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TITLE: Neurophysiologic Mechanisms of Freezing of Gait: Disentangling Phenotypic Heterogeneity with Mobile EEG and Wearable Kinematic Sensors

PRINCIPAL INVESTIGATOR: Kathryn Cross

CONTRACTING ORGANIZATION: University of California Los Angeles

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14. ABSTRACT Freezing of gait (FOG) is a disabling complication of Parkinson's disease (PD) characterized by episodes of difficulty continuing or initiating walking. The goal of this research is to identify neural correlates of freezing susceptibility, onset and recovery, and how these mechanisms relate heterogeneity in FOG phenotypes using state of the art mobile brain body imaging (MOBI) techniques. 60 patients with PD perform a walking task employing multiple trigger types (dual task, doorway, initiation, turning, cluttered environment) during high density electroencephalography (EEG) and movement kinematic recordings under three conditions: no cues, visual cues and auditory cues. The project is in the data collection phase, and we have enrolled and completed data collection in 18 patients with Parkinson disease. Interim analyses of individual subject data demonstrate expected gait-related neural activity modulation and modulation of gait kinematics by sensory cues, indicating adequate data quality for planned group analyses relating gait kinematics and EEG data across the cohort.					
15. SUBJECT TERMS Parkinson's disease, freezing of gait, electroencephalography, external cues, mobile brain body imaging					
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1. INTRODUCTION:

Freezing of gait is a disabling and poorly understood complication of Parkinson's disease characterized by episodes of difficulty continuing or initiating walking that contributes to poor quality of life and is often refractory to treatment. A significant barrier to the development of effective FOG neuromodulation therapies is the poor understanding of the underlying neurophysiology of FOG. The goal of this research is to identify neural correlates of freezing susceptibility, onset and recovery. In addition, we examine how these mechanisms relate to the large heterogeneity observed in FOG phenotypes, such as the diverse freezing triggers and variability in efficacy of rehabilitation strategies used to overcome freezing episodes. Our overarching hypothesis is that abnormal neural activity in dissociable cognitive and motor cortical networks contribute to different freezing phenotypes and that behavioral strategies to overcome freezing differentially affect these networks. In Aim 1, 60 patients with PD (40 with FOG, FOG+ and 40 without freezing, NF) perform a walking task employing multiple trigger types (dual task, doorway, initiation, turning, cluttered environment) during high density electroencephalography (EEG) and movement kinematic recordings. Here we identify neurophysiologic correlates associated with freezing episodes elicited by distinct triggers. In Aim 2, the same group performs the walking task with auditory and visual cues (separately) to determine how these modulate gait kinematics and associated neural correlates. By relating electrophysiological activity to kinematic measures of cueing benefits, we will elucidate mechanisms associated with cueing efficacy, rather than simply the neural correlates of walking in the presence or absence of cues.

2. KEYWORDS:

Parkinson's disease, freezing of gait, electroencephalography, external cues, mobile brain body

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Aim 1: To identify neural signatures of freeze-free walking and freezing episodes using high density mobile EEG and simultaneous kinematic measurements in ambulating subjects with and without FOG.

Aim 2: To determine how sensory cues modulate cortical network activity during successful cueing

Milestone 1: Human subjects IRB/HRPO approval (target: 12/31/21, actual: 8/9/21)

Milestone 2: ½ data collection complete (both aims) = 30 patients (target 9/29/21, current: 18 pts = 60%)

Milestone 3: data collection complete (both aims) = 60 patients (target 7/30/22, current: 30%)

What was accomplished under these goals?

As described in the SOW, the planned activities for the first year of this project focused on implementation of mobile EEG experiments and data collection. I set up my independent lab including hiring and training a research assistant for this project; obtained regulatory approval for the human subjects research; implemented the mobile EEG experiment; initiated data collection for both aims; and established much of the preprocessing and analysis pipeline for individual subject data processing. Implementation of the tasks required establishing and testing millisecond level synchronization between multiple devices (mobile EEG system, kinematic measurements, visual and auditory cues).

Data collection was initiated 3 months behind schedule due to recruitment delays caused by the COVID-19 Omicron surge, during which limitations on human subjects research without direct benefit to patients were in place. After recruitment started and recruitment strategies were established in our clinics, we have enrolled and completed data collection at a rate of 8 patients per quarter, slightly below the goal of 10 patients per quarter.

The pipeline for preprocessing EEG data has been developed based on best practices in the field of mobile brain body imaging (Figure 1). Preliminary analyses of individual subject data have been implemented to (1) quantify how auditory and visual cues affect spatiotemporal gait parameters and (2) how EEG power is modulated by the gait cycle under these same cueing conditions.

