Title: Altering Activation Patterns Post-stroke
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Analysis: Spasticity will be quantified using the MCP angular position and torque data from the trials of imposed MCP rotation [27, 66-68]. Namely, the nominally passive torque curve (recorded during the 10°/s trial) will be subtracted from the total torque curve (recorded during the 300°/s). Mean reflex torque will then be computed from the resulting signal by averaging across a 300-ms period beginning at the end of stretch. The EMG data, normalized by the values recorded during maximum contraction, will be used to confirm that a reflex occurred. The FDS signal must surpass a threshold of 5% of maximal contraction for classification as a spastic stretch reflex and subsequent evaluation. Coactivation during voluntary tasks will be computed from the ratio of normalized EDC/FDS for flexion and FDS/EDC for extension. Values closer to 0 indicate less coactivation. Relaxation time will be estimated as the elapsed time from cessation of the auditory tone to the FDS signal dropping below a threshold level equal to three standard deviations of the resting signal [34]. Active isometric flexion and extension torque will be found by subtracting the initial, passive torque from the peak torque recorded during the respective trials.

Statistical analyses will be employed to assess the effect of cyproheptadine on these outcome measures. We will perform repeated measures analysis of variance (rmANOVA) with the between-subject factor Drug (cyproheptadine, placebo) and the within-subject factor evaluation Session (pre-administration, week 1, week 2, week 3 - see Fig. 1). To test the first hypothesis, addressing efficacy in reducing hyperexcitability, the measures spastic reflex, FDS relaxation time, and coactivation ratio will be used as dependent variables in a MANOVA. Should evidence of a significant effect appear, i.e., a Wilk's lambda value < 0.05, we will perform subsequent post-hoc ANOVAs to test the effects on individual dependent variables. To examine the second hypothesis, regarding loss of strength, separate rmANOVAs will be conducted for extension and flexion strength. Similarly, as we wish to minimize Type II errors for these potentially negative outcomes, separate rmANOVAs will be run for ESS and BDI-II without correction. Normality of the residuals will be tested for these parametric tests and non-parametric tests will be run if normality assumptions are violated.

We will have 50 subjects in each of our Drug groups (cyproheptadine/placebo) in accordance with the power analysis performed for the whole study (see ***Aim 2: Analysis***). Thus, we will be able to detect an effect size of 0.22 with a power of 80% for an α of 0.05 (G*Power 3.0 software [69]). In our pilot study examining a single dose of cyproheptadine, we observed a much greater effect size of 0.60 for the reduction in relaxation time. Importantly, the targeted subject numbers will allow us to detect even moderate decreases in strength or increases in somnolence.