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

Victor Pando-Naude [1] & Lau Møller Andersen [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.

Email: lmandersen@cc.au.dk

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

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.

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Abstract

Parkinson's disease 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.

To probe cerebellar and basal ganglia responses, we used a somatosensory timing paradigm, while recording magnetoencephalography. Beta-band (14-30 Hz) activity was of special interest, as we have shown that it is relevant to timing in the cerebellum. Parkinson's disease participants and controls were presented with tactile stimuli in non-jittered or jittered sequences, with the last on-time position of the sequence being omitted to probe prediction-related processes.

We find prediction-related differences in the cerebellum and the basal ganglia before the omissions, but no differences in cerebellar evaluation responses after the omissions. In Parkinson's disease participants, basal ganglia activity favor jittered sequences over non-jittered, whereas the reverse is seen in the controls. Moreover, the alterations in cerebellar beta-band responses correlate with symptom severity in Parkinson's disease participants. Finally, we find an interaction in functional connectivity within a sensory-integration network between the two participant groups and the regularity of the stimuli.

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

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 also involved in monitoring and evaluation of its own predictions (3,4). Thus, one might conjecture that neurodegenerative diseases associated with loss of motor control, such as Parkinson's disease, would be associated with altered prediction mechanisms (5).

The Role of the Cerebellum and Basal Ganglia in Temporal Prediction and Evaluation

The cerebellum has been increasingly recognized as a key structure in sensory prediction, particularly in the somatosensory domain (6). Beyond its traditional role in motor coordination, the cerebellum is thought to generate forward models that predict the timing and nature of sensory feedback from motor actions (7). These predictive functions are crucial for adapting to changes in the environment and for smooth execution of movements (8).

Cerebellar beta-band activity (14–30 Hz) has been identified as a key contributor to timing functions (9). Studies using magnetoencephalography 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).

Compatible with this view, we demonstrated in Andersen & Dalal (2021) (10) that cerebellar beta-band activity following omissions of expected tactile stimuli is influenced by the regularity of preceding tactile stimuli. Specifically, stronger cerebellar responses were observed when omissions followed non-jittered sequences, suggesting an engagement in *evaluating* prediction outcomes. Andersen & Dalal (2024a) (18) expanded on this by linking cerebellar activity to behavioral performance, showing that cerebellar evaluation activity correlates with detection accuracy in near-threshold stimuli tasks. Such findings suggest that cerebellar dysfunction may disrupt the formation of predictions, which may be particularly relevant in conditions such as Parkinson's disease, as smooth movement is facilitated by having accurate predictions (19–22).

Parkinson's Disease and Timing

Parkinson's disease is primarily characterized by dopaminergic degeneration in the substantia nigra pars compacta, disrupting basal ganglia-thalamo-cortical circuitry and impairing motor functions (23,24). While

the basal ganglia have been traditionally emphasized in Parkinson's disease pathophysiology, recent studies have further indicated the cerebellum's involvement in compensatory mechanisms and its potential role in exacerbating motor and cognitive symptoms (5,25), including timing (26).

By comparing Parkinson's disease 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 (27). At the same time, this comparison can help reveal potential cerebellar dysfunction specifically linked to Parkinson's disease. To meet these three ends, we used magnetoencephalography.

Magnetoencephalography

Due to its unmatched temporal resolution, magnetoencephalography allows precise differentiation of activity occurring *before* versus *after* an expected but omitted stimulus. Magnetoencephalography captures millisecond-scale neural dynamics, complementing the high spatial but limited temporal resolution of magnetic resonance imaging. Magnetoencephalography has traditionally been regarded as mainly being sensitive to the cerebral cortex, but recently it has been shown that the cerebellum is within reach of magnetoencephalography (28,29). The sensitivity of magnetoencephalography to the basal ganglia, on the other hand, is low, especially in situations where the cerebral cortex is activated simultaneously (30). Some studies, however, have indicated that the basal ganglia may contribute to the magnetic field (31,32).

