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Brain structural connectivity increases concurrent with functional improvement: Evidence from diffusion tensor MRI in children with cerebral palsy during therapy

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ABSTRACT

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 (Bax et al., 2005). Because of its serious long-term consequences, effective interventions that can help improve motor function, independence, and quality of life are critically needed. 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 2 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. In this report, diffusion tensor imaging (DTI) and subsequent brain connectome analyses were performed in a subset of children enrolled in the clinical trial ($n = 17$), who all exhibited positive but varying degrees of functional improvement over the first 2-year period of the study. Strong correlations between increases in white matter (WM) connectivity and functional improvement were demonstrated; however no significant relationships between either of these factors with the age of the child at time of enrollment were identified. Thus, our data indicate that increases in brain connectivity reflect improved functional abilities in children with CP. In future work, this potential biomarker can be used to help differentiate the underlying mechanisms of functional improvement, as well as to identify treatments that can best facilitate functional improvement upon un-blinding of the timing of autologous cord blood transfusions at the completion of this study.

1. Introduction

Cerebral Palsy (CP) is estimated to affect 3–4 out of 1000 children (Yeargin-Allsopp et al., 2008) and consists of disordered movement, often in conjunction with deficits in sensation, cognition, communication, and behavior (Bax et al., 2005; Aisen et al., 2011). A variety of disturbances in the developing fetal or infant brain may lead to CP, with the resulting neurological deficits correlated with degree and location of damage to brain structure (Accardo et al., 2004). Brain damage in CP often consists of diffuse damage and/or focal lesions in white matter (WM), which are often most severe in periventricular regions (Haynes et al., 2003). While CP is typically diagnosed via neurological assessment, neuroimaging techniques such as T_2-weighted imaging, and more recently diffusion MRI, have been used to characterize WM abnormalities associated with functional deficits in this disorder at a single time point (for a systematic review see Scheck et al. (2012)).

There is extensive literature on neuroimaging studies concerned with functional recovery in brain disorders, (Staudt et al., 2006; Sawaki et al., 2008; Sharma et al., 2009; Pajonk et al., 2010; Bosnell et al., 2011; Johansen-Berg, 2012; Madhavan et al., 2014). Neuroimaging studies specifically in CP have indicated relationships between functional and structural changes within discrete anatomical regions, mostly focusing on sensorimotor regions of interest (ROIs) (Trivedi et al., 2008; Jain et al., 2014). Additionally, initial evaluations of the efficacy of experimental treatments for CP – including autologous stem cell therapy – have been performed (Bae et al., 2012; Lee et al., 2012; Min et al., 2013), also

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using neuroimaging metrics derived from discrete brain regions to demonstrate structural changes associated with functional improvement.

However, there have been several studies demonstrating damage to WM tracts throughout the brain (Nagae et al., 2007), as well as diffuse connectivity deficits associated with severity of functional impairment (Englander et al., 2013; Pannek et al., 2014) at a single time point. Furthermore, CP is a heterogeneous disorder with multiple causes and clinical manifestations, meaning that the specific structural changes that may underlie improved function are likely to be unique to each patient. These factors indicate that longitudinal studies in CP should explore structural change throughout the brain on an individualized basis, in addition to examining specific changes within the sensorimotor network.

Therefore, in this report we use diffusion tensor imaging (DTI) and whole brain connectome analyses to investigate connectivity changes throughout the brain in relation to functional outcomes in children with CP. To maximize the potential for functional improvement, all children in this trial received autologous cord blood transfusions in conjunction with more standard physical and occupational therapies. The aim of this report was to investigate neuroimaging biomarkers that would reflect diffusely distributed and heterogeneous changes in connectivity in relation to improved functional outcomes following therapy. In future analyses, this biomarker can be used to determine the underlying mechanisms of these functional improvements, potentially helping to identify the treatments that best facilitate better functional outcomes.

2. Materials and methods

In this report we used diffusion tensor imaging (DTI) and whole brain connectome analysis to investigate connectivity changes throughout the brain in relation to functional outcomes in 17 children with CP, who all showed positive but varying degrees of functional improvement over the first 2 years of a longitudinal study. We specifically investigated whether brain connectivity changes could serve as a biomarker for improved functional outcomes during therapy in children with CP.

