotor beta power in PD patients when the movement was externally cued could be interpreted as an indication that cueing promoted the integration of sensory information[60-62] and the maintenance of the motor state, reducing the uncertainty on the feedforward estimation[55]. Taken together, these results open new routes to the investigation of how cueing supports motor behavior in neurodegenerative disease. The present study represents a first step in gaining understanding of the brain's cortical response to cueing in Parkinson's disease. The reported findings warrant further investigations to promote the development of targeted strategies in rehabilitation settings.

Notably, however, the pattern of beta modulation seen in the present study appears to be different from those seen in our previous work[44], where we found reduced beta power in Parkinson's disease patients compared to healthy controls both before and after crossing an obstacle while walking. Indeed, in Mustile et al.[44] we found reduced beta power suppression when preparing gait adjustment to step over an obstacle on the floor, signaling a deficit in the planning

a motor adjustment in Parkinson's disease compared to healthy age-matched controls. Moreover, we found an attenuated beta rebound[63] after crossing the obstacle, indicating an impaired reactive strategy after a change in motor response. Instead, the current study revealed a large power increase in the beta range in Parkinson's disease when they had to stand from a sitting position in response to the cue, compared to when they had to voluntarily initiate the movement. The different findings likely reflect a distinct role of beta oscillations in motor control processes, related to the specificity of the movement performed and the demands of the task employed. Indeed, whereas in our previous work participants were required to walk and adjust their gait to avoid obstacles on the floor, in the present study participants were asked to stand from a sitting position which places different demands. Additionally, we cannot exclude that the distinct findings might also be due to the severity and disease stage, as the present study recruited patients who were unable to walk for the duration that patients did in our previous study. The reduced beta modulation found in our previous study would therefore signal compromised motor and cognitive processes underlying complex motor behavior for obstacle avoidance, whereas the large increase in beta seen in the present study might be associated with a specific response of the brain to external cueing.

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 cue onset in the Parkinson's disease group, compared to healthy participants. Frontal theta oscillations are regarded as an index of a top-down cross-modal multisensory control system[45,46] that plays a key role in supporting cognitive processing and

organizing activity across cortical areas[45,64]. Previously [43,44], we observed a significant theta power increase when participants encountered unexpected obstacles while walking, consistent with the notion that theta oscillations serve the continuous updating of information[47,48]. The present results indicate that PD patients exhibited greater theta activity compared to healthy participants in response to the auditory cue, which provides neural evidence for the idea that the most relevant benefit of external cueing in the rehabilitation of Parkinson's disease is to promote an effective boost of cognitive during task performance[12,29].

Furthermore, regardless of whether the movement was cued or not, the present study showed that Parkinson's disease patients exhibited attenuated theta power modulation compared to healthy controls when they started to stand from the sitting position, which points towards a rather limited availability of cognitive resources at this stage of the sit-to-stand movement. 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 pedaling[65] or during obstacle avoidance[44]. Other studies[50,66] also systematically reported reduced modulation in theta frequency band in response to cue during the performance of standard cognitive control tasks, not involved in movement, in Parkinson's disease patients with cognitive impairments and dementia, compared to controls and Parkinson's disease patients without cognitive deficits. Additionally, Singh et al. [50] also found that diminished modulation delta range (1-4 Hz) along diminished theta, seemingly related to cognitive decline in Parkinson's disease.

One striking feature of the present findings is how similar the pattern of theta modulations is to those reported in our previous work[44], where we found evidence of reduced theta power increase in Parkison's disease patients compared to controls before crossing an obstacle on the floor while walking. The increase of theta power found when planning gait adaptation to step over an unexpected obstacle in healthy participants[43,44], is likely associated with proactive control mechanisms underlying the monitoring of behavioral output in response to a change of the motor plan. Therefore, the diminished theta power modulation consistently found in both our works in Parkinson's disease participants compared to healthy age-matched controls, likely indicates general impaired integration of sensory and motor information[67,68], or difficulty in monitoring the action plan at the moment of behavioral decision[69,70].

An interesting question raised by the current results was whether the changes in EEG signals observed in the present study were systematically related to the degree of behavioral benefit of cueing in Parkinson's disease patients. Although the current study was not designed to provide a behavioral measure to quantify the degree of benefit caused by cueing, an important aim for future studies will be to generate and compare behavioral and neural indexes of externally cued movements. This might clarify the neural changes underlying external cueing drive positive adjustments in Parkinson's disease motor behavior. Importantly, the identification of EEG signals associated with behavioral indices of cueing might reveal new objective measures independent of subjective assessment by clinicians or self reports by patients, providing useful diagnostic markers for motor disorders.

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 markers of Parkinson's patients' response to the cue indexed by a specific pattern in high beta power, as well as the markers on cognitive resource allocation indexed by theta power, 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 approaches[70]. While this data provides new insight into the understanding of the beneficial effects of cueing, further investigations are needed to elucidate the links between brain oscillations and behavioral responses. In the present study we did not employ sensitive behavioral indexes 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 to provide suggestions for the design of the most effective personalized 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 administration might have independent effects on cognitive and cortical processes in Parkinson's disease.

Conclusion

To the best of our knowledge, this is the first study investigating 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. The cue-related beta power increases support the maintenance of the motor state, most likely reflecting both greater effort in sensory integration and increased confidence in the estimation of motor output, whereas the enlarged theta power, immediately following cue onset 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 at https://osf.io/r67zh/?view_only=8a2e8f3148ee4e28b74d98c4acfa7418.

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MM, MI, DK, DV, MP, EP contributed to the design and conception of the project: MM contributed to the organization 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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595

596 # Figure legends

597 **FIG 1.** Representation of the experimental conditions.

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

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

608 **FIG 4. Top:** Spectrograms of a representative frontal channel (Fz) per condition and per group. Dashed
609 lines (time 0) indicate the onset of the movement. **Bottom left:** Scalp maps of theta activity per group and
610 condition in the different time bins. **Bottom right:** Graph of % change in theta activity per condition in the
611 two groups over time.

612 **FIG 5. Left:** Cue-locked averaged theta activity over a representative central channel (Cz) in the two groups
613 in the CUED condition. Dashed lines (time 0) indicate the onset of the cue. As we can see, PD participants
614 (blue line) presented an enlarged theta response to the cue compared to HC participants (red line). **Right:**

615 Scalp maps of theta activity in HC (top topography) and PD group (bottom topography) in the time bin
616 immediately after the cue (0 to 250 ms).