Somatosensory timing and cerebellar-basal ganglia beta-band interactions in Parkinson's disease

Victor Pando-Naude, MD, PhD [1] & Lau Møller Andersen, PhD [2,3]*

[1] Department of Clinical Medicine, Center for Music in the Brain, Aarhus University and The Royal Academy of Music Aarhus/Aalborg, Universitetsbyen, 3-0-17, 8000, Aarhus C, Denmark

[2] Center of Functionally Integrative Neuroscience (CFIN), Aarhus University, Universitetsbyen 3, Building 1710, 8000 Aarhus C, Denmark

[3] Department for Linguistics, Cognitive Science and Semiotics, Aarhus University, Jens Chr. Skous Vej 2, Building 1485, 8000 Aarhus C, Denmark

*Corresponding author

Lau Møller Andersen

Address: Universitetsbyen, 3-0-17, 8000, Aarhus C, Denmark

Telephone: +45 87169032

Email: lmandersen@cc.au.dk

ORCID: LMA - https://orcid.org/0000-0001-7323-0614; VPN - https://orcid.org/0000-0003-1963-5068

Word count: 3,695

Running title: Cerebellar timing in Parkinson's disease

Funding agencies: V.P.N. is funded by the Center for Music in the Brain (MIB), supported by the Danish National Research Foundation (DNRF 117). L.M.A. was funded by the Lundbeck Foundation (R322-2019-1841). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of Interest: The authors declare no conflict of interest for this work.

Classification: Biological Sciences - Neuroscience

Keywords: Cerebellum, Basal Ganglia, Somatosensory, Timing, Parkinson's Disease, Beta-Band

Abstract

Background: Parkinson's disease (PD) has traditionally been viewed through the lens of basal ganglia dysfunction, yet emerging research also implicates the cerebellum and its connections to the basal ganglia.

Objective: To investigate cerebellar and basal ganglia beta-band responses during a somatosensory timing task, with a focus on prediction- and evaluation-related activity in individuals with PD compared to controls.

Methods: Using magnetoencephalography (MEG), we presented participants with tactile stimuli in regular (non-jittered) and irregular (jittered) sequences. In each trial, the final expected stimulus was omitted to probe prediction-related activity before the omission and evaluation-related activity after it. We analyzed beta-band responses and functional connectivity across cerebellum, basal ganglia, thalamus, and motor cortex.

Results: We found prediction-related differences between PD and controls in cerebellum and basal ganglia *before* the omissions, but no differences between PD and controls in the cerebellar evaluation responses *after* the omissions. In PD participants, basal ganglia activity favored jittered sequences over non-jittered, whereas the reverse was seen in the controls. Moreover, alterations in cerebellar beta-band responses correlated with symptom severity in PD participants. Finally, we found an interaction in functional connectivity within a sensory-integration network between the two participant groups and the regularity of the stimuli.

Conclusion: We interpret these findings as indicating that the cerebellum may play a compensatory role in predictive timing in PD and that in challenging conditions, the jittered condition, the wider sensory-integration network is harder at work in PD in trying to predict upcoming stimuli.

1. Introduction

Prediction is a fundamental aspect of sensory processing, allowing the brain to efficiently anticipate incoming stimuli based on prior experience. Across modalities – visual, auditory, and somatosensory – predictive mechanisms enhance adaptation and response efficiency. In the somatosensory system, prediction has been found to facilitate motor control and to inform perception [1,2]. To update and refine such predictions, a monitoring and evaluative system is also needed, especially when sensory feedback disconfirms the predictions. Evidence suggests that the cerebellum is involved in monitoring and evaluating its own predictions [3,4]. Thus, one might conjecture that neurodegenerative diseases associated with loss of motor control, such as Parkinson's disease (PD), would be associated with altered prediction mechanisms [5].

The cerebellum, traditionally linked to motor coordination, is now recognized as crucial for generating predictive models of sensory feedback [6,7], particularly in the somatosensory domain [8]. Cerebellar beta-band activity (14–30 Hz) has been identified as a key contributor to timing functions [9]. Studies using magnetoencephalography (MEG) show that the cerebellum responds not only to tactile stimuli but also to the omission of expected stimuli, suggesting its involvement in maintaining temporal predictions [10,11]. Additionally, the basal ganglia are also implicated in the timing of sensory and motor events, coordinating with cortical areas to refine predictions based on temporal patterns [12].

While debates persist about the differential roles of the basal ganglia and the cerebellum in timing operations, a theory proposes that the basal ganglia are responsible for supra-second timing while the cerebellum manages sub-second timing [13]. Alternatively, the basal ganglia may handle regular time intervals while the cerebellum processes irregular time intervals [14,15]. In Andersen & Dalal (2024b) [16], we offered yet another view, arguing that the basal ganglia perform core timing computations, while the cerebellum integrates timing information with spatial and sensory cues to generate spatiotemporal predictions. Our model emphasizes that the cerebellum is not directly involved in timing per se but serves as an integrative hub within a broader basal ganglia-cerebellum-thalamus-M1 system [16]. This integrated network plays a fundamental role in *predicting* when, where, and what sensory stimuli will occur. From this it follows that timing capabilities may thus be lost due to incapacitation of *either* basal ganglia *or* cerebellum, as also indicated by a recent lesion study [17].

We previously showed that cerebellar beta-band responses to omitted tactile stimuli are modulated by the regularity of preceding input, with stronger responses following non-jittered sequences, reflecting prediction evaluation [10]. This activity correlates with detection accuracy [18], suggesting that cerebellar dysfunction may impair predictive mechanisms critical for smooth movement in PD [19–22].

PD is primarily characterized by dopaminergic degeneration in the substantia nigra pars compacta, disrupting basal ganglia-thalamo-cortical circuitry and impairing motor functions [23,24], including timing [25]. By comparing PD participants to controls, we can gain insights into the fundamental mechanisms of (1) sensory processing, (2) temporal prediction and evaluation, and (3) cerebellar beta-band activity [26]. At the same time, this comparison can help reveal potential cerebellar dysfunction specifically linked to PD. To meet these three ends, we used MEG.

Due to its unmatched temporal resolution, MEG allows precise differentiation of activity occurring *before* versus *after* an expected but omitted stimulus. MEG captures millisecond-scale neural dynamics, complementing the high spatial but limited temporal resolution of magnetic resonance imaging. MEG has traditionally been regarded as mainly sensitive to the cerebral cortex, but recently it has been shown that the cerebellum is within reach of MEG [27,28]. The sensitivity of MEG to the basal ganglia, on the other hand, is low, especially in situations where the cerebral cortex is activated simultaneously [29]. Some studies, however, have indicated that the basal ganglia may contribute to the magnetic field [30,31].

