Pallidal Spectral and Phase-Amplitude Coupling Differences in Parkinson's Disease Locomotor States

Josephine J. Wallner[a*], Nicholas Druck[a*], Harsh P. Shah[b], Leslie J. Cloud[c,d], Kathryn L. Holloway[b], and Dean J. Krusienski[a]

[a]Biomedical Engineering, Virginia Commonwealth University. 601 W Main St, Richmond, VA 23220.
[b]Department of Neurosurgery, Virginia Commonwealth University Health System. 417 N 11th St, Richmond, VA 23298.
[c]Parkinson's and Movement Disorders Center, Virginia Commonwealth University. 11958 W Broad St, Henrico, VA 23233.
[d]Department of Neurology, Virginia Commonwealth University Health System. 417 N 11th St, Richmond, VA 23298
[*]authors contributed equally

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Corresponding author: Nicholas Druck. Department of Biomedical Engineering. 800 E Leigh St, Richmond, VA 23298, (804) 828-7929. Email: druckn@vcu.edu

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Author emails:
Josephine Wallner: wallnerj@vcu.edu,
Nicholas Druck: druckn@vcu.edu,
Harsh Shah: harshpshahmd@gmail.com,
Leslie Cloud: leslie.cloud@vcuhealth.org,
Kathryn Holloway: kathryn.holloway@vcuhealth.org,
Dean Krusienski: djkrusienski@vcu.edu

Abstract

Background: Deep brain stimulation of the subthalamic nucleus or Globus Pallidus internus is an established therapy for Parkinson's Disease that is sub-optimally managed with medication. While post-operative motor studies have defined neurophysiological signatures of the subthalamic nucleic local field potentials, comparable studies in the Globus pallidus internus are needed. Recent work shows that bandpower and phase-amplitude coupling in the subthalamic nucleus reliably distinguish locomotor states, motivating parallel investigation in the Globus pallidus internus.

Objectives: To characterize pallidal bandpower and phase-amplitude coupling across locomotor states (sitting, standing, and overground walking) in Parkinson's, and relate to clinical motor scores.

Methods: Bandpower and phase-amplitude coupling from pallidal signals of six adults with Parkinson's were compared across locomotor states; inter-state differences were correlated with clinical scores.

Results: High beta and gamma power differentiated sitting from walking, while delta power distinguished standing from walking. Phase-amplitude coupling between lower phases and gamma amplitude decreased during walking. Standing-to-walking delta-power modulation strongly correlated with Unified Parkinson's Disease Rating Scale scores ($R = 0.9$, $p < 0.05$). Standing-to-walking beta-gamma phase-amplitude coupling modulation highly correlated with freezing-of-gait scores ($R = 0.86$, $p < 0.05$).

Conclusions: This study provides the first detailed characterization of Globus pallidus internus activity in these locomotor states in Parkinson's. The coupling between lower frequencies and gamma was lower during walking as compared to sitting and standing, revealing an inverse relationship to what has been reported in the subthalmic nucleus. These findings suggest that movement coordination in the Globus pallidus internus may rely on a balance of single- and cross-frequency mechanisms.

1 Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by bradykinesia, rigidity, tremor, and gait impairment [1]. When motor symptoms become inadequately controlled by dopaminergic medication, deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus internus (GPi) offers an effective therapeutic alternative. While STN remains the predominant target, GPi-DBS has gained increasing clinical interest due to its favorable effects on levodopa-induced dyskinesias and a potentially more straightforward programming profile [2].

Advances in DBS technology now permit chronic recording of local field potentials (LFPs) from implanted electrodes, providing a window into the oscillatory dynamics of basal ganglia circuits. Extensive work in the STN has identified pathological beta-band (13–30 Hz) synchronization as a robust electrophysiological marker of the parkinsonian state, with beta power correlating with bradykinesia and rigidity severity [3]. Beyond single-frequency measures, cross-frequency interactions, particularly phase-amplitude coupling (PAC) between beta phase and gamma amplitude, have emerged as candidate biomarkers. Beta-gamma PAC has been shown to reflect cortico-basal ganglia communication, motor network dysfunction, and changes in gait patterns [3–11].