Aims and Hypotheses

This study aims to investigate cerebellar dysfunction in Parkinson's disease, focusing on the role of cerebellar beta-band activity in somatosensory prediction. Using magnetoencephalography, we examine beta-band activity in response to regular and irregular sequences of tactile stimuli and omissions, comparing Parkinson's disease participants to controls without Parkinson's disease. Due to the temporal resolution of magnetoencephalography, 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. Parkinson's disease 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. Parkinson's disease 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.

To foreshadow the results, we found differential basal ganglia activations to omissions between Parkinson's disease participants and controls. We believe that the veracity of this differential activation is supported by: (**1)** us using a beat-based timing paradigm, which preferentially activates the basal ganglia (14,15); **(2)** us using omissions to elicit activity, which do not activate the cerebral cortex to the same degree that sensory stimulation does, thus, the MEG signal of the basal ganglia is more likely to be visible (30); and **(3)** basal ganglia activation being expected to be altered in Parkinson's disease.

Results

Magnetoencephalography was recorded while 24 participants with Parkinson's disease and 25 age-matched controls passively received right-index-finger pulse trains (**Figure 1, Table 1**). Each train comprised six 100-µs electrical stimuli separated by 1.497 s; in the non-jittered (0 %) condition all pulses were on time, whereas in the jittered (15 %) condition, pulses 4–6 were shifted randomly by ±225 ms, and the seventh event was always omitted to probe predictive processing. Participants fixated on a silent nature film to minimize eye and body movements. MEG signals were band-passed at 14–30 Hz (beta band), epoched around each stimulus or omission, and reconstructed to source space with linearly constrained minimum-variance beamforming. Condition- and group-dependent beta-power and envelope-correlation metrics were then extracted for cerebellum, basal ganglia, thalamus, and primary motor cortex, as proposed by Andersen & Dalal (2024b) (16).

