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# Assessment of the structural brain network reveals altered connectivity in children with unilateral cerebral palsy due to periventricular white matter lesions

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ABSTRACT

*Background:* Cerebral palsy (CP) is a term to describe the spectrum of disorders of impaired motor and sensory function caused by a brain lesion occurring early during development. Diffusion MRI and tractography have been shown to be useful in the study of white matter (WM) microstructure in tracts likely to be impacted by the static brain lesion.
*Aim:* The purpose of this study was to identify WM pathways with altered connectivity in children with unilateral CP caused by periventricular white matter lesions using a whole-brain connectivity approach.
*Methods:* Data of 50 children with unilateral CP caused by periventricular white matter lesions (5–17 years; manual ability classification system [MACS] I = 25/II = 25) and 17 children with typical development (CTD; 7–16 years) were analysed. Structural and High Angular Resolution Diffusion weighted Images (HARDI; 64 directions, b = 3000 s/mm$^2$) were acquired at 3 T. Connectomes were calculated using whole-brain probabilistic tractography in combination with structural parcellation of the cortex and subcortical structures. Connections with altered fractional anisotropy (FA) in children with unilateral CP compared to CTD were identified using network-based statistics (NBS). The relationship between FA and performance of the impaired hand in bimanual tasks (Assisting Hand Assessment—AHA) was assessed in connections that showed significant differences in FA compared to CTD.
*Results:* FA was reduced in children with unilateral CP compared to CTD. Seven pathways, including the corticospinal, thalamocortical, and fronto-parietal association pathways were identified simultaneously in children with left and right unilateral CP. There was a positive relationship between performance of the impaired hand in bimanual tasks and FA within the cortico-spinal and thalamo-cortical pathways ($r^2$ = 0.16–0.44; $p < 0.05$).
*Conclusion:* This study shows that network-based analysis of structural connectivity can identify alterations in FA in unilateral CP, and that these alterations in FA are related to clinical function. Application of this connectome-based analysis to investigate alterations in connectivity following treatment may elucidate the neurological correlates of improved functioning due to intervention.


## 1. Introduction

Cerebral palsy (CP) has been defined as "a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing foetal or infant brain" (Rosenbaum et al., 2007). It is a condition with myriad clinical manifestations and functional limitations. Structural magnetic resonance imaging (MRI), such as T1- or T2-weighted imaging, can be used to assess the location and size of brain lesions in children with cerebral palsy, and can be used to

*Abbreviations:* AHA, assisting hand assessment; CDGM, cortical and deep grey matter; CP, cerebral palsy; CTD, children with typical development; DROP-R, detection and replacement of outliers prior to resampling; FA, fractional anisotropy; FMAM, fit model to all measurements; GMFCS, gross motor function classification system; HARDI, high angular resolution diffusion imaging; HOMOR, higher order model outlier rejection; MACS, manual ability classification system; NBS, network based statistic; PWM, periventricular white matter.

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elucidate the aetiology or pathogenesis of CP (Krägeloh-Mann and Horber, 2007). It is, however, difficult to establish a relationship between structural MRI and clinical function (Arnfield et al., 2013). While larger brain lesions typically indicate higher severity of impairments, similarly severe impairments can be seen in children with small lesions in functionally relevant areas or even in those with apparently normal structural MRI (Krägeloh-Mann and Horber, 2007; Miller, 2005). An assessment of the microstructural properties of the white matter is therefore required for an improved understanding of the relationship between brain microstructure and clinical function.

Diffusion MRI provides a non-invasive tool to probe white matter microstructure. The diffusion of water molecules in the brain is hindered and restricted by the presence of axons in the brain. Changes in water diffusion are associated with changes in myelination, axon density and diameter, and coherence (Scholz et al., 2009). Tissue microstructural properties are frequently characterised using the quantitative diffusion metrics fractional anisotropy (FA) and mean diffusivity (MD); see Basser and Ozarslan (2010) for a review. In addition, diffusion MRI allows the delineation of white matter pathways by tractography, and subsequent assessment of microstructure within three-dimensional tracts rather than two-dimensional regions of interest. Both diffusion MRI and tractography have previously been used to investigate CP in paediatric populations (see Scheck et al., 2012 for a systematic review).

Perhaps not surprisingly, the corticospinal tract – the major descending motor pathway in the brain – has been the most frequent target of tractography investigations in CP (Chang et al., 2012; Chaturvedi et al., 2012; Glenn et al., 2007; Holmström et al., 2011; Hoon et al., 2002; Koerte et al., 2011; Rha et al., 2012; Rose et al., 2011; Son et al., 2007, 2009; Thomas et al., 2005; Trivedi et al., 2010; Yoshida et al., 2010), with a recently increased interest in ascending sensory pathways (Chaturvedi et al., 2012; Hoon et al., 2002; Rha et al., 2012; Rose et al., 2011; Thomas et al., 2005; Trivedi et al., 2010; Yoshida et al., 2010). Other projection, association and commissural pathways have been investigated less frequently (Koerte et al., 2011; Thomas et al., 2005). In the majority of these studies, the identification of pathways associated with CP was limited by the use of the diffusion tensor model to drive tractography, as well as the necessity of a priori hypotheses concerning the pathways to be investigated.