These neurophysiological signatures have motivated the development of adaptive DBS (aDBS), which modulates stimulation delivery based on real-time LFP features [12, 13]. The recent FDA approval of aDBS systems has accelerated efforts to identify biomarkers suitable for closed-loop control. In the STN, beta power during naturalistic locomotion has shown promise as an aDBS control signal [14]. However, analogous GPi biomarkers for aDBS remain underexplored.

The GPi serves as the primary output nucleus of the basal ganglia, integrating signals from the direct and indirect pathways before projecting to the thalamus and motor cortex. Prior work suggests that the STN and GPi exhibit reciprocal oscillatory patterns, with distinct and opposing modulation across these structures [15, 16]. Early intraoperative studies demonstrated that pallidal beta power and PAC with high-frequency oscillations were modulated during upper-limb movement [17]. Whether similar modulation occurs during whole-body locomotion, and whether such signatures relate to clinical motor scores, has not been extensively examined in the GPi.

In this study, we recorded GPi LFPs from six individuals with PD during a post-operative overground walking protocol. We characterized spectral power and PAC across three locomotor states: sitting, standing, and walking, and examined correlations with clinical motor assessments. Our objectives were to (1) identify GPi electrophysiological signatures that distinguish locomotor states, (2)

compare these patterns to established STN findings, and (3) evaluate the potential of GPi spectral features as biomarkers for clinical motor dysfunction.

2 Methods

2.1 Participants and DBS devices

Six participants diagnosed with PD were recruited for the study. All participants reported persistent FoG following DBS implantation. The study design was approved by the Institutional Review Board of Virginia Commonwealth University, and informed consent was obtained for experimentation with human subjects. All participants were implanted with the Percept (Medtronic, Minneapolis, MN) DBS system in the GPi (unilateral or bilateral, based on clinical indication - see table in Figure S1) [18]. Each electrode shaft consists of four contacts, forming three bipolar recording channels (i.e., C0-C2, C1-C3, C0-C3). The Percept system records LFPs digitized at 250 Hz. All data was recorded using the Percept's Indefinite Streaming mode, which is done with stimulation off. Patient demographics, clinical characteristics, and device set up can be found in Figure S1.

2.2 Data Collection

The participants walked an obstacle course that was originally designed to elicit FoG. Minimal freezing data were obtained during the experimental sessions, and excluded from the subsequent analysis. The course consisted of five scenarios while LFPs were recorded: (1) passing a narrow archway, (2) 540° turn, (3) approaching a visual target, (4) dual-task (performing calculations while walking), and (5) a time-sensitive task (answering a distant ringing phone). Data were collected off medication and with stimulation off. A summary of data length across participants is listed in Table 1.

During the experimental sessions, participants donned ankle-mounted inertial monitoring units (IMUs), which were temporally aligned with GPi LFP recordings through the injection of a controlled external artifact. Transcutaneous electrical nerve stimulation (TENS) electrodes were positioned on the lateral neck, over the subcutaneous DBS leads, and on the contralateral mastoid. Surface EMG electrodes placed adjacent to the DBS leads detected the TENS artifact. Both EMG and IMU data streams were routed to a laptop via Lab Streaming Layer (LSL) for synchronized acquisition [19]. The TENS artifact, present in both the IMU and LFP signals, enabled offline temporal alignment.

Video recordings were acquired concurrently and synchronized to IMU and LFP data using timestamps and audio markers. Additionally, an external audio signal was transmitted through LSL to serve as a secondary synchronization marker across the video and IMU recordings. Based on the synchronized IMU and video data, the LFP recordings were manually segmented into three locomotor states: sitting, standing, and walking.

Condition \ **Participant**	**A**	**B**	**C**	**D**	**E**	**F**
Sit	120	127	10	38	60	102
Stand	120	12	120	30	51	20
Walk	120	130	130	120	98	120

Table 1: Seconds of data collected in each locomotor state across participants A–F.

