Supplementary Materials

Methodological Details

Randomization was done after children completed the pre-intervention assessments, but before the intervention began. Before randomization, children in each year's intervention were assigned to one of two equal-sized groups, such that each group had a similar age and baseline Jebsen-Taylor Test of Hand Function score. After groups were made, an offsite collaborator blinded to all study information assigned each group to one therapy. All interventionists, parents, children, and motor skill assessors were blinded to therapy group and study hypotheses.

Intervention description

Materials: Both types of therapy used toys, board games, art supplies, craft supplies, and sports equipment. Children brought items to the intervention for practicing functional goals, such as a shirt with buttons or shoes with laces.

Procedures: Children were randomized to receive structured or unstructured bimanual therapy. Participants engaged in age-appropriate training 6 hours/day for 15 days (90 hours).

Providers and Location: Therapy was provided by trained interventionists, paired 1:1 with a child. There were 20 interventionists, one per child, plus approximately 10 additional trained interventionists who assisted in the therapy rooms during the intervention. Interventionists were blinded to study hypotheses. Supervision was provided throughout training. Therapy was provided in rooms at a university, with 4-5 children per room. Each room had one supervisor at all times, and each day camp had an additional overall supervisor. While children were not present, supervisors met with interventionists to emphasize protocol fidelity daily.

Duration of therapy: Therapy for both groups was provided 6 hrs/day for three weeks (15 days, 90 hrs total).

Tailoring of therapy: In both therapy groups, activities were selected for each child based on the child's interests and their therapy goals. In only the structured HABIT group, skill demands of activities were changed as a child's skill improved (see above).

Modifications and Adherence: The therapy was not modified during the course of the study. Adherence was tracked in several ways, and was high. Interventionists kept daily logs of each activity done by the child. Supervisors provided feedback while the children were present and while the children were not present, to emphasize protocol fidelity.

Participants in both groups engaged in bimanual activities at home (1 hour/day) during the intervention and for six months following. Participants submitted weekly logs documenting activities performed and time spent on each activity.

Magnetic Resonance Imaging (MRI) and Transcranial Magnetic Stimulation (TMS) Colocalization

Each child had a structural MRI to allow motor mapping that was consistent between each time point. Children received a structural T1-weighted MRI on a Phillips 3T scanner at Columbia University Medical Center. Frameless stereotaxy (Brainsight: Rogue Research, Montreal, Canada) was used to guide the position of the TMS stimulating coil relative to a child's MRI. This system used an infrared camera to monitor the positions of reflective markers attached to the child's head with a headband. The position of each stimulation point was marked on the child's MRI, which enabled maintenance of precision and accuracy of stimulating the same points on different testing days. Even if a child had an irregular lesion, we mapped over

the scalp over the lesion. We never found a response to TMS when mapping over spaces filled with cerebrospinal fluid, but did find responses in cortical regions adjoining the lesion or in the contralesional hemisphere.

TMS Motor Mapping Details

We chose to measure the FDI muscle because it is commonly used in TMS assessments , is easy to access in isolation, and is commonly activated during hand movements. We chose to measure the FCR muscle because it is easy to target with surface EMG, and is used in many upper extremity movements.

To prepare skin for electrode placement, skin was cleaned with alcohol and a gentle exfoliator (Nu-Prep, Weaver, CO). Surface bipolar electrodes (Coviden, Mansfield, MA) were then applied to FDI and FCR muscles bilaterally. For each muscle, the positive electrode was placed over the belly of the muscle, while the negative electrode was placed on the muscle tendon. A ground electrode was placed on the wrist overlying the ulnar styloid process. Electrodes were connected to a Brainvision ExG amplifier (NeuroConn, Germany) (gain 600 V/V, high pass filter 10 Hz, low pass filter 1000 Hz). EMG was recorded simultaneously at 4000 Hz from all electrodes, from 400ms before TMS pulse onset to 400ms after the pulse.

Single-pulse TMS was delivered using a Magstim 200 stimulator and a 70 mm figure-of-8 coil. Pulses were delivered at an intensity of 60-80% maximum stimulator output, at a frequency less than 0.1 Hz. The coil was moved along the head in 1cm increments between each pulse. If an MEP of the affected FDI or FCR was not found, the stimulator output was increased by 2%, and stimulation was repeated. This process of searching for an MEP continued until an MEP was found or until a stimulus intensity of 85-90% device output was reached.

The same mapping grid was used before and after training. In nearly all cases, a complete post-training map was found within the region of the grid that was drawn during the pre-training map. If responsive sites were found at the border of the grid, another grid ring was added until the map border was found. No more than one additional ring needed to be added for any case.

TMS Data Analyses

EMG data were imported into MATLAB (Mathworks, Natick, MA). A MATLAB script was written to identify the peak-to-peak amplitude of each MEP. For each grid point, average MEP strength and latency were calculated. Each grid point was categorized as a digit, wrist, or duel digit-wrist response site by the presence or absence of an MEP in the FDI or FCR at that site, with latency <40ms.

FDI map size, for each map, in cm^2 was determined by counting the number of sites in which an FDI response was found, and dividing the number by map density (1 site/cm^2). FCR map size in cm^2 was determined by counting the number of sites in which an FCR response was found, and dividing the number by map density. Total map size in cm^2 was determined by counting the number of sites in which an FDI or FCR response was found, and dividing the number by map density.

