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# The effect of injury timing on white matter changes in the corpus callosum following unilateral brain injury ☆

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## ARTICLE INFO

## ABSTRACT

Motor impairments following unilateral brain injuries may be related to changes in the corpus callosum. The purpose of this study was to determine if the corpus callosum is impacted differently in pediatric versus adult hemiplegia. Diffusion tensor imaging was completed on 41 participants (11 pediatric hemiplegia, 10 adult hemiplegia, 10 pediatric control and 10 adult control). Fractional anisotropy values and cross-sectional areas for five regions of the corpus callosum were compared between subject groups. Additionally, the amount of involuntary activity in the paretic elbow was quantified during non-paretic elbow flexion tasks for a subset of pediatric hemiplegia participants. Fractional anisotropy values were reduced in pediatric hemiplegia compared to pediatric control subjects in callosal regions corresponding to premotor and supplementary motor areas, primary sensory cortex, and parietal, temporal, and occipital cortices. Differences in fractional anisotropy between adult stroke and adult controls were only found in the region corresponding to parietal, temporal, and occipital cortices. Cross-sectional area was affected in all regions of the corpus callosum in pediatric hemiplegia, but only in the primary sensory region in adult hemiplegia. Additionally, changes in the cross-sectional areas were correlated with involuntary mirror movements in the pediatric hemiplegia group. In conclusion, the corpus callosum is affected to a greater extent in pediatric compared to adult hemiplegia, which may explain why unsuppressed mirror movements and difficulty with bimanual coordination are greater problems in this population.

## 1. Introduction

The motor impairments observed following unilateral brain injuries are typically thought to be caused by damage to motor cortices and descending motor pathways, however, changes in other brain areas including the corpus callosum may also be a factor. Specific to motor functions, the corpus callosum is necessary for bimanual coordination as well as providing interhemispheric inhibition during unimanual tasks (Fling and Seidler, 2012; Gallea et al., 2011; Koerte et al., 2009). Lesions in the corpus callosum have also been linked to gait disturbances including reduced step heights, wide base of support, and reduced cadence (Giroud and Dumas, 1995). Degeneration of callosal fibers has been previously reported in adults following a stroke (Gupta et al., 2006; Wang et al., 2011), as well as in children with early unilateral brain injuries including stroke (Kulak et al., 2008; Moses et al., 2000). More specifically, in adult stroke, the degeneration of transcallosal fibers connecting higher order sensorimotor areas has been correlated with greater bilateral motor area activation during paretic hand movements and poorer motor outcomes (Wang et al., 2011). In children with hemiplegia, mirror movements and difficulties with discrete bimanual tasks are commonly reported (Kuhtz-Buschbeck et al., 2000; Sukal-Moulton et al., 2013; Utley and Steenbergen, 2006).

The purpose of this study was to determine if unilateral lesions occurring early in life compared to in adulthood affect the corpus callosum differently. We hypothesized there would be greater microstructural changes of the callosal white matter in earlier injuries, due to the developmental trajectory of the corpus callosum. The degree of callosal involvement may help to explain the differences in motor deficits that exist between pediatric and adult hemiplegia.

## 2. Methods

Forty-one participants were recruited for this study into one of four groups: pediatric hemiplegia (n = 11), pediatric control (n = 10), adult hemiplegia (n = 10), and adult control (n = 10). The pediatric hemiplegia group consisted of children who sustained unilateral brain injuries before the age of ten years. The etiologies of this group were

mixed and therefore represent the wide range of individuals clinically labeled as hemiplegic due to unilateral motor deficits. Etiologies included intraventricular hemorrhage, internal capsule ischemic damage, middle cerebral artery infarct, intracranial bleeds, and arteriovenous malformations. The average age of the children in this group was $10.12 \pm 1.96$ years, with six female and five male participants. Eight of the children had clinical presentations of right hemiplegia (due to

left sided lesion), with the remaining three having left hemiplegia. Within the pediatric hemiplegia group, five participants had prenatally acquired lesions (late second to early third trimester), four had perinatally acquired lesions (late third trimester to two months after birth), and two had postnatally acquired lesions (6 months to 10 years). Injury timing was determined by review of medical records. The Upper Extremity Fugl-Meyer scores for the pediatric hemiplegia group ranged