2.3 Data Analysis

2.3.1 Preprocessing

To provide a balanced comparison across participants with differing number of implants, a single hemisphere was chosen for analysis. For those with bilateral implants, GPi contacts contralateral to hemibody with worse (ie., greater) UPDRS-III scores at the time of collection were chosen. One participant had equal UPDRS-III scores bilaterally; for this participant, the initially affected hemisphere per prior clinical documentation was used. For all participants, the C1 and C2 contacts were confirmed to be located in the GPi by a neurosurgeon via post-operative imaging using Stealth MRI (Medtronic, Minneapolis, MN) [20]. From these contacts, two bipolar channels based on the C0-C2

and C1-C3 contact pairs were used for the subsequent analyses. Channel C0-C3 was not analyzed due to the lower spatial specificity and overlap with the selected channels. The raw LFP data and power spectra were screened to confirm the absence of motion artifacts, and for EKG contamination using the Perceive toolbox [21]. Dual-tasking walking data was excluded to avoid confounding effects in the signals. While some participants had shorter lengths of clean LFPs, the subsequent analysis techniques have been shown to be robust for these segment lengths [22].

2.3.2 Frequency Bandpower

Bandpower estimates were calculated to quantify the relative contributions of physiological frequencies across locomotor states. The power spectral densities (PSDs) were estimated for each locomotor state using Welch's method via the *pwelch* function in MATLAB2024a (MathWorks Inc., Natick, MA). The LFPs were partitioned into 1-second Hamming-windowed epochs with 50% overlap. Due to the lowpass filter characteristics of the Percept, the resulting PSDs were processed and visualized up to 100 Hz.

To reveal differences in bandpower between locomotor states, the *bandpower* function in MATLAB2024a was used across canonical frequency bands (i.e., Delta: 0.5-4 Hz, Theta: 4-8 Hz, Alpha: 8-12 Hz, Beta: 13-30 Hz, and Gamma: 30-100 Hz). Based on prior work suggesting functionally relevant subdivisions of the beta band in the GPi, low beta (13-20 Hz) and high beta (21-30 Hz) were also analyzed [17].

Pairwise statistical comparisons between locomotor states were performed separately for each frequency band using the Wilcoxon signed-rank test, a nonparametric test that does not assume normality. P-values were adjusted for multiple comparisons using Benajmini-Hochberg correction (significance threshold: 0.05).

2.3.3 Phase-Amplitude Coupling

Phase–Amplitude Coupling (PAC) is a measure of cross-frequency coupling where the phase of a low-frequency oscillation modulates the amplitude of a higher-frequency oscillation. PAC was quantified using the modulation index (MI) based on Kullback–Leibler divergence, a widely-used method in LFP studies [17, 22, 23]. LFP signals were bandpass filtered to estimate phase frequencies from 1–30 Hz (1 Hz steps, 2 Hz bandwidth) and amplitude frequencies from 40–100 Hz (2 Hz steps, 10 Hz bandwidth). Instantaneous phase and amplitude were extracted using the Hilbert transform. Specifically, for every 20-degree interval of the instantaneous phase distribution, the entropy of the instantaneous amplitude envelope distribution was computed.

MI values were computed between each phase–amplitude frequency pair and visualized as comodulograms. To obtain summary PAC metrics, MI values were summed across canonical phase-frequency ranges, consistent with prior DBS work [5]:

$$\text{PAC} = \sum_{\text{phase range}} MI \tag{1}$$

where *phase range* represents the range of phase frequencies used for the summation of MI values. This process was repeated for each locomotor state.

Pairwise statistical comparisons between locomotor states were performed using Wilcoxon signed-rank tests with Benjamini–Hochberg correction (significance threshold: 0.05).

2.3.4 Clinical Correlations

The resulting bandpower and PAC comparisons that yielded statistically significant differences were linearly correlated to the clinical motor scores (UPDRS-III, nFoG-Q) using robust linear regression. Specifically, the difference between each significant bandpower or PAC combination was calculated for all GPi contacts and averaged within each participant.

3 Data Sharing

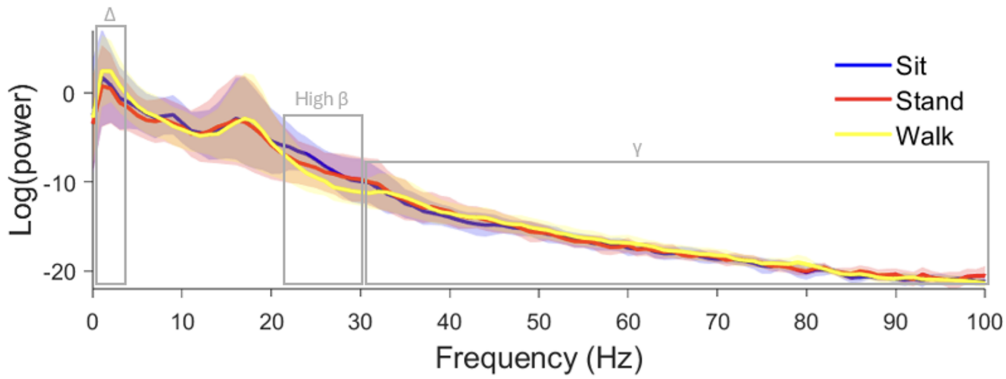
Data are available upon request.

