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ORIGINAL ARTICLE

# Interhemispheric and intrahemispheric connectivity and manual skills in children with unilateral cerebral palsy

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**Abstract** This study investigated patterns of motor brain activation, white matter (WM) integrity of inter- and intrahemispheric connectivity and their associations with hand function in children with unilateral cerebral palsy (CP-U). Fourteen CP-U (mean age 10.6 ± 2.7 years) and 14 typically developing children (TDC) underwent magnetic resonance imaging. CP-U underwent extensive motor evaluation. Pattern of brain activation during a motor task was studied in 12 CP-U and six TDC, by calculating laterality index (LI) and percent activation in the sensorimotor areas (around the central sulcus), and quantifying the activation in the supplementary motor area (SMA). Diffusivity parameters were measured in CP-U and eight other TDC for the corpus callosum (CC), affected and less affected cortico-spinal tracts (CST), and posterior limb of the internal capsule (PLIC). Abnormal patterns of brain activation were detected in areas around the central sulcus in 9/12 CP-U, with bilateral activation and/or reduced percent activation. More activation in areas around the central sulcus of the affected hemisphere was associated with better hand function. CP-U demonstrated more activation in the SMA when moving the affected hand compared to the less affected hand. CP-U displayed reduced WM integrity compared to TDC, in the midbody and splenium of the CC, affected CST and affected PLIC. WM integrity in these tracts was correlated with hand function. While abnormal pattern of brain activation was detected mainly when moving the affected hand, the integrity of the CC was correlated with function of both hands and bimanual skills. This study highlights the importance of interhemispheric connectivity for hand function in CP-U,

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which may have clinical implications regarding prognosis and management.

**Keywords** Cerebral palsy · FMRI · Tractography · Corpus callosum · Cortico-spinal tract

**Abbreviations**

| | |
|---|---|
| WM | White matter |
| CP-U | Unilateral cerebral palsy |
| TDC | Typically developing children |
| MRI | Magnetic resonance imaging |
| fMRI | Functional MRI |
| DTI | Diffusion tensor imaging |
| MD | Mean diffusivity |
| FA | Fractional anisotropy |
| Da | Axial diffusivity |
| Dr | Radial diffusivity |
| LI | Laterality index |
| CC | Corpus callosum |
| CST | Cortico-spinal tracts |
| PLIC | Posterior limb of the internal capsule |
| M1 | Primary motor areas |
| CIMT | Constraint induced movement therapy |
| HABIT | Hand-arm bimanual intensive therapy |

## Introduction

Unilateral cerebral palsy (CP-U) is caused by various brain pathologies that occur early in the course of development and is characterised by motor impairments predominantly lateralised to one side of the body (Bax et al. 2006; Odding et al. 2006). The prevalence of CP is 1–2 per 1,000 live births, of which children with hemiplegia make up approximately 26 % of cases (Bax et al. 2006; Reid et al. 2011; Rice et al. 2009). The effects of brain injury during childhood have profound consequences across the lifespan with significant therapeutic challenges (Bax et al. 2005, 2006; Green and Wilson 2012).

Magnetic resonance imaging (MRI) has been shown to be useful in the evaluation of children with CP-U (Cioni et al. 1999). Yet, when using conventional MRI, not all children show evidence of structural abnormalities nor can white matter (WM) damage be characterised and the radiologic description of ‘severity’ does not always correlate with behavioural performance (Lee et al. 2011; Son et al. 2007; Holmefur et al. 2013; Okereafor et al. 2008). Advanced MRI methods, including diffusion tensor imaging (DTI) and functional MRI (fMRI), have improved the understanding of brain behaviour correlations in several developmental disorders, including childhood epilepsy, attention deficit hyperactivity disorder, autism and CP (van Ewijk et al. 2012; Weinstein et al. 2011; Yang et al. 2012; Liston et al. 2011; Staudt et al. 2004).

fMRI studies using motor tasks in children with CP-U demonstrated abnormal pattern of activation, which included reduced activation in the affected hemisphere and existence of ipsilateral activation (Guzzetta et al. 2007; Sutcliffe et al. 2007, 2009; You et al. 2005). Most studies focused on the relation between brain activation and motor function (Guzzetta et al. 2007; Staudt et al. 2002) or the effects of intervention on brain activation (Golomb et al. 2010; Sutcliffe et al. 2009; Walther et al. 2009; You et al. 2005; Cope et al. 2010). Ipsilateral activation has been shown to indicate poor recovery in adult stroke patients (Cramer 2004; Turton et al. 1996) and a shift to contralateral activation was detected following constraint induced movement therapy (CIMT) in children with CP-U (Sutcliffe et al. 2009). In the present study, we used fMRI to investigate the spatial distribution and level of activation, during a motor task in children with CP-U.

The pathomechanisms underlying the impaired motor performance and abnormal pattern of brain activation following early brain injury are unclear. Do they result from the existence of ipsilateral cortico-spinal connections (Holmström et al. 2010; Staudt et al. 2002) or due to damage to the CC influencing inhibitory control (Meyer et al. 1998)? To approach these questions, we used DTI, which is a non-invasive, sensitive method for the study of WM maturation, integrity and pathology (Basser et al. 1994; Fan et al. 2006; Huang et al. 2006; Wakana et al. 2004). DTI offers various diffusivity indices, reflecting microstructural information. The most common parameters are mean diffusivity (MD) and fractional anisotropy (FA), which describe the degree by which water diffusion is restricted in one direction relative to all others, reflective of axonal maturation; axial diffusivity (Da), considered to reflect diffusivity parallel to WM fibres and to be sensitive to axonal growth and injury and radial diffusivity (Dr), considered to reflect diffusivity perpendicular to the axon, and to be sensitive to myelination and demyelination processes (Budde et al. 2009; Dubois et al. 2006; Song et al. 2002). During normal development, MD, Da and Dr values decrease along with increases in the FA values, indicating brain maturation and increased integrity.

DTI studies in children with hemiplegia have mainly focused on the intrahemispheric tracts and reported reduced WM integrity in the affected cortico-spinal tracts (CST) (Glenn et al. 2003, 2007; Son et al. 2007; Yoshida et al. 2010; Nagae et al. 2007). Fewer studies have focused on the integrity of the CST, or assessed the cerebral peduncle asymmetry, in relation to motor function (Bleyenheuft et al. 2007; Duque et al. 2003; Holmström et al. 2011; Murakami et al. 2008). The involvement of the corpus callosum (CC), which has a central role in motor functions, was studied mainly in children with periventricular leucomalacia (PVL) and/or with bilateral spastic CP, (Davatzikos et al. 2003; Koerte et al. 2011; Murakami et al. 2008; Nagae et al. 2007). These studies reported ambiguous results with some reporting reduced callosal integrity (Davatzikos et al. 2003; Koerte et al. 2011; Nagae et al. 2007) and others that did not detect differences between children with bilateral CP compared to controls (Murakami et al. 2008). Since these studies investigated interhemispheric connectivity mainly in children with bilateral CP and used limited measures of hand function, it is difficult to interpret the results specifically in relation to the inter-hemispheric connectivity in children with CP-U. One study, on five subjects with CP-U, did not detect a significant decrease in number of fibres of the CC as compared with controls, but did report reduced WM integrity in the body of the CC. This study included a limited number of subjects and did not relate to hand function (Thomas et al. 2005). Therefore, another aim of this study was to investigate the integrity of both interhemispheric and intrahemispheric connectivity, their relation with each other, with motor hand function and their role in abnormal pattern of activation.

