A longitudinal resting state functional MRI study of children with hemiplegic cerebral palsy treated with constraint therapy

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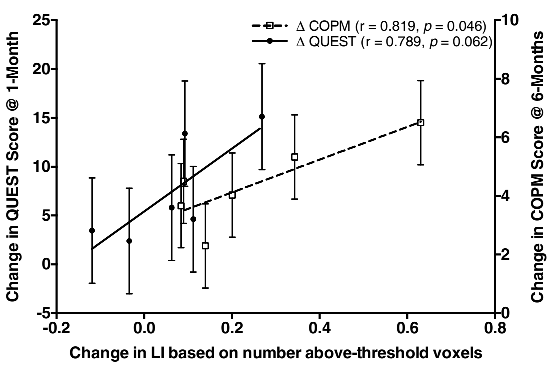
Introduction: Hemiplegic cerebral palsy (CP) is characterized by unilateral upper extremity impairment as a result of subcortical and/or cortical damage sustained prenatally or in early life. Children often exhibit learned non-use where they opt to perform tasks with their unaffected limb. Constraint-induced movement therapy (CIMT) attempts to directly combat this mechanism with repetitive practice with the hemiplegic limb while the other arm is restrained. Resting state fMRI could be a useful tool in understanding this reorganization, predicting clinical outcome following therapy, and understanding CIMT-induced neuroplasticity.

Purpose: The objective of this study was to quantify the sensorimotor resting state network (RSN) before and after CIMT to (a) determine baseline measures that predict clinical improvements and (b) compare these clinical changes with any RSN reorganization.

Methods: Eleven children with hemiplegic CP (7 treated, 4 control) were recruited from three different facilities, all with Gross Motor Function Classification System and Manual Ability Classification System Level I and between the ages of 6 and 18. Treated subjects were evaluated at baseline, 1-month later following CIMT, and 6-months follow-up while control subjects were assessed at baseline and 1-month later. Standard clinical tests included the Canadian Occupational Performance Measure (COPM), Quality of Upper Extremity Skills Test (QUEST), and a Jebsen-Taylor Test of Hand Function (JTTHF) task (occupational therapists identified lifting a large, but light object as being the most sensitive a priori). All MRI data was acquired on a 3T MR scanner (Tim Trio; Siemens, Erlangen, Germany) using a 32-channel human head coil. Two different anatomical images were taken for registration purposes and in order to best delineate the lesions; an axial T2-weighted turbo spin echo sequence (TE/TR = 95/7770 ms, flip angle (FA) = 120˚, matrix size = 320x225, FOV = 256x200 mm, # slices = 35, slice thickness = 3mm) and an axial T2-weighted turbo inversion recovery fluid attenuated inversion recovery (TIRM-FLAIR) sequence (TE/TR = 120/8000 ms, FA = 130˚, matrix size = 256x232, FOV = 220x200 mm, # slices = 35, slice thickness = 4mm). Two 5 minute resting state fMRI gradient echo echo-planar imaging (GE-EPI) sequences (TE/TR = 30/2350 ms, FA = 90˚, matrix size = 80x80, FOV = 240x240 mm, # slices = 40, slice thickness = 3mm) were performed while the patient was simply asked to remain still and not fall asleep. Image preprocessing and analysis was done using FSL FMRIB software. Independent component analysis (ICA) was applied to cleaned, concatenated data to identify the sensorimotor resting state network (RSN). Dual regression algorithms were used to back-reconstruct the sensorimotor RSN connectivity layout at each time point and from this various laterality indices (LI) were calculated and compared to clinical changes.

Results: All clinical scores improved after therapy, and COPM remained significantly improved 6-months after baseline, while control subject's remained unchanged. There was a significant correlation between the LI calculated from the number of above-threshold voxels in the baseline sensorimotor RSN and the change in COPM (r=-0.81, p=0.03) and JTTHF scores 1-month after baseline (r=0.72, p=0.07). The LI tended to approach 0 (equal contributions from both hemispheres) in the CIMT-treated group after therapy while the control group remained unchanged (with a preference to the unaffected side). The LI was significantly different from baseline values at 6-months (p=0.03) using a paired samples t-test. Figure 1 shows a representative subject's sensorimotor RSN reorganization after CIMT with increased activation in ipsilesional motor areas. The LI and QUEST scores had correlated changes between baseline and 1-month post-CIMT (r=0.79,p=0.06) and the changes in LI and COPM scores at 6-months were significantly correlated (r=0.82,p=0.05).

Conclusions: The predictor relationships indicate that children with more unilateral sensorimotor RSN at baseline improved the most following CIMT. Constraint therapy may improve motor function by releasing the increased interhemispheric inhibition upon the affected hemisphere. A larger group of subjects with a wider range in symptom severity is needed to confirm the RSN predictors and reorganization found in this pilot study. The correlated changes between sensorimotor RSN reorganization and clinical improvements provide further evidence of CIMT-induced neuroplasticity.



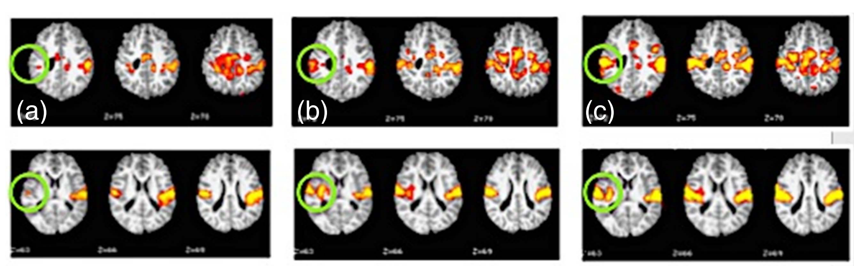


Figure 1: (Left) Correlated changes between RSN reorganization and clinical scores 1 and 6 months post-CIMT. Figure 2: (Above) The sensorimotor RSN in two CIMT-treated subjects at (a) baseline, (b) 1-month, and (c) 6-months.