Neural Biomarkers of Cognitive Impairment in Parkinson' Disease

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Abstract: Electrophysiological analysis reveals that dual-task walking impairs response inhibition and alters brain network dynamics in Parkinson's disease and aging. These neural biomarkers highlight disrupted connectivity and compensatory mechanisms, supporting the development of closed-loop DBS for improved motor-cognitive outcomes.

Keywords: EEG, Neurodegeneration

Introduction

Cognition emerges from the dynamic interplay of large-scale brain networks, with efficient communication and adaptive reorganization underpinning core processes such as attention, executive function, and response inhibition. Recent years have witnessed a surge in the use of electrophysiological methods to unravel the temporal and spatial dynamics of these networks during cognitive and motor tasks. This approach has proven especially valuable in elucidating how neurological conditions disrupt the balance and integration of brain circuits, leading to cognitive deficits.

A growing body of research has demonstrated that cognitive challenges, such as dual-task walking, elicit distinct changes in neural activity. These changes manifest as shifts in event related potentials (ERPs), spectral power across frequency bands and as alterations in network connectivity, particularly within frontoparietal and cortical-subcortical circuits. Notably, studies employing graph-theoretical analyses have revealed that cognitive load is often accompanied by reduced global efficiency and reorganization of network clustering, reflecting a dynamic recalibration of information processing strategies.

Importantly, these neural dynamics are not only observed in healthy individuals but are also markedly altered in various neurological conditions, such as Parkinson's disease (PD). Such alterations are associated with deficits in attention and inhibitory control and may serve as sensitive biomarkers for cognitive dysfunction. Furthermore, interventions such as motor training have been shown to modulate task-related network properties, highlighting the plasticity of the brain's cognitive architecture even in clinical populations. Together, these findings underscore the critical role of brain network dynamics in supporting cognition and offer promising avenues for the development of electrophysiological biomarkers to track cognitive health and impairment. This work synthesizes current evidence from EEG-based studies [1-3] to provide an integrated perspective on the neural mechanisms underlying cognitive function and dysfunction in both health and disease.

Methods

Studies included both healthy individuals and Parkinson's disease patients, who performed cognitive and motor tasks while undergoing EEG recording [1-3]. The studies received approval from the local ethical committee in accordance with the Declaration of Helsinki principles, and all participants provided informed written consent prior to participation.

64-channel EEG was used to capture ongoing brain activity during task performance. Electrode placement followed standard international systems (10-20 system), and signals were sampled at 250Hz. Raw EEG data underwent preprocessing steps to remove artifacts and enhance signal quality. This included: (1) Band-pass filtering, (2) Removal of artifacts such as eye blinks and muscle activity using independent component analysis (ICA), (3) Segmentation of the continuous EEG into epochs time-locked to task events or stimuli.

EEG analysis included calculation of P300 and N2 amplitude and latency [1], spectral analysis [2], source localization with interpolation and parcellation [2], and connectivity analysis [3]. Spectral power was computed for each epoch and region of interest using fast Fourier transform (FFT) or wavelet decomposition, allowing quantification of frequency bands (delta: 1–4 Hz, theta: 4–8 Hz, alpha: 8–13 Hz, beta: 13–30 Hz). Event-related spectral perturbation (ERSP) analysis was also employed to assess changes in power relative to baseline during task. The standardized current source density in the gray matter and the hippocampus of the MNI-reference brain was evaluated for each trial in 6239 brain voxels using sLORETA. Next, the source activity was interpolated onto an AAL atlas in MNI coordinates, containing 116 regions of interest (ROIs), and subsequently parcellated using Fieldtrip toolbox for MATLAB. Functional connectivity between brain regions was estimated using coherence, resulting in connectivity matrices for each condition1. These matrices were analyzed using graph-theoretical approaches to extract network metrics. Clustering coefficient was used to quantify the degree to which nodes cluster together. Degree was performed to measure the number of connections for each node. Global efficiency was applied to reflect the integration capacity of the network. Statistical analysis tested group differences and task effects using mixed-model or repeated-measures ANOVA, with corrections for multiple comparisons. Covariates such as age and medication status were included where relevant.

