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Diffuse reduction of white matter connectivity in cerebral palsy with specific vulnerability of long range fiber tracts

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ABSTRACT

Cerebral palsy (CP) is a heterogeneous group of non-progressive motor disorders caused by injury to the developing fetal or infant brain. Although the defining feature of CP is motor impairment, numerous other neurodevelopmental disabilities are associated with CP and contribute greatly to its morbidity. The relationship between brain structure and neurodevelopmental outcomes in CP is complex, and current evidence suggests that motor and developmental outcomes are related to the spatial pattern and extent of brain injury. Given that multiple disabilities are frequently associated with CP, and that there is increasing burden of neurodevelopmental disability with increasing motor severity, global white matter (WM) connectivity was examined in a cohort of 17 children with bilateral CP to test the hypothesis that increased global WM damage will be seen in the group of severely affected (Gross Motor Function Classification Scale (GMFCS) level of IV) as compared to moderately affected (GMFCS of II or III) individuals. Diffusion tensor tractography was performed and the resulting fibers between anatomically defined brain regions were quantified and analyzed in relation to GMFCS levels. Overall, a reduction in total WM connectivity throughout the brain in severe versus moderate CP was observed, including but not limited to regions associated with the sensorimotor system. Our results also show a diffuse and significant reduction in global inter-regional connectivity between severity groups, represented by inter-regional fiber count, throughout the brain. Furthermore, it was also observed that there is a significant difference ($p = 0.02$) in long-range connectivity in patients with severe CP as compared to those with moderate CP, whereas short-range connectivity was similar between groups. This new finding, which has not been previously reported in the CP literature, demonstrates that CP may involve distributed, network-level structural disruptions.

1. Introduction

Cerebral palsy (CP) refers to a group of heterogeneous disorders characterized by the impairment of movement and posture with resultant limitation of activity (Bax et al., 2005). CP remains the most prevalent motor disorder affecting children (Clark and Hankins, 2003), and the common co-morbid deficits in sensation, cognition, communication, and behavior contribute immensely to the burden of the disorder in these patients (Bax et al., 2005; Volpe, 2008). A variety of disturbances in the developing fetal or infant brain may lead to CP with an individual's clinical presentation likely determined by the spatial pattern and extent of gray matter (GM) and white matter (WM) involvement (Folkerth, 2005; Volpe, 2008). Standard clinical neuroimaging identifies gross patterns of injury in 70–90% of cases and provides some useful prognostic information; however, tremendous clinical heterogeneity still exists that limits the utility of this neuroimaging data on an individual basis (Benini et al., 2013; Korzeniewski et al., 2008; Krageloh-Mann and Horber, 2007; Martinez-Biarge et al., 2011; Towsley et al., 2011; Woodward et al., 2006).

Multi-modal and advanced neuroimaging techniques such as diffusion tensor imaging (DTI) show great promise for providing increased sensitivity and specificity of the underlying structure–function relationships related to the neurobehavioral deficits in CP. These advanced neuroimaging techniques are also being explored for the more immediate clinical needs of subgroup classification, prognostication, targeting treatment strategies and treatment monitoring (Benini et al., 2013; Hoon, 2005; Shimony et al., 2008). The latter has become increasingly necessary as more neuroprotective and rehabilitative treatment trials

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are underway. Thus far, neuroimaging data have shown early promise as treatment response biomarkers in neuroprotective therapeutic hypothermia (Porter et al., 2010; Rutherford et al., 2010), stem cell therapies (Lee et al., 2012; Min et al., 2013) and rehabilitative trials within this population (Sutcliffe et al., 2009; Trivedi et al., 2008).

Diffusion weighted imaging techniques, including DTI and diffusion tensor tractography (DTT), are particularly well-suited for the detection of WM microstructural changes (Gerig et al., 2004; Mori and Zhang, 2006) that are thought to contribute heavily to the clinical manifestations of CP. In the last several years, many groups have reported DTI-based ultra-structural WM differences in this population. The majority of studies have predominately focused on regions of the brain associated with putative sensorimotor function and demonstrate variable deficits (Chang et al., 2012; Hoon et al., 2002; Ludeman et al., 2008; Murakami et al., 2008; Rose et al., 2007; Scheck et al., 2012; Trivedi et al., 2010) (for systematic review see Scheck et al. (2012)). For the most part, these studies used similar approaches and typically measure diffusivity and anisotropy within a priori selected WM ROIs related to sensorimotor function. Additional studies utilizing tractography methods were likewise focused on the identification of a priori sensorimotor tracts as ROIs for quantification of diffusivity measurements (Rha et al., 2012; Rose et al., 2011; Thomas et al., 2005; Yoshida et al., 2010).