4 Results

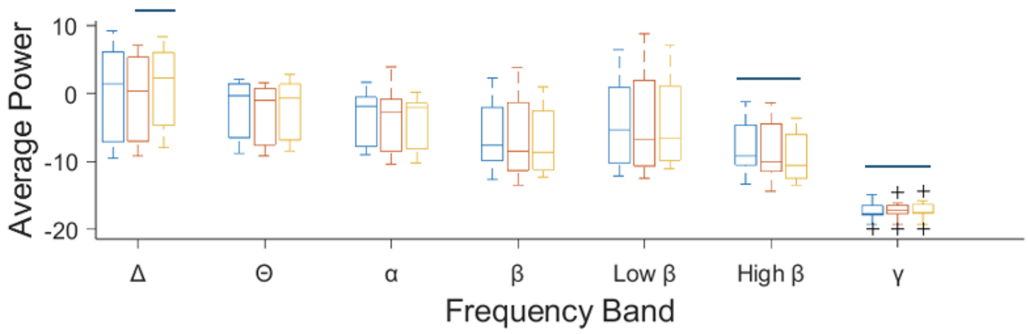
4.1 Differences in frequency bandpower across locomotor states

Figure 1a shows average PSD across all participants for all three locomotor states: sit, stand, and walk. The power in specific frequency bands was averaged for each participant and each state, and displayed as box plots in Figure 1b. Individual PSD for all GPi contacts can be found in Figure S2.

Pairwise comparisons between locomotor states revealed increased delta power during walking relative to standing. Power in both high beta and gamma frequency ranges differentiated between sitting and walking: walking was associated with decreased high beta and increased gamma. Notably, the beta power modulation between sitting and walking was not apparent when analyzing the entire beta range as a single band.



(a) Power spectral densities for each locomotor state, averaged across participants. Solid lines indicate mean, with shaded regions indicating 95% confidence intervals. The boundaries of the frequency ranges exhibiting significant differences between states are highlighted with gray boxes.



(b) Box plots of the bandpower distributions across participants for each frequency band. Horizontal bars indicate statistically significant differences ($p < 0.05$)

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Figure 1: Summary of bandpower analysis across locomotor states.

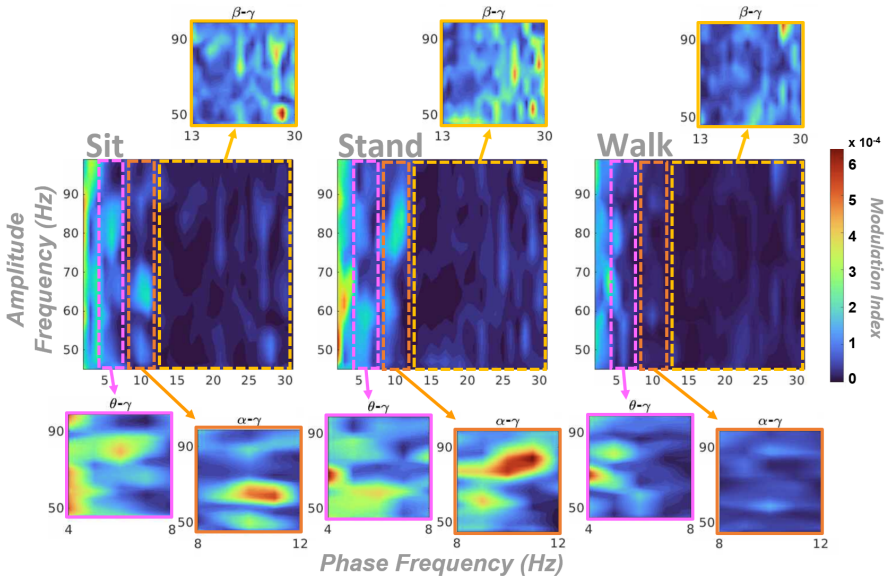
4.2 Differences in phase-amplitude coupling across locomotor states

Figure 2a provides example comodulograms for one contact from one participant across locomotor states. The insets highlight the coupling between the phase of canonical frequency ranges (i.e., theta, alpha, beta) and the gamma amplitude. PAC values from these comodulograms were summarized into locomotor-state-specific boxplots, as shown in Figure 2b. Individual comodulograms for GPi contacts across all participants can be found in Figure S3.

