Priming the Brain for Rehabilitation: Brain Stimulation Followed by Constraint-Induced Movement Therapy in Adults with Severe Arm Paresis after Stroke

Study Protocol & Statistical Analysis Plan

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Outline of Study Design and Procedures

1. **Overall Goals**
   1.1. Demonstrate the feasibility of combining intermittent theta burst stimulation (iTBS; a form of TMS) with an expanded form of Constraint-Induced Movement therapy (eCIMT) for treating adults after stroke with chronic, severe upper-extremity impairment.
   1.2. Get a preliminary read on whether stimulating a brain region that controls movement of the more-affected arm with iTBS boosts the effect of eCIMT on use of the more-affected arm in everyday life and on the motor capacity of that arm.
2. **Specific Aims**
   2.1. To gather preliminary data on the therapeutic effect of eCIMT plus iTBS in adults with severe, chronic hemiparesis after stroke. If the data are promising, they will be used to inform decisions about the appropriate sample size and other logistics for a RCT to be proposed to NIH that will compare the efficacy of eCIMT+iTBS to a) eCIMT alone and b) usual care.
   2.2. To establish feasibility for using magnetic resonance spectroscopy (MRS) to identify the cellular basis of any neuroplastic changes we might observe after eCIMT+iTBS. Our labs already have expertise in magnetic resonance imaging (MRI) methods that will permit detection of changes in brain activity (fMRI) and grey matter (MRI) and white matter structures (diffusion weighted imaging; DWI). If any changes in brain activity or structure take place, MRS will permit examination of the changes in the cellular composition of those regions. As noted, grey and white matter changes have been observed after the original form of CIMT.
3. **Study Design**
   3.1. Baseline Testing→ No treatment for 3 weeks→ Pre-treatment Testing→ eCIMT+iTBS for 3 weeks→ Post-treatment Testing→ 4-weekly follow-up phone calls→ → → 12-month follow-up.
4. **Participants**
   4.1. Twenty adults more than 1-year after stroke with severe impairment of their more-affected arm, i.e., plegic or nearly plegic hands
      4.1.1. Grade 4 or Grade 5 with stipulation that patient can perform reliable, active extension of wrist to permit collection of fMRI data
      4.1.2. Participants from whom MRI would be contraindicated will be excluded
         4.1.2.1. This covers all of the exclusion criteria for the iTBS procedure but one, which is exclusion of any candidates with a history of seizures.
5. **Intervention**
   5.1. eCIMT: Expanded CIMT (eCIMT) combines CIMT with neurodevelopmental techniques (NDT) for managing tone.
   5.2. iTBS: Intermittent theta burst stimulation is a form of excitatory transcranial magnetic stimulation (TMS) that involves delivery of magnetic pulses in bursts and at a frequency that mimics the frequency of theta brain waves. It has robust evidence of promoting long-term potentiation, whereas more standard forms of TMS do not.
      5.2.1. Initial stimulation threshold determined with FDI muscle in less-affected hand

5.2.2. Hotspot for stimulation of cortical area controlling movement of more-affected hand/wrist identified with support of fMRI images obtained during movement of more-affected wrist.

5.3. Treatment period: 15 consecutive weekdays

5.4. Treatment setting: iTBS in Sparks Rm 405, eCIMT in Taub Therapy Clinic.

5.4.1. Participant will be transported from Taub Therapy Clinic to iTBS facility and back using wheel chair.

5.5. Typical Treatment Day (4-4.5 hours):

5.5.1. eCIMT- Transfer Package component (structured interview on arm use, review of daily diary, problem-solving, etc... ; 15-20 min typically but substantially longer on first day)

5.5.2. iTBS (20-40 minutes on first treatment day, 10-15 minutes thereafter)

5.5.3. eCIMT- NDT, i.e., facilitation/tone management component: stretching, weight-bearing, oscillation, icing, vibration (60 minutes)

5.5.4. iTBS (10-15 minutes)

5.5.5. eCIMT- shaping component, i.e., training on tasks with frequent, positive feedback and raising of the bar for reward in progressive, small increments; simulated ADL practice (60 minutes)

5.5.6. iTBS (10-15 minutes)

5.5.7. eCIMT- shaping component, i.e., training on tasks with frequent, positive feedback and raising of the bar for reward in progressive, small increments; simulated ADL practice (60 minutes)eCIMT- Transfer Package component (structured interview on arm use, review of daily diary, problem-solving, etc... ; 15-20 min typically but substantially longer on first day)

5.5.8. eCIMT- Transfer Package component (assignment of home skill assignment, etc... ; 5-10 min typically but substantially longer on first day)

5.5.9. eCIMT- padded safety mitt will be worn on less-affected to discourage its use both during treatment and at home. Time that mitt is worn will be determined by safety considerations and the degree to which the patient needs to use the less-affected arm to accomplish tasks that are typically bilateral.

5.5.10. eCIMT- splinting and orthotic devices will introduced during eCIMT sessions on an as needed basis to support use of the more-affected arm to complete tasks.

6. Motor Function Testing

6.1. Occasions: Baseline, Pre-treatment, Post-treatment, 12-month follow-up

6.2. Setting: Taub Therapy Clinic and Blinded Testing Room ("Pink Room," SRC R056). Grade 4/5 WMFT will be conducted in Pink Room to permit collection of kinematic data.

6.3. Tests

6.3.1. Grade 4/5 Motor Activity Log (everyday use of more-affected arm)

6.3.2. Canadian Occupational Performance Measure (everyday use of arms)

6.3.3. Grade 4/5 Wolf Motor Function Test (motor capacity of that arm)

7. Data Analysis

7.1. Primary outcome is change from baseline to post-treatment on MAL

7.2. If the enrollment target is met, a repeated measures ANOVA will be used to evaluate whether statistically significant improvement is present on the primary outcome. The repeated measures factor will be Testing Occasion (baseline, pre-treatment, post-treatment, 12-month follow-up). If the omnibus test is significant, specific contrast statements will be used to test when improvement takes place.

7.3. Parallel methods will be used to evaluate the secondary outcomes.
7.4. If the sample size is substantially smaller than projected, changes on the primary outcome will be characterized using descriptive statistics.