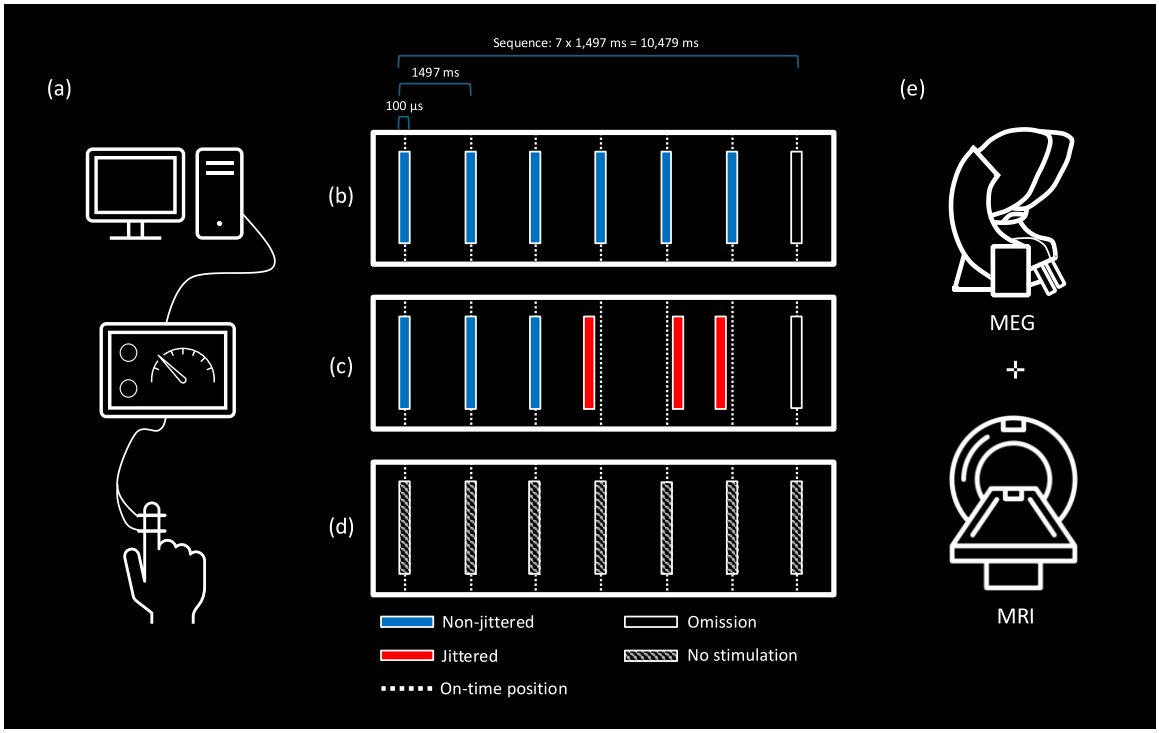

Figure 1. Experimental paradigm. (a) *Tactile stimuli were administered via ring electrodes placed on the right index finger, delivering sequences of six pulses with a duration of 100µs and inter-stimulus interval of 1,497ms. PsychoPy controlled the stimulation, while participants watched a nature program 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.*

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.

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 2**). Clear somatosensory evoked responses were observed in both Parkinson's disease participants and controls, with the expected SI (53 ms) and SII (132 ms) components following electrical stimulation.

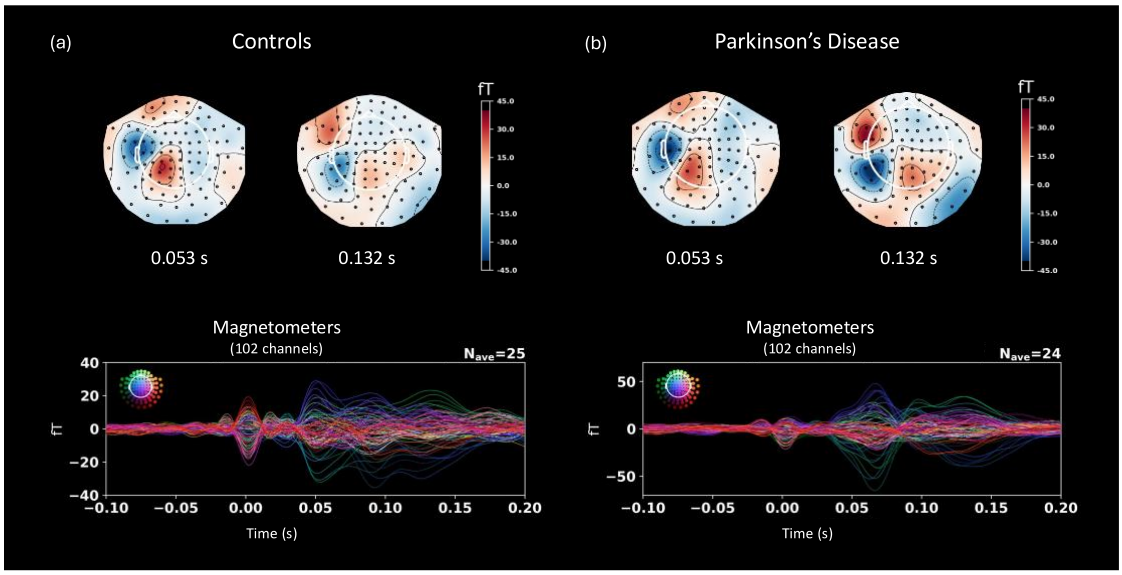

Figure 2. Somatosensory responses *for SI (53 ms) and SII (132 ms); (**a**) Controls, n=25; (**b**) Parkinson's disease, n=24.*

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 3**). Note that this region and time did not show a significant interaction $F_{1,48}$ = 0.41, p = 0.53.