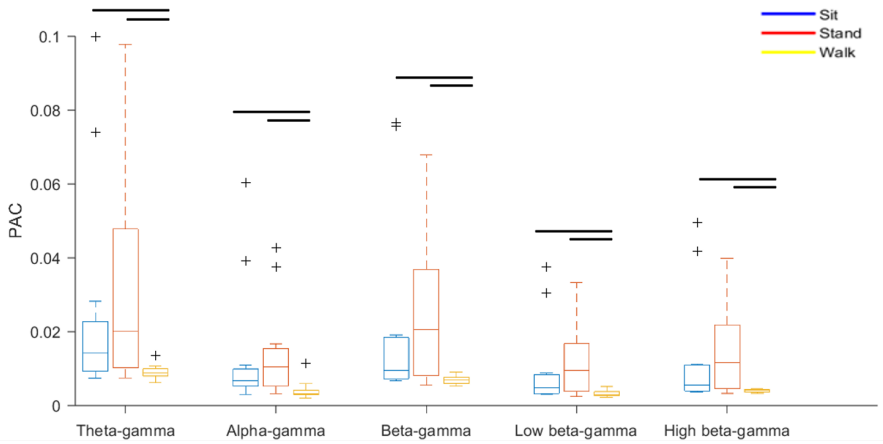
No significant differences in PAC were observed between sitting and standing. However, compared to sitting and standing, walking was consistently associated with a decrease in PAC between all lower

frequency bands and gamma. Standing-related PAC is highest at low phase frequencies and gradually declines with increasing phase frequency, similar to the typical 1/f-like decay in neural power spectra; however, these PAC patterns cannot be fully accounted for by frequency-dependent changes in power [24]. This difference across locomotor states was present whether or not the beta band was partitioned into low and high beta; therefore, subsequent PAC comparisons were done so using the entire beta band without sub-divisions.

Figure 3 compares the current GPi beta–gamma PAC results with previously published STN findings from Farokhniaee et al. (2024) [5]. To enable an analogous comparison, the beta–gamma PAC values from Figure 2b were min–max normalized to match the scale in the STN analysis. In this STN study, beta-gamma PAC was positively modulated during walking across their participants; whereas in this GPi cohort, a reciprocal trend was observed where beta-gamma PAC was negatively modulated during walking.



(a) Locomotor state-specific comodulograms for one contact from an example participant. The larger three comodulograms labeled "Sit", "Stand", and "Walk", share the displayed color scale. The insets highlight the coupling between the phase of canonical frequency ranges (i.e., theta, alpha, beta) and the gamma amplitude. MI values across locomotor states, and within a frequency range, were re-normalized to better visualize coupling dynamics that are otherwise obscured by the shared color scale. The PAC value for each GPi contact during a given locomotor-state is defined as the sum of all MIs in the comodulogram over the specified phase range, using Eq. 1.



(b) Box plots of the PAC values for all participants and for each frequency band pair. Horizontal bars indicate statistically significant differences ($p < 0.05$, with Benjamini-Hochberg correction).

Figure 2: Summary of the current GPi PAC results with an analogous comparison between the current GPi beta-gamma PAC results and prior STN beta-gamma PAC work.

