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Structural connectivity of the anterior cingulate in children with unilateral cerebral palsy due to white matter lesions

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ABSTRACT

In this work we investigate the structural connectivity of the anterior cingulate cortex (ACC) and its link with impaired executive function in children with unilateral cerebral palsy (UCP) due to periventricular white matter lesions.

Fifty two children with UCP and 17 children with typical development participated in the study, and underwent diffusion and structural MRI. Five brain regions were identified for their high connectivity with the ACC using diffusion MRI fibre tractography: the superior frontal gyrus, medial orbitofrontal cortex, rostral middle frontal gyrus, precuneus and isthmus cingulate. Structural connectivity was assessed in pathways connecting these regions to the ACC using three diffusion MRI derived measures: fractional anisotropy (FA), mean diffusivity (MD) and apparent fibre density (AFD), and compared between participant groups. Furthermore we investigated correlations of these measures with executive function as assessed by the Flanker task.

The ACC–precuneus tract had significantly different MD ($p < 0.0001$) and AFD ($p = 0.0072$) between groups, with post-hoc analysis showing significantly increased MD in the right hemisphere of children with left hemiparesis compared with controls. The ACC–superior frontal gyrus tract had significantly different FA ($p = 0.0049$) and MD ($p = 0.0031$) between groups. AFD in this tract (contralateral to side of hemiparesis; right hemisphere in controls) showed a significant relationship with Flanker task performance ($p = 0.0045$, $\beta = -0.5856$), suggesting that reduced connectivity correlates with executive dysfunction.

Reduced structural integrity of ACC tracts appears to be important in UCP, in particular the connection to the superior frontal gyrus. Although damage to this area is heterogeneous it may be important in early identification of children with impaired executive function.

1. Introduction

Cerebral palsy (CP) is a non-progressive disability caused by a heterogeneous group of brain pathologies. The clinical phenotype has been classically described in terms of motor impairment (Krägeloh-Mann and Cans, 2009), and consequently there has been a large focus in neurological research around motor regions of the brain in these children (Krägeloh-Mann and Cans, 2009; Arnfield et al., 2013; Krägeloh-Mann and Horber, 2007; Scheck et al., 2012). There has been increasing interest in exploring cognitive and social functioning in children with CP (Whittingham et al., 2014; Bodimeade et al., 2013; Weierink et al., 2013; Bjorgaas et al., 2012; Caillies et al., 2012; Hustad et al., 2012; Iwata et al., 2012), showing impairments across multiple executive function domains (Bodimeade et al., 2013) with considerable impact on everyday life (Whittingham et al., 2014). Up to 50% of children with CP have an intellectual disability (Novak et al., 2012) and 25–50% have attention deficit disorder or attention deficit hyperactivity disorder (Bjorgaas et al., 2012; Novak et al., 2012). Despite extensive research on the impact of cognitive and social impairment on the lives of people with CP, there is little understanding of the underlying neuropathology (Weierink et al., 2013).

Abbreviations: ACC, anterior cingulate cortex; AFD, apparent fibre density; CP, cerebral palsy; CTD, children with typical development; DTI, diffusion tensor imaging; FA, fractional anisotropy; FOD, fibre orientation distribution; HARDI, high angular resolution diffusion imaging; MD, mean diffusivity; MRI, magnetic resonance imaging; ROI, region of interest; SIFT, spherical deconvolution informed filtering of tractograms; UCP, unilateral cerebral palsy; WM, white matter.

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Lesions in CP typically involve periventricular white matter (56%) or either cortical or deep grey matter (18%), with global maldevelopments being less common (9%) (the remaining 17% are non-specific) (Krägeloh-Mann and Horber, 2007). In the present study we assess children with periventricular white matter (WM) lesions. Early WM damage evident on structural MRI at term equivalent age is a significant predictor of executive function in very preterm children (Iwata et al., 2012), and diffusion properties of multiple WM regions have been shown to correlate with neuropsychological scores in children with spastic diplegia (Rai et al., 2013). In a whole brain connectome study in children with unilateral CP with WM lesions we have shown that the integrity of tracts connecting to the anterior cingulate cortex (ACC) may be compromised (Pannek et al., 2014).

The ACC is a bilateral cortical structure in the medial wall of the brain, important for both cognitive and social functioning (Bush et al., 2000). Functional MRI studies have shown that the ACC plays a central role within the executive function brain network (Botvinick et al., 1999), being highly connected with the prefrontal cortex, premotor and supplementary motor areas and parietal cortex (Paus, 2001; Devinsky et al., 1995).

To investigate WM integrity, we used two models derived from diffusion weighted MRI: the diffusion tensor model; and constrained spherical deconvolution. Multiple MRI measurements of Brownian motion of water molecules (Stejskal, 1965) are acquired for each voxel, used to derive a mathematical model from which various properties can be extracted, relating to underlying tissue. The majority of diffusion MRI studies in children with CP to date have utilised the diffusion tensor model (see review Scheck et al., 2012) which characterises diffusion within each voxel using a single tensor ellipsoid (Basser et al., 1994). From the tensor, quantitative measures such as fractional anisotropy (FA; often reported as a surrogate marker for white matter 'integrity') and mean diffusivity (MD) can be computed (Basser and Pierpaoli, 1996). Tractography algorithms can also exploit tensor-derived fibre orientation information to estimate fibre bundle trajectories (Mori et al., 1999). Surrogate markers for tract based 'connectivity' can then be computed by averaging quantitative measures within voxels traversed by tractography streamlines.