The aim of this study was to identify pathways associated with unilateral cerebral palsy from the structural network of connections in an automated fashion. This approach requires no a priori hypotheses regarding the tracts of interest, and has the potential of identifying pathways of altered microstructure that were not previously investigated in unilateral CP. To achieve this, we calculated the structural connectomes of children with unilateral left and right CP caused by periventricular white matter (PWM) lesions, as well as children with typical development (CTD) using High Angular Resolution Diffusion Imaging (HARDI) tractography, and investigated differences in FA between participant groups using a network-based statistics approach. We further hypothesised that a relationship would exist between FA of the identified pathways and performance of the impaired hand in bimanual tasks.

## 2. Methods

### 2.1. Participants

Study participants included children who were recruited and assessed at baseline as part of ongoing cohort studies of children with unilateral CP at our centre, investigating executive function (Bodimeade et al., 2013), the effect of web-based multimodal training (Mitii) (Boyd et al., 2013a), and the effect of constraint induced movement and bimanual therapy (CoMBiT) (Boyd et al., 2013b) on brain structure and function in children and adolescents with unilateral CP. Children with mild to moderate unilateral CP (congenital spastic hemiplegia; Gross Motor Function Classification System I–II, Manual Ability Classification System I–II), aged between 5 and 18 years, with sufficient cooperation and cognitive understanding to participate in therapy activities (Boyd et al., 2013a,b), and no contraindication for MRI and no epilepsy were eligible for recruitment.

A total of 80 children with unilateral CP (age 5–17 years), of whom 38 presented with left unilateral CP and 42 presented with right unilateral CP, as well as 21 children with typical development (CTD, age 7–16 years) recruited from the community with no indication for brain MRI participated in one or more of the abovementioned studies and had MRI performed at baseline (see Table 1 for participant demographics).

The University of Queensland and Children's Health Queensland ethics committees granted ethical approval. Informed parental consent was obtained from all participants.

### 2.2. Clinical testing

Performance of the impaired hand in bimanual tasks was assessed using the Assisting Hand Assessment (AHA; (Krumlinde-Sundholm and Eliasson, 2003)). The AHA assesses the effectiveness with which a child uses their impaired hand in bimanual activities. The school kids version of the AHA has previously been shown to have excellent inter-rater and intra-rater reliability (intraclass correlation 0.97; (Holmefur et al., 2007)), and is sensitive to change due to intervention (Eliasson et al., 2005). An alternate form of the AHA was used for adolescents older than 12 years provided by the developers, however its reliability has not yet been assessed. A certified rater scored the AHA. Raw AHA scores are based on 22 items scored from 1 to 4; hence raw AHA scores range from 22 to 88. Raw AHA scores were converted to scaled logit (log odds probability units) AHA scores, which range from 0 to 100 (Krumlinde-Sundholm, 2012).

### 2.3. MRI

To prepare children for the MRI scan, a “practice session” with a mock scanner was organised prior to the real MRI scan to familiarise children with the scanner conditions.

MRI data were acquired using a 3 T Siemens Tim Trio scanner (Siemens, Erlangen, Germany) with TQ gradients (45 mT/m, slew rate 200 T/m/s), using a 12 element Tim head array. A high-resolution structural image was acquired using a 0.9 mm isotropic 3D T1 Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence. The imaging parameters were: field of view 23 × 23 × 17.3 cm; TR/TE/TI 1900/2.32/900 ms; and flip angle 9°. The acquisition time for the MPRAGE was 4.5 min.

Diffusion images were acquired using a commercial single shot twice-refocussed echo planar multi-directional diffusion weighted sequence (SS-EPI; Reese et al., 2003). The imaging parameters were: 60 axial slices; 2.5 mm slice thickness; field of view 30 × 30 cm; TR/TE 9500/116 ms; and acquisition matrix 128 × 128, resulting in an in-plane resolution of 2.34 × 2.34 mm. Parallel imaging was employed with an acceleration factor of 2 to reduce susceptibility distortions. Sixty-four diffusion weighted images were acquired at $b = 3000$ s/mm$^2$, in which the encoding gradients were distributed in space using the electrostatic approach (Jones et al., 1999), along with one minimally diffusion weighted image ($b = 0$). A field map for diffusion data was acquired using two 2D gradient-recalled echo images (36 axial slices; 3 mm slice thickness with 0.75 mm gap; field of view 19.2 × 19.2 cm; TR/TE1/TE2 488/4.92/7.38 ms; acquisition matrix 64 × 64) to assist in the correction for residual distortions due to susceptibility inhomogeneities. The combined acquisition time for diffusion data and field map was 10 min.

A Fluid Attenuated Inversion Recovery (FLAIR) image was acquired for lesion classification (25 axial slices; 4 mm slice thickness with 1.2 mm gap; field of view 22 × 22 cm; TR/TE/TI 7000/79/2500 ms; acquisition matrix 256 × 192 interpolated to 512 × 512). The acquisition time for the FLAIR image was 2 min.