In this study, we used a combined assessment of hand function, functional activation via fMRI, and WM integrity via DTI to provide a more comprehensive picture of the relationships between these variables and better understanding of the reorganization of the brain following perinatal injury. We hypothesized that children with CP-U would show a different pattern of activation and reduced integrity of inter and intra WM tracts compared to TDC. In addition, we hypothesized that the imaging variables, both structural and functional, will be correlated to motor performance. On the basis of the role of the CC in inhibitory control, we hypothesized that reduced WM integrity in the CC may be associated with bilateral motor activation when moving the affected hand, and thus will contribute to the understanding of the pathomechanism underlying impaired performance. Results from this study may have clinical implications regarding prognosis and evaluation of the benefits of intervention in these children.

## Materials and methods

### Participants

#### *Patient population*

Fourteen children with CP-U (eight boys, mean age 10.6 ± 2.7 years; range 7–14 years) underwent MR imaging alongside clinical motor assessments. Children with CP-U were recruited from a regional hospital and/or child development centres. Inclusion criteria were clinical signs of spastic hemiplegia (due to early brain injury), attending regular education and independently mobile. Exclusion criteria were any overt seizure activity, administration of treatment (aimed at improving range of upper extremity movements) such as botulinum toxin injections or surgery in the previous 6 months, and any contra-indications to MR imaging. We intentionally included children with mild to severe limitations of movement in the affected hand, yet with preserved cognitive abilities to examine a range of abilities. For clinical details of the children see Table 1.

#### *Control group*

Fourteen typically developing children (TDC) were included: six children (four boys, mean age 13.8 ± 3.1 years) served as controls in the fMRI analysis and eight children served as controls in the DTI analysis (six boys, mean age 12.1 ± 2.9 years). Requirements for eligibility were no brain anomalies on conventional MRI, normal developmental history, attendance of an age-appropriate educational facility, no prior history of head injury and no clinical evidence of neurological dysfunction. There were no significant differences in age between children with CP-U and TDC in the DTI analysis $t(20) = -1.531$, $p = 0.141$, but in the fMRI analysis TDC were significantly older than children with CP-U $t(18) = -2.58$, $p = 0.019$.

This study was approved by the Institutional Review Board of the Ministry of Health and the hospital, and fully informed consent was obtained from parents and/or children aged over 18 years.

### Clinical assessment of hemiparesis

All children with CP-U underwent comprehensive motor assessment on the day of the MRI. Baseline data of severity of motor disorder and co-existing conditions were documented at assessment and verified via medical records.

Severity of movement difficulties was reflected by higher scores on the Manual Ability Classification Level (MACS) and the Modified Ashworth Scale (MAS). The MACS classifies a young person's ability to handle objects in important daily activities across a five point scale. Children at level I handle most objects easily and at level V are severely limited in their ability (Eliasson et al. 2006; Gunel et al. 2009; Kuijper et al. 2010). The MAS further characterised the children by documenting severity of movement restriction due to spasticity across the elbow, wrist, fingers and thumb (0 indicating no movement restriction, to 4 reflecting rigidity/severe contracture). The

Table 1 Subject characteristics

| Sub. | Gender | Preterm/term | Birth weight (g) | Age at MRI | Hemi paretic side | Type of injury | Time of injury | Extent of damage | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | WM | GM |
| 1 | M | Term | 3,470 | 8y6m | R | Intracranial haemorrhage | Perinatal | 3 | Cortex, deep grey matter |
| 2 | F | Preterm | 960 | 13y | R | IVH IV | Perinatal | 2 | – |
| 3 | F | Preterm | 1,000 | 14y3m | R | IVH IV | Perinatal | 1 | – |
| 4 | M | Term | 2,770 | 9y2m | R | MCA infarct | Perinatal | 2 | Basal ganglia |
| 5 | M | Term | 3,555 | 7y2m | R | MCA infarct | Perinatal | 3 | Cortex, basal ganglia |
| 6 | M | Preterm | 1,460 | 10y2m | L | PVL | Perinatal | 1 | – |
| 7 | F | Preterm | 800 | 14y | R | IVH IV | Perinatal | 3 | Cortex, basal ganglia, thalamus |
| 8 | M | Term | 3,900 | 14y1m | R | MCA Infarct (partial) | Perinatal | 1 | – |
| 9 | M | Preterm | 1,298 | 7y2m | L | PVL | Perinatal | 1 | Cortex |
| 10 | F | Term | 2,360 | 7y3m | R | MCA infarct | Perinatal | 3 | Cortex, basal ganglia, thalamus |
| 11 | F | Term | 3,245 | 10y2m | R | MCA Infarct (partial) | Perinatal | 1 | Deep grey matter |
| 12 | M | Preterm | 2,000 | 9y2m | R | IVH IV | Perinatal | 3 | Thalamus |
| 13 | M | Term | 3,765 | 7y2m | R | MCA Infarct | Perinatal | 3 | Basal ganglia, thalamus |
| 14 | F | Term | 3,330 | 13y | L | Infancy-age 3 m | | 3 | – |

*Sub.* subject, *M* male, *F* female, *Preterm* ≤31 weeks, range 26–31 weeks, *y* years, *m* months, *R* right, *L* left, *IVH* intraventricular haemorrhage, *MCA* middle cerebral artery, *WM* white matter volume loss: 1 = mild, 2 = moderate, 3 = severe, *GM* grey matter

MAS was selected due to its use in corresponding clinics and ease of administration (Scholtes et al. 2006) despite adequate reliability in children only for the spasticity ratings of elbow flexors (interrater intra class correlation coefficient [ICC] >0.75 and intrarater ICC = 0.50–0.75 (Clopton et al. 2005).

The Assisting Hand Assessment (AHA; version 4.3) is a standardised test of spontaneous use and performance of a weaker/affected hand during bimanual interactions in functional/play based tasks with good reliability and validity (Eliasson et al. 2005; Krumlinde-Sundholm et al. 2007). The AHA is scored from video recordings across 22 predefined items using a four-point rating scale. Test–retest reliability is reported as 0.99, ICCs between scales 0.99 with smallest detectable difference of 3.89 logit scale score and interrater ICCs for summed scores were high: 0.98 (2-rater design) and 0.97 (20-rater design; Holmefur et al. 2009; Holmefur et al. 2007). Raw scores are transformed into logits via Rasch analysis and converted to a 0-100 AHA scale, higher scores representing better bimanual skills (Holmefur et al. 2009). Assessments were undertaken by trained therapists and evaluations from video were made by a trained therapist blinded to medical history and/or other test results.

The Jebsen Taylor Test of Hand Function (JTTHF; Jebsen et al. 1969) is a standardised timed test measuring manual dexterity (modified by eliminating the writing task) with reliability and normative data reported for children with test–retest reliability of 0.83–0.99 (Taylor et al. 1973). Maximum time allowable to complete each task successfully was capped at 3 min, thus maximum time for all six items was 1,080 s. Lower scores reflect better unimanual skills. Age and gender JTTHF adjusted scores were derived by adjusting each child's raw score by the difference between the mean of the each age band from the total mean per gender from the normative group (Taylor et al. 1973). Age Adjusted JTTHF score = child's raw score ± (mean total for gender − mean per age band by gender).

Children's Hand Experience Questionnaire (CHEQ) is a 29-item questionnaire exploring independent participation and skilled use of an affected/hemiplegic hand in daily bimanual activities with good item-fit statistics using Rasch analysis (Skold et al. 2011). Children or parents completed the English version if they were fluent in English or the Hebrew translation. The extent to which children's affected hand was used in daily bimanual activities was calculated as a percentage of the 29 activities in which the affected hand was used to stabilize or grip items with scores ranging from 0 to 100 (Green et al. 2013).

Mirror Movement Assessment: Videos of the motor task in the MRI and 5 min of the AHA tasks of cutting and drawing (involving repetitive, sequential movements) were rated using the Woods and Teuber scales (Woods and Teuber 1978) to obtain estimated measures of presence/

extent of mirror movements (0 = no clear imitative movement to 4 = movement equal to that expected for the intended hand).