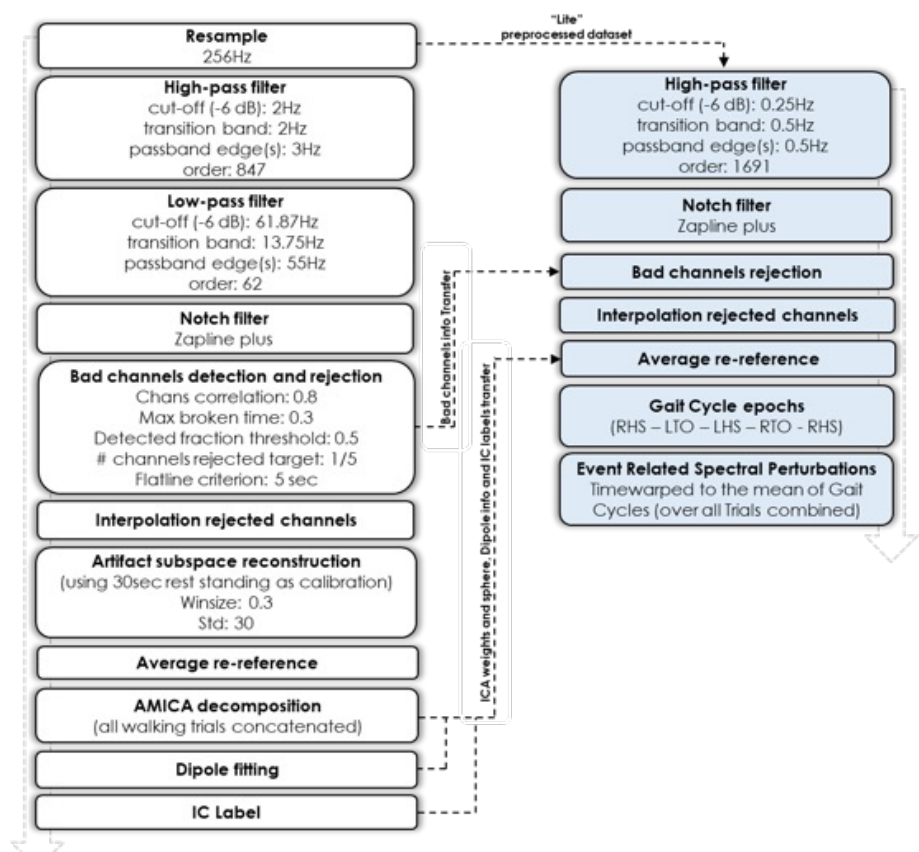


Figure 1. Flow chart of EEG preprocessing pipeline

As shown for one example subject (Figure 2), we observe expected power modulation of high beta and gamma (20-60 Hz) power in vertex electrode across the gait cycle in the uncued condition (left panel). This gait-related cortical power modulation is affected differentially by auditory and visual cues, with more prominent high beta/gamma (30-60Hz) power modulation during walking without cues and walking with auditory cues as compared to walking with visual cues. In addition, alpha power peak during normal walking is suppressed by both cueing conditions.

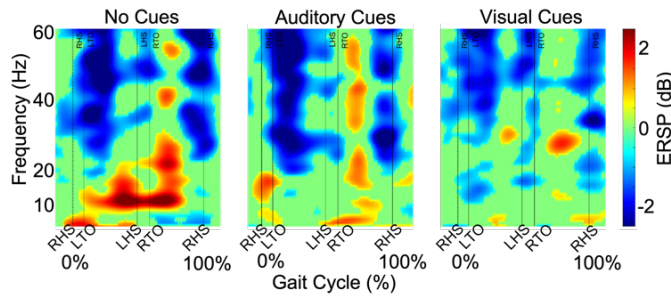


Figure 1. Example EEG data from one patient. Event Related Spectral Perturbations (ERSPs, dB change in power relative to average across complete gait cycle) from the CZ electrode time-locked to gait cycle events defined as Right Heel Strike (RHS) – Left Toe Off (LTO) - Left Heel Strike (LHS) – Right Toe Off (RTO) -- Right Heel Strike (RHS). Plots are masked for significance relative to average power across full gait cycle after bootstrapping permutations (alpha = 0.05). 3 walking conditions are depicted from left to right: walking normally (without cues), walking with a metronome, stepping over laser lines.

