Study Protocol and Statistical Analysis Plan

Title: Improvements in upper extremity function following intensive training are independent of corticospinal tract organization in children with unilateral spastic cerebral palsy: A clinical randomized trial.

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Study Objectives
This study aims to test the hypothesis that improvements in upper extremity function following either constraint induced movement therapy (CIMT) or bimanual training depend on corticospinal tract (CST) laterality and type of training (unimanual vs. bimanual) in children with unilateral spastic cerebral palsy (USCP). Specifically, we predict that children with a maintained contralateral CST will respond equally to CIMT and bimanual training, while children with ipsilateral CST laterality will be less responsive to CIMT than bimanual training.

Study Design
All study procedures will be approved by the Institutional Review Boards of Teachers College, Columbia University, where the treatments will be conducted, the Burke Medical Research Institute, where TMS evaluations will be performed, and Weill Cornell Medicine, where magnetic resonance imaging (MRI) will be performed.

We will recruit participants from clinics in the NYC area, our website (http://www.tc.edu/centers/cit/), ClinicalTrials.gov (NCT02918890), and online support groups. We will obtain written informed consent and assent from children and their caregivers.

We will randomize participants to receive either 90 hours of CIMT or Hand-Arm Bimanual Intensive Training (HABIT) after they complete all baseline outcome measures. Block randomization will be implemented for each cohort of participants, with each cohort stratified by age, sex, baseline hand function and CST connectivity pattern as closely as possible. Randomization will occur offsite using concealed allocation to receive either CIMT or HABIT. Intervention will be delivered in a day-camp model for 6 hours/day over 15 days for a total of 90 hours.

The inclusion criteria will be: 1) ages 6 to 17 years, 2) diagnosed with USCP 3) capable of participating in a 15 day, 6 hours/day day camp while separated from caregiver(s), 4) capable of following directions regarding hand use and testing, 5) capable of communicating needs, 6) mainstreamed in age-appropriate school classroom, and 7) able to lift the more affected arm 15cm above a table surface and grasp light objects. The exclusion criteria will be: 1) unwillingness to comply with instructions or other behavioral issues making delivery of an intensive therapy infeasible, 2) health problems unassociated with hemiplegia, 3) visual impairment that could interfere with participation, 4) orthopedic surgery on the more affected hand within 1 year, 5) presence of metallic objects in the body, and 6) botulinum toxin in the more affected upper extremity within the past 6 months or intended treatment within the study period, 7) seizures after the age of 2 years, 8) family history of seizure disorders, 9) current medication use to lower the seizure threshold, 10) claustrophobia, or 11) pregnancy.

We aim to recruit 82 participants based on sample size calculations from results of the Assisting Hand Assessment (AHA) and Jebsen-Taylor Test of Hand Function (JTTHF) outcomes of a prior CIMT/HABIT randomized controlled trial and pilot data.

Methodology
Children will participate in an intensive hand training intervention using either one (CIMT) or both (HABIT) hands. During the intervention, children will be paired with a trained interventionist, with an interventionist:child ratio of at least 1:1. We will recruit and train physical and occupational therapists, graduate students in kinesiology/neuroscience, speech pathology, and psychology, and undergraduates to be interventionists. Interventionists will be supervised by experienced PT/Ots. Both the interventionists and supervisors will be blinded to CST connectivity patterns. Prior to the intervention, a training session will be conducted by the supervisors for standardization based on the established manual of procedures for CIMT and HABIT. Fidelity will be reinforced by supervisors during the day camp and daily post-camp meetings. Participants receiving CIMT and HABIT will be located in separate rooms, with each room being supervised by experienced PTs/OTs who will model and ensure uniformity of treatment. Each day, interventionists will attend team meetings to discuss the progress and needs of each child.

Participants will work one-on-one with their interventionist or in groups, and activities will be divided into whole and part task practice. Whole task practice involves sequencing successive movements within the context of activities (e.g., games, arts and crafts, goal training). The activities will be performed continuously for at least 15 to 20 minutes. Targeted movements and spatial and temporal coordination will be practiced within the context of completing the task. Part task practice will involve breaking down motor skills into smaller components and reinforcement of successive approximations of the desired behavior (e.g., card turning to promote forearm supination) while increasing repetitions and progressing skill requirements. This approach will also serve to increase treatment intensity by requiring as many repetitions as possible over repeated 30 second intervals (typically a minimum of 5 intervals).

Constraint-Induced Movement Therapy
CIMT will be modified to be child-focused, using a cotton sling fastened to the child's trunk with the distal end enclosed to prevent using the less affected arm or hand as an assist. The sling will be continuously worn throughout the intervention, and breaks of up to 30 minutes will be given as requested. To engage the child in the intervention and to maintain engagement, we will establish a list of fine motor and manipulative gross motor activities that elicit movement behaviors of interest that include a battery of age-appropriate, unimanual functional and play activities. Interventionists will select tasks based on which train the targeted hand impairments and the child's interest. Task difficulty will be progressed as children improved by requiring greater speed, accuracy, or movement repetition.