This study aims to investigate cerebellar dysfunction in PD, focusing on the role of cerebellar beta-band activity in somatosensory prediction. Using MEG, we examine beta-band activity in response to regular and irregular sequences of tactile stimuli and omissions, comparing PD participants to controls without PD. Due to the temporal resolution of MEG, we can tell apart effects that happen *before* the expected but omitted stimulus, i.e. related to the *prediction* of upcoming stimuli, from effects that happen *after* the expected but omitted stimulus, i.e. related to the *evaluation* of predictions.

The hypotheses of interest were:

1. PD participants exhibit altered cerebellar beta-band responses to omitted tactile stimuli in jittered versus non-jittered sequences of stimulation, i.e. an interaction between group and regularity of stimulation.
2. PD participants show altered basal ganglia beta-band activity during predictable somatosensory stimulation, indicating disrupted timing mechanisms.

For exploratory reasons we also estimated the functional connectivity in the beta-band between the cerebellum, the basal ganglia, the thalamus, and the primary motor cortex. We have suggested that these areas together comprise a temporal integration network enabling proactive action [16]. The basal ganglia provide the temporal information; the cerebellum integrates the temporal information with other kinds of information, such as spatial information and intensity information, into predictions; and the thalamus [18] passes that information on to primary motor cortex to enable proactive action.

2. Materials and Methods

Participants

Participants in the study were right-handed individuals diagnosed with PD as well as an age-matched control group without PD, henceforth "controls". The study was approved by the regional ethics committee (De Videnskabsetiske Komitéer for Region Midtjylland) in accordance with the Declaration of Helsinki. Participants were recruited following ethical guidelines and provided informed consent before participating in the study. Detailed demographic information was recorded for each participant (**Table 1**). Participants were screened for mild cognitive impairment using the Montreal Cognitive Assessment (MoCA) [32] and depression symptoms using the Major Depression Inventory (MDI) [33] and were excluded if they scored less than 26 and higher than 24, respectively. None were excluded based on these scores.

To assess the severity of PD, the motor examination of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (UPDRS-III) [34] was performed by the team physicians. PD participants were asked to take their daily medication as normal, without interruption. Fifty-six participants were recruited for the project. Of these, 3 had metal plates in their body that disturbed MEG recordings, 3 were revealed to be left-handed, and one had atrophy in the cerebellum, resulting in a final sample of 49 participants.

Table 1. Demographics

	Controls	PD
Participants (n)	25	24
Gender (females)	16	8
Age (mean/SD years)	60.2 ± 9.43	66.0 ± 7.77
MDI (median/range points)	3 (0-19)	8 (0-17)
MoCA (median/range points)	29 (26-30)	29 (26-30)
PD dx (median/range years)	-	4 (1-17)
UPDRS-III (median/range points)	-	31 (13-47)
Hoehn and Yahr (median/range points)	-	2 (1-2)

PD, Parkinson's disease; MDI, Major Depression Inventory; MoCA, Montreal Cognitive Assessment; PD dx, years since PD diagnosis; UPDRS-III, Motor Examination of the Movement Disorder Society Unified Parkinson's Disease Rating Scale.

Stimuli and Procedure

Tactile stimulation was administered using two ring electrodes powered by an electric current generator (Stimulus Current Generator, DeMeTec GmbH, Germany). These ring electrodes were affixed to the tip of the right index finger, with one placed 10 mm below the bottom of the nail and the other 10 mm below that.

Stimuli were delivered using PsychoPy (version 3.2.4) [35] on a Linux operating system running Ubuntu Mate (kernel version 4.15.0-126). Six short breaks were administered throughout the session to ensure participant comfort and to verify their well-being through verbal communication with the experimenter.

Stimuli were presented in sequences of six, with an inter-stimulus interval of 1,497 ms to prevent synchronization with the 50 Hz power line interference. Each pulse had a duration of 100 µs, and the level of current was individually adjusted for each participant. In each sequence, the sixth stimulus was followed by an omission, marking the start of a new stimulation train. Thus, a 2,994 ms interval elapsed between the last stimulus of one train and the first stimulus of the next. Three types of sequences were administered (**Figure 1**):

1. Non-Jittered Sequence: All stimuli occurred precisely on time (0% jitter).
2. Jittered Sequence: Stimuli 4–6 were jittered by 15%, occurring from -225 ms to +225 ms relative to the steady sequence. The jitter administered on a given stimulus is drawn from a uniform distribution in steps of 1 ms.
3. Non-Stimulation Sequence: A train of seven non-stimulations, each lasting 1,497 ms, occurred after every fifteen stimulation sequences.

Each stimulation sequence type was administered 150 times, while the non-stimulation sequence was administered 30 times. The sequences were pseudorandomly interleaved and counterbalanced to mitigate order effects. Participants were instructed to watch a nature program with sound from panel speakers during the stimulation procedure and were instructed to focus on the center of the screen, remain motionless, and disregard the finger stimulation.