Where complex WM architecture exists, multiple fibres may cross within each voxel, and single ellipsoid tensor orientations can no longer be reliably used for tractography. FA results in these regions can be unintuitive and difficult to interpret (Douaud et al., 2011; Pierpaoli et al., 2001). A higher order model of the diffusion signal is therefore more appropriate (Jones, 2010). The fibre orientation distribution (FOD), computed via constrained spherical deconvolution, is one such model (Tournier et al., 2004, 2007). By resolving multiple fibres within each voxel, the FOD provides more accurate fibre directions for tractography in addition to tract specific quantification of white matter. The apparent fibre density (AFD), a recently developed fibre specific metric derived from the FOD lobe parallel to the direction of the streamline (Raffelt et al., 2012a; Raffelt et al., 2013) allows a result that reflects the individual tract being analysed, in contrast with the diffusion tensor model which provides a voxel-average FA or MD value. The AFD has been used to identify tracts with reduced fibre density in Motor Neurone Disease (Raffelt et al., 2012a), Alzheimer's disease (Raffelt et al., 2012b), epilepsy (Vaughan et al., 2013), infants born preterm (Tournier et al., 2013), adolescents born preterm (Raffelt et al., 2014a), grey matter heterotopia (Farquharson et al., 2014), and Dravet Syndrome (Raffelt et al., 2014b).

In this work we set out to analyse the connectivity of the ACC using both AFD and traditional tensor-derived measures (as this is the currently accepted approach in the majority of diffusion imaging studies in CP). We expect that due to anatomical location, WM tracts projecting from the ACC will pass through a high number of voxels with multiple fibre orientations and therefore AFD analysis will be more specific to the tracts being analysed than diffusion tensor-based analysis. We also aim to determine whether performance in an executive function task correlates with connectivity measures of these tracts.

2. Methods

2.1. Participants

A total of 71 children were identified through a population-based research database, recruited for one or more clinical studies requiring baseline MRI and clinical assessment (prior to any study specific intervention). Selection criteria included age 3–17 years, a confirmed diagnosis of unilateral cerebral palsy, attendance at a mainstream school, and a score of II (two) or below in both the Gross Motor Function Classification System (GMFCS) (Russell et al., 1989) and Manual Ability Classification System (MACS) (Eliasson et al., 2006) as assessed by an occupational therapist (scores shown in Table 1).

Of these children, 53 were selected based on MRI brain image classification. Images were reviewed by a child neurologist (SF) and classified according to the Krageloh-Mann classification system (Krägeloh-Mann and Horber, 2007) as periventricular white matter lesions (the remainder included 16 with cortical or deep grey matter lesions and 2 with brain malformations). Of these, 52 children were able to be adequately parcellated by the software as outlined below. These children were aged 5–17 years, and included 25 with left hemiparesis and 27 with right hemiparesis.

Seventeen children with typical development (CTD) without brain pathology were also included in all analyses as controls. The institutional review board approved the study and written informed consent was obtained from a parent or guardian, as well as verbal assent from each child.

2.2. Flanker task

A subset of children (7 left hemiparesis, 10 right hemiparesis, 14 CTD) participated in the Flanker task (Eriksen and Eriksen, 1974), which has previously been shown to be strongly linked to the ACC using functional MRI (Brown, 2009). This involved five symbols displayed in a horizontal line on a computer screen. The central symbol was either a left or right facing arrow. The remaining four symbols (the "Flanker" objects) were either congruent (e.g. ← ← ← ← ←); incongruent (e.g. → → ← → →); or neutral (e.g. – – ← – –). Subjects were given 5 s to press either the right or left button on a handheld control (using their preferred hand) to indicate the direction of the central arrow. This was repeated 120 times, with a 30 s break every after each set of 40 trials. To eliminate any group differences in motor performance, we used the mean time taken for a correct answer in the neutral condition as a baseline, and reported the mean additional time needed for a correct answer in the incongruent condition as a measure of executive function (increased additional time representing poorer executive function). Results were statistically corrected for age (and gender where significant) using a general linear model (see Statistical analysis below). We assessed the relationship between task performance and diffusion derived metrics (FA, MD and AFD) in both hemispheres, labelled as "contralateral" or "ipsilateral", referring to the side of hemiparesis. For CTD ipsilateral was arbitrarily taken as the left hemisphere (as this is ipsilateral to the non-dominant hand in right handers, but still the non-dominant hemisphere in most left handers (Knecht et al., 2000)).

Table 1
Participant information. Age given as mean ± standard error. CTD — children with typical development. GMFCS — Gross Motor Function Classification System. MACS — Manual Ability Classification Scale.

			Gender		GMFCS		MACS	
Group	n	Age	F	M	I	II	I	II
CTD	17	10.6 ± 0.5	10	7	n/a	n/a	n/a	n/a
Left hemiparesis	25	9.9 ± 0.6	10	15	20	5	15	10
Right hemiparesis	27	11.4 ± 0.6	10	17	18	9	11	16