Statistical Analysis Plan

Study: Effects of intermittent theta-burst stimulation on neurophysiological and neuromuscular recovery from fatigue in Parkinson's disease: a randomized, sham-controlled pilot crossover trial

1. Design
Single-blind, randomized, sham-controlled, two-period crossover pilot study. 10 PD patients and 10 age/sex-matched healthy controls, each completing an iTBS and a sham session in randomized order, separated by a one-week washout. Randomization: stratified permuted-block (stratum: group; block size 2).

2. Objectives and outcomes
Primary: within-subject change in isometric maximal voluntary contraction (MVC, kg) from pre-exercise baseline, compared between iTBS and sham conditions.
Secondary: power, velocity, voluntary activation, corticospinal excitability (MEP/Mmax, absolute MEP amplitude), cortical silent period, resting/active motor thresholds, and EMG time- and frequency-domain measures (RMS, median frequency, spectral power in three frequency bands), all as change from baseline.
All outcomes assessed at baseline and 5, 12, and 20 minutes post-exercise/intervention, under both conditions.

3. Primary analysis
Because no assessment was available between the fatiguing exercise and the intervention, all primary inferences are based on the within-subject difference between the iTBS and sham conditions (Δ = iTBS − sham) at each post-exercise timepoint, which cancels the unobserved post-fatigue state. Between-group comparisons and within-group contrasts against zero are assessed using exact permutation tests: label-exchange permutation (enumerating all C(20,10) = 184,756 possible allocations) for two-group comparisons, and sign-flip permutation (enumerating all 2^{10} = 1,024 possible sign reversals) for one-sample contrasts. These do not rely on asymptotic approximations or estimated degrees of freedom and are appropriate at n=10 per group. Effect sizes are reported as Hedges' *g* (between-group) or Cohen's *dz* (within-subject), with 95% confidence intervals from non-parametric bootstrap (5,000 resamples).

4. Secondary and exploratory analyses
Baseline equivalence between sham and iTBS visits: paired sign-flip permutation, per outcome.
Peripheral neuromuscular stability: maximal M-wave amplitude tested for statistical equivalence across conditions and groups using two one-sided tests (TOST; margin ±5% of baseline).
Associations between neurophysiological and fatigue measures: repeated-measures correlation (rmcorr), preferred over Pearson/Spearman correlation to avoid conflating within- and between-subject variance in this repeated-measures design.

5. Sensitivity analyses
Treatment-order and carry-over effects (Grizzle test), applied to all outcomes.
Leave-one-subject-out re-analysis of the primary outcome interaction and the cortical silent period interaction.

Consistency of corticospinal excitability findings across normalization approaches (MEP/Mmax ratio vs. absolute MEP amplitude).

6. Multiplicity
Given the pilot, hypothesis-generating nature of the study, all outcomes are reported without correction for multiplicity. Effect sizes and 95% confidence intervals, rather than dichotomous significance, are the primary basis for interpretation; secondary outcomes are regarded as exploratory.

7. Missing data
No missing data

8. Significance threshold
Two-tailed $P < 0.05$.

9. Software
R (v 4.6.1), custom implementations of exact permutation, bootstrap, and repeated-measures correlation procedures.