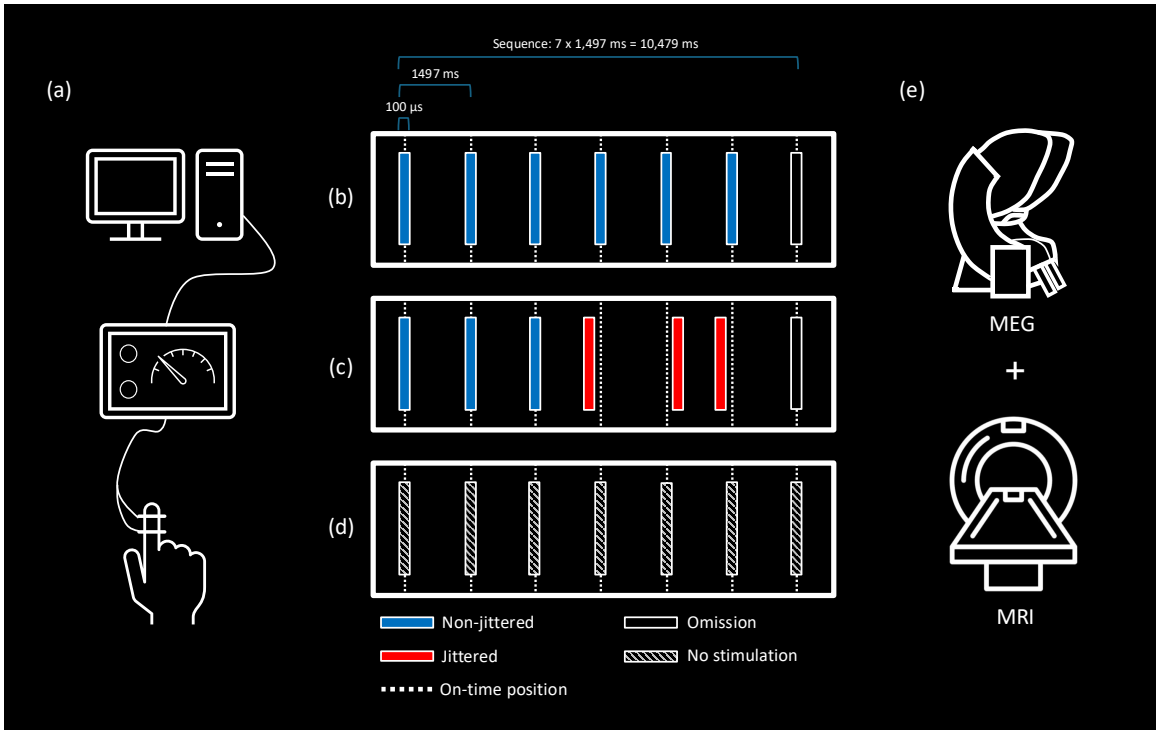

Figure 1. Experimental paradigm. (a) *Tactile stimuli were administered via ring electrodes placed on the right index finger, delivering sequences of six pulses with a duration of 100µs and inter-stimulus interval of 1,497ms. PsychoPy controlled the stimulation, while participants watched a nature program and remained motionless. EOG, ECG, and EMG recordings were collected to monitor eye movements, heart activity, and muscle tension. Stimulus sequences included* ***(b)*** *non-jittered,* ***(c)*** *jittered (15%), and* ***(d)*** *non-stimulation sequences.* ***(e)*** *MEG was acquired during the paradigm and structural MRI was acquired another day within the next two weeks.*

Preparation of Participants

Participants underwent standard MEG preparation, including Electrooculography (EOG), electrocardiography (ECG), electromyography (EMG), and respiration recordings to monitor eye movements, cardiac activity, muscle tension, and breathing. EOG electrodes were placed around the eyes, ECG on the collarbones, and EMG on the splenius muscles. Four HPI coils were attached to the head, and head shape digitization was performed using Polhemus FASTRAK, including fiducials and ~200 extra points. Participants were positioned supine in the MEG scanner with ring electrodes secured to the right index finger. Stimulation current was individually adjusted: starting at 1.0 mA, increased until perceptible but not irritating, and then fine-tuned for comfort.

Data Acquisition

Data was acquired at Aarhus University Hospital (AUH), Denmark. MEG data was acquired using an Elekta Neuromag TRIUX system located within a magnetically shielded room (Vacuumschmelze Ak3b). The sampling frequency was 1,000 Hz; online filtering was applied to the acquired data, consisting of a low-pass filter with a cutoff frequency of 330 Hz and a high-pass filter with a cutoff frequency of 0.1 Hz.

MEG Data Processing

MEG data were processed using MNE-Python [36] following Andersen (2018) [37]. Bad channels (mean = 0.22 per participant) were excluded based on power spectral inspection. For evoked responses, data were low-

pass filtered at 40 Hz [one-pass, noncausal, finite impulse response; zero phase; upper transition bandwidth: 10.00 Hz (−6 dB cutoff frequency: 45.00 Hz; filter length 331 samples; a 0.0194 passband ripple and 53 dB stopband attenuation)], epoched (−200 to 600 ms), baseline-corrected (-100 ms – 0 ms(, and averaged by condition. Beta-band responses (14–30 Hz) were extracted by band-pass filtering [14–30 Hz; lower transition bandwidth: 3.50 Hz (−6 dB cutoff frequency: 12.25 Hz); upper transition bandwidth: 7.50 Hz (−6 dB cutoff frequency: 33.75 Hz); filter length 943 samples; passband ripple: 0.0194; stopband attenuation: 53 dB)], Hilbert transforming, and epoching from −750 to +750 ms around each stimulus or omission (baseline correct (-750 ms to 750 ms).

Source Reconstruction

Neural source activity was estimated using beamforming to achieve high spatial resolution. Each participant underwent structural MRI (Siemens Magnetom Prisma 3T, 1 mm isotropic MPRAGE). The pulse sequence parameters were as follows: 1 mm isotropic resolution; field of view, 256 × 240 mm; 192 slices; slice thickness, 1 mm; bandwidth per pixel, 290 Hz/pixel; flip angle, 9°; inversion time (TI), 1,100 ms; echo time (TE), 2.61 ms; and repetition time (TR), 2,300 ms. We furthermore acquired T2-weighted 3D images. The pulse sequence parameters were as follows: 1 mm isotropic resolution; field of view, 256 × 240 mm; 96 slices; slice thickness, 1.1 mm; bandwidth per pixel, 780 Hz/pixel; flip angle, 111°; echo time, 85 ms; and repetition time, 14,630 ms. These images were processed with FreeSurfer [38,39] to segment the head and brain surfaces. A volumetric source space (~4,000 sources, 7.5 mm spacing) was generated using MNE-C's watershed algorithm [40]. Single compartment boundary element method (BEM) models were constructed, and MRI–MEG co-registration was performed using Polhemus FASTRAK fiducials and head shape points. Forward models were computed from co-registered data.

Source estimation used a linearly constrained minimum variance (LCMV) beamformer [41] with unit-noise-gain constraint, applied separately to evoked and beta-band data. The data covariance matrix was estimated from post-stimulus periods for the evoked responses and for the full epoch for the beta-band responses and used without regularization due to good conditioning of the covariance matrices. Magnetometer data were prioritized for optimal sensitivity to deep sources.

Statistical Analysis

Statistical analyses focused on identifying significant differences in beta-band responses between the two omission conditions (non-jittered and jittered) in source space. Regions of interest were chosen based on previous experiments [10,18] and theory [16]. The regions of interest were the cerebellum crus I [10,18] and the basal ganglia [16]. Statistical maps for omissions were plotted for these regions, showcasing respectively the interaction between Group (PD and controls) and Regularity (non-jittered and jittered), the main effect of Group and the main effect of Regularity. The time range of interest was chosen to be from 100 ms before the expected stimulus to 100 ms after the expected stimulus. The difference between the non-jittered and the jittered conditions were calculated as the following ratio: $\frac{(x_1 - x_2)}{(x_1 + x_2)}$. Interactions were of special interest as these highlight where there are differences between the two groups in terms of how they build expectations under ideal (non-jittered) and less than ideal (jittered) conditions.

Envelope correlations

To test functional connectivity between regions of interest, we used envelope correlation [42]. We investigated the envelope correlations in the beta-band from –100 ms to 100 ms the omitted stimulation. Regions of interest were based on the proposed network of sensory prediction from Andersen & Dalal (2024b) [16], which is constituted of basal ganglia, thalamus, cerebellum and the primary motor cortex. We included these areas bilaterally – and explored the functional connectivity within this proposed network. For descriptive purposes, we estimated the all-to-all connectivity between these nodes.