MRI protocol

Brain scans were performed on a 3 T GE (GE Signa EXCITE, Milwaukee, WI, USA) scanner preceded by training in a mock scanner. The MRI protocol included: high-resolution anatomical 3D fast spoiled gradient echo sequence (FSPGR), (slice thickness/gap = 1/0 mm; field of view (FOV)/matrix: 240 mm/256 × 256; Time to repeat (TR)/Time to echo(TE) = 8.6/3.3 ms); fMRI performed with $T_2$*-weighted gradient echo echo-planar imaging (GE-EPI) sequence (slice thickness/gap = 3.5/0.3 mm; FOV/matrix = 240 mm/128 × 128; TR/TE/flip angle = 2,250/29 ms/79°); DTI acquired along 19 diffusion gradient directions ($b = 1{,}000$ s/mm$^2$) and one with no applied diffusion gradient, (slice thickness/gap = 3/0 mm; FOV/matrix = 220 mm/128 × 128; TR/TE = 11,000/91 ms).

*Conventional MRI assessment*

An experienced paediatric radiologist assessed the extent of WM damage (1 = mild, 2 = moderate, 3 = severe) and grey matter (GM) involvement, cortex, deep grey matter, thalamus and basal ganglia.

*fMRI motor paradigm*

A block-design fMRI motor task was used based on (Golomb et al. 2010; McDonald and Saykin 2010; West et al. 2011) in which children were asked to clench and extend all fingers of one hand in synchrony with 2-Hz paced tones. The total task duration was 4 min and 48 s, with alternations between six epochs of rest, six epochs for right hand and six epochs for left hand, each epoch was 14 s. Children were instructed to do the best they could move only the affected or less affected hand in isolation. Range of movement was limited by a soft plastic sponge ball (50 cm diameter) placed in children's palms. Video recordings of the motor task in the MRI were made to objectively assess and monitor mirror movements using the Woods and Teuber scale (Woods and Teuber 1978).

*fMRI analysis*

fMRI analysis was performed using BrainVoyager QX 2 software package (http://www.brainvoyager.com). Preprocessing included head movement assessment (scans with head movement >3 mm were rejected), high-frequency temporal filtering, and removal of low-frequency linear trends. To allow for $T_2$* equilibration effects, the first six volumes of each functional scan were rejected. Pre-processed functional images were incorporated into the high-resolution 3D anatomy images through trilinear interpolation. Since the study group displayed substantial brain abnormalities, they were not transformed into a standard space (e.g., Talairach space) rather using each subject's native space. Three-dimensional statistical parametric maps were calculated separately for each subject using a general linear model (GLM) in which all stimuli conditions were positive predictors. To account for a hemodynamic response, predictors were convolved with 6-s hemodynamic response filter for all participants. Two contrasts were studied: contrast 1 = affected hand vs. baseline and contrast 2 = less affected hand vs. baseline. We used the false discovery rate (FDR) procedures for the selection of thresholds, which was found to be an effective technique, selecting thresholds automatically and adaptively across subjects (Benjamini et al. 2001; Genovese et al. 2002). The FDR ($q$ value) chosen in the present study was 0.005. The numbers of voxels within left and right areas around the central sulcus and within the supplementary motor area (SMA) were quantified separately. This broader definition of primary motor areas, which may have included some sensory areas, was used in this study, since brain plasticity, including significant shifts in brain structures, has been shown to occur following brain injury early in life (Eyre 2007).

*Laterality index (LI)* LI was calculated for each contrast and for each subject, according to the following commonly used formula (Sutcliffe et al. 2007): LI = (contralateral − ipsilateral)/(contralateral + ipsilateral), where contralateral and ipsilateral equal the total number of voxels activated above threshold in areas around the central sulcus contralateral or ipsilateral to the moving hand. An LI closer to one indicates a more unilateral pattern of activation (as expected TDC), while an LI closer to zero indicates a more bilateral pattern of activation, and a negative LI indicates more ipsilateral activation.

*Percent activation* Percent activation was used to overcome variability between subjects in physiological and imaging parameters, by normalizing the number of voxels. It was calculated as: number of voxels in areas around the central sulcus of the affected hemisphere (when moving the affected hand)/number of voxels in areas around the central sulcus of the unaffected hemisphere (when moving the unaffected hand) × 100.

These two measures provide complimentary information. The LI takes into account contralateral and ipsilateral activation when moving one hand and does not provide information regarding individual differences in extent of activation. Percent activation takes into account only contralateral activations and indicates the activation of the affected hand in relation to the activation potential, which is reflected by the activation of the less affected hand. Therefore this measure relates also to the extent of activation.

*DTI analysis*

DTI analysis was performed using DTIStudio software (Johns Hopkins University, Baltimore, MD, USA). First, the diffusion tensor was estimated on a voxel-by-voxel basis and Da, Dr, MD and FA maps were calculated. The main interhemispheric fibre (the CC) and intrahemispheric motor tracts (the CST) were reconstructed using streamline fibre tracking method with Fibre Assignment by Continuous Tracking (FACT) algorithm (Mori et al. 1999). Fibre tracking was terminated when it reached a pixel with an FA value lower then 0.25, or when the turning angle was >70°. The CC was extracted using a single region of interest (ROI) defined on a colour coded mid-sagittal FA image (Mori et al. 1999; Mori and van Zijl 2007; Wakana et al. 2004). Further segmentation of the CC into three segments was performed based on Witelson parcellation scheme (Witelson 1989): genu—comprising the anterior third, midbody—comprising the anterior and posterior midbody and the isthmus, and splenium—comprising the posterior one-fifth. The CST tracts were extracted using a multiple ROI approach, defining fibres that pass through the unilateral pons, posterior limb of the internal capsule (PLIC), and motor and premotor cortex. In addition, ROI analysis was performed for the left and right PLIC using ROIEditor software (Johns Hopkins University, Baltimore, MD, USA). A number of fibres and mean values of Da, Dr, MD and FA were calculated for each fibre/ROI. We decided to include the number of fibres measured, although this measure has large variability and is less reliable than other diffusivity values (Wang et al. 2012), in order to reflect structural differences in addition to the microstructural differences.

Statistical analysis

Descriptive and inferential statistics were performed using SPSS software (SPSS 19.0 Chicago, IL, USA). For the analysis of pattern of activation, mean and standard deviation (SD) of LI and percent activation of TDC were primarily calculated and then difference in SD from the mean of TDC was calculated for each child with CP-U. This enabled us to assess each child's pattern of activation individually and not mask the individual differences by combining all children with CP-U into one group. Normality of distribution was assessed for LI, percent activation, DTI parameters and motor function (AHA, CHEQ, JTTHF and mirror movements) using skewness and kurtosis measures. Paired $t$ tests were performed to compare the right and left CST. Multivariate general linear model (GLM) analysis was used to compare children with CP-U to TDC with number of fibres and diffusion values (Da, Dr, MD, FA) of the CC segments, affected and less affected CST and PLIC as the dependent variables and group as the fixed factor. Partial correlations using age as a covariate were calculated between variables with normal distribution, and Spearman correlations were calculated for variables without normal distribution and ordinal data (mirror movements).

## Results

The demographic and clinical characteristics of the participants are presented in Table 1. Children with CP-U varied in type of injury: six children had middle cerebral artery stroke, four children had intraventricular haemorrhage grade IV, two children had intracranial haemorrhage and two children had periventricular leucomalacia. One child (subject 7) showed more extensive bi-hemispheric lesion with motor signs observed in both lower limbs but with unilateral upper limb involvement. Ten children had grey matter injury that included one or more of the following: cortex, basal ganglia, thalamus and deep grey matter (see Fig. 1 for representation of extent of damage and intersection of regions of interest). Six children were born preterm with gestational age <31 weeks.[1] The extent of motor involvement of the hemiplegia ranged from 1 to 3 on MACS and 0 to 4 on MAS.