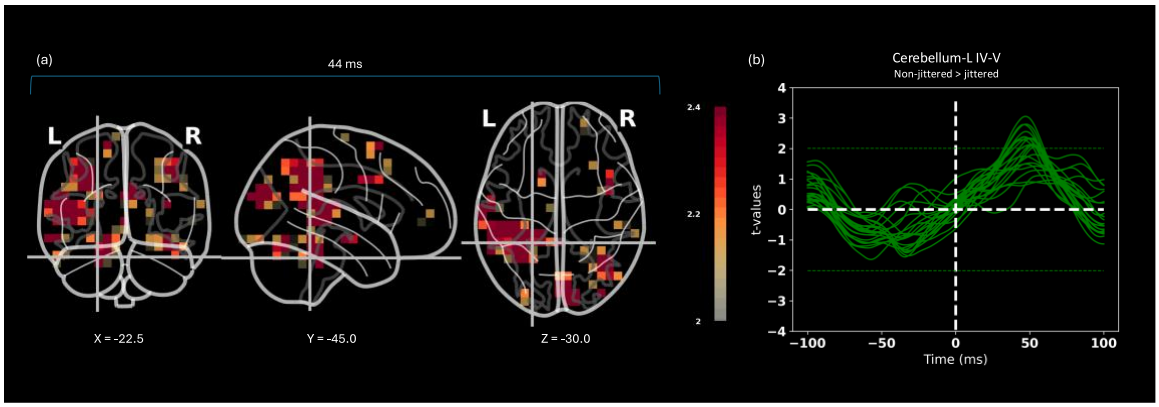

***Figure 3. Replication**. **(a)** Main effect of regularity (non-jittered vs. jittered); **(b)** t-values (df=48) peaking at left cerebellum IV-V at t = 44 ms, similar to earlier studies (10,18) – thresholded at critical t-value for p=0.05. the lines in the panel indicate averages for the sources in the region of interest, not subjects.*

When plotting the interaction, significant effects were revealed 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 and the 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 4a**).

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 Parkinson's disease participants, t_{23} = 2.61, p = 0.016 (**Figure 4d**).

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 Parkinson's disease participants, t_{23} = -3.33, p = 0.0029 **(Figure 4e).**

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 Parkinson's disease 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 (Parkinson's disease vs controls) and regularity (non-jittered vs jittered), indicating altered timing mechanisms in Parkinson's disease.

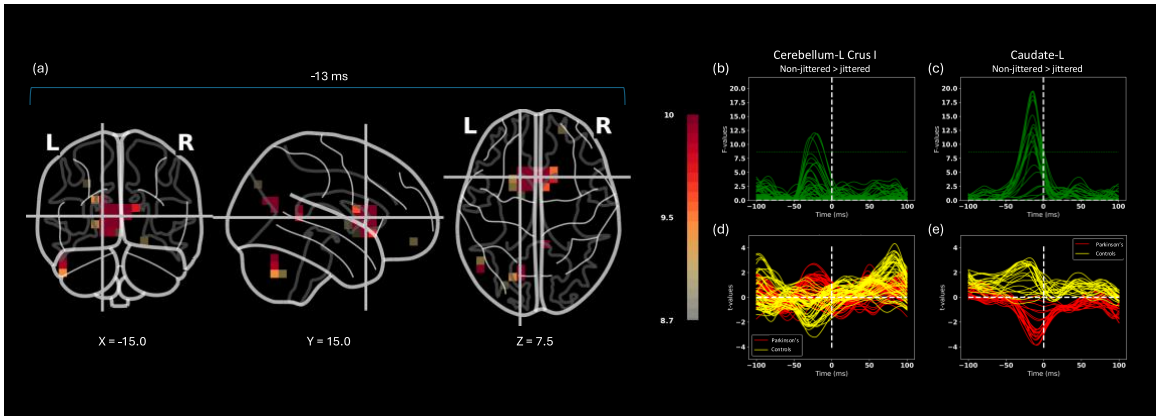

Figure 4. Interaction *between group (PD vs controls) and regularity (non-jittered vs jittered)**. (a)*** *Thresholded at p=0.005 at t = –13 ms. Color shows F-values. Of note are the caudate and cerebellar findings.* ***(b)*** *An interaction in Cerebellar-L Crus I, peaking at –23 ms.* ***(c)*** *An 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.*

To test the link between Parkinson's disease related symptoms and the reported interaction in the cerebellum (**Figure 5a**) and the basal ganglia (**Figure 5b**), we correlated the peak ratio difference for each participant with the UPDRS-III score at –23 ms and –13 ms respectively.