3. Results

As an initial validation of our data processing pipeline, we analyzed evoked responses in the primary and secondary somatosensory cortices (S1 & S2) across all participants (**Figure S1**). Clear somatosensory evoked responses were observed in both PD participants and controls, with the expected SI (53 ms) and SII (132 ms) components following electrical stimulation.

We then investigated whether we could replicate the results from Andersen & Dalal (2021, 2024a) [10,18] which showed that the left cerebellar lobule VI showed a significant increase in beta-band activity (14-30 Hz) for omissions following non-jittered sequences compared to omissions following jittered sequences, i.e. the main effect of regularity. In both cases [10,18], the peak of this difference was found at 44 ms after the stimulation should have happened. This is also what we report here, however in the neighboring lobule, IV-V: t_{48} = 2.36, p = 0.022, (MNI152: x = -22.5 mm, y = -45.0 mm, z = -30.0 mm) (**Figure 2**). Note that this region and time did not show a significant interaction $F_{1,48}$ = 0.41, p = 0.53.

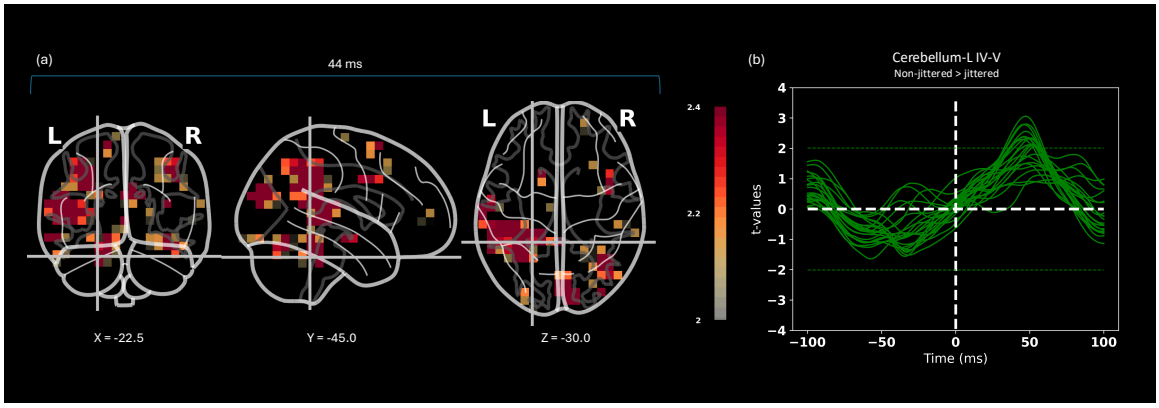

***Figure 2. Replication**. **(a)** Main effect of regularity (non-jittered vs. jittered); **(b)** t-values (df=48) peaking at left cerebellum IV-V at t = 44 ms, similar to earlier studies (10,18) – thresholded at critical t-value for p=0.05. the lines in the panel indicate averages for the sources in the region of interest, not subjects.*

When plotting the interaction (**Figure 3a**), significant effects were revealed in Cerebellum-L Crus I (MNI152: x = -52.5 mm, y = -67.5 mm, z = -37.5 mm; t = -23 ms), $F_{1,48}$ = 11.3, p = 0.0015 (**Figure 3b**), and in Caudate-L (MNI152: x = -15.0 mm, y = 15.0 mm, z = 7.5 mm; t = -13 ms), $F_{1,48}$ = 17.9, p = 0.00010 (**Figure 3c**). When testing for the direction of the interaction for the Cerebellum-L Crus I (t=-23 ms), we found that controls responded more strongly to the jittered omissions than to the non-jittered omissions, t_{24} = -2.20, p = 0.038, whereas the opposite pattern was found for PD participants, t_{23} = 2.61, p = 0.016 (**Figure 3d**). When testing for the direction of the interaction for Caudate-L (t = -13 ms), we found that controls responded more strongly to the non-jittered omissions than to the jittered omissions, t_{24} = 2.78, p = 0.010, whereas the opposite pattern was found for PD participants, t_{23} = -3.33, p = 0.0029 **(Figure 3e).** To test the link between PD related symptoms and the reported interaction in the cerebellum (r = 0.405, p = 0.0499)(**Figure 3f**) and the basal ganglia (r = 0.209, p = 0.326) (**Figure 3g**), we correlated the peak ratio difference for each participant with the UPDRS-III score at –23 ms and –13 ms respectively.

In summary, our results indicate that Cerebellum-L IV-V shows differential beta-band activity to omissions following respectively non-jittered and jittered sequences in both PD participants and controls for the peak at 44 ms *after* the expected, but omitted, stimulus, similar to what has been reported twice before [10,18]. In contrast, *before* the expected, but omitted, stimulus, basal ganglia (Caudate-L) (-13 ms) and Cerebellum-L Crus I (-23 ms) beta-band activity differ between group (PD vs controls) and regularity (non-jittered vs jittered), indicating altered timing mechanisms in PD.