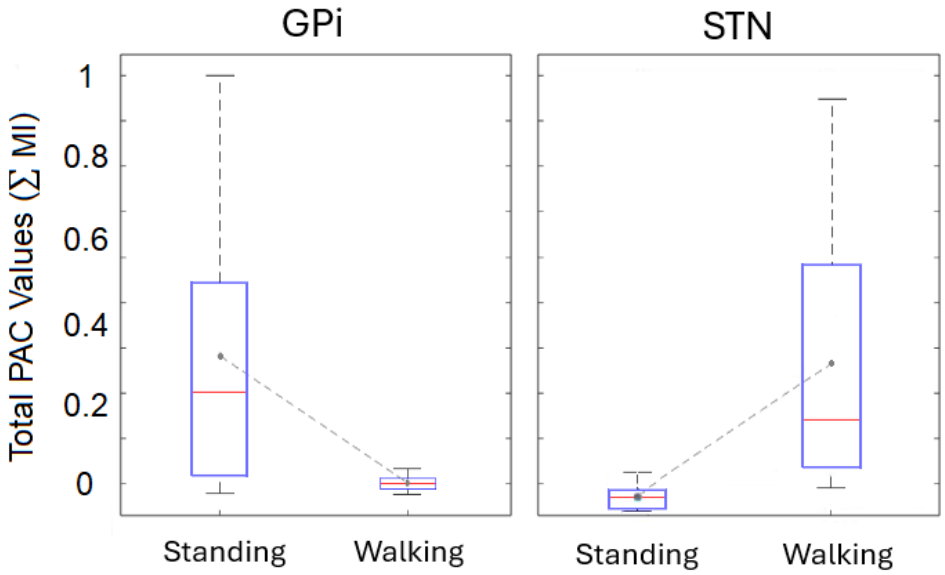
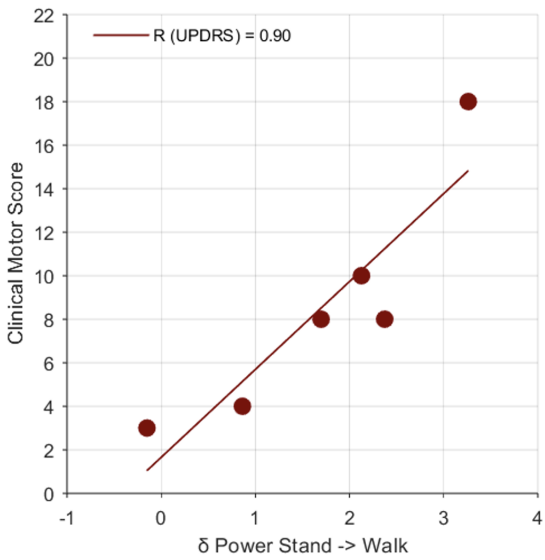


Figure 3: Min-max normalized changes in beta-gamma PAC between standing and walking, compared between the present GPi participants and a separate STN cohort from Farokhniaee et al., 2024. Beta-gamma PAC between standing and walking exhibits a reciprocal relationship across STN and GPi.

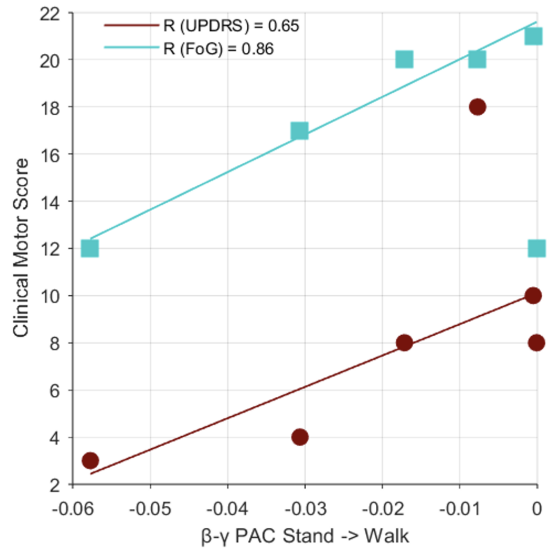
4.3 Correlations between spectral features and clinical motor scores

Statistically significant spectral features (i.e., delta power modulation and beta–gamma PAC differences) were averaged across each participant's GPi contacts to yield a single representative value per participant. These spectral features were then correlated with clinical motor scores using MATLAB's built-in *fitlm* function with the *RobustOpt* parameter set to *on*. Results of robust regression correlations across all spectral features can be found in Figure S5.

In Figure 4a, the correlation between standing-to-walking delta modulation with UPDRS-III scores is shown. In Figure 4b, the correlations between standing-to-walking beta-gamma PAC modulation and clinical motor scores is shown.



(a) Robust linear regression between delta power modulation from standing to walking with UPDRS scores. Individual points represent the averaged delta modulation for each participant (p_{fog} = 0.01).



