Hemiplegic cerebral palsy and constraint-induced movement therapy: Resting state functional magnetic resonance and diffusion tensor imaging predictors and neuroplastic changes

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Introduction: Hemiplegic cerebral palsy (CP) is characterized by unilateral upper extremity impairment as a result of subcortical injury due to stroke or trauma prenatally or in early life. Due to the early onset of the disease, patients experience learned non-use where the hemiplegic arm is further inhibited from healthy development as most tasks are done with the unaffected arm. Constraint-induced movement therapy (CIMT) directly combats learned non-use by restraining the unaffected limb, forcing the patient to repetitively use the hemiplegic limb[1]. There is currently little understanding of the neurological basis behind this therapy and functional MRI (fMRI) experiments have focused on variable task-based studies[2]. Resting state fMRI and diffusion tensor imaging (DTI) are useful tools to explore *global* network reorganization, neuronal integrity, and neuroplasticity.

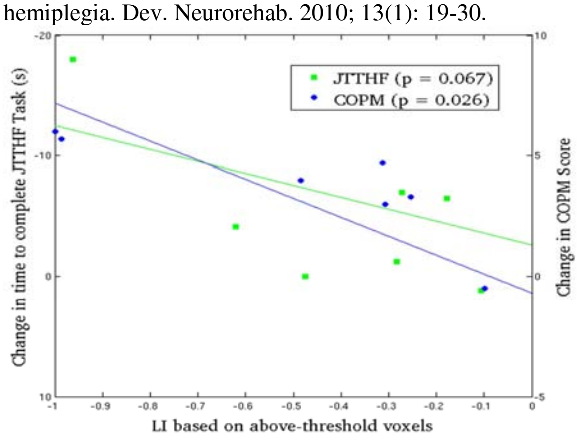
Objectives: The objective of this study was to evaluate hemiplegic CP patients using various standard clinical assessments and MRI to (a) determine baseline fMRI resting state and diffusion quantitative measures that accurately predict a positive response to CIMT, and to (b) better understand the relationship between CIMT-induced functional changes and neuroplasticity. To the best of our knowledge, this is the first work aimed to identify resting state and diffusion neuroimaging predictors and correlated changes following CIMT in hemiplegic CP patients.

Methods: Twelve hemiplegic CP patients (7 treated, 5 control) from two different facilities were evaluated at baseline and 1-month after CIMT. The patients were clinically assessed using the Quality of Upper Extremity Skills Test (QUEST), a Jebsen-Taylor Test of Hand Function (JTTHF) task (occupational therapists identified lifting a large, but light object as being the most sensitive task), and the Canadian Occupational Performance Measure (COPM). All MRI data was acquired on the 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, No. 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, No. 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, No. slices = 40, slice thickness = 3mm) were performed while the patient was simply asked to remain still and not fall asleep. And finally, a spin echo (SE) DTI sequence (TE/TR = 85/6800 ms, matrix size = 100x100, FOV = 200x200 mm, No. slices = 56, slice thickness = 2mm, $b_1 = 0$, $b_2 = 1000$ s/mm^2, gradient directions = 30) was used for creating diffusion-weighted images. 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, where: $LI = \frac{Ipsilesional - Contralesional}{Ipsilesional + Contralesional}$. The eddy current corrected DTI data was used to find the fractional anisotropy (FA) and mean diffusivity (MD) at the posterior limb of the internal capsule (PLIC), midbrain and the pons along both the right and left corticospinal tracts (CST).

Results: There was a significant correlation between the LI calculated from the number of above-threshold voxels in the sensorimotor RSN and the change in COPM score from baseline to 1-month (r=-0.814, p=0.026), as well as a trend with the change in time to complete the JTTHF task (r=0.722,p=0.067). (Figure 1) There was also a significant correlation between the change in the time to complete the JTTHF task and the MD of the PLIC in the ipsilesional hemisphere (r=-0.832, p=0.020) and a trend with the LI based on average CST FA values (r=0.747,p=0.054). The LI based on the number of above-threshold voxels and QUEST scores had correlated changes between baseline and 1-month post-CIMT (r=0.748,p=0.053). Figure 2 shows a representative subject and sensorimotor RSN reorganization after CIMT with increased activation in ipsilesional motor areas.

Conclusions: Both of the predictor relationships indicate that patients with more unilateral sensorimotor RSN and a further compromised ipsilesional CST improved the most as measured using both COPM and JTTHF assessments. This result could be influenced by a ceiling effect because of our high-performing baseline subjects. A further range of subjects is needed to confirm predictors based on disease severity and baseline MRI measures. The correlated changes between sensorimotor RSN reorganization and QUEST clinical measures provide further evidence of neuroplasticity.

References: 1. Mark VW, Taub E, Morris DM. Neuroplasticity and Constraint-induced Movement Therapy. Eura Med. 2006; 42(3): 269-284.
2. Cope S, Liu X, Verber MD, et al. Upper limb function and brain reorganization after constraint-induced movement therapy in children with hemiplegia. Dev. Neurorehab. 2010; 13(1): 19-30.



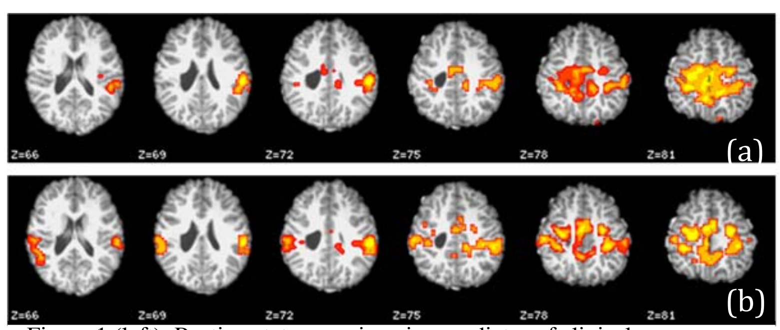


Figure 1 (left): Resting state neuroimaging predictor of clinical success following CIMT. Figure 2 (above): An ICA-derived sensorimotor RSN (a) before and (b) after CIMT displaying evidence of neuroplasticity.