**Table 1**

Pediatric hemiplegia participant information. Anatomical (T1-weighted) MRI images for each participant in the pediatric hemiplegia group, as well as gender, age, and side of hemiparesis (lesion on contralateral side). Asterisks indicate inclusion in the assessment of involuntary mirror movements.
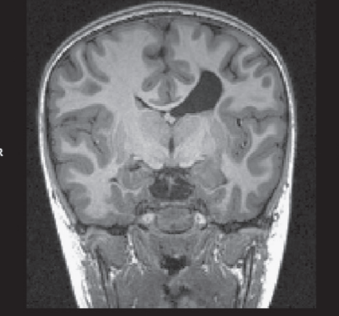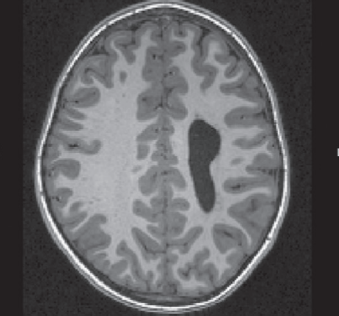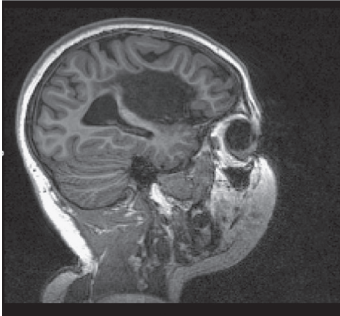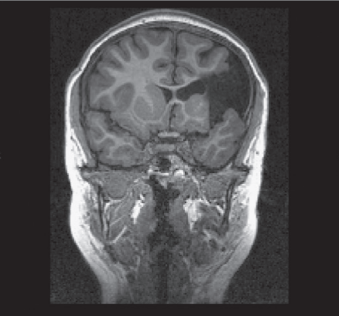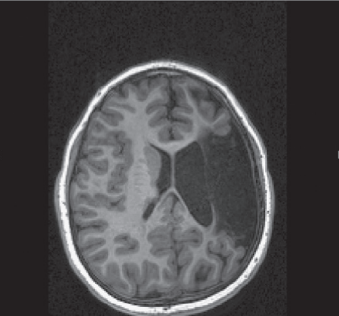