The auditory and visual cues also modulate spatiotemporal gait parameters differentially in this subject (Figure 3). Stride length is increased significantly by visual and auditory cues, and moreso for visual cues. Cadence significantly increases with auditory cues but not with visual cues and variability in cadence is reduced (e.g. gait rhythmicity improves) with auditory cues only.

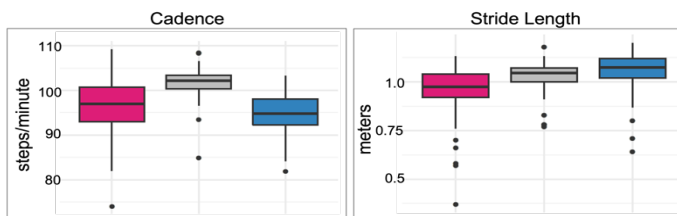


Figure 2. Gait cadence and stride length from the same patient are modulated differentially by sensory cues. Cadence variability decreases and magnitude increases with metronome set 10% faster than baseline walking pace; no increase in cadence is observed with visual cueing. In contrast, both auditory and visual cues increase stride length.

Overall, preliminary individual subject results indicate that our manipulation is successful in modulating gait and neural parameters of interest. Once the full cohort has been collected, analysis relating kinematic changes to neural changes will be performed at the group level to draw conclusions regarding neural correlates of cueing benefits in patients with and without freezing of gait. Recruitment of more patients with FOG and development of the analysis of the neural correlates of freezing episodes is ongoing.

What opportunities for training and professional development has the project provided?

For this early career grant, direct training in mobile brain body imaging – from experimental design to implementation and analysis – was obtained through one-on-one meetings with the mentor, Dr. Nanthia Suthana as well as participation in her lab meetings. In particular, her expertise and guidance was instrumental in successfully accomplishing synchronization across recording modalities and she also assisted with assessment and preprocessing pipelines for artifact reduction. She has also provided career mentorship including ongoing discussions planning future R01 submission to obtain independent funding to continue the Parkinson disease gait research initiated here.

For professional development, I attended the 4th International Conference on Mobile Brain/Body Imaging in July of 2022 which included (1) a 4-day workshop on best practices in mobile brain body imaging (e.g. mobile EEG) run by leaders in the field and (2) a 3-day scientific conference on mobile brain body imaging providing networking opportunities. Training in advanced electrophysiology techniques was further supported by attendance at weekly Electrophysiology Affinity Group Seminars at UCLA, in which invited outside speakers, UCLA faculty and UCLA trainees present ongoing work or journal club style presentations. In addition, I attended the virtual International Movement Disorder Society conference in September 2021

How were the results disseminated to communities of interest?

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?

Data collection will be continue and be completed. This will require recruitment of 41 patients with the majority being patients with freezing of gait. In parallel with completion of data collection, we will implement the remaining individual subject analyses examining neural correlates of freezing episodes and gait initiation and their modulation by external auditory and visual cues. Once the full cohort has been collected, individual subject data will be entered into group analyses comparing activity in patients with and without freezing, patients with and without cueing benefits, and regression analyses to examine the relationship between spatiotemporal gait parameters and cortical activity from which we can draw final conclusions

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

Initiation of data collection was delayed by the COVID-19 Omicron surge, as our population is generally high risk due to majority being of advanced age. In addition, enrollment of patients with freezing of gait is slower than expected. No changes in the protocol or scope of work are planned. To compensate for delays in initiation of data collection and to enrich the population with patients who have freezing of gait, additional recruitment strategies to are currently being initiated. Specifically, we will begin advertising outside of UCLA to the broader Parkinson disease community through online advertisements and engagement with local support groups and rehabilitation service providers.

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

Nothing to report

Books or other non-periodical, one-time publications.

Nothing to report

Other publications, conference papers and presentations.

Nothing to report

- **Website(s) or other Internet site(s)**

Nothing to report

- **Technologies or techniques**

Nothing to report

- **Inventions, patent applications, and/or licenses**

Nothing to report

- **Other Products**

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Ipek Talu
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID): n/a
Nearest person month worked: 10
Contribution to Project: Ms. Talu has performed work in patient recruitment, data collection and data entry.
Funding Support:

Name: Federico Genarro
Project Role: Post-doctoral Fellow
Researcher Identifier (e.g. ORCID ID): n/a
Nearest person month worked: 2
Contribution to Project: Dr. Genarro has performed data collection and data analysis.
Funding Support: PI unrestricted funds (research start-up)

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS: *None*

9. APPENDICES: *None*