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PRINCIPAL INVESTIGATOR: Dr. Kathryn Cross, MD

CONTRACTING ORGANIZATION: University of California Los Angeles

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Dr. Kathryn Cross, MD

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Office of Research Administration
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13. SUPPLEMENTARY NOTES

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 20 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 9/29/22, actual: 9/7/2023)
Milestone 3: data collection complete (both aims) = 60 patients (target 7/30/2023, actual: 55%).
Milestone 4: complete group analysis and disseminate results (both aims). (Original target 9/30/23, no-cost extension approved, new target: 9/30/24).

What was accomplished under these goals?

During this reporting period, we have continued data collection with a total of 32 patients with Parkinson disease acquired to date. We have finalized the individual subject processing pipelines for EEG and kinematic data, allowing for preliminary results to be analyzed at the group level and presented at national and international conferences.

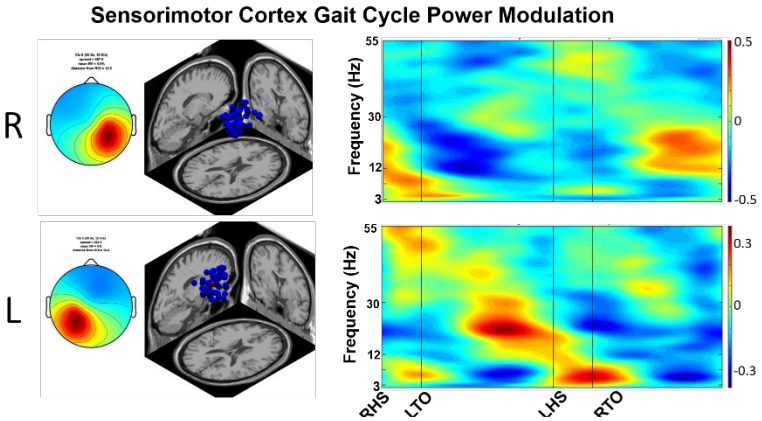

Figure 1. Power modulation in right (R, top row) and left (L, bottom row) sensorimotor clusters. Clear modulation of beta (12-30 Hz) power with the gait cycle is evident in both legs with suppression during the contralateral leg swing phase (LTO->LHS in R cortex, RTO->RHS in L cortex).

As part of **Aim 1**, we have identified neural signatures of freeze-free walking in the preliminary group of patients. High density EEG data are decomposed into independent components of spatially distinct activity. Shared clusters across the group are identified using source localization techniques. This has demonstrated that in motor cortex, supplementary motor area and parietal regions activity is modulated in phase with the gait cycle. In sensorimotor cortex, this is most prominent in the beta frequency band (12-35 Hz), where beta suppression occurs during the swing phase of the contralateral leg, consistent with beta reflecting movement-related activity of the contralateral leg (Figure 1). Upon completion of 20 participants per group (FOG+ and NF), we will have sufficient data to make group comparisons of freeze-free walking to understand neural correlates of freezing susceptibility.

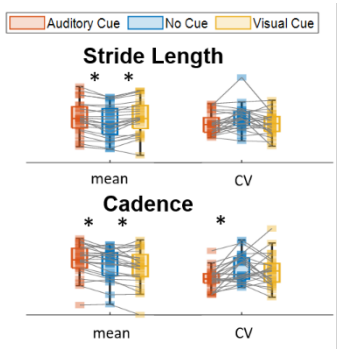

Figure 2. Gait parameters improve with visual and auditory cues at the group level and in a majority of patients.

For **Aim 2** we compare gait-cycle related activity during normal walking to walking with auditory and visual cues. Importantly, we will look specifically at how these changes are related to changes in gait parameters, to identify potential compensatory activity related to benefits from external cues, rather than simply changes related to cue processing that are not related to gait improvement. Auditory and visual cues both improve gait at the group level, but to varying degrees across subjects and with some differences in parameters affected (Figure 2). Synchronizing gait to rhythmic auditory cues improves stride length, cadence and cadence variability whereas stepping over lasers improves stride length but does not improve cadence, but may even slow cadence. These behavioral changes are accompanied by amplification of gait-cycle modulation of beta power (Figure 3) leading to greater movement-related suppression and stance phase resynchronization during visually cued walking as compared to walking with no cues (Figure 1, R panel arrow). This is consistent with our hypothesis that using external cues increases recruitment of cortical

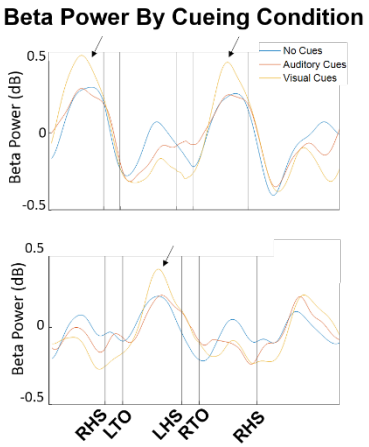

Figure 3. *Sensorimotor b*eta power modulation is amplified during visual as compared to uncued condition

"voluntary" motor systems as a potential compensatory mechanism for walking impairments due to abnormal basal ganglia function. In contrast for auditory cues theta band activity in SMA is related to gait improvement. This is consistent with the hypothesis that engagement of cortical sensorimotor synchronization networks may mediate the effects of auditory cues on improvement of PD gait.