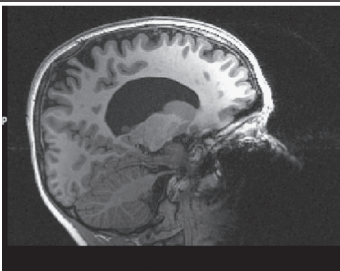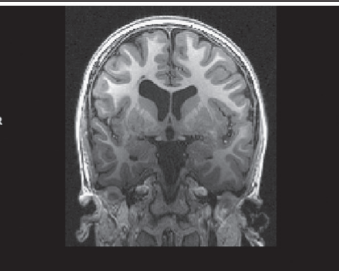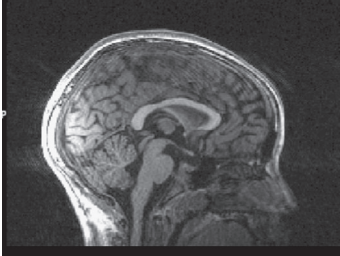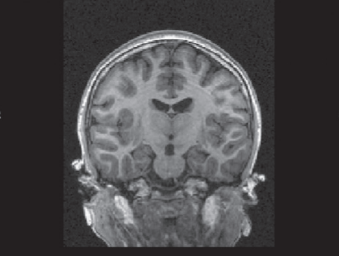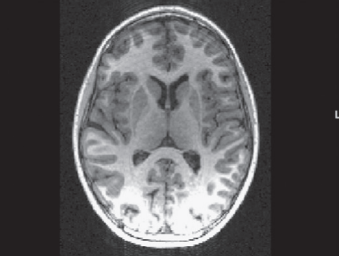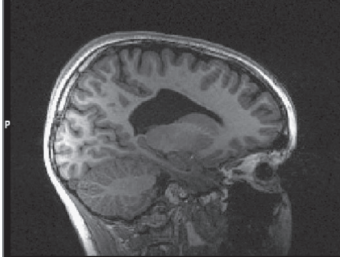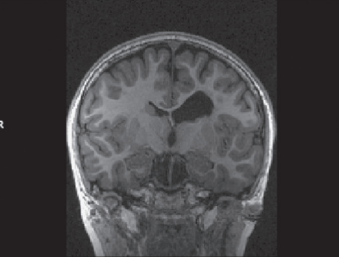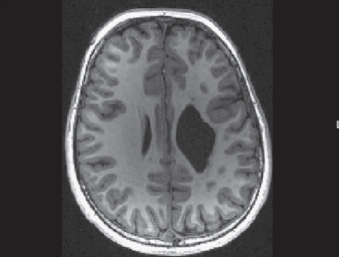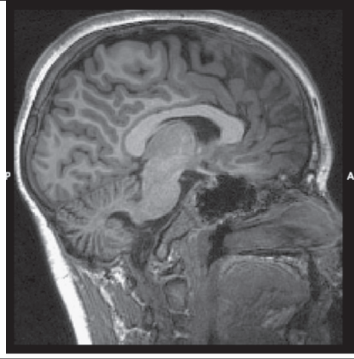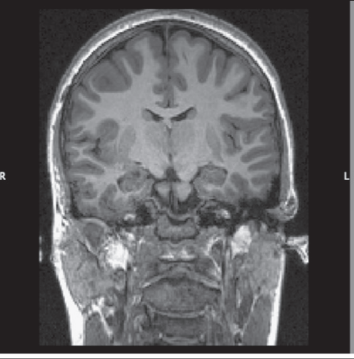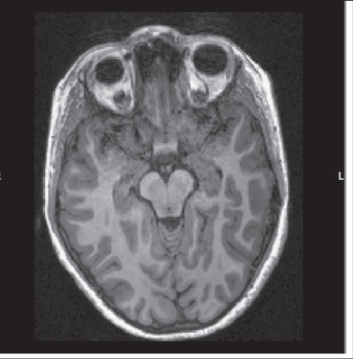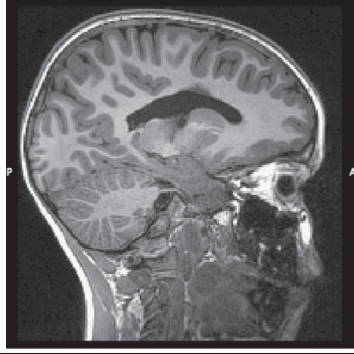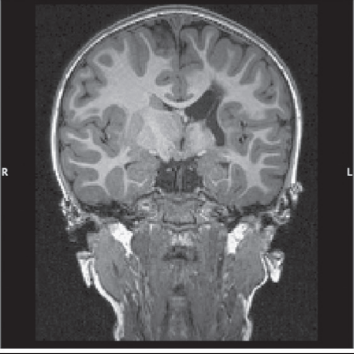