## Motor assessment

Bimanual performance on the AHA varied widely between children (mean 52.2; SD 18.6; range 30–90), and similarly large differences were evident in the extent to which children used their affected hand in daily tasks on the CHEQ (mean two-handed use = 13.6; SD = 9.4; range = 0–29). Large variations were also seen in uni-manual capacity on the JTTHF with four children unable to complete any task with their affected hand (mean = 574.1; SD = 418.6; range 44–1,080 s). See Table 2 for details of hand function per child. Variations were also seen in the use of the less affected hand (mean 43.9; SD 18.4; range 19–94.5 s), with six children displaying significant impairment (≥2 SD) in their less affected hand, based on the norms of the JTTHF (Taylor et al. 1973). Therefore, in this study, we referred to

[1] One child, subject 14, acquired her brain lesion at 3 months of age and all analyses were run excluding her data with no significant differences in results.

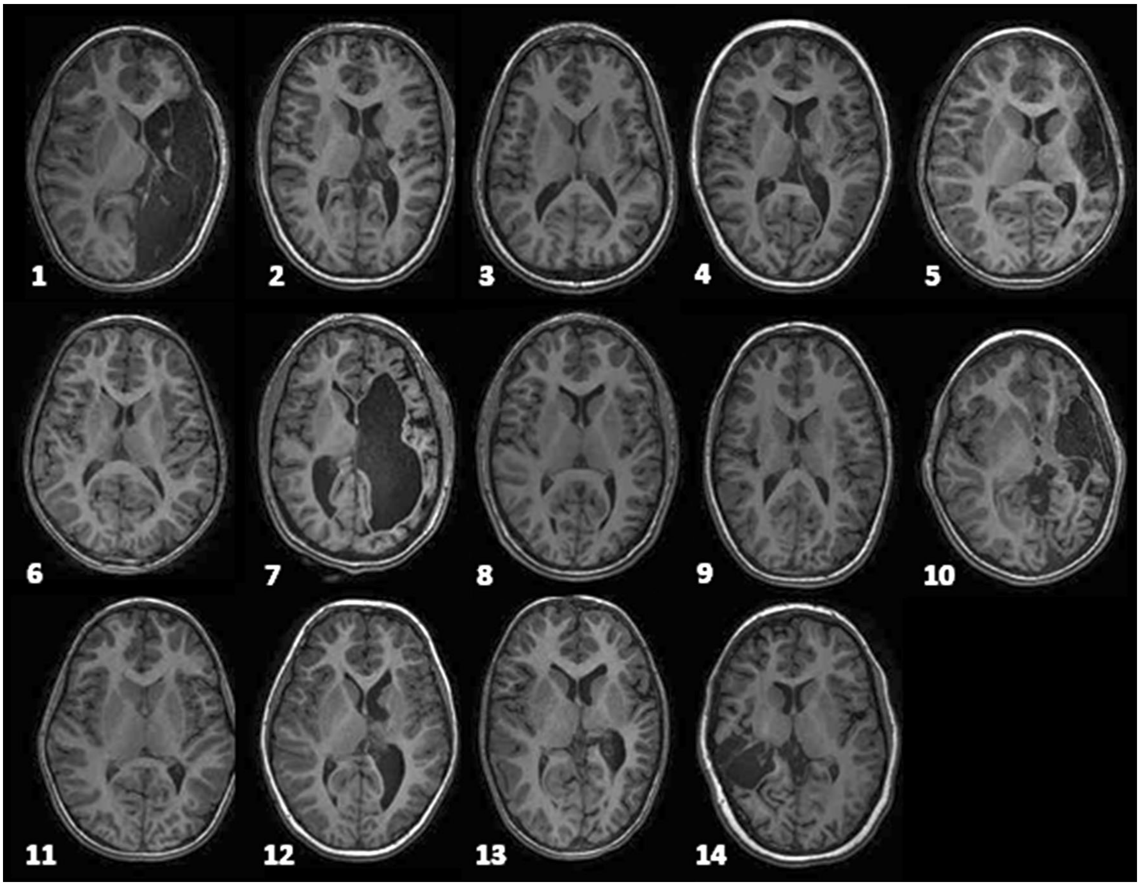


**Fig. 1** Axial T1 images of children with unilateral CP

the non-plegic hand as "less affected" rather than "unaffected" in line with previous studies that showed impairment in the non-plegic hand (Brown et al. 1987; Gordon et al. 1999). Fifty percent of the children with CP-U exhibited minimal mirror movements during the AHA and/or during motor fMRI task; subject 4 exhibited moderate-severe mirror movements in both tasks.

## Motor brain activation

The data of subject 5 and subject 13 were excluded due to major head movement (>3 mm). In general, children with CP-U ($n = 12$) displayed abnormal patterns of activation compared to TDC subjects ($n = 6$). Results of brain activation in all subjects, including LI and percent activation calculated based on activations around the central sulcus, are presented in Table 3. Mean LI was similar for both right and left hands in TDC subjects (right hand 0.90 ± 0.15; left hand 0.92 ± 0.12), with no significant difference between hands ($t(5) = -1.17$, $p = 0.29$). In contrast, children with CP-U displayed significantly lower LI values when moving the affected hand compared to the less affected hand [mean values: affected LI = 0.5 ± 0.6, less affected LI = 0.8 ± 0.3, ($t(11) = -2.85$, $p = 0.016$)]. Lower LI values indicate a pattern of greater bilateral activation. Moreover, there was substantial variance in the LI scores, especially when moving the affected hand; 7/12 children with CP-U showed an apparent pattern of bilateral activation (>2 SD of the mean LI of TDC) while five children showed a unilateral activation pattern, as would be expected in TDC (Staudt et al. 2002). When moving the less affected hand, only 3/12 children showed bilateral activation.

The mean percent activation in areas around the central sulcus in TDC was 80 ± 15 %, and in children with CP-U was 62 ± 30 %, indicating a trend of reduced number of active voxels when using the affected hand compared to the less affected hand. Although this difference was not significant between groups ($F(1,16) = 1.79$, $p = 0.20$), 6/11 children with CP-U showed abnormal percent activation (different in more than 2 SD of the mean of TDC).

Children with CP-U demonstrated increased number of voxels in the SMA when moving the affected hand (mean # of voxels ± SD. error: 1,618 ± 609) compared to when moving the less affected hand (652 voxels ± 237)

**Table 2** Hand-arm function

| Case no. | MAS | MACS | AHA (logit scale) | CHEQ | | JTTHF affected | JTTHF less affected | Mirror movement |
|---|---|---|---|---|---|---|---|---|
| | | | | Independent | 2 hand | | | |
| 1 | 4 | 3 | 30 | 18 | 10 | 1,080 | 35.1 | $0^{\gamma}$ |
| 2 | 1 | 2 | 48 | 22 | 11 | 300.5 | 53.2* | 1 |
| 3 | 3 | 2 | 50 | 25 | 22 | 841.7 | 36.0* | 1 |
| 4 | 1 | 2 | 63 | 22 | 20 | 348.4 | 40.9 | 3 |
| 5 | 4 | 3 | 30 | 12 | 8 | 854.7 | 35.4 | $0^{\gamma}$ |
| 6 | 1 | 1 | 58 | 21 | 21 | 91.5 | 53.9* | 0–1 |
| 7 | 4 | 3 | 32 | 13 | 1 | 1,080 | 64.8* | $0–1^{\gamma}$ |
| 8 | 1 | 1 | 90 | 29 | 29 | 44.1 | 34.5* | 0 |
| 9 | 0 | 1 | 77 | 25 | 25 | 143.8 | 19.0 | 0 |
| 10 | 2 | 2 | 42 | 15 | 6 | 1,080 | 42.1 | 0–1 |
| 11 | 1 | 1 | 71 | 21 | 20 | 72.6 | 39.9 | $0–1^{\gamma}$ |
| 12 | 3 | 2 | 55 | 1 | 0 | 609.2 | 28.2 | 0 |
| 13 | 1 | 3 | 32 | 16 | 3 | 1,080 | 37.1 | 0–1 |
| 14 | 4 | 2 | 53 | 19 | 14 | 411.3 | 94.5* | 0 |
| Mean (SD) | 2.1 (1.5) | 2.0 (0.78) | 52.2 (18.6) | 18.5 (7.0) | 13.6 (9.4) | 574.1 (418.6) | 43.9 (18.4) | |
| Range | 0–4 | 1–3 | 27–90 | 1–29 | 0–29 | 44–1,080 | 19–94.5 | 0–3 |