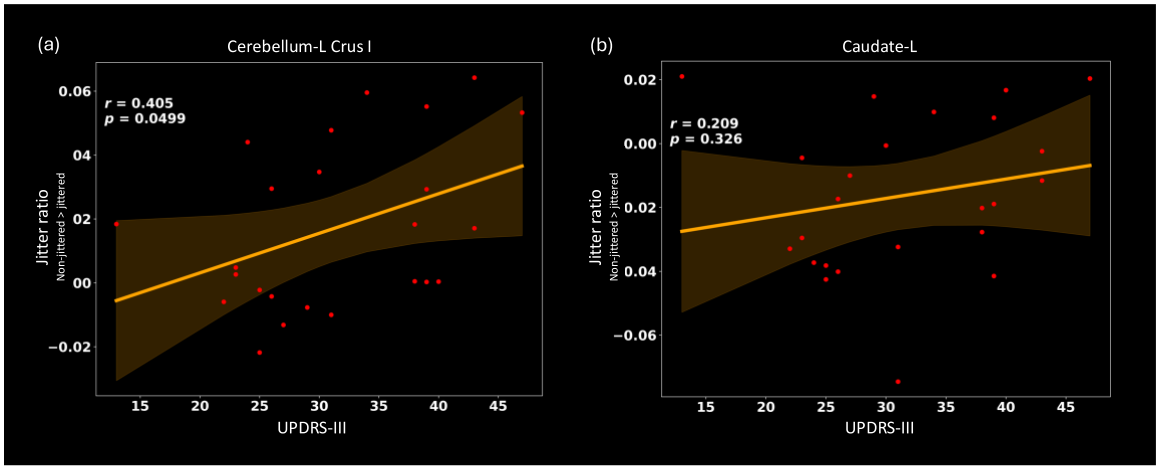

Figure 5*:* ***Correlations*** *between UPDRS-III scores and the ratio between non-jittered and jittered beta-band activity for the maximum source peaking* ***(a)*** *at peak time (-23 ms) for Cerebellum-L Crus I and* ***(b)*** *at peak time (-13 ms) for Caudate-L. Shaded areas are 95 % confidence intervals.*

To explore differences in connectivity, we first plotted the difference of differences of the envelope correlation, i.e. the interaction, in all-to-all connections in the regions of interest (**Figure 6a**). Specifically, we calculated the difference in connectivity between non-jittered omissions and jittered omissions for both Parkinson's disease participants and controls and took the difference of those two differences.

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 6a**) 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 Parkinson's disease.