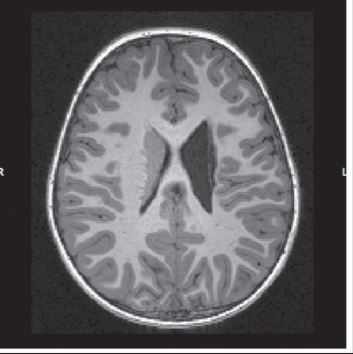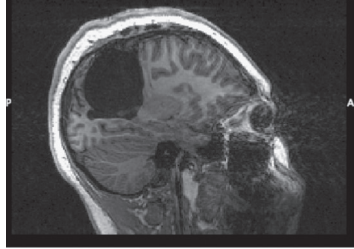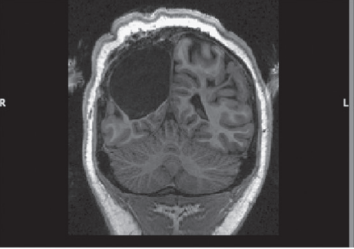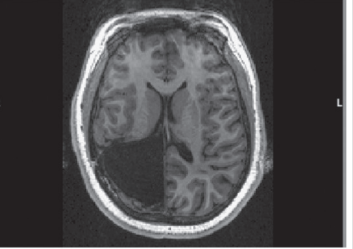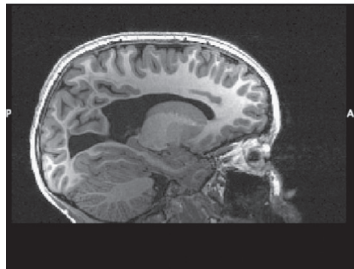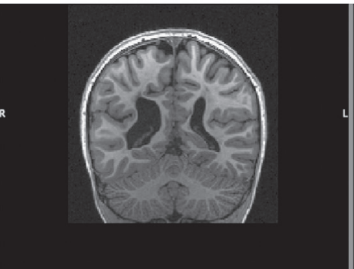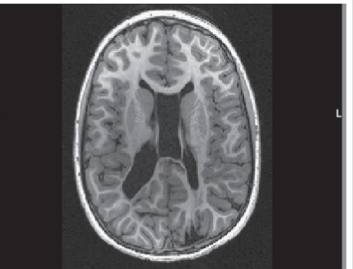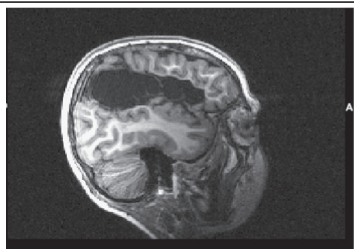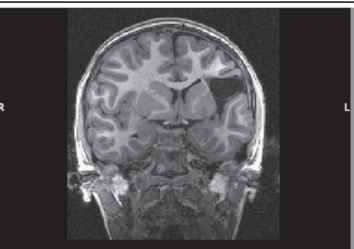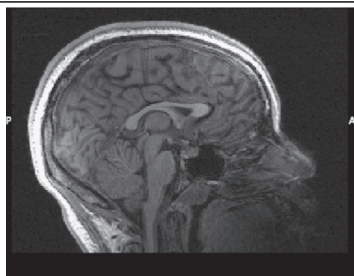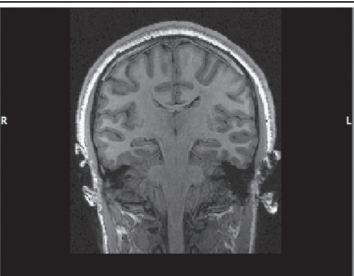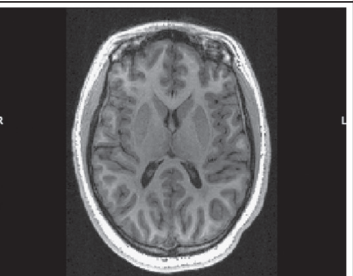
**Table 1** (*continued*)

