Brain Connectivity Increases Concurrent with Functional Improvement: Evidence from Connectome MRI in Children with Cerebral Palsy during Therapy

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Target Audience: Researchers and clinicians interested in creating biomarkers of treatment efficacy using brain structural connectome analyses.

Purpose: Cerebral palsy (CP) refers to a heterogeneous group of permanent but non-progressive movement disorders caused by injury to the developing fetal or infant brain[1]. Because of its serious long-term consequences, effective interventions that can help improve motor function, independence, and quality of life are critically needed, and our ongoing longitudinal clinical trial to treat children with CP is specifically designed to meet this challenge. To maximize the potential for functional improvement, all children in this trial received autologous cord blood transfusions (with order randomized with a placebo administration over two years) in conjunction with more standard physical and occupational therapies. As a part of this trial, magnetic resonance imaging (MRI) is used to improve our understanding of how these interventions affect brain development, and to develop biomarkers of treatment efficacy.

Methods: Neuroimaging and functional data was obtained from a subset of 17 children (mean age = 2.6 ± 1.2 at time of enrollment) enrolled in our ongoing clinical trial. These children had a clinical diagnosis of CP, with either unilateral or bilateral impairment. MRI and functional assessments were scheduled at three time points over a two-year period, each separated by one year. The children were assessed for functional abilities at time of enrollment using the Gross Motor Function Classification (GMFCS) levels, and the Gross Motor Function Measure (GMFM-66) was used to assess functional change. All children were scheduled to receive an autologous cord blood transfusion in the first or second year with the order randomized with placebo administration, however the researchers analyzing the imaging data were blind to the time point at which this experimental treatment was administered. All children had received a transfusion by the time of the final MRI session. Diffusion tensor imaging (DTI) and whole brain connectome analysis was used to investigate connectivity changes throughout the brain in relation to functional outcomes. Diffusion weighted images were acquired on a 3 Tesla GE MR750 scanner (25-directions, b=1000 s/mm^2, TE=70.5ms, TR=12,000 ms, 2 mm^3 resolution). T1-weighted images were obtained with an inversion-prepared 3D FSPGR sequence (TE=2.5 ms, TI=450 ms, TR=6.5 ms, 1 mm^3 resolution). In the structural connectome analysis, gray matter ROIs are defined as "nodes" and the connectivities between pairs of nodes (proportional to the volume of voxels containing the streamlines originating and terminating within a pair of gray matter ROIs) are defined as "edges". Baseline connectivity was determined by normalizing the edge values with the total WM volume for each child, at the time of enrollment. Similarly, baseline fractional anisotropy (FA) was obtained by averaging the FA within the voxels that make up the edges at the time of enrollment. The total change in connectivity over two years was calculated for each child by obtaining the difference in the sum of edge values, normalized by the change in total WM volume, and scaled by the maximum increase in total connectivity across the cohort. The aim of this report was to Alleassess the changes in brain connectivity resulting from combined therapy. We visualized the individual connectivity changes throughout the brain in each individual by plotting edges with increased connectivity relative to change in total WM volume as connectome maps.

Results: A statistically significant relationship between total connectivity change and GMFM-66 score change (p = 0.020) (Fig. 1) was observed. The age of the child at the time of enrollment was not significantly correlated with total connectivity change (p = 0.944). Furthermore, no relationship between enrollment ages and GMFM-66 score changes was observed in this cohort (p = 0. 979). However, children with the most improved functional scores (GMFM-66 score changes > 10) demonstrated significantly higher (p = 0.007) baseline connectivity as compared to children who showed more moderate functional improvement over the two-year period (GMFM-66 score changes <10). Additionally, children with the most improved functional scores demonstrated significantly (p = 0.007) higher baseline FA than children who showed more modest functional improvement. Children who showed the greatest functional improvements were classified at lower GMFCS levels at time of enrollment (indicating higher levels of gross motor function) than did children who improved more modestly, and the difference in mean GMFCS levels was highly significant (p = 0.005). Fig. 2 shows connectome maps representing the two-year connectivity changes in four representative individuals (subjects 8 and 9 for significant responders, and subjects 1 and 11 for moderate responders) (Fig. 2). In subjects with significant functional improvements (e.g. subjects 8 and 9), the numbers of edges showing increased connectivity are far greater than those in moderate responders (e.g. subjects 1 and 11). These improvements are diffusely distributed throughout the brain, and include connections that are associated with a variety of functional networks, well beyond only the sensorimotor network.
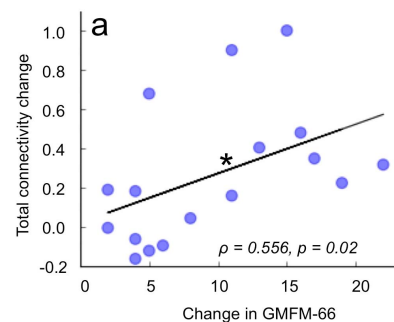

Fig 1. Total connectivity change is significantly correlated with functional changes measured by GMFM-66 score changes.
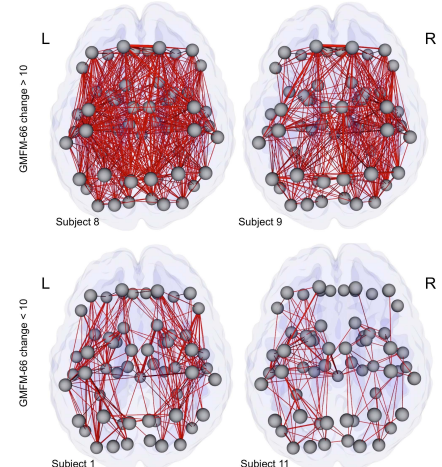

Fig 2. Diffuse positive changes in WM connectivity in four representative subjects during therapy. Subjects 8,9 responded significantly to treatment, whereas subjects 1 and 11 showed a more moderate response.

Discussion: Our results reveal statistically significant relationships between brain connectivity changes and functional outcomes in children with CP. The observed changes were diffuse (not limited to the sensorimotor network), consistent with prior evidence of diffuse structural deficits in CP[2]. The fact that changes in the GMFM-66 are correlated with diffuse changes in connectivity may reflect the fact that functional movement of the body as a whole, in coordination with the environment, may require coordinated use of the brain, rather than the isolated use of what is classically considered the sensorimotor network. Furthermore, it was found that enrollment ages were not correlated with functional or structural outcomes, however it was demonstrated that children with higher connectivity and FA at the time of enrollment showed better functional outcomes after two years.

Conclusion: Our findings indicate that children with greater structural connectedness and WM health at the time of enrollment are likely to achieve more favorable functional outcomes following therapy, at least within the two-year time period and with the treatments in this study. We have identified that brain connectivity change can serve as a biomarker of functional change in children with CP.

References:

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