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 6b).**

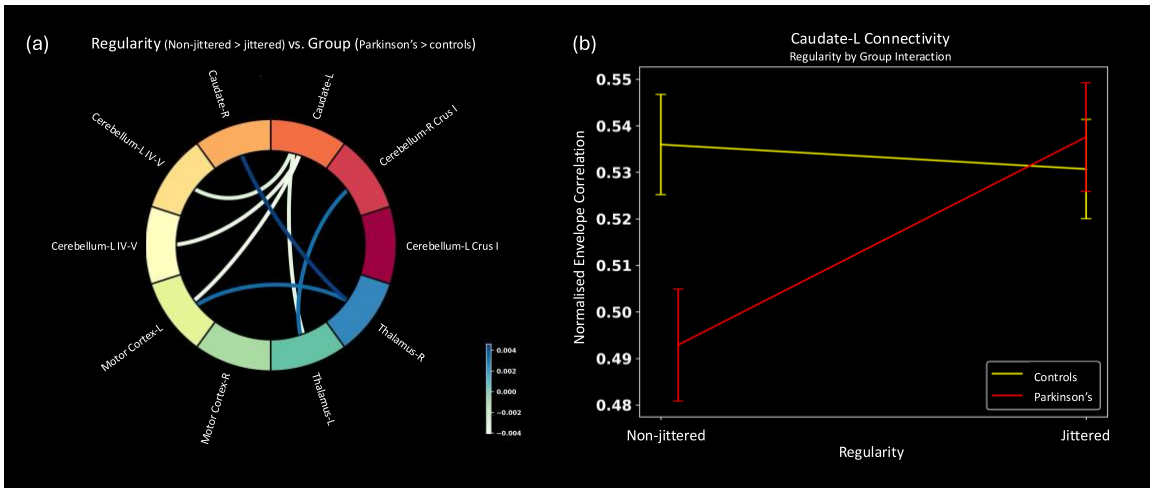

***Figure 6**. **Functional Connectivity.** Envelope correlation findings: **(a)** all-to-all differences in connectivity between regions of interest, thresholded to show only the 7 greatest differences (the minimum number of connections required to reveal all functional links to the proposed network (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.*

Discussion

Summary of Key Findings

This study investigated cerebellar and basal ganglia beta-band (14-30 Hz) activity in medicated Parkinson's disease 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 Parkinson's disease participants.
4. Parkinson's disease participants showed an increase in functional connectivity for the jittered relative to the non-jittered sequences.

Explication of interactions

To lay out the interactions between Parkinson's disease participants and controls, we first describe the findings in the control group. The basal ganglia results – specifically, the finding of a preferential response to non-jittered sequences – are in line with previous reports using functional magnetic resonance imaging (fMRI) (33,34).

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 interpretation is in line with Grahn & Rowe's (2009) (34) findings that

the cerebellum reacts more strongly to non-beat sequences than sequences with a beat. In contrast, when the sequence is jittered, the cerebellum is more active, because it is attempting to identify a pattern. Overall, the reported pattern for the controls in terms of their cerebellar and basal ganglia activity is compatible with the study by Teki et al. (2011) (15), wherein they show, using fMRI, that the cerebellum responds more strongly to irregular sequences and the basal ganglia respond more strongly to regular sequences.

Why then do we see opposite patterns in Parkinson's disease? In Parkinson's disease, the basal ganglia may not be capable of distinguishing the non-jittered and jittered sequences as purely 'rhythmic' vs. 'arrhythmic'. The increased beta activity for the jittered sequences could thus reflect the basal ganglia attempting to find a pattern (i.e. 'trying harder' to generate an internal beat in response to the irregular timing). This is compatible with Grahn & Rowe's (2009) (34) findings showing that the basal ganglia respond more strongly to rhythmic sequences that require internal generation of a beat to predict upcoming stimuli. That is, when the beat is accented, the basal ganglia respond less than when the beat is unaccented. Thus, it is possible to suggest that the basal ganglia of Parkinson's disease participants may activate more in the jittered case, because it is trying harder in generating an internal beat that would be compatible with the jittered condition being rhythmic.

Notably, we found that for Parkinson's disease participants, the cerebellum showed increased activity during non-jittered sequences. Since the basal ganglia do not provide accurate timing information for the regular sequences, the timing of the next stimulus is no longer precisely predictable. As the sequence, to the cerebellum, is not marked as a beat sequence by the basal ganglia, the cerebellum steps in in a compensatory manner to in line with its preference for non-beat sequences (34).

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 Parkinson's disease 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 Parkinson's disease.

Several studies have supported the idea that the cerebellum contributes to the prediction of sensory events rather than the explicit measurement of time intervals. Ivry & Keele (1989) (35) demonstrated that cerebellar lesions impair the ability to adapt to sensory prediction errors without affecting fundamental time perception. This was further corroborated by Spencer et al. (2003) (36), who showed that cerebellar patients struggled with tasks requiring temporal prediction, but not with tasks involving simple interval timing.