*MAS* modified Ashworth Scale, *MACS* Manual Ability Classification Level, *AHA* Assisting Hand Assessment, *CHEQ* Children's Hand Experience Questionnaire, *JTTHF* Jebsen Taylor Test of Hand Function (age adjusted)

* Significant impairment in less affected hand based on the norms in Taylor et al. 1973. $^{\gamma}$ Spasticity high and very little movement observed – mirror movements possibly reflected in increased fisting and/or elbow flexion

($t(11) = 2.12$, $p = 0.05$). No significant differences in SMA activation were detected in TDC when moving the dominant vs. non dominant hand ($t(5) = 0.431$, $p = 0.68$). Figure 2 illustrates the brain activation in areas around the central sulcus and in the SMA during the hand clenching task.

## Interhemispheric connectivity

DTI parameters detected in the various WM tracts and segments in children with CP-U compared to TDC are presented in Table 4. In two children (subject 1 and subject 7), all segments of the CC could not be reconstructed due to the large size of the lesion, and also in subject 10 the midbody of the CC could not be reconstructed. These children were excluded from this analysis. Overall, children with CP-U ($n = 11$) displayed reduced WM integrity in the CC compared to TDC ($n = 8$). There were significantly less number (#) of fibres detected in all CC segments in children with CP-U compared to TDC (Genu: $F = (1,17) = 4.85$, $p = 0.042$; Midbody: $F(1,17) = 11.97$, $p = 0.003$; Splenium: $F(1,17) = 5.04$, $p = 0.038$) (see Table 4). In addition to the structural differences, significant microstructural differences were detected with significantly higher MD ($F(1,17) = 5.36$, $p = 0.03$) and Dr ($F(1,17) = 6.31$, $p = 0.02$) and lower FA ($F(1,17) = 5.86$, $p = 0.027$) values in the midbody of the CC in children with CP-U compared to TDC.

## Intrahemispheric connectivity

In two children (sub 1 and sub 7), the affected CST and affected PLIC could not be reconstructed due to the large size of the lesion. Overall, children with CP-U ($n = 12$) displayed reduced WM integrity in the affected CST and PLIC compared to TDC ($n = 8$). Significant differences were detected between the # of fibres ($t(11) = -3.50$, $p = 0.006$), Dr ($t(11) = 4.29$, $p = 0.001$), MD ($t(11) = 3.75$, $p = 0.003$) and FA ($t(11) = -3.20$, $p = 0.009$) of the affected CST as compared with the less affected CST in children with CP-U. No significant differences were detected between the right and left CST in TDC for all diffusivity parameters ($1.86 < t(7) < 0.27$, $0.1 < p < 0.8$). Children with CP-U displayed reduced # of fibres and integrity of the affected CST and PLIC compared to TDC indicated by significantly reduced # of fibres ($F(1,18) = 9.051$, $p = 0.008$), higher MD ($F(1,18) = 7.135$, $p = 0.017$) and Da ($F(1,18) = 6.527$, $p = 0.021$) in the affected CST and decreased FA ($F(1,18) = 9.063$, $p = 0.008$) in the PLIC. No significant differences were detected between the less affected CST and PLIC in children with CP-U compared to TDC in all diffusivity

**Table 3** Lateralization index and percent activation in areas around the central sulcus

| Case | LI affected | | LI less affected | | Percent activation | |
|---|---|---|---|---|---|---|
| | LI | Diff in SD | LI | Diff in SD | % activ. | Diff in SD |
| 1 | 1.00 | 0.64 | 0.76 | −1.34 | 35 | −3 |
| 2 | 0.49 | −2.70 | 0.85 | −0.57 | 48 | −2 |
| 3 | 0.51 | −2.63 | 0.66 | −2.17 | 47 | −2 |
| 4 | −0.01 | −6.02 | 0.43 | −4.10 | 64 | −1 |
| 5 | NA | NA | NA | NA | NA | NA |
| 6 | 0.39 | −3.37 | 1.00 | 0.65 | 79 | 0 |
| 7 | 1.00 | 0.64 | 1.00 | 0.65 | 38 | −3 |
| 8 | 1.00 | 0.64 | 1.00 | 0.65 | 76 | 0 |
| 9 | 1.00 | 0.64 | 1.00 | 0.65 | 94 | 1 |
| 10 | 0.55 | −2.32 | 1.00 | 0.65 | 8 | −5 |
| 11 | 0.78 | −0.83 | 1.00 | 0.65 | 78 | 0 |
| 12 | −1.00 | −12.59 | 0.23 | −5.82 | * | |
| 13 | NA | NA | NA | NA | NA | NA |
| 14 | 0.16 | −4.95 | 1.00 | 0.65 | 115 | 2 |
| TDC | LI Rhand | Diff in SD | LI Lhand | Diff in SD | % activ. | Diff in SD |
| 1 | 1.00 | 0.64 | 1.00 | 0.65 | 77 | 0 |
| 2 | 1.00 | 0.64 | 1.00 | 0.65 | 99 | 1 |
| 3 | 1.00 | 0.64 | 1.00 | 0.65 | 72 | −1 |
| 4 | 0.75 | −1.02 | 0.76 | −1.33 | 95 | 1 |
| 5 | 1.00 | 0.64 | 1.00 | 0.65 | 77 | 0 |
| 6 | 0.67 | −1.53 | 0.77 | −1.26 | 59 | −1 |

*LI* laterality index, *diff in SD* difference in standard deviations from mean of controls, *% activ.* percent activation, *Rhand* right hand, *Lhand* left hand

* No activation in affected hemisphere when moving affected hand

parameters. Figure 3 illustrates the reduced WM integrity in a child with CP-U in contrast to TDC via tractography.

## Normality distribution of the variables

The LI, percent of activation, Da, Dr, MD and FA in all WM tracts and segments and the AHA, JTTHF and CHEQ were distributed normally. The # of fibres in the WM tracts did not distribute normally. The mirror movement measure is an ordinal variable.

## Relationship between interhemispheric and intrahemispheric connectivity

Children with CP-U ($n = 11$) displayed significant correlations, corrected for age, between all diffusivity parameters

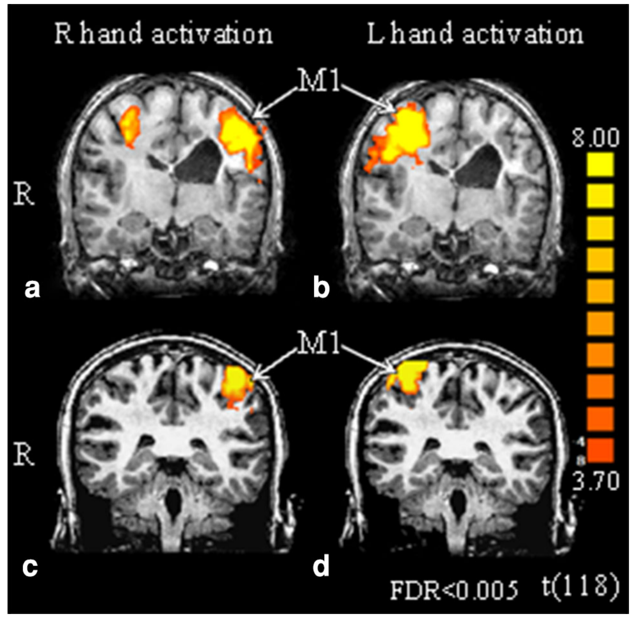


**Fig. 2** Brain activation in areas around the central sulcus and in the SMA during the hand clenching task from a 13-year-old female with right unilateral CP due to PVL with bilateral activation detected when moving affected hand (**a**) and unilateral activation detected when moving less affected hand (**b**). 10-year-old male TDC with unilateral activation detected when moving either the right hand (**c**) or left hand (**d**)

in the midbody of the CC, and diffusivity parameters of the affected CST and affected PLIC ($0.63 < r < 0.94$, $0.0001 < p < 0.035$), except with the Da of both regions and MD of the affected CST and FA of the midbody of the CC ($0.06 < r < 0.41$, $0.23 < p < 0.87$); (see Fig. 4a). In addition, the Da and MD of the genu of the CC were also significantly correlated with the MD and FA of the affected PLIC ($0.70 < r < 0.76$, $0.007 < p < 0.016$).