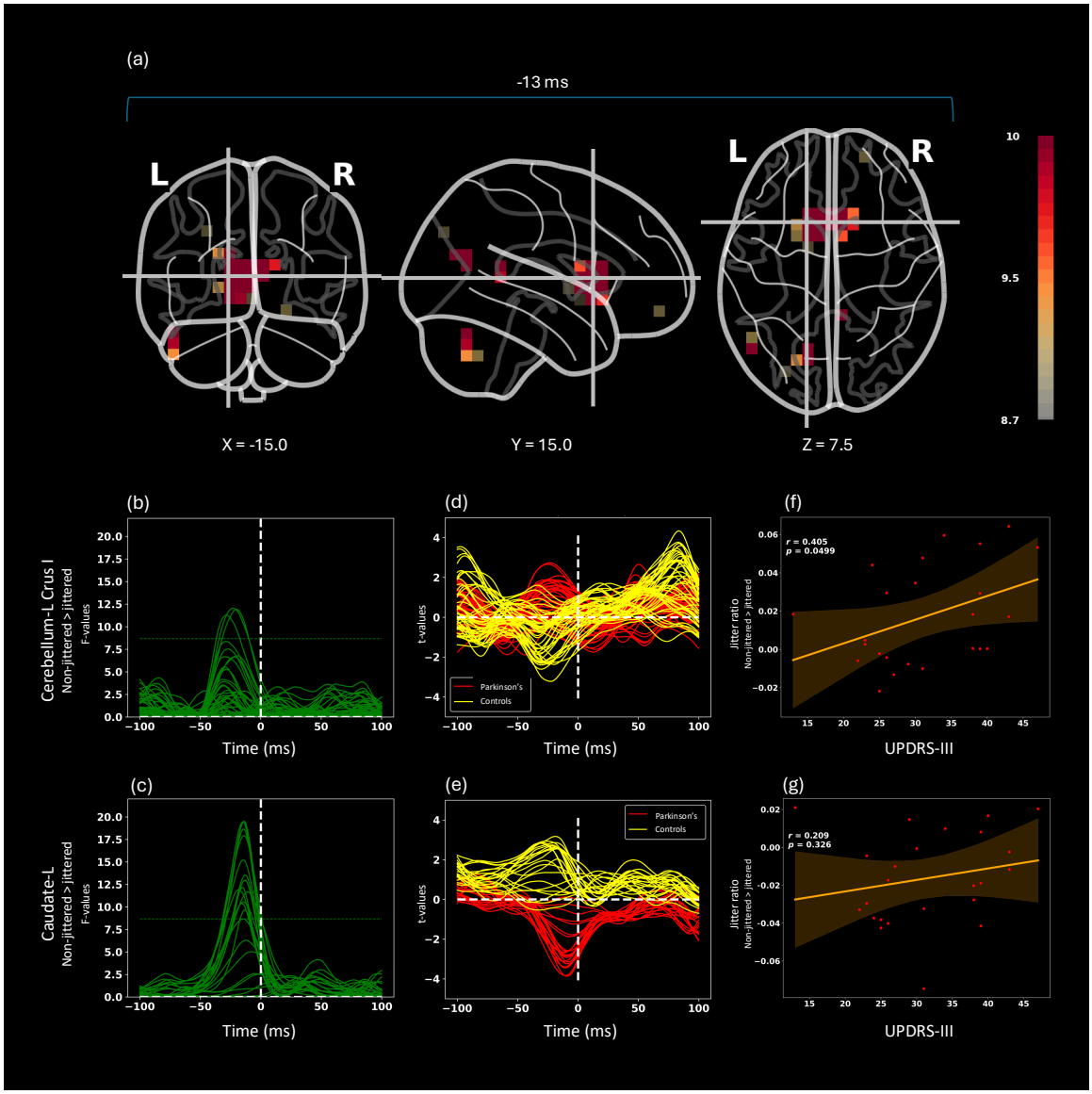

Figure 3. Interaction *between group (PD vs controls) and regularity (non-jittered vs jittered)****. (a)*** *Thresholded at p=0.005 at t = –13 ms. Color shows F-values. Of note are the caudate and cerebellar findings.* ***(b)*** *An interaction in Cerebellar-L Crus I, peaking at –23 ms.* ***(c)*** *An interaction in Caudate-L, peaking at –13 ms.* ***(d)****: Cerebellum-L Crus I t-test: in controls, beta-band activity is higher in the jittered condition than in the non-jittered condition. Parkinson's disease participants show the opposite pattern.* ***(e)****: Caudate-L t-tests: in controls, beta-band activity is higher in the non-jittered condition than in the jittered condition. Parkinson's disease participants show the opposite pattern. The lines in panels b, c, d, and e indicate averages for the sources in the region of interest, not subjects.* ***Correlations*** *between UPDRS-III scores and the ratio between non-jittered and jittered beta-band activity for the maximum source peaking* ***(f)*** *at peak time (-23 ms) for Cerebellum-L Crus I and (****g****) at peak time (-13 ms) for Caudate-L. Shaded areas are 95 % confidence intervals.*

To explore, whether the envelope analysis supported an interaction between Group and Regularity, we chose Caudate-L as a seed and included bilaterally, the cerebellar regions found in the current analysis (Cerebellum-L IV-V and Cerebellar-L Crus I) and the regions specified in earlier work (Motor Cortex and Thalamus and Caudate) [16]. This was, in part, motivated by the descriptive plot (**Figure 4a**) showing that the greatest differences were connections involving the caudate, and, in part, motivated by the *a priori*

knowledge that the basal ganglia should be involved due to PD. By running an ANOVA testing for the interaction between Group and Regularity while controlling for Region of Interest (10 levels), we found the following significant interaction: $F_{1,967} = 4.99$, $p = 0.0258$ **(Figure 4b).**

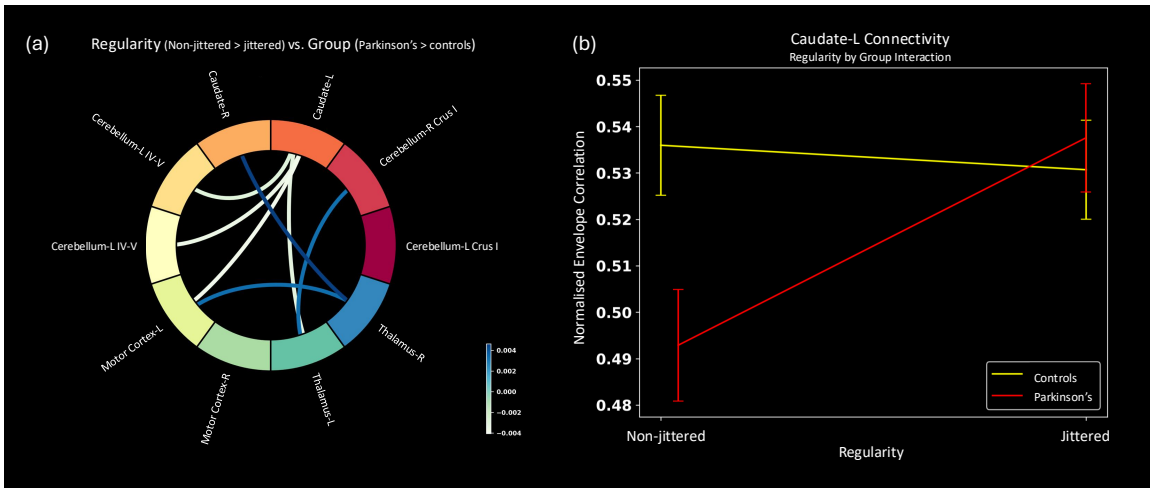

***Figure 4**. **Functional Connectivity.** Envelope correlation findings: **(a)** all-to-all differences in connectivity between regions of interest, thresholded to show only the 7 greatest differences (the minimum number of connections required to reveal all functional links to the proposed network (16) involving the left caudate). Left caudate shows differences to all regions of the proposed network, i.e. cerebellum, thalamus and the motor cortex. **(b)** Group by Regularity interaction for the connections that involve left caudate. PD participants show higher connectivity during the jittered condition than during the non-jittered condition. Error bars are standard errors of the mean.*

4. Discussion

Summary of Key Findings

This study investigated cerebellar and basal ganglia beta-band (14-30 Hz) activity in PD participants compared to controls during a somatosensory prediction task. Our findings revealed that:

1. *After* the expected but omitted stimulus (44 ms), the cerebellum reacted more strongly to omissions following non-jittered than jittered sequences, *across groups*.
2. *Before* the expected but omitted stimulus, the group and regularity factors interacted in a non-linear manner for the basal ganglia (-13 ms) and the cerebellum (-23 ms).
3. Cerebellar activity (-23 ms) correlated with symptom severity (UPDRS-III) in PD participants.
4. PD participants showed an increase in functional connectivity for the jittered relative to the non-jittered sequences.