There are a few DTI studies investigating more global WM deficits in CP, also demonstrating changes in mean diffusivity (MD) and fractional anisotropy (FA) (Lee et al., 2011; Rai et al., 2013). In a tractography study, Nagae et al. found multiple and wide-spread differences in a qualitative assessment of 26 manually defined fiber tracts (Nagae et al., 2007). These studies suggest a more diffuse pattern of white matter injury, and indicate the need for a more comprehensive whole-brain characterization of white matter damage in CP.

Thus far, there have been no DTI studies in CP aimed at quantifying WM connectivity throughout the whole brain using a comprehensive and standardized set of ROIs. Given the neuropathologic evidence of diffuse gross and ultra-structural WM pathology in CP patients (Folkerth, 2005; Hoon, 2005; Volpe, 2003) we investigated the spatial pattern and extent of WM tract differences using whole-brain connectivity analysis in children with CP. Specifically, WM connectivity measures were compared between groups of individuals with severe versus moderate CP (grouped by GMFCS level), in order to test the hypothesis that WM connectivity is affected throughout the brain in proportion to the severity of the disorder.

2. Methods

2.1. Subjects

Participants included children, ages 1 to 5 years, with a clinical diagnosis of bilateral CP and Gross Motor Function Classification System (GMFCS) level of II, III or IV. Participants were part of a randomized, placebo controlled trial of autologous cord blood infusions in children with CP. As part of the study, baseline MRI and functional assessments were performed. The data presented here are the results from baseline imaging findings in a subset of children enrolled in the clinical trial. The subset was restricted to children with predominantly spastic bilateral CP in order to minimize clinical heterogeneity in an effort to identify brain pathologies specific to this discrete population and relatable to functional deficits. Thus, patients were excluded if they had hemiparetic CP (unilateral involvement), predominant dystonic CP, seizure disorder, brain dysmorphogenesis, or known genetic disease. The main structural MRI findings in this cohort are enlarged ventricles accompanied by gross white matter atrophy, and none of these individuals showed evidence of perinatal stroke as the primary etiology. Patients underwent neurological testing of motor control, muscle tone and spasticity, overall flexibility and reflexes, as well as cognitive assessment if able (see below). The physical examinations were performed by two senior clinicians experienced with clinical care of patients with CP. Demographic information is presented in Table 1.

The cohort in this report consists of 17 children (age = 2.4 years ± 1.18). Individuals were divided into two groups based on GMFCS level, a severe group (GMFCS of IV, n = 9, mean age = 1.83 years ± 0.77), and a moderate group (GMFCS of II or III, n = 8, mean age = 3.10 years ± 1.23). The moderate and severe group distinction used here separates the participants according to the precursors of their eventual levels of self-mobility. According to the GMFCS levels, individuals at levels II or III will be able to walk with limitations (possibly with a hand held assistance or mobility device) after age 4, however individuals classified at level IV have more limited self-mobility. GMFCS assessment can be performed on children prior to age 4 and is predictive and reliable of functional abilities throughout development (Palisano et al., 1997, 2007).

Of the 17 children in this cohort, 13 were between 0 and 3 years of age and qualified for neuropsychometric testing with the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) (Bayley, 2005). The other 4 children were older than 3 years of age at the time of testing; of these, two were too impaired to be tested,

Table 1
Demographic information of the CP patient cohort.

Subject	GMFCS level	Age (at scan, years)	BSID-III cognitive composite	Abnormal movements	Typography	Gestational age (weeks)
1	IV	1.83	55	Spastic predominant with dystonia	Q	38
2	II	2.5	105	Spastic	D	35
3	IV	1.25	55	Spastic predominant with dystonia	Q	30
4	III	4.42	N/T[b]	Spastic	D	27
5	III	2.08	90	Spastic predominant with dystonia	Q	31
6	IV	1.5	N/T[b]	Spastic predominant with dystonia	Q	31
7	IV	3.75	N/T[a]	Spastic	Q	31
8	II	2.08	100	Spastic	D	41
9	II	4.83	N/T[b]	Spastic	D	38
10	II	2.83	100	Spastic	D	32
11	IV	1.42	90	Spastic	Q	32
12	IV	1.92	55	Spastic predominant with dystonia	Q	32
13	II	4.3	69[c]	Spastic predominant with dystonia	D	38
14	IV	1.17	55	Spastic predominant with dystonia	D	39
15	IV	1.7	N/T[b]	Spastic	Q	40
16	IV	1.95	55	Spastic	Q	30
17	II	1.73	80	Spastic predominant, mixed unspecified	Q	35

[a] Not tested due to language barrier.
[b] Too severely disabled to complete testing.
[c] Tested using WISC-III.