## Intra- and interhemispheric connectivity and brain activation

Significant correlation, corrected for age, was detected between the FA in the affected PLIC and LI calculated when moving the affected hand ($n = 11$, $r = 0.89$, $p = 0.003$) demonstrating that increased WM integrity of the PLIC in the affected hemisphere is associated with greater unilateral activation.

## Correlations between imaging and behavioural measures

*Brain activation and motor behaviour*: Significant correlation, corrected for age, was detected between percent activation and the JTTHF of the affected hand ($n = 11$;

**Table 4** DTI parameters in CC, CST and PLIC

| Fibre/ROI | Da ($\times 10^{-3}$ mm$^2$/s) | | Dr ($\times 10^{-3}$ mm$^2$/s) | | MD ($\times 10^{-3}$ mm$^2$/s) | | FA (a.u.) | | # Fibres | |
|---|---|---|---|---|---|---|---|---|---|---|
| | CP-U | TDC | CP-U | TDC | CP-U | TDC | CP-U | TDC | CP-U | TDC |
| CC-genu | 1.634 ± 0.10 | 1.594 ± 0.08 | 0.536 ± 0.05 | 0.502 ± 0.03 | 0.909 ± 0.07 | 0.866 ± 0.06 | 0.6 ± 0.03 | 0.618 ± 0.03 | 940 ± 408* | 1685 ± 952* |
| CC-midbody | 1.58 ± 0.11 | 1.514 ± 0.05 | 0.608 ± 0.12* | 0.498 ± 0.03* | 0.932 ± 0.11* | 0.836 ± 0.03* | 0.554 ± 0.05* | 0.603 ± 0.03* | 439 ± 296* | 1341 ± 800* |
| CC-splenium | 1.626 ± 0.10 | 1.596 ± 0.05 | 0.505 ± 0.12 | 0.441 ± 0.03 | 0.879 ± 0.11 | 0.826 ± 0.03 | 0.641 ± 0.07 | 0.665 ± 0.02 | 674 ± 405* | 1503 ± 1095* |
| CST-affected | 1.459 ± 0.07* | 1.393 ± 0.06* | 0.499 ± 0.06 | 0.458 ± 0.03 | 0.819 ± 0.05* | 0.769 ± 0.03* | 0.601 ± 0.03 | 0.608 ± 0.03 | 98 ± 76* | 250 ± 127* |
| CST-less affected | 1.401 ± 0.08 | 1.408 ± 0.03 | 0.443 ± 0.03 | 0.456 ± 0.03 | 0.762 ± 0.03 | 0.773 ± 0.03 | 0.623 ± 0.03 | 0.614 ± 0.02 | 231 ± 124 | 312 ± 98 |
| PLIC-affected | 1.446 ± 0.09 | 1.468 ± 0.06 | 0.457 ± 0.09 | 0.411 ± 0.03 | 0.815 ± 0.07 | 0.763 ± 0.03 | 0.587 ± 0.07* | 0.660 ± 0.03* | | |
| PLIC-less affected | 1.397 ± 0.20 | 1.49 ± 0.06 | 0.405 ± 0.06 | 0.421 ± 0.02 | 0.736 ± 0.09 | 0.771 ± 0.01 | 0.665 ± 0.04 | 0.659 ± 0.03 | | |

*CP-U* unilateral cerebral palsy ($n = 14$), *TDC* typically developed controls ($n = 8$), *CC* corpus callosum, *CST* cortico-spinal tract, *PLIC* posterior limb of internal capsule, *Da* axial diffusivity, *Dr* radial diffusivity, *MD* mean diffusivity, *FA* fractional anisotropy, *a.u.* arbitrary units

Mean ± standard deviation, *$p < 0.05$

$r = -0.76$, $p = 0.011$) and AHA ($n = 11$; $r = 0.63$, $p = 0.050$), indicating that the greater the activation in areas around the central sulcus in the affected hemisphere, the better the unimanual and bimanual motor performance (see Fig. 4b). LI scores did not correlate with behavioural assessments including mirror movements ($p > 0.33$). Number of voxels in the affected and less affected SMA did not correlate with motor behaviour ($n = 13$; $-0.003 < r < 0.42$, $0.15 < p < 0.97$).

*Interhemispheric connectivity and motor behaviour*: Diffusivity values in the CC were significantly associated with motor assessments. Significant negative correlation was evident between # of fibres of the midbody and performance in the JTTHF when using the less affected hand ($n = 11$; $r = -0.74$, $p = 0.010$) and with mirror movements ($n = 11$; $r = -0.71$, $p = 0.014$).

Within the splenium of the CC, significant correlation was evident between # of fibres of the splenium of the CC and AHA scores ($n = 12$; $r = 0.59$, $p = 0.045$); (see Fig. 4c). Significant correlations, corrected for age, were detected between the Dr ($n = 12$; $r = -0.83$, $p = 0.011$), MD ($n = 12$; $r = -0.75$, $p = 0.031$) and FA ($n = 12$; $r = 0.80$, $p = 0.017$) and CHEQ scores. Furthermore, significant negative correlations were detected between the FA in the splenium and performance (faster time) in the JTTHF when using the less affected hand ($n = 12$; $r = -0.83$, $p = 0.011$) and positive correlation between Dr ($n = 12$; $r = 0.86$, $p = 0.007$) and MD ($n = 12$; $r = 0.81$, $p = 0.015$) in the splenium of the CC and performance in the JTTHF when using the less affected hand. Overall, reduced # of fibres and reduced WM integrity were associated with poorer hand function.

*Intrahemispheric connectivity and motor behaviour*: Significant correlations were detected between # of fibres of the affected CST and mirror movements ($n = 11$; $r = -0.72$, $p = 0.013$) and between # of fibres of the less affected CST and AHA ($n = 14$; $r = 0.56$, $p = 0.039$). When looking specifically at the PLIC, correlations, corrected for age, were evident between FA values in the affected PLIC and CHEQ ($n = 12$; $r = 0.76$, $p = 0.010$); (see Fig. 4d). No significant correlations were detected between diffusivity values in the less affected PLIC and other behavioural assessments ($n = 14$; $0.01 < r < 0.52$, $0.17 < p < 0.99$).