Explication of interactions

To clarify the group interaction, we first consider the control group. As expected, the basal ganglia showed stronger responses to non-jittered sequences, consistent with prior functional magnetic resonance imaging (fMRI) studies [43,44].

In terms of the cerebellar activity *before* the expected stimulus, i.e. that beta-band power is greater following jittered sequences than following non-jittered sequences, it is likely that the cerebellum shows less activity for the non-jittered sequences, as the timing of the upcoming, expected, but omitted, stimulus is highly predictable. This aligns with findings that the cerebellum responds more strongly to non-beat or irregular sequences, while the basal ganglia prefer beat-based, regular input [15,44].

In PD, this pattern was reversed. The basal ganglia showed stronger responses to jittered sequences, possibly reflecting compensatory effort to extract rhythmicity in the absence of clear timing cues—consistent with prior work showing greater basal ganglia activation when internally generating a beat [44]. Conversely, the cerebellum in PD showed stronger responses to non-jittered sequences, suggesting a compensatory mechanism: when basal ganglia fail to label regular input as beat-based, the cerebellum steps in, consistent with its preference for processing non-beat sequences.

Cerebellum and temporal processing: *Evaluation* vs. *Prediction*

Our findings indicate that the cerebellum displays a beta-band response peaking at 44 ms *after* the omitted stimulus in both PD participants and controls. This result replicates earlier findings [10,18] and aligns with the proposal by Andersen & Dalal (2024b) [16] that the cerebellum is not directly responsible for timing functions but plays a key role in integrating sensory predictions with sensory feedback. Thus, the *evaluative* role of the cerebellum seems preserved in PD.

However, the observed differences in cerebellum crus I *before* the omitted stimulus suggest that, while the cerebellum may not be directly involved in beat-based timing in the otherwise healthy brain, it may play a compensatory role in PD. This is supported by the correlation between symptom severity and the magnitude of the cerebellar responses to non-jittered versus jittered omissions.

Our findings contribute to a growing body of literature suggesting that the cerebellum plays a role in building sensory predictions rather than directly controlling the timing of sensory events. The observed differences in cerebellar regions in PD participants *before* the omitted stimulus indicate potential compensatory mechanisms that are disrupted in the disease, underscoring the cerebellum's broader role in temporal prediction and motor control.

Basal Ganglia Dysfunction and Altered Timing Mechanisms in Parkinson's disease

The significant alteration in beta-band activity in the caudate nucleus between PD participants and controls underscores the basal ganglia's pivotal role in temporal processing. The basal ganglia, particularly the caudate and putamen, have long been implicated in the regulation of motor control and timing [12]. Our findings are consistent with a large body of literature showing that PD impairs both motor and perceptual timing tasks. Notably, the basal ganglia dysfunction plays a central role in these deficits [26].

Beta-band activity within the basal ganglia is thought to maintain the current motor state and suppress voluntary movements until the appropriate time for action [45]. This rhythmic activity is crucial for the fine-tuning of temporal predictions and the execution of time-sensitive motor behaviors [46]. The different beta-band responses observed in PD suggest a failure in the basal ganglia's ability to appropriately modulate these timing signals.

Furthermore, neuroimaging studies have demonstrated that the basal ganglia are critical for interval timing and the perception of temporal sequences [25,47,48]. These studies indicate that the caudate nucleus is particularly involved in the processing of temporal expectations and the updating of internal models based on sensory feedback. Our findings extend this understanding by showing that PD participants exhibit altered beta-band activity in the caudate during tasks requiring precise temporal predictions, suggesting a diminished capacity to adjust timing based on sensory input.

Beta-Band Connectivity between Basal Ganglia and Cerebellum, Thalamus and Motor Cortex

We find evidence that the connectivity in the beta-band between the caudate and cerebellum, thalamus and motor cortex specifically changes for PD. Compared to controls, PD participants showed an increase in connectivity for the jittered condition compared to the non-jittered condition. Similarly, in PD we found that the caudate reacted more strongly to the jittered stimuli than the non-jittered stimuli. These

increases may reflect the underlying network (basal ganglia, cerebellum, thalamus and motor cortex) synchronizing more tightly to integrate timing information with action plans [18]. In other words, the network is 'trying harder' to generate an internal beat to interpret the jittered sequence as rhythmic [44].

Limitations

One limitation concerns the participant sample, while comparable to similar neurophysiological studies, we may have limited statistical power for detecting smaller effect sizes. Our study included only medicated PD participants, which means that the effects of dopaminergic medication on beta-band activity cannot be ruled out.

The second limitation is that despite MEG being a powerful tool for investigating neural activity with high temporal resolution, it has limited sensitivity to central brain structures, such as the basal ganglia. This limitation is mitigated by the observation that our magnetoencephalographic basal ganglia findings in controls concord with what is found in functional magnetic resonance imaging studies [15,44,48,53], namely that the basal ganglia preferentially respond to non-jittered stimuli. It is furthermore mitigated by the *a priori* knowledge that this is exactly where PD participants should show dysfunctional activity, which is precisely what our results show. Finally, as we relied on omissions to elicit activity, cortical activity of the cerebrum, which might otherwise mask sub-cortical activity, was kept to a minimum [29].

Conclusion

In conclusion, the cerebellum shows preserved evaluative beta-band responses in PD, while basal ganglia dysfunction alters predictive timing signals. Increased cerebellar activity before predicted stimuli, correlating with symptom severity, suggests a compensatory role. PD also disrupts connectivity within a sensory-integration network involving the cerebellum, basal ganglia, thalamus, and motor cortex.

Author Contributions:

VPN: Investigation, Writing – Original Draft, Writing – Review & Editing, Visualization.

LMA: Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualization, Supervision, Project Administration, Funding Acquisition.

Financial Disclosures of all authors (for the preceding 12 months):

V.P.N. is funded by the Center for Music in the Brain (MIB), supported by the Danish National Research Foundation (DNRF 117). L.M.A. was funded by the Lundbeck Foundation (R322-2019-1841). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors declare that there are no conflicts of interest relevant to this work, and that there are no additional disclosures to report.

Data sharing:

The raw MRI data underlying this study contain sensitive personal information and cannot be fully shared publicly due to restrictions imposed by the General Data Protection Regulation (GDPR) and Danish national data protection laws. However, analysis scripts and code used for data processing and visualization are available at (https://github.com/ualsbombe/pd_cerebellum). Requests for access to the raw MRI data can be submitted to the corresponding author and will require a formal data-sharing agreement and approval from the relevant parties. The raw MEG data will be shared upon reasonable request to the corresponding author.