Hand-Arm Bimanual Intensive Therapy
We will establish a list of age-appropriate fine and gross motor activities that require use of both hands. Activities will be chosen by taking into consideration the role of the more affected upper extremity (UE) increasing in complexity from passive assist to active manipulator. Children will be asked to use the more affected UE in the same manner as that of the non-dominant limb of a typically developing child. Directions will be provided

to the child before the start of each task to avoid use of compensatory strategies, specifying how each hand will be used during the activity.

Outcome Measures

We will use several measures of hand function to capture different aspects of manual ability. All measures will be administered immediately before treatment (pre-test), within two days after (post-test), and 6 months after treatment (follow-up). Assessments will be administered by an experienced physical or occupational therapist who is blinded to the treatment allocation and CST connectivity of each child.

The primary outcome measures will be the Assisting Hand Assessment (AHA) and Jebsen-Taylor Test of Hand Function (JTTHF). The AHA will measure bimanual hand use, while the JTTHF will measure unimanual dexterity of the affected hand.

AHA: The AHA is a validated test for measuring bimanual hand use in children with UE impairments. The AHA measures the use of the more affected hand in bimanual activities during a play-like testing session. Sessions will be videotaped and scored off-site by a blinded evaluator. The AHA has excellent validity, reliability (0.97-0.99) and responsiveness to change. The AHA units will be used for the analysis. The smallest detectable difference (SDD) for AHA is an improvement of at least 5 units.

JTTHF: The JTTHF measures the time taken to complete six unimanual tasks, which include flipping cards, moving small objects, and lifting cans. The total score is the amount of time taken to complete all tasks. The test will be performed on both the more affected and less affected hands. The JTTHF is well-validated and has excellent reliability.

Several secondary outcome measures will also be used. The Box and Blocks Test (BBT) will measure unimanual dexterity. The Canadian Occupational Performance Measure (COPM) will measure caregiver perceptions of a child's performance of functional goals, and satisfaction with how well the child can perform the goal. The ABILHAND-Kids is a parent-report of child's manual ability. The Pediatric Evaluation of Disability Inventory (PEDI) will be used to measure functioning in the home environment.

BBT: The BBT measures how many blocks (2.5 cm^3) an individual can move from one box, over a barrier, to an adjacent box in one minute. Both hands will be tested. The BBT is valid and reliable for children with CP.

COPM: The COPM is a structured interview in which the individuals are asked to identify up to five functional goals. In this study, parents will report their child's functional goals in terms of how they perform each goal (COPM-Performance), and how satisfied they are with the child's performance (COPM-Satisfaction). The same caregiver will be interviewed at all time points. A change of 2 or more points in each scale of COPM is considered a minimum clinically important difference (MCID). The COPM has been validated for parents of children with disabilities.

ABILHAND-Kids: The questionnaire measures the ability of a child to perform specific 21 daily tasks which require hand use, according to the parent's perspective. It has been validated for children with CP over the age of 6 and it is a reliable test.

PEDI: Caregivers will be interviewed to assess children's daily functioning using the PEDI, a valid/reliable test focusing on child's functioning in daily living activities at home. Children's functional skills (PEDI-FS) and caregiver assistance (PEDI-CA) in self-care will be assessed.

Determination of CST Laterality
We will determine CST laterality in two ways. 1) TMS (primary approach): We will determine which hemisphere evokes muscle activation of the affected hand when TMS is applied to the primary motor cortex (M1); 2) DTI (secondary approach): We will use DTI to visualize the affected CST only in children whose CST laterality cannot be determined with TMS. We have shown that DTI is an accurate surrogate measure of CST laterality.

Transcranial Magnetic Stimulation
Single-pulse transcranial magnetic stimulation (TMS) will be used to determine which hemisphere's M1 controls movement of the child's more affected hand. We will record EMG from the first dorsal interosseous (FDI) muscle in both hands. Skin will be cleaned with rubbing alcohol and a mild abrasive (NuPrep, Weaver and Company, Aurora, CO). Electrodes will be placed on the FDI muscle belly. Reference electrodes will be placed on the muscle tendon, and a ground electrode will be placed on the wrist styloid process. EMG will be recorded with Neuroconn hardware and software (Neuroprax, Germany). The Neuroconn will receive a trigger input from the TMS stimulator, such that the relative timing of an EMG response to a stimulus can be measured and visualized. The EMG response to TMS is a motor evoked potential (MEP).