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 Parkinson's disease. 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 Parkinson's disease 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 Parkinson's disease 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 Parkinson's disease impairs both motor and perceptual timing tasks. Notably, the basal ganglia dysfunction plays a central role in these deficits (27).

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 (37). This rhythmic activity is crucial for the fine-tuning of temporal predictions and the execution of time-sensitive motor behaviors (38). The different beta-band responses observed in Parkinson's disease 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 (26,39,40). 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 Parkinson's disease 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.

Our findings provide evidence that basal ganglia dysfunction, particularly in the caudate nucleus, leads to altered beta-band activity in Parkinson's disease.

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 Parkinson's disease. Compared to controls, Parkinson's disease participants showed an increase in connectivity for the jittered condition compared to the non-jittered condition. Similarly, in Parkinson's disease 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 (34).

Limitations

While this study provides important insights into cerebellar and basal ganglia beta-band activity in Parkinson's disease, two limitations should be considered when interpreting the results.

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 Parkinson's disease participants, which means that the effects of dopaminergic medication on beta-band activity cannot be ruled out. The second limitation is that despite magnetoencephalography 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 (15,34,40,45), 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 Parkinson's disease 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 was kept to a minimum (30).

Conclusion

In conclusion, our study provides evidence that the cerebellum exhibits similar beta-band (14-30 Hz) activity in Parkinson's disease participants and controls, supporting the notion that the cerebellum performs evaluation of predictions *after* being exposed to disconfirming evidence. In contrast, basal ganglia dysfunction in Parkinson's disease leads to altered beta-band activity *before* predicted stimuli, highlighting its critical role in temporal processing. Moreover, differences in cerebellar activation *before* predicted stimuli suggest a compensatory role of the cerebellum in generating temporal predictions – one that correlates with symptom severity. Finally, the Parkinsonian brain exhibits notable differences in connectivity in a sensory-integration network comprising the basal ganglia, the cerebellum, the thalamus, and the primary motor cortex.

Materials and Methods

Participants

Participants in the study were right-handed individuals diagnosed with Parkinson's disease as well as an age-matched control group without Parkinson's disease, 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, including age, gender distribution, disease severity, and medication status, was recorded for each participant. Participants were screened for mild cognitive impairment using the Montreal Cognitive Assessment (MoCA) (51) and depression symptoms using the Major Depression Inventory (MDI) (52) and were excluded if they scored less than 26 and higher than 24, respectively. None were excluded based on these scores (**Table 1**).

To assess the severity of Parkinson's disease, the motor examination of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (UPDRS-III) (53) was performed by the team physicians. Parkinson's disease 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. Of these, 24 were participants with Parkinson's disease (Mean age: 66.0 y; SD: 7.77 y; 16 men; 8 women; UPDRS-III: Mean score: 31.5; SD: 8.28) and 25 were controls (Mean age: 60.2 y; SD=9.43 y; 9 men; 16 women).

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) (54) 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.

Preparation of Participants

Prior to data acquisition, participants underwent preparation procedures to ensure accurate and comfortable measurement conditions. Electrooculography (EOG), electrocardiography (ECG), and electromyography (EMG) were recorded during the procedure. Additionally, respiration was measured using a respiratory belt for exploratory purposes. Each participant had two pairs of EOG electrodes positioned horizontally and vertically around the eyes to monitor eye movements. ECG was recorded using a pair of electrodes placed on each collarbone. Additionally, two pairs of EMG electrodes were attached to either side of the splenius muscles to monitor muscle activity related to neck tension.

Four head-position indicator (HPI) coils were affixed to the participants, with two placed behind the ears and two on the forehead. The ground electrode was positioned on the wrist of the right arm above the ring electrode. Subsequently, participants' head shapes were digitized using a Polhemus FASTRAK system. Three fiducial points, including the nasion and the left and right pre-auricular points, were digitized, along with the positions of the HPI coils. Approximately 200 extra points were digitized to capture additional details of each participant's head shape.