References:

1. Blakemore, S.-J., Wolpert, D. M. & Frith, C. D. Central cancellation of self-produced tickle sensation. *Nat. Neurosci.* **1**, 635–640 (1998).
2. Clark, A. Whatever next? Predictive brains, situated agents, and the future of cognitive science. *Behav. Brain Sci.* **36**, 181–204 (2013).
3. Kakei, S. *et al.* Contribution of the Cerebellum to Predictive Motor Control and Its Evaluation in Ataxic Patients. *Front. Hum. Neurosci.* **13**, (2019).
4. Peterburs, J. & Desmond, J. E. The role of the human cerebellum in performance monitoring. *Curr. Opin. Neurobiol.* **40**, 38–44 (2016).
5. Caligiore, D. *et al.* Parkinson's disease as a system-level disorder. *NPJ Park. Dis.* **2**, 16025 (2016).
6. Miall, R. C., Weir, D. J., Wolpert, D. M. & Stein, J. F. Is the cerebellum a smith predictor? *J. Mot. Behav.* **25**, 203–216 (1993).
7. Wolpert, D. M. & Kawato, M. Multiple paired forward and inverse models for motor control. *Neural Netw. Off. J. Int. Neural Netw. Soc.* **11**, 1317–1329 (1998).
8. Schmahmann, J. D. & Pandya, D. N. The cerebrocerebellar system. *Int. Rev. Neurobiol.* **41**, 31–60 (1997).
9. Gross, J. *et al.* The neural basis of intermittent motor control in humans. *Proc. Natl. Acad. Sci.* **99**, 2299–2302 (2002).
10. Andersen, L. M. & Dalal, S. S. The cerebellar clock: Predicting and timing somatosensory touch. *NeuroImage* **238**, 118202 (2021).
11. Tesche, C. D. & Karhu, J. J. T. Anticipatory cerebellar responses during somatosensory omission in man. *Hum. Brain Mapp.* **9**, 119–142 (2000).
12. Coull, J. T., Hwang, H. J., Leyton, M. & Dagher, A. Dopamine Precursor Depletion Impairs Timing in Healthy Volunteers by Attenuating Activity in Putamen and Supplementary Motor Area. *J. Neurosci.* **32**, 16704–16715 (2012).
13. Buhusi, C. V. & Meck, W. H. What makes us tick? Functional and neural mechanisms of interval timing. *Nat. Rev. Neurosci.* **6**, 755–765 (2005).
14. Grube, M., Cooper, F. E., Chinnery, P. F. & Griffiths, T. D. Dissociation of duration-based and beat-based auditory timing in cerebellar degeneration. *Proc. Natl. Acad. Sci. U. S. A.* **107**, 11597–11601 (2010).
15. Teki, S., Grube, M., Kumar, S. & Griffiths, T. D. Distinct Neural Substrates of Duration-Based and Beat-Based Auditory Timing. *J. Neurosci.* **31**, 3805–3812 (2011).
16. Andersen, L. M. & Dalal, S. S. The role of the cerebellum in timing. *Curr. Opin. Behav. Sci.* **59**, 101427 (2024).
17. Criscuolo, A., Schwartze, M., Nozaradan, S. & Kotz, S. A. Basal ganglia and cerebellar lesions causally impact the neural encoding of temporal regularities. *Imaging Neurosci.* **3**, imag_a_00492 (2025).
18. Andersen, L. M. & Dalal, S. S. Detection of Threshold-Level Stimuli Modulated by Temporal Predictions of the Cerebellum. *eneuro* **11**, ENEURO.0070-24.2024 (2024).
19. Arnal, L. H. Predicting "When" Using the Motor System's Beta-Band Oscillations. *Front. Hum. Neurosci.* **6**, (2012).
20. Te Woerd, E. S., Oostenveld, R., Bloem, B. R., De Lange, F. P. & Praamstra, P. Effects of rhythmic stimulus presentation on oscillatory brain activity: The physiology of cueing in Parkinson's disease. *NeuroImage Clin.* **9**, 300–309 (2015).
21. Vinding, M. C. *et al.* Attenuated beta rebound to proprioceptive afferent feedback in Parkinson's disease. *Sci. Rep.* **9**, 2604 (2019).
22. Vinding, M. C. *et al.* Oscillatory and non-oscillatory features of the magnetoencephalic sensorimotor rhythm in Parkinson's disease. *Npj Park. Dis.* **10**, 1–13 (2024).
23. DeLong, M. R. & Wichmann, T. Circuits and circuit disorders of the basal ganglia. *Arch. Neurol.* **64**, 20–24 (2007).
24. Kalia, L. V. & Lang, A. E. Parkinson's disease. *Lancet Lond. Engl.* **386**, 896–912 (2015).