| | |
|---|---|
| PH06<br>Male<br>11.78 yrs<br>L hemi |  |
| PH07*<br>Female<br>7.71 yrs<br>R hemi |  |
| PH08<br>Female<br>11.36 yrs<br>L hemi |  |
| PH09*<br>Male<br>9.53 yrs<br>R hemi |  |
| PH10<br>Male<br>6.94 yrs<br>R hemi |  |
| PH11<br>Female<br>13.79 yrs<br>R hemi |  |

from 24 to 65, with an average of 37.7 ± 11.2 out of 66 possible points (Fasoli et al., 2009). The Gross Motor Functional Classification System (GMFCS) classified all participants as either GMFCS Level I (n = 6) or Level II (n = 5) (Rosenbaum et al., 2008). The Manual Ability Classification System (MACS) levels ranged from I–III (I: n = 2; II: n = 7; III: n = 2) (Eliasson et al., 2006). The pediatric control group consisted of convenience sample of typically developing children with no history of neurological diagnoses. The average age of the pediatric control group was 12.3 ± 3.89 years, with three female and seven male participants. All pediatric control participants were right-hand dominant. There was no significant difference between the ages of the pediatric hemiplegia and pediatric control groups (p = 0.136). The average age

**Table 2**
Adult hemiplegia participant information. Anatomical (T1-weighted) MRI images for each participant in the adult hemiplegia group, as well as gender, age, and side of hemiparesis (lesion on contralateral side).
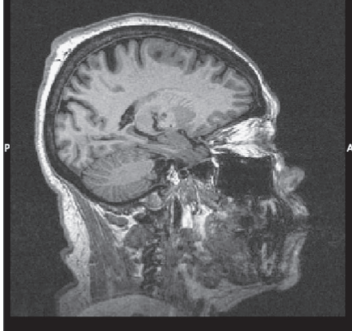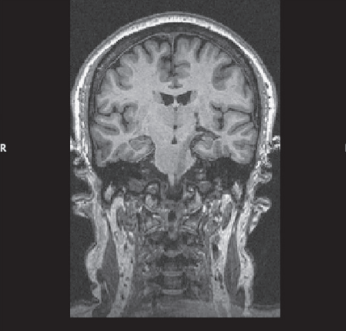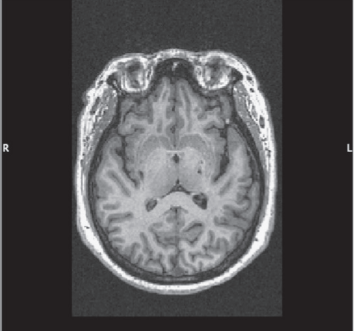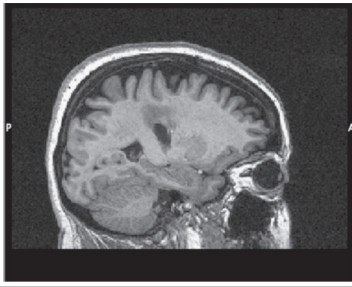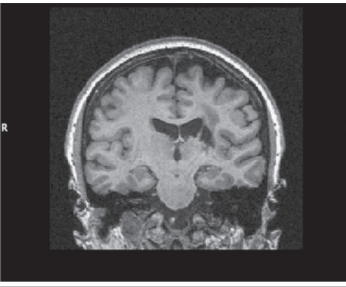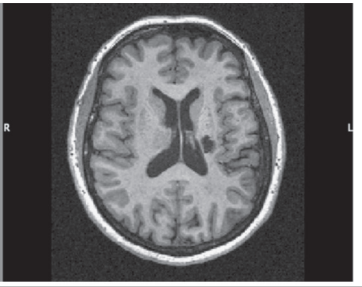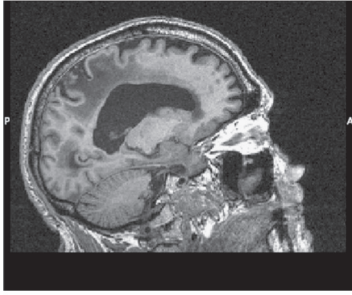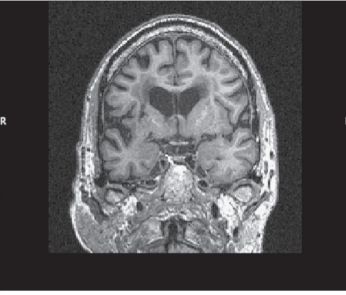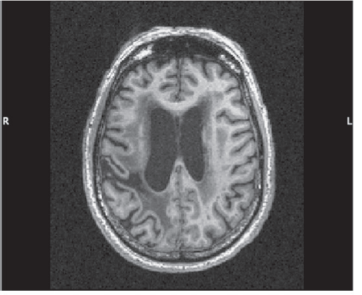