Stability of Motor Maps in the Absence of Intervention

In a subset of children across groups (n=8), we performed two motor maps before the beginning of the hand training. We examined FDI map size, FCR map size, and average FDI and FCR MEPs for the center 1cm region of the map across the two timepoints before treatment

began. The average difference between the two maps was ±3.3% for hand map size, ±3.7% for FDI map size, ±6.7% for FCR map size, ±8.4% for FDI MEP, and ±16.3% for FCR MEP. Some measures went up in the two pre-training maps in some children, while others went down. There were no systematic patterns in the changes from one map to the next (i.e. which map was bigger, first or second), and no statistical differences ($p>0.1$).

Challenges and Constraints of Multi-Modal Studies in Children with USCP

In this study, we performed multiple types of testing in children with CP: MRI, TMS, and motor function assessments. This testing paradigm held several challenges for the study team as well as participants and their families. Here we briefly share insights to assist others who may be planning similar assessments.

A key element of successful pediatric research, especially using methods unfamiliar to most children, is thorough informed consent. We provide children and families with age-appropriate written descriptions of all methods, as well as flyers and videos about TMS and MRI (viewable at http://friellab.org/?page_id=30). Special care must be taken to familiarize children with the experimental environment.

Children were provided a "Research Passport" containing a description of each procedure on each page of the passport. After the child completed a step of the protocol, they received a stamp in their passport and a small prize.

Helpful strategies for specific protocols:

MRI: Before the MRI, children were given a tour of MRI center. Children were given the opportunity to lie in a play tunnel and listen to a recording of the MRI sounds. Children wore a baseball catcher's face mask during the simulated MRI to mimic the feeling of having the MRI

head coil around their head during the MRI. During the MRI, we played a movie of the child's choice that the child could see from their position in the scanner. We also allowed parents to be with the child in the scan room if the parent met all MRI inclusion/exclusion criteria regarding presence of metallic objects in the body.

TMS: Before TMS, children were given the opportunity to tour the lab. Children were seated in a comfortable, child-sized armchair. Pillows were used to position the child's arms on the lab to minimize any muscle tension in the child. We provided parent-approved snacks and drinks during the session, and allowed for ample breaks. During TMS, children were able to watch a movie. Since visual input and excitement can influence TMS responses, care was taken to provide the same type of movie during all testing sessions. Although an ideal environment would be void of such visual and auditory input, maintaining a restful pose in each child during a TMS session required distractions for the child. While we wish we could have obtained even more measures for each child, a 2-3 hour session was the limit of what was feasible.

A common concern of children was the removal of the electrodes at the end of the session. We found that application of an alcohol-based hand sanitizer sufficiently loosened the adhesive to make removal painless.

one child. A2-C2. Unstructured practice, representative maps of the affected hand from one child. D. Quantification of map changes. The size of the motor map of the affected hand increased significantly only in the structured training group (* $p<0.05$).

Figure 4. Changes in magnitude of motor evoked potentials in TMS maps after structured skill training. A1-C1. Maps of the affected hand located contralateral to the affected hemisphere in a representative case. Red color indicates stronger MEP response. A2-C2. Representative maps of the affected hand in a representative case from the unstructured practice group. D-E. MEP amplitude of the representation of the affected FDI increased significantly after structured but not unstructured training (* $p<0.05$).

Supplementary Figure 1. Relationship between change in COPM Performance and change in size of the affected hand motor map. Overall, children in the structured skill group who had the largest gain in COPM Performance also had the largest increase in size of the motor map of the affected hand ($F(1,8)=5.6$, $p=0.045$, $r=0.64$, $r^2=0.41$).

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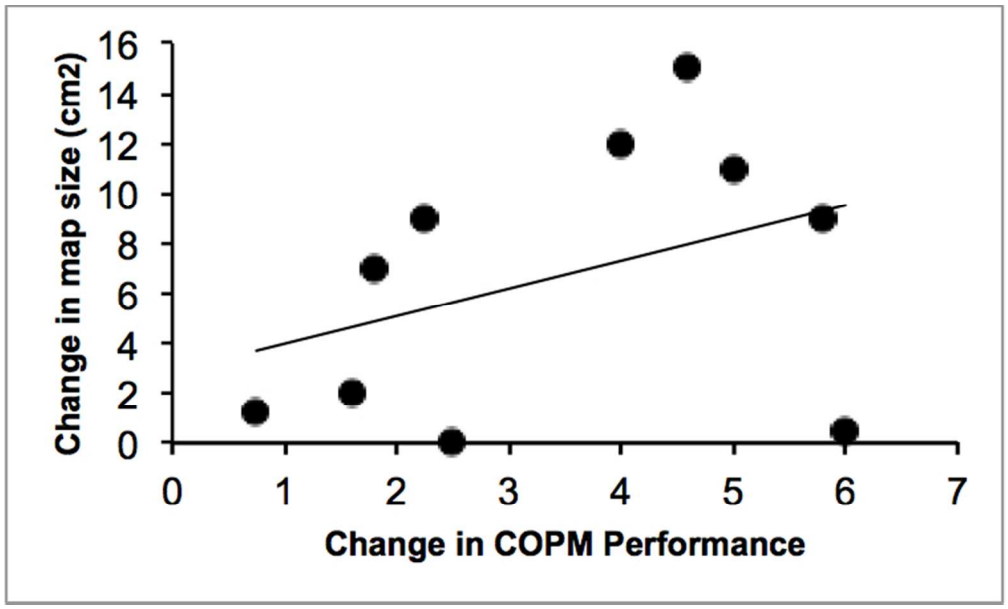

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127x76mm (150 x 150 DPI)