Despite development of a walking task with many different types of cueing triggers, we have elicited freezing episodes in only 30% of patients who report freezing in daily life. This is similar to previous descriptions of freezing of gait research noting the difficulty of eliciting freezing in research settings when attention is directed to gait. We have found that our aim to improve freezing elicitation by performing a walking task with multiple different ecological freezing triggers has not solved this challenge. While we will still be able to examine freezing-related activity (**Aim 1**) in this subset of patients once the cohort is complete, there will likely not be sufficient power to compare across different freezing trigger types as we had initially planned. As a result, this work has motivated a novel approach using immersive VR in which we can reliably elicit freezing using an adaptable, patient-specific freezing triggers which we believe will allow us to identify freezing neurophysiological signatures in future work.

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 – has been obtained through direct mentorship from Dr. Nanthia Suthana. She has assisted with implementation of the experimental setup as well as analysis of gait-related neural activity. She has also provided career mentorship including ongoing discussions and collaboration for an R01 using VR to improve freezing elicitation planned for submission in February, 2024. For professional development, I have attended the UCLA CTSI Junior Faculty lecture series. In addition, attendance at the weekly Electrophysiology Affinity Group Seminars has included lectures in mobile brain body imaging and advanced electrophysiology analysis. The post-doctoral fellow who is working on the project has also received training in advanced computational techniques. He attended the EEGLab and cuttingEEG Brainstorm Workshops, which are led by experts in the field of EEG and mobile brain body imaging and provided training in multivariate analysis of high dimension EEG and kinematic data.

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 completed (28 subjects, 2-3 per month) and group analysis will be finalized with the complete cohort of patients. In addition to expanding the analyses described in the "Accomplishments" section to the full cohort, we will examine neural correlates of freezing episodes in the subset of patients who demonstrate freezing during the study. Results will also be submitted for publication. As described in detail below, we have modified recruitment plans to improve enrollment.

4. IMPACT:

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

Our preliminary results suggest that specific changes in neural activity can be related to gait improvement in response to external cues. Should these results hold upon completion of the full study cohort, the identified neural signatures will provide targets for future neuromodulation strategies that augment the observed activity (e.g. gait-related SMA theta modulation or sensorimotor beta modulation). Though prior work has examined the effect of different types of external cues on gait or on brain activity, it has not linked the cue-related neural activity to actual improvements in gait. This is particularly problematic given that we know that patients have variable improvement with cues. As such, it is unclear whether previous results are related to gait improvements, or simply to processing of the cues absent any improvement in gait. Our work will fill this important gap.

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

Our recruitment has unfortunately been slower than planned, despite expanding our strategies during the last year to reach patients outside of the UCLA movement disorders program using third party online advertising. While this did generate significantly more interest in the study, a small number of the identified participants were eligible. Specifically, the presence of freezing and ability to complete the study OFF dopaminergic meds results in a relatively narrow target patient population. In recent months, we again adapted our recruitment strategies to improve enrollment and allow us to complete the study during the recently granted no cost extension. Specifically, instead of online advertising, we will contact our Movement Disorders, neurology and physical therapy colleagues and referring practices directly with specific eligibility criteria. We believe this will be more successful than the less targeted approach we relied upon in the 2nd year of the project given the relatively narrow target population

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.

Gennaro F, Talu I, Cross K. *Gait cycle-related neural activity during cued and uncued gait in Parkinson's disease patients.* International Congress of Parkinson's Disease and Movement Disorders. 1213. Copenhagen, Denmark, Aug 2023. *Movement Disorders, 38, S538.*

Ma L, Talu I, Cross KA. *Auditory and Visual Cues Elicit Different Cortical Responses in Parkinson's Disease Patients during Walking.* Platform Accepted for American Physical Therapy Association Combined Sections Meeting. 42393. 2024. Boston, MA.

Ma L, Talu I, Cross KA. *Alpha and theta activity in the supplementary motor area correlates with gait benefits from auditory cues in Parkinson's Disease and their healthy counterparts.* Poster Accepted for Society for Neuroscience 2023. Washington, DC.

- **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:	This Award

Name:	Leo Ma
Project Role:	Post-doctoral Fellow
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	6
Contribution to Project:	Dr. Ma 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*