25. Jones, C. R. G. & Jahanshahi, M. Motor and Perceptual Timing in Parkinson's Disease. in *Neurobiology of Interval Timing* (eds. Merchant, H. & de Lafuente, V.) 265–290 (Springer, New York, NY, 2014). doi:10.1007/978-1-4939-1782-2_14.
26. Harrington, D. L. *et al.* Neurobehavioral Mechanisms of Temporal Processing Deficits in Parkinson's Disease. *PLOS ONE* **6**, e17461 (2011).
27. Andersen, L. M., Jerbi, K. & Dalal, S. S. Can EEG and MEG detect signals from the human cerebellum? *NeuroImage* **215**, 116817 (2020).
28. Samuelsson, J. G., Sundaram, P., Khan, S., Sereno, M. I. & Hämäläinen, M. S. Detectability of cerebellar activity with magnetoencephalography and electroencephalography. *Hum. Brain Mapp.* **41**, 2357–2372 (2020).
29. Krishnaswamy, P. *et al.* Sparsity enables estimation of both subcortical and cortical activity from MEG and EEG. *Proc. Natl. Acad. Sci.* **114**, E10465–E10474 (2017).
30. Attal, Y., Maess, B., Friederici, A. & David, O. Head models and dynamic causal modeling of subcortical activity using magnetoencephalographic/electroencephalographic data. **23**, 85–95 (2012).
31. Piastra, M. C. *et al.* A comprehensive study on electroencephalography and magnetoencephalography sensitivity to cortical and subcortical sources. *Hum. Brain Mapp.* **42**, 978–992 (2021).
32. Nasreddine, Z. S. *et al.* The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* **53**, 695–699 (2005).
33. Olsen, L. R., Jensen, D. V., Noerholm, V., Martiny, K. & Bech, P. The internal and external validity of the Major Depression Inventory in measuring severity of depressive states. (2003) doi:10.1017/S0033291702006724.
34. Goetz, C. G. *et al.* Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale Presentation and Clinimetric Testing Results. *Mov. Disord.* (2008) doi:10.1002/mds.22340.
35. Peirce, J. W. Generating stimuli for neuroscience using PsychoPy. *Front. Neuroinformatics* **2**, (2009).
36. Gramfort, A. *et al.* MEG and EEG data analysis with MNE-Python. *Front. Neurosci.* **7**, (2013).
37. Andersen, L. M. Group Analysis in MNE-Python of Evoked Responses from a Tactile Stimulation Paradigm: A Pipeline for Reproducibility at Every Step of Processing, Going from Individual Sensor Space Representations to an across-Group Source Space Representation. *Front. Neurosci.* **12**, (2018).
38. Dale, A. M., Fischl, B. & Sereno, M. I. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *NeuroImage* **9**, 179–194 (1999).
39. Fischl, B. FreeSurfer. *NeuroImage* **62**, 774–781 (2012).
40. Gramfort, A. *et al.* MNE software for processing MEG and EEG data. *NeuroImage* **86**, 446–460 (2014).
41. Sekihara, K., Hild, K. E., Dalal, S. S. & Nagarajan, S. S. Performance of prewhitening beamforming in MEG dual experimental conditions. *IEEE Trans. Biomed. Eng.* **55**, 1112–1121 (2008).
42. Hipp, J. F., Hawellek, D. J., Corbetta, M., Siegel, M. & Engel, A. K. Large-scale cortical correlation structure of spontaneous oscillatory activity. *Nat. Neurosci.* **15**, 884–890 (2012).
43. Grahn, J. A. & Brett, M. Rhythm and beat perception in motor areas of the brain. *J. Cogn. Neurosci.* **19**, 893–906 (2007).
44. Grahn, J. A. & Rowe, J. B. Feeling the beat: Premotor and striatal interactions in musicians and nonmusicians during beat perception. *J. Neurosci.* **29**, 7540–7548 (2009).
45. Engel, A. K. & Fries, P. Beta-band oscillations--signalling the status quo? *Curr. Opin. Neurobiol.* **20**, 156–165 (2010).
46. Jenkinson, N. & Brown, P. New insights into the relationship between dopamine, beta oscillations and motor function. *Trends Neurosci.* **34**, 611–618 (2011).
47. Jones, C. R. G. & Jahanshahi, M. Contributions of the Basal Ganglia to Temporal Processing: Evidence from Parkinson's Disease. *Timing Time Percept.* **2**, 87–127 (2014).
48. Rao, S. M., Mayer, A. R. & Harrington, D. L. The evolution of brain activation during temporal processing. *Nat. Neurosci.* **4**, 317–323 (2001).
49. Friston, K. A theory of cortical responses. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **360**, 815–836 (2005).

50. Fujioka, T., Trainor, L. J., Large, E. W. & Ross, B. Internalized Timing of Isochronous Sounds Is Represented in Neuromagnetic Beta Oscillations. *J. Neurosci.* **32**, 1791–1802 (2012).
51. Large, E. W. & Jones, M. R. The dynamics of attending: How people track time-varying events. *Psychol. Rev.* **106**, 119–159 (1999).
52. Kühn, A. A., Kupsch, A., Schneider, G.-H. & Brown, P. Reduction in subthalamic 8-35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease. *Eur. J. Neurosci.* **23**, 1956–1960 (2006).
53. Grahn, J. A. & Rowe, J. B. Finding and feeling the musical beat: Striatal dissociations between detection and prediction of regularity. *Cereb. Cortex* **23**, 913–921 (2013).
54. Kotz, S. A., Ravignani, A. & Fitch, W. T. The Evolution of Rhythm Processing. *Trends Cogn. Sci.* **22**, 896–910 (2018).
55. Manto, M. *et al.* Consensus Paper: Novel Directions and Next Steps of Non-invasive Brain Stimulation of the Cerebellum in Health and Disease. *The Cerebellum* **21**, 1092–1122 (2021).
56. Pando-Naude, V., Jespersen, K. V., Johnsen, E. & Vuust, P. Rhythmic auditory stimulation for motor rehabilitation in Parkinson's disease. *Cochrane Database Syst. Rev.* **CD015759**, (2024).
57. Thaut, M. H. *et al.* Rhythmic auditory stimulation in gait training for Parkinson's disease patients. *Mov. Disord. Off. J. Mov. Disord. Soc.* **11**, 193–200 (1996).
58. Wang, L. *et al.* Effects of Rhythmic Auditory Stimulation on Gait and Motor Function in Parkinson's Disease: A Systematic Review and Meta-Analysis of Clinical Randomized Controlled Studies. *Front. Neurol.* **13**, 818559 (2022).

Supplementary Information

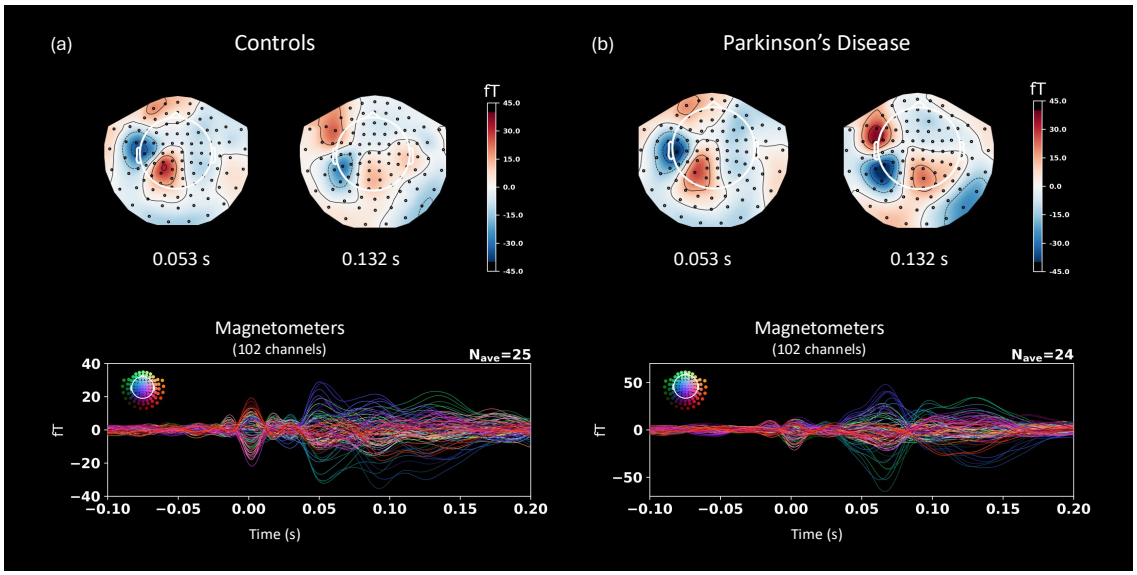

Figure S1. Somatosensory responses *for SI (53 ms) and SII (132 ms);* ***(a)*** *Controls, n=25;* ***(b)*** *Parkinson's disease, n=24. Signal Space Projection (first four SSPs) was applied to reduce environmental noise.*