Neural and Kinematic Features of Freezing of Gait for Adaptive Neurostimulation

Statistical Analysis Plan

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Data Analysis

Concurrent Kinematic and Neural Recording: The kinematic signals from the wireless Opal sensors and tri-axial accelerometer are sampled at 128 Hz and 1 kHz, respectively. Video recordings (thirty frames/second) are acquired concurrently with the LFP signals (sampled at 1 kHz) using our data acquisition interface and Spike software. The data from the wireless Opal sensors is collected using Mobility Lab software (APDM, Inc., Portland, OR).

Neural Signal Analysis: Signal analysis will be performed in MATLAB (version 8.2, The MathWorks, Inc., Natick, MA, USA). Prior to analysis, the data will be parsed into rest, movement, and various stimulation state epochs using Spike software, with care being taken to exclude any sections containing signal or movement artifacts from further analysis. Spectrograms of LFP epochs will be generated using a short-time Fourier transform of a one second Hann filtered sliding window and 50% overlap. The power spectral density (PSD) estimate will be calculated using Welch's method with the aforementioned windows and overlap parameters. Phase-amplitude coupling (PAC) between pairs of frequency (i.e. phase and amplitude components) will be calculated using Tort's modulation index (MI). Signals will be band-pass filtered using a two-way least square FIR filter with 1 Hz frequency resolution for phase and 2 Hz frequency resolution for amplitude; frequencies will be used to account for correcting the frequency leakage in higher frequencies. A surrogate data analysis will be performed to assess the statistical significance of MI values extracted for each frequency pair and MI values will be converted to z-scores. A PAC map will be formed to show PAC values (z-scores) between each frequency pair (phase and amplitude) for each subject.

Kinematic Analysis: During the FW and TBC tasks, the wireless Opal sensors will be used to measure gait speed, stride and swing duration, gait arrhythmicity and asymmetry, and the number and duration of freezing episodes, as detailed in Section During the SIP task, we will evaluate the stepping cycle rhythmicity and symmetry and the number and duration of freezing episodes on force plates[1].

Power analysis

Thirteen/fifteen (~87%) freezers had at least one freezing episode during the SIP task (mean number of freezes = 4.9, STD=+/- 2.47)[1]. Previous studies found an average of 66% improvement in freezing metrics between ineffective and effective stimulation conditions[2]. A power analysis (paired t-test) using the mean number of freezes with ineffective/NO DBS (4.9, STD +/- 2.47, from above) and a 65% improvement from effective stimulation shows that the largest sample size required for significant outcomes is 9 subjects with freezing during SIP (alpha=0.05, power=0.8, assuming only 87% of patients will freeze during tasks).

Comparison of characteristics at baseline

Student's t-tests were used to compare age, disease duration, pre-op and post-op Unified Parkinson's disease Rating Scale (UPDRS) between the Freezer and Non-Freezer groups.

Analysis of primary outcome

The number and percentage of occurrences of treatment-related adverse events (AE) will be reported for each treatment arm of continuous DBS (cDBS), adaptive DBS (aDBS) and off DBS.

Analysis of secondary outcomes

For Alpha/beta power and Sample Entropy (SampEn): Alpha/beta power varied across subjects sometimes by orders of magnitudes. Relative alpha and beta power was calculated by dividing the summed absolute alpha or beta power by the summed power in the 40- 70 Hz band during the resting state, and allowed comparison across subjects, whose raw signal magnitude can vary by one or two orders of magnitude, see Supplementary information. The FW task was analyzed by excluding the turning periods at the end of the 10 m of straight walking. As a result, each FW task had 4 trials. Similarly, as the TBC task had four trials, it was also analyzed as four separate time periods for each patient. The SIP task had one trial per patient. Asymmetry and arrhythmicity were assessed individually using a linear mixed effect model in Freezers and Non-Freezers during FW, while a one-way ANOVA was used in SIP. A one way ANOVA and a Kruskal-Wallis test by ranks was also used to determine if alpha or beta power and SampEn changed significantly between Freezers and Non-Freezers in SIP, while a linear mixed effects model was used for both TBC and FW, in order to account for the four trials. Freezer or Non-Freezer type was a fixed effect and a factor variable with 2 levels (Freezer and Non-Freezer). Subject STN was a random effect, and a random intercept was used in the model. Residuals were assessed for homoscedasticity and normality, and all statistical assumptions were met.

To compare arrhythmicity, asymmetry, or stride time between groups, a one-way ANOVA was used. Paired t-tests were used to com- pare the effects of different stimulation frequencies on arrhythmicity, asymmetry, and stride time within each group for each task. Post hoc analyses were completed to compare between stimulation conditions. All statistical testing was performed in SigmaPlot (Systat Software, San Jose, CA) using two- tailed tests with significance levels of $P < .05$.

References

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3. Syrkin-Nikolau, J., Koop, M. M., Prieto, T., Anidi, C., Afzal, M. F., Velisar, A., ... & Bronte-Stewart, H. (2017). Subthalamic neural entropy is a feature of freezing of gait in freely moving people with Parkinson's disease. Neurobiology of disease, 108, 288-297.

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