We will identify the spot at which a single TMS pulse evokes the strongest MEP in the affected FDI muscle (the motor "hotspot"). To identify the motor hotspot, single TMS pulses will be delivered to the child's scalp, starting approximately 4 cm from midline above the ear. The initial TMS stimulus intensity will be 50% stimulator output. If an MEP is not found, the coil position will be moved in 1cm increments to stimulate the scalp above motor cortex on both hemispheres. Stimulus intensity will be increased in 2-5% increments until an MEP is found. We will stimulate up to 80% stimulator output, because higher stimulation can be painful to participants. If we are unable to find an MEP in the motor strip, we will stimulate at 80% stimulator output at 50 points across frontal and parietal cortices in one hemisphere. If no MEP is found at any of these sites, we will classify that hemisphere as having no direct control of the movement of either upper extremity.

After the motor hotspot is found, the resting motor threshold (rMT) will be determined. The rMT is defined as the minimum stimulus intensity needed to evoke an MEP in the affected FDI in 6 of 10 trials. Stimuli will be delivered at a frequency <0.1Hz. If an MEP

is found after 6 of 10 pulses, the stimulus intensity will be lowered 2% until an MEP is no longer found in 6 of 10 trials.

We will then place a circular grid over the hemisphere, centered over the hotspot, using Brainsight. The grid will have a 10cm diameter, with five concentric rings, each gridpoint placed 1cm apart. The grid will be centered over the hotspot for that hemisphere. We will stimulate each site 1-3 times at 110% the participant's rMT to thoroughly search for all motor cortex representations of the upper extremities. Responses are sites at which a TMS stimulus evoked an MEP 50μV or larger. We will calculate the ratio between the number of responses in the more affected FDI obtained from the lesioned and contralesional hemispheres. This ratio is the laterality index (LI).

Participants will be categorized as having a contralateral CST connectivity pattern if the LI is between 0.9 and 1; i.e., 90% to 100% of the responses in the more affected hand come from the lesioned hemisphere. Participants will be categorized as having an ipsilateral CST connectivity pattern if the LI is between 0 and 0.1; i.e., 0% to 10% of the responses in the affected hand come from the lesioned hemisphere. Participants will be categorized as having a bilateral CST connectivity pattern if the LI is between 0.1 and 0.9.

Transcranial Magnetic Stimulation Analysis
The latency and peak-to-peak amplitude of each TMS pulse will be measured using a suite of custom-written MATLAB (Mathworks, Waltham, MA) scripts. If the latency of the MEP is longer than 40ms after the TMS pulse, that trial will be excluded from analysis. Additionally, if high levels (>100μV) of background EMG activity are seen before the MEP, the trial will be excluded from analysis.

Magnetic Resonance Imaging
Each child will receive a structural MR scan (MP-RAGE, 3D, T1-weighted) and diffusion tensor imaging scan, without sedation prior to participation. The structural MRI will be used to co-register TMS stimulation targets with specific brain landmarks, using a frameless stereotaxic neuronavigation system (Brainsight Frameless, Rogue Research, Montreal, QC, Canada). For TMS localization, there is normal variability in brain topography relative to scalp landmarks. MR scans will be done on a Siemens Prisma MRI Scanner (Malvern, PA) in the Citigroup Biomedical Imaging Center (CBIC). Structural scans (165 slices) will be taken at a resolution of 256 x 256 px. The structural MRI will be used to identify the lesion type and extent, as well as to localize the TMS coil (i.e., neuronavigation). The DTI scan will be done during the same session as the structural MRI. For DTI, a 65-direction protocol will be used, 75 slices per direction at a resolution of 112 x 112 px each.

Diffusion Tensor Imaging Analysis
DT images for participants whose CST laterality cannot be determined with TMS due to excessively high threshold or safety reasons will be imported into DTI Studio (Johns Hopkins University) software for processing and analyses. This has been shown to be a reliable surrogate for TMS in determining CST laterality. Image series for each

participant will be screened for movement artifact, and slices showing artifact will be removed. Since images are obtained using 65 gradients, up to 30% of slices may be removed without compromising feasibility of tract reconstruction. Using DTI Studio, we will place region of interest seeds in the affected motor cortex and cerebral peduncle, and later in the unaffected motor cortex and cerebral peduncle. We will use tractography to find tracts that pass through both regions of interest. We will categorize each CST as present or absent. If there is a present CST on the affected side, the child will be categorized as having a contralateral CST. If there is not a CST present on the affected side, and a CST present on the other side, the child will be categorized as having an ipsilateral CST.

Statistical Analysis Plan

This will be an intention-to-treat study. If a child misses their 6 month follow-up assessment, we will impute their missing data based on the average change data for other participants in their subgroup. Statistical analyses will be performed using SPSS (IBM). A treatment (CIMT, HABIT) x CST connectivity pattern (contralateral, ipsilateral, bilateral) x test session (pre-, post-, 6 month) ANOVA with repeated measures on test session will be performed on all measures and Newman-Keuls post hoc tests will be performed where appropriate. Regression analyses will be done to determine predictors of outcomes. For children with a bilateral CST, correlations will be done between the LI and changes in outcome measures. Statistical significance will be considered at the $p<0.05$ level.