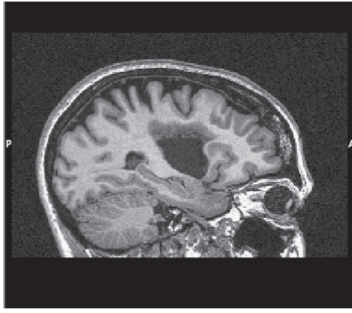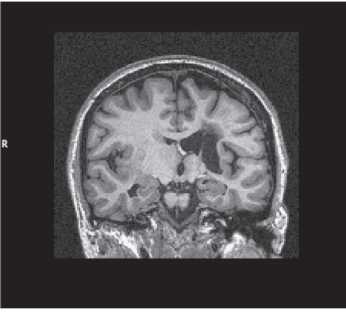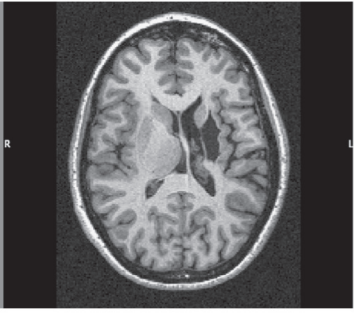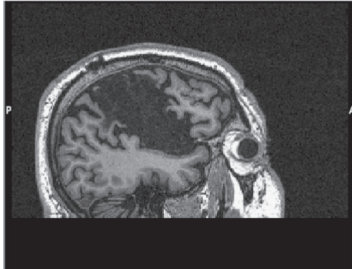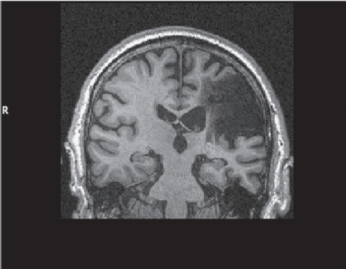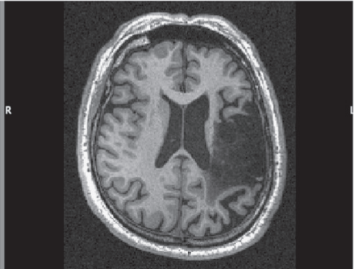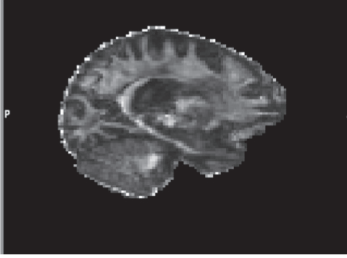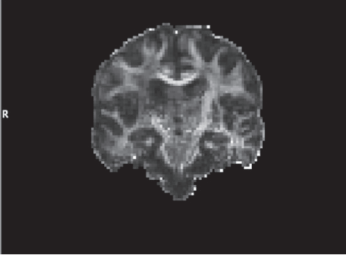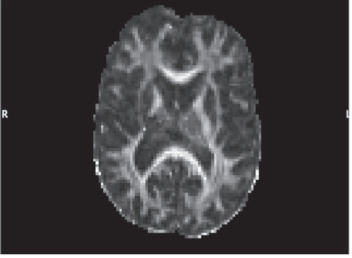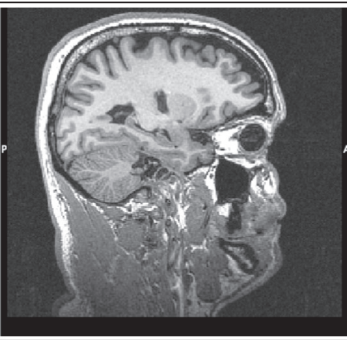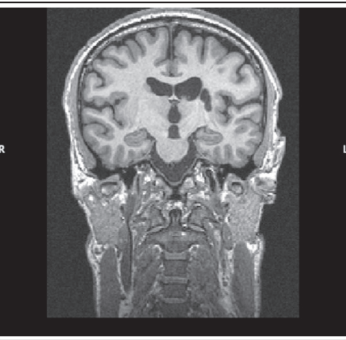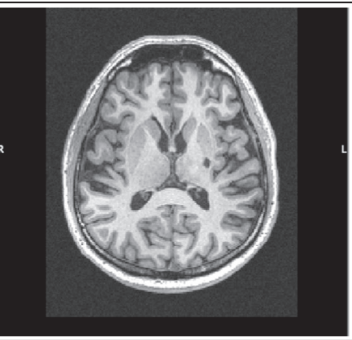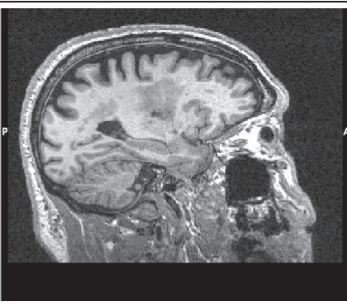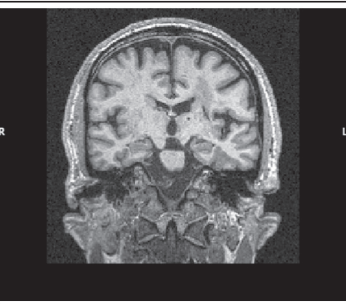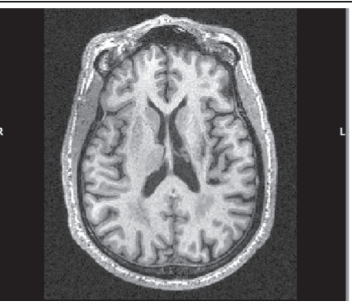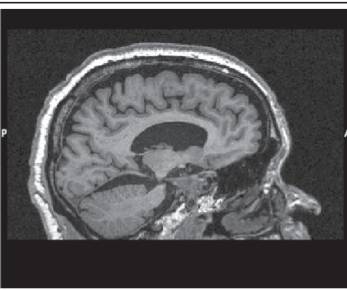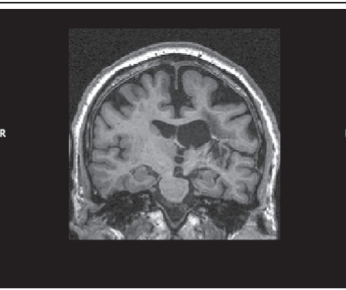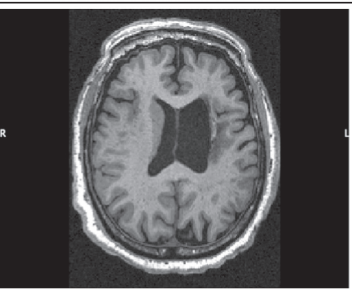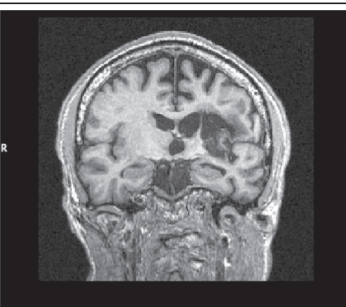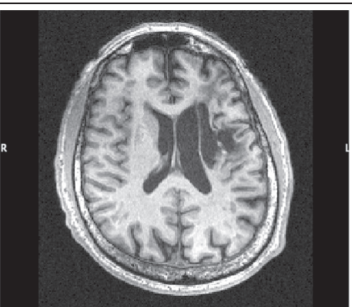
**Table 2** (*continued*)

