A randomised trial of Botulinum toxin A and upper limb training in children with congenital hemiplegia: a serial fMRI study

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Objective: To date, there have been no serial functional Magnetic Resonance Imaging (fMRI) motor studies on children with cerebral palsy before and after upper limb training with or without intramuscular injections of Botulinum toxin A (BTX-A). We wished to examine the changes in central activation using fMRI accompanying two motor tasks in the impaired limb over a 12 week period in children with congenital hemiplegia.

Methods: Thirty children with congenital hemiplegia (n = 20 right sided, 20 girls) aged 5 - 15 yrs were studied. All children undertook at least one training session in a 'mock scanner', prior to the real scan. High-resolution whole-brain fMRI studies (Gradient-Echo EPI at 3-Tesla) were conducted at baseline, 3 and 12 weeks, without sedation. T1-weighted anatomical and MR-angiographic images were also acquired. Two motor paradigms were used, each two-condition block designs with task (finger tapping or wrist extension) at 2.0 Hz alternating with rest. In each paradigm the task and rest periods were 20 seconds and the block was repeated four times. In order to minimize the possible adaptation/learning the paradigm was practiced only briefly prior to each session. The actual movements performed in the scanner were rated for number of repetitions to determine speed over each task in the activation period, the range of motion and presence of mirror movements in the contralateral hand or general body movements. All movements were recorded on video for independent analysis to confirm the movement parameters during each task. After baseline assessment on a validated functional test (Melbourne Unilateral Upper limb assessment, MUUL) and fMRI children were randomly allocated within pairs to receive six weeks of upper limb training with or without intramuscular injections of Botulinum toxin A (BTXA) to the spastic forearm muscles (1-4U Botox/kg/muscle). Image analysis was preformed using iBrain® (Brain Research Institute, Melbourne, Australia) and SPM99 (Wellcome Department of Cognitive Neurology, London, UK) software. After image realignment, a t-test was performed at each voxel location to look for differences between task and rest states. The maps were qualitatively reviewed by a neurologist blinded to group allocation. Studies rated as poor quality (scored less than 2 out of a maximum 5) were excluded from the quantitative analysis. Region of interest (ROI) analysis was undertaken by a rater who was blinded to group allocation on statistical maps generated at p<0.0005 uncorrected. ROI focused on activation in the contralateral and ipsilateral Primary Motor cortex (PM1) and the supplementary motor area (SMA). Quantitatively we compared voxel counts between baseline and three weeks and baseline and twelve weeks fitting a regression model with an interaction term between study group and a three-level factor indicating time of measurement. Changes in the laterality index were also plotted over the 12 weeks by treatment group to note the incidence of brain reorganisation. Here we report the quantitative data for the finger task over time and the changes in the laterality index. As the raw data were skewed a log of the pixcel count was analyzed between the groups.

Results: Twenty-seven of the thirty children undertook all three serial fMRI studies including three five year old children. Three children refused the real fMRI after practice in a mock scanner, but continued in the remainder of the study completing the functional outcome measures. Post hoc quantitative comparison of pixel counts between the randomly allocated groups at baseline demonstrated no significant differences between the groups (est. mean difference 0.65, 95%CI -0.88, 2.2; *NS*) so that the groups had similar activation prior to training and/or BTXA. Both groups improved at 3 week follow-up but the groups were not significantly different. At 12 week follow up there was significantly greater activation for the BTX-A treated group compared to the upper limb training alone treated group in the contralateral PM1 (est. mean diff = 1.15, 95% CI -0.002, 2.29, p = 0.05) (figure 2). This was accompanied by a significantly greater functional improvement on the MUUL assessment (est. mean diff. 12.9; 95%CI 6.12, 19.8; p < 0.0001). In the BTX-A treated group these activation changes were accompanied by reorganisation to the ipsilateral cortex shown by a negative laterality index in four cases at 3 week follow up which was sustained in three of the cases at 12 week follow up. In contrast the upper limb training alone treated group had only one case of reorganisation following treatment. The laterality index was consistently negative for one case in each group and activations in these patients were accompanied by mirror movements.

Figure 1: fMRI maps (at p<0.005) of a right finger task for a 7 yr old girl with right hemiplegia treated with BTX-A and UL training at (I) baseline, (ii) 3 wks (iii) 12 weeks.

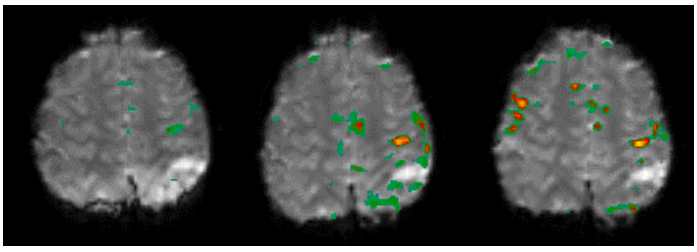
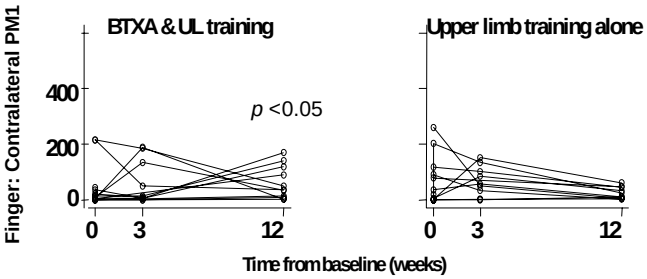


Figure 2: Contralateral PMI by group. Group difference was significant at 12 wks but not at baseline & 3 weeks.



Conclusions: In a matched pairs single blind randomised trial there was a treatment effect with Botulinum toxin A superior to upper limb training alone in young children with hemiplegic cerebral palsy. These increases in central activation on fMRI where accompanied by significant increases in functional behaviour. The period of retained neurovascular changes at 12 weeks was after the period of peak chemodenervation effect of BTX-A (3 weeks) suggesting that plasticity of neurovascular changes may have occurred beyond the pharmacological effect of BTX-A. In addition three children in the BTX-A treated group had increases in brain reorganisation to their ipsilateral motor cortex. These data provide evidence for brain reorganisation in response to Botulinum toxin A injections with upper limb training that was superior to upper limb training alone.

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