## Discussion

In this study, we tried to better understand the relationships between inter and intrahemispheric connectivity, motor brain activation and manual motor performance in children with CP-U. Abnormal patterns of activation were detected in most children with CP-U, which were associated with

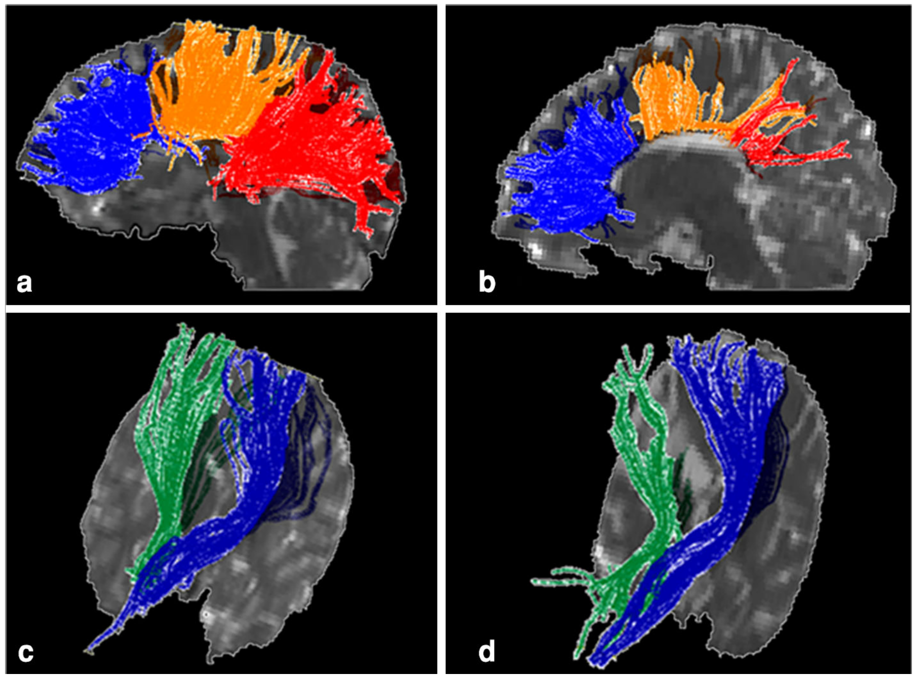


**Fig. 3** Tractography of the CC (genu *blue*, midbody *orange*, splenium *red*) and CST (right *green*, left *blue*): **a** CC and **c** CST of TDC; **b** CC and **d** CST of children with unilateral CP

poorer hand function performance. Reduced WM integrity of intrahemispheric connections was associated with impaired hand function, as has already shown in previous studies. Our key findings are reduced WM integrity in the CC in children with CP-U compared to TDC which was associated with reduced function of both the affected and less affected hands and with poorer bimanual skills. This study highlights the impaired interhemispheric connectivity in children with CP-U and its relationship with hand function.

In our study abnormal patterns of activation were detected in most of the children with CP-U, including increased bilateral activation in areas around the central sulcus, increased activation of the SMA and/or reduced percent activation when moving the affected hand. This is in line with several fMRI studies that detected bilateral activation in participants with hemiplegia both in motor and sensory areas (Staudt et al. 2002; Guzzetta et al. 2007; Sutcliffe et al. 2009; You et al. 2005). In typically developed subjects, unilateral activation is expected in the primary motor cortex of the contralateral hemisphere to the hand engaged in movement. Bilateral activation may result from the existence of lack of inhibition mediated transcallosally, mirror movements and/or ipsilateral projections (Kim et al. 2003).

The mid and posterior body of the CC is typically responsible for mediating interhemispheric inhibition between the motor cortices (Meyer et al. 1998) resulting in refined unilateral activation. Impaired integrity of the body of the CC might affect inhibition, which may result in bilateral activation. We hypothesized that reduced transcallosal integrity would result in increased bilateral motor activation due to lack of interhemispheric inhibition. However, we did not detect linear correlation between WM integrity of the midbody and LI. It has also been argued that interhemispheric connections are necessary for the performance of motor functions and in particular bimanual functions (Gooijers et al. 2013; Johansen-Berg et al. 2007). Lower FA of transcallosal motor fibres, evidence of mirror movements and a coherent tendency towards decreased interhemispheric inhibitory competence was demonstrated in children with bilateral spastic CP/PVL (Koerte et al. 2011). In the current study reduced transcallosal fibre integrity was associated with lower performance in bimanual tasks in children with CP-U. Therefore, although we did not detect direct association between WM integrity of the CC and LI, we suggest that reduced transcallosal inhibition plays a major role in motor impairment in children with CP-U.

Another explanation for the bilateral activation pattern may be mirror movements. Around 50 % of the children with CP-U in our study displayed mild mirror movements, mostly when moving the affected hand. Previous studies have suggested that mirror movements tend to impede functional performance in the most bimanual tasks with equivocal evidence regarding the relationship of mirror movements to severity of movement impairment (Kim et al. 2003; Meyer et al. 1998; Nelles et al. 1998). In our study, mirror movements were not correlated with LI, indicating that the bilateral activation detected in children with CP-U did not necessarily directly stem from actual movement of the less affected hand. We demonstrated that

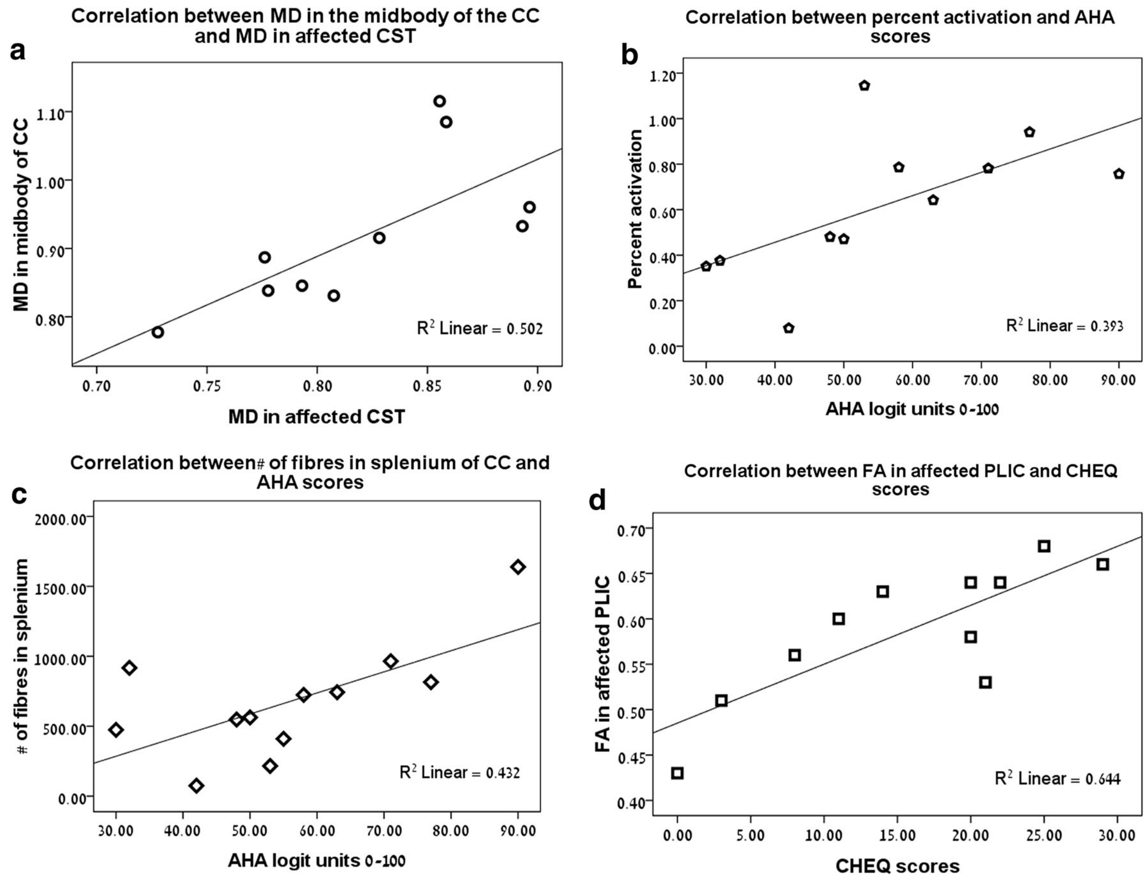


**Fig. 4** Scatter graphs of associations between imaging parameters and behaviour: **a** correlation between MD in the midbody of the CC and MD in affected CST; **b** correlation between percent activation and AHA scores; **c** correlation between # of fibres in splenium of CC and AHA scores; **d** correlation between FA in affected PLIC and CHEQ scores

higher extent of mirror movements were associated with reduced number of fibres in the midbody of the CC and in the affected CST. This suggests that mirror movements, along with other factors, may indirectly affect bilateral activation pattern through reduced WM integrity in both inter and intrahemispheric tracts in children with CP-U.