(b) Robust linear regression between the beta-gamma PAC modulation from standing to walking with both UPDRS-III and nFoG-Q scores. Individual points represent the averaged beta-gamma PAC modulation from standing to walking for each participant (p_{updrs} = 0.18, p_{fog} = 0.04).

Figure 4: Robust linear correlations between selected statistically-significant spectral and PAC features and clinical motor scores.

5 Discussion

The present study, to our knowledge, provides the first detailed characterization of GPi LFP dynamics during naturalistic sitting, standing, and overground walking in individuals with PD. High-beta and gamma power differentiated sitting from walking, while delta power distinguished standing from walking. PAC between lower-frequency phases (theta, alpha, beta) and gamma amplitude was consistently reduced during walking compared to static states. Standing-to-walking delta modulation correlated strongly with motor scores (UPDRS-III), and beta-gamma PAC modulation correlated with freezing-of-gait scores (nFoG-Q).

The observed reduction in high-beta power during walking aligns with the well-established phenomenon of movement-related beta desynchronization, which has been extensively documented in the STN and is considered a hallmark of healthy motor output [25, 26]. Notably, this effect was only apparent when analyzing high-beta separately from low-beta, suggesting that beta sub-bands may reflect distinct functional processes in the GPi, as previously proposed for the STN [27, 28].

The increased activity in the 1-8 Hz range during walking, which has also been reported in the pedunculopontine nucleus, suggests that low-frequency oscillations may be a shared gait-related signature across interconnected nodes of the motor network [29]. The accompanying increase in gamma power during walking further indicates that multiple oscillatory components reconfigure as participants transition between static and dynamic states, underscoring the distributed, multi-frequency nature of motor control in basal ganglia circuits.

A key finding was the global reduction in PAC between all lower-frequency phases and gamma amplitude during walking. This pattern where sit $\approx$ stand $>$ walk suggests that cross-frequency coupling across a broad frequency range in the GPi may encode a movement-related control signal. Cross-frequency coupling has been proposed to reflect dynamic gating mechanisms that regulate when neural populations become synchronized in response to behavioral context [30, 31]. The observed reduction during active movement could reflect the release of an inhibitory signal from the GPi, facilitating motor execution.

Notably, the direction of beta-gamma PAC modulation in this GPi cohort was opposite to that

reported in the STN, where PAC increases during walking [5]. This reciprocal pattern is consistent with previous work in the STN and GPi, which reported inverse oscillatory dynamics in response to therapeutic interventions [15, 32]. While the present study did not include simultaneous STN recordings, future work employing dual-target acquisition could directly test this reciprocal relationship during locomotion.

The identification of locomotor-state-dependent spectral features in the GPi carries implications for aDBS development. Incorporating multi-band, state-aware biomarkers, such as delta modulation or beta-gamma PAC, may enhance adaptive control by accounting for the specific motor context. Furthermore, longitudinal tracking of these markers could provide physiological indices of disease progression or short-timescale fluctuations in motor state, potentially guiding individualized parameter adjustments over time.

5.1 Limitations

The sample size (n = 6) restricts generalizability and statistical power, particularly for the clinical correlation analyses, which should be interpreted as hypothesis-generating in the absence of a larger cohort. Participants exhibited variable disease duration and medication regimens, which may have influenced basal ganglia activity. Additionally, the slow dissipation of stimulation effects in the GPi likely contributed to inter-subject variability [33]. Finally, while PAC has shown discriminatory value across locomotor states, the observed broadband coupling suggests that PAC may not be optimally identifying processes that drive these differences.

5.2 Summary and conclusion

This study demonstrates that GPi LFPs encode locomotor-state-dependent information through both single-frequency power and cross-frequency coupling mechanisms. The reciprocal PAC modulation relative to the STN suggests that movement coordination in the pallidum may involve distinct, and potentially reciprocal, oscillatory dynamics. The observed correlations with clinical motor scores, while preliminary, support continued investigation of GPi spectral features as candidate biomarkers for pallidal aDBS and as potential indices of motor dysfunction in PD.

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7 Authors' Roles

Conceptualization and study design: JW, HS, LC, KH, DJK; Data collection: JW, ND, HS, LC, KH; Formal analysis: JW, ND; Manuscript preparation: JW, ND, DJK; Manuscript review & editing: JW, ND, HS, LC, KH, DJK

8 Financial Disclosures

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