2.1. Subjects

Neuroimaging and functional data were analyzed in a subset of children enrolled in our ongoing clinical trial to evaluate the impact of various treatments (including autologous cord blood infusions) for CP. 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 2-year period, each separated by one year. The children received an autologous cord blood transfusion in either the first or second year, with a placebo administered in the alternate year. The time point at which the experimental treatment was administered was randomized across subjects, and the researchers analyzing the imaging data were blind to the time point at which the treatment was administered. All children had received a transfusion by the time of the final MRI session. Patients underwent neurological testing of motor control, muscle tone and spasticity, overall flexibility and reflexes. Children were sedated for the MRI scans to limit subject discomfort and motion artifacts. Written informed consent was obtained from the parents of each participant, and study related procedures were approved by the Duke University Medical Center Institutional Review Board.

Children were excluded from this report if they had a seizure disorder, brain dysmorphogenesis, or genetic disease. An additional exclusion criterion was significantly abnormal brain anatomy (such as in the case of perinatal stroke) that would prohibit robust image registration or parcellation. 25 subjects had completed the functional and neuroimaging assessments at both time points, however 8 subjects for which an accurate anatomical parcellation could not be achieved were not included in further analyses. These subjects had major anatomical abnormalities due to stroke. Therefore, 17 children (median age = 2.4 years, age range 1.1–5.1 years at time of enrollment) are included in this report. Demographic information for these children is presented in Table 1.

2.2. Rehabilitative therapies

In addition to autologous cord blood transfusions, the children in this study received rehabilitation services in their home communities which may have included physical therapy (PT), occupational therapy (OT), developmental therapy, (DT), speech/language therapy (LT), hippotherapy, vision or hearing therapy, and the use of orthotic intervention and adaptive equipment, as are typically included in the comprehensive management of CP. A comprehensive list of therapies is included in Table 2.

2.3. Functional outcome measures

The Gross Motor Function Classification System (GMFCS) levels are used to evaluate functional impairment at the time of enrollment. The GMFCS is a five level classification system (Levels I–V) appropriate for the assessment of young children, with distinctions between the levels based on functional limitations and the need for assistive mobility devices (Palisano et al., 1997). Children classified at Level I have the least impaired motor function, whereas children classified at Level V show the most severe functional impairment.

The Gross Motor Function Measure-66 (GMFM-66), the most commonly utilized functional outcome measure in children with CP (Wang and Yang, 2006; Alotaibi et al., 2014), is used to assess changes in functional abilities during treatment in this study. The GMFM-66 includes the assessment of quality of movement in addition to the acquisition of age related isolated skills (Russell, 2002). Children in this report demonstrated GMFM-66 score changes ranging from 2 to 22 points. Here we use a GMFM-66 score change of 10 as a threshold to stratify the subjects into two groups, a moderate improvement group (GMFM-66 score change < 10) and a significant improvement group (GMFM-66 score change > 10). These groups separate subjects based on their levels of functional improvement over the 2-year period. This threshold was chosen based on the distribution of GMFM-66 score changes in the cohort, and it allowed for balanced numbers within each group as well as a highly significant ($p = 0.0003$) difference in the mean change scores associated with each group. The group of children with GMFM-66 change scores < 10 ($n = 9$) had a mean GMFM-66 change score of 4.44 ± 1.77, and the group of children with GMFM-66 change scores > 10 ($n = 8$) had a mean GMFM-66 change score of 15.5 ± 3.61. This group distinction allowed us to assess whether structural characteristics and functional abilities at the time of enrollment have an impact on responsiveness to therapy.

2.4. Image acquisition

Diffusion weighted images were acquired on a 3 Tesla GE MR750 scanner (Waukesha, WI) using a 25-direction gradient encoding scheme at $b = 1000$ s/mm^2 with 3 non-diffusion-weighted images. An echo time (TE) of 70.5 ms and a repetition time (TR) of 12,000 ms were used. An isotropic resolution of 2 mm^3 was achieved using a 96×96 acquisition matrix in a field of view (FOV) of 192×192 mm^2. T_1-weighted images were obtained with an inversion-prepared 3D fast spoiled-gradient-recalled (FSPGR) pulse sequence with a TE of 2.5 ms, an inversion time (TI) of 450 ms, a TR of 6.5 ms, and a flip angle of 12°, at a 1 mm^3 isotropic resolution.

2.5. Region of interest parcellation

Region of interest (ROI) parcellation was performed by warping the JHU-DTI-MNI "Eve" atlas template (Oishi et al., 2009; Faria et al., 2010; Faria et al., 2011) into each subject's DTI image space via the Advanced