Results

The results demonstrated significant group differences in response inhibition and neural dynamics during walking. Behavioral data showed lower VGNG accuracy in PD patients compared to young and older adults, with prolonged N2 latency during walking versus sitting across all groups ($p=0.013$). PD patients exhibited longer P300 latency during walking compared to sitting ($p<0.001$), particularly in NoGo trials [1]. Moreover, the young adults showed the smallest number of electrodes for which a significant differential activation between sit to walk was observed, while PD patients showed the largest with N2 being more strongly manifested in bilateral parietal electrodes during walking and in frontocentral electrodes while seated [Figure 1A]. Source localization analysis showed alterations in activity within a distributed network of brain areas associated with attention and inhibition operations, including a circuit pathway connecting frontal and temporal/parietal regions and the limbic network [2]. The alterations in activity were associated with task complexity (single- or dual- task) and group (PD or controls) and encompassed spatial, temporal and spectral dimensions [Figure 1B & 1C]. The functional connectivity analysis showed that PD patients had: (1) Higher δ/θ band power but lower α/β power (group×band interaction: $p<0.001$), (2) increased within-network connections ($p<0.034$), and (3) elevated cluster coefficient in graph analysis (group×band: $p<0.001$). These findings correlated with worse GO/NOGO task performance in PD ($p<0.001$) [3].

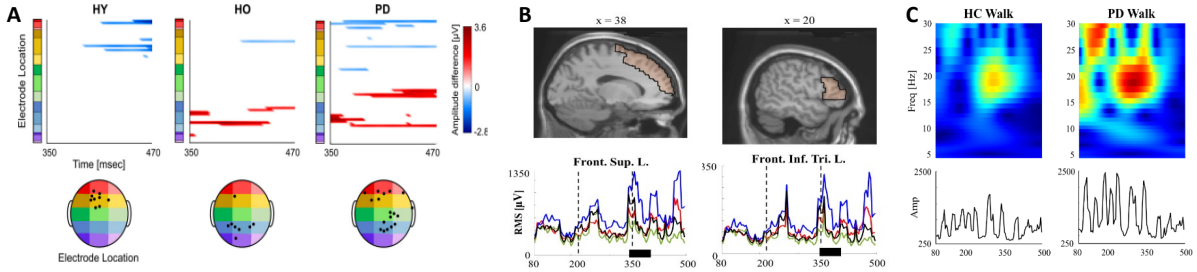

Figure 1: Event-related potentials (ERPs) during the Go-NoGo task during sitting and walking in healthy and PD. (A) Significant electrode-time points for P300 amplitude differences are color-coded; black circles indicate electrodes with significant effects [1]. (B) Sagittal brain sections highlight parcels with significant group and condition effects, with mean parcel activation curves for each group/condition; black bars denote significant differences [2]. (C) Spectrograms display right frontal superior gyrus activity during NoGo events, with average post-stimulus activity (80–500 ms) shown below [2].

Discussion

Our results indicate that response inhibition during walking is impaired in both older adults and Parkinson's disease (PD) patients, with increased cognitive load during dual-task walking leading to significant changes in parietal and frontocentral scalp electrical activity. We observed robust, group- and condition-dependent differences in the amplitude, latency, and distribution of ERP components associated with both early (automatic) and late (cognitive) phases of inhibitory control. These findings highlight the involvement of distinct neural circuits in single- and dual-task conditions and suggest that PD patients may recruit additional attentional resources during walking as a compensatory mechanism. Furthermore, alterations in brain network dynamics—such as increased δ and θ activity, reduced α and β activity, and changes in connectivity—underscore the network-level underpinnings of cognitive deficits in PD. Future work will employ source localization and connectivity analyses to further delineate the neural pathways underlying normal and impaired inhibitory control.

Conclusions

These findings have important implications for the clinical management of Parkinson's disease. Electrophysiological biomarkers identified in this study can inform the development of adaptive, closed-loop DBS systems, enabling real-time, personalized adjustments to stimulation parameters and ultimately improving the efficacy of neuromodulation therapies for motor-cognitive symptoms in PD.

Acknowledgements

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