The bilateral activation pattern can also be explained by ipsilateral projections. Emerging evidence using transcranial magnetic stimulation (TMS) shows that some children with hemiplegia retain ipsilateral connectivity from the undamaged hemisphere to the affected limb influencing functional skills and that the timing of the injury may have an impact on re-organisation (Eyre et al. 2007; Staudt et al. 2002, 2004). Prior studies report that children with ipsilateral projections had the most impaired motor function (Eyre 2007; Holmström et al. 2010; Kuhnke et al. 2008). Our results indicated that better WM integrity of the affected PLIC was associated with unilateral brain activation (higher LI values), and better hand function. Yet, our current methodology does not allow distinction of PLIC fibres that are part of the ipsilateral projections from those that belong to the contralateral projections of the CST and, therefore, we cannot conclude if the bilateral activation stemmed from ipsilateral connections. Stimulation techniques such as TMS and transcranial direct-current stimulation along with DTI may go some way to answer these questions.

Next we set to explore the associations between the functional and structural imaging parameters and motor hand function. The reduced percent activation in the affected hemisphere was associated with poorer hand function while the SMA activation did not correlate with motor behaviour nor with mirror movements. These results indicate that children with hemiplegia recruited additional motor areas compared to TDC when performing the task with their affected hand, supporting motor brain plasticity following early injury to try and compensate for the damage.

Intrahemispheric connectivity differed significantly between children with hemiplegia and age-matched TDC in the affected CST tract, but not in the less affected tract. These findings are in line with several previous studies (Glenn et al. 2003, 2007; Holmström et al. 2011; Lee et al. 2011; Son et al. 2007; Yoshida et al. 2010). Motor performance was correlated with MD in the affected CST and FA in the affected PLIC. The PLIC region has been shown to demonstrate the highest FA and lowest MD values along the tract already in preterms (Partridge et al. 2004). Moreover, asymmetrical signal intensity of the PLIC in newborn infants with intraventricular haemorrhage (IVH) was found to be an early predictor of future hemiplegia (De Vries et al. 1999), and FA values in this area were found to be positively correlated with motor function in children with hemiplegia (Holmström et al. 2011). These results suggest that the PLIC may be a more sensitive area for detection of injury within the CST.

Defining characteristics of brain activation and connectivity may give important clues to the adaptive capacities of the brain in response to early injury, and also provide indicators for prognosis and differential response to different therapeutic approaches. Two common therapeutic interventions for children with CP-U are the constraint-induced movement therapy (CIMT) and hand-arm bimanual intensive therapy (HABIT) (Gordon et al. 2011). A few studies which investigated the type of corticospinal reorganization (identified by TMS) and interhemispheric connectivity demonstrated different response to treatment in relation to predominance of ipsi- versus contra-lateral CST connectivity (Kuhnke et al. 2008). Other fMRI studies demonstrated a shift to a more unilateral motor activation pattern post CIMT intervention (Sutcliffe et al. 2007). However, consideration as to the inter-relationship between CST projections, interhemispheric connectivity and patterns of motor brain activation to HABIT approach has not been explored. Our findings may have potential clinical implications on choosing the appropriate intervention. Green et al. (2013) demonstrated the efficacy of the HABIT approach on children with CP-U. We suggest that this intervention may be beneficial for children with predominant ipsilateral connection and reduced integrity of the CC, accompanied by bilateral motor activation, as it encourages both inter and intrahemispheric functions for performing bimanual tasks.

WM integrity in the midbody of the CC was highly correlated with the integrity of the affected PLIC. This important relation has gained little attention in children with CP-U. Our cohort included only children with injury early in life. Therefore, this result may indicate abnormal development of both the CC and CST which were associated with impaired motor function. In addition, abnormal development of the CC may also affect connectivity between other brain areas, not only the sensory-motor areas, that can explain additional deficits common in children with CP-U. Of interest are our findings regarding the splenium and its relationship to motor skills (Muetzel et al. 2008). WM integrity in the splenium was associated with the use of the affected hand in daily bimanual tasks (CHEQ) and in unimanual tasks that require grasp and release of the less affected hand (JTTHF), but was not associated with bimanual use within a clinical setting (AHA assessment). One possible explanation is that this finding results from visuo-spatial impairments that are often detected in children with hemiplegia (Barca et al. 2010). Visual projections pass through the splenium of the CC (Dougherty et al. 2005); therefore, WM injury in the splenium may affect visuo-spatial skills that are needed to achieve independence in performance of daily activities. Although we did not focus on visuo-spatial skills in our assessment, impaired pattern reasoning scores (mean scores of $7.13 \pm 2.9$; one standard deviations below mean) were available from the Kaufman Assessment Battery for Children (KABC) for seven children in our cohort. This test includes abstract visual stimuli and requires no motor coordination. The splenium may, therefore, play an important role, not only in visual spatial accuracy for dexterity but also in mediating spatial awareness and body image supporting use of a weaker hand.

In this study we measured diffusivity parameters that reflect microstructural characteristics within the CC, CST and PLIC. Significant differences were detected between children with hemiplegia and TDC in several diffusivity parameters, Da, Dr, MD and FA, in the above-mentioned WM areas and these measures corresponded with hand function. These findings indicate impaired WM integrity, yet the specific type of WM injury, such as abnormal myelination or axonal injury is to be determined. Further studies with a larger number of subjects may enable correlation of the specific microstructural injury to the subtype of brain damage, such as PVL, infarcts or traumatic brain injury and to the timing of the injury (pre or post natal).

There were a number of limitations to our study which should be considered in the overall interpretation. Firstly, the lack of control for absolute range and force of movement during the active fMRI task may have influenced activation levels/region. To minimize differences in range and force of movement along the fMRI task, an average value was taken across the six trials for each condition (left/right hand). Secondly, unlike other segments of the study, fMRI controls were somewhat older than the children with CP-U. However, brain activation is less expected to be influenced by age in the age range of our two groups. Thirdly, given the limited numbers of children additional analyses based on subtypes, such as time of injury (preterm vs. term), different severity rankings of hemiplegia and different types of injury were precluded. An additional limitation was that the presence of lesions had an impact on tractography, in two children with large lesions the CC and affected CST could not be reconstructed. Finally, due to the small sample size and exploratory nature of our study, we did not adjust for multiple comparisons due to risk of Type

II error. Nevertheless, the relations found were fairly strong (in the order of 0.7–0.9) and hence are less likely to be incidental. Further studies with a larger sample, across age and severity are warranted.

In conclusion, abnormal WM integrity may adversely affect connectivity between brain regions and may be linked to some of the behavioural impairments seen in children with hemiplegia. Abnormal patterns of activation were further detected in our cohort, and were related to poorer hand function. This study emphasizes the importance of interhemispheric connectivity for motor hand function of both the affected and less affected hands in children with CP-U. The abnormal pattern of brain activation, detected in children with CP-U, is suggested to be mediated through a mechanism of reduced callosal inhibition along with involvement of ipsilateral projections and mirror movements. Understanding the pathomechanism of abnormal brain activation in children with CP-U is of great importance to the understanding of the structure–function relationship and may have implications on intervention planning. This is particularly applicable with respect to whether to emphasize forced use of the affected hand (via restraint/CIMT) or enhance bimanual training (HABIT).

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