| | | | |
|---|---|---|---|
| AH06<br>Male<br>57.51 yrs<br>L hemi |  |  |  |
| AH07<br>Male<br>36.48 yrs<br>R hemi |  |  |  |
| AH08<br>Male<br>52.91 yrs<br>R hemi |  |  |  |
| AH09<br>Male<br>62.14 yrs<br>R hemi |  |  |  |
| AH10<br>Male<br>60.84 yrs<br>R hemi |  |  |  |

of the adult hemiplegia group was $59.1 \pm 11.6$ years, and consisted of three females and seven male participants; 8 with right sided hemiplegia and 2 with left sided hemiplegia. Adult hemiplegia participants all had a single unilateral stroke at least one year prior to participation in the study with remaining upper extremity deficits. Upper Extremity Fugl-Meyer scores ranged from 12 to 40, with an average of $19.9 \pm 9.0$ out of 66 points. The adult control group consisted of a convenience sample of right-handed adults with no neurological history. Anatomical MRIs depicting the lesion locations for both the pediatric hemiplegia and adult hemiplegia groups can be found in Tables 1 and 2. All participants (or legal guardians) provided written consent. Procedures were in accordance with institutional guidelines, and this study was approved by Northwestern University's Institutional Review Board.

All subjects underwent diffusion tensor imaging on a 3 T Siemens TIM Trio scanner. An echo-planar based diffusion imaging sequence was used with diffusion weighting of 1000 s/mm$^2$ in 60 different directions, as well as 8 scans without diffusion weighting. The scan parameters used were: TR = 5 s; TE = 85 ms, matrix = $128 \times 128$; FOV =
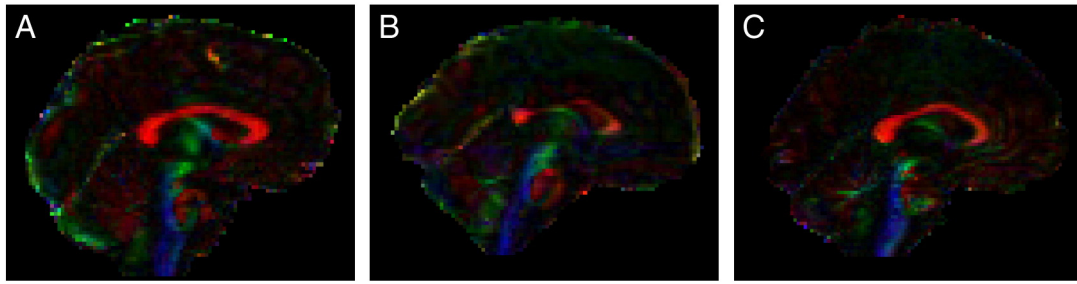
**Fig. 1.** Representative diffusion color maps. A) Adult control, B) pediatric hemiplegia, C) adult hemiplegia. Colors represent primary diffusion (fiber) direction (blue: superior/inferior; green: anterior/posterior; red: left/right). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

256 mm, and 72 slices with thickness 2 mm. Additionally, T1 weighted images were collected, using an MP-RAGE sequence with the following acquisition parameters: TR = 2.3 s, TE = 3 ms, TI = 900 ms, matrix = 256 × 256 and FOV = 256 × 256 mm.

Images were processed using the FMRIB Software Library. A diffusion tensor model was fit at each voxel, from which voxelwise values for fractional anisotropy (FA) were calculated. For each participant, masks were hand-drawn on the corpus callosum at the midsagittal slice using a directional color map as a guide. The corpus callosum was sectioned anteriorly to posteriorly into five regions corresponding with the location of the cortical projections (I: prefrontal cortex; II: pre-motor and supplementary motor areas; III: primary motor cortex; IV: primary sensory cortex; and V: parietal, occipital, and temporal regions) as previously described (Hofer and Frahm, 2006). For each region, the average FA was calculated as a measure of white matter microstructure, with higher values indicating more coherent and intact white matter. FA for each region was compared between groups using one-way ANCOVAs with age as a covariate. When significance was found between groups with the ANCOVA, groups were compared post-hoc using Fisher's LSD t-tests to correct for multiple comparisons. To investigate the differential effect of injury timing, two-