Participants were then positioned in the supine position within the MEG system, ensuring their comfort and preventing neck tension. The ring electrodes were securely fastened to the tip of the right index finger.

Before starting the experimental procedure, individualized stimulation currents were determined for each participant. The initial current was set to 1.0 mA and gradually increased in steps of 1 mA until the participant reported feeling the current. Subsequently, the current was adjusted in increments of 0.5 mA until the participant found it to be irritating. The current was then reduced in steps of 0.5 mA until it was no longer perceived as irritating. Participants were instructed that the stimulation should be clearly perceptible but not painful or irritating.

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 set to 1,000 Hz to capture high-resolution neural activity. To ensure data quality, online filtering was applied to the acquired data, including 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

We extracted evoked and beta-band (14-30 Hz) responses from the acquired MEG data. All data processing procedures were implemented using MNE-Python (55), and followed a pipeline based on Andersen (2018) (56). Signal Space Projection (SSP) was employed to project out the first four SSPs for sensor space analyses. This correction mitigated the impact of gradients on the magnetometers, thereby enhancing data quality by reducing environmental noise and artifacts. The raw MEG data were inspected to ensure data quality. Visual inspection of sensors was conducted by examining the power spectral densities of the raw data. On average, across all participants, 0.22 magnetometers were marked as bad channels (range: 0-4) and removed from subsequent analysis.

For the extraction of evoked responses, the data were subjected to a series of steps. Initially, the raw data were low-pass filtered at 40 Hz using a one-pass, non-causal finite impulse response filter with zero-phase characteristics. Following filtering, the data were segmented into epochs of 800 ms duration, consisting of a 200 ms pre-stimulus baseline and a 600 ms post-stimulus period. Offsets were corrected by demeaning based on the average activity during the pre-stimulus baseline. Subsequently, the epochs were averaged across trials to generate evoked response waveforms for each stimulation condition.

Beta-band responses were extracted through similar procedures but involved additional. After band-pass filtering the raw data into the beta-band (14–30 Hz), the filtered data were Hilbert transformed. Epochs of 1,500 ms duration (pre-stimulus 750 ms and post-stimulus 750 ms) were extracted for both stimulation and omission conditions.

Source Reconstruction

Source reconstruction using beamforming was employed to estimate the neural sources underlying the recorded MEG signals, enabling the investigation of activity across the brain with high spatial resolution.

Structural MRI images were acquired for each participant using a Siemens Magnetom Prisma 3T MRI system, providing high-resolution anatomical information of the brain. The MPRAGE sequence parameters were: 1 mm isotropic resolution; field of view: 256 x 256 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; repetition time (TR): 2,300 ms.

These images were processed using FreeSurfer (57,58) to segment the head and brain surfaces, which were subsequently delineated using the watershed algorithm from MNE-C (59). From the brain surface, we generated a volumetric source space consisting of approximately 4000 sources with a spacing of 7.5 mm.

Single compartment boundary element method (BEM) solutions were computed from the segmented brain surfaces to construct volume conduction models. Co-registration of the structural MRI images with the MEG sensor positions was performed using fiducial points and head shape information obtained from Polhemus FASTRAK digitization. Finally, a forward model was generated based on the volume conduction model, MEG sensor positions, and volumetric source space with sources spaced 7.5 mm apart.

For source estimation, a linearly constrained minimum variance (LCMV) beamformer approach (60) was employed using the unit-noise-gain constraint. The beamformer was applied separately to both evoked and beta-band responses. To compute the spatial filter weights for the beamformer, the data covariance matrix was estimated based on the relevant post-stimulus period for each type of response. No regularization was applied to the covariance matrix, as it was well-conditioned. The beamformer spatial filter weights were then applied to the MEG data to estimate the neural activity at each source location. Source reconstruction focused on magnetometer data, which are most sensitive to deep non-neocortical 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 (Parkinson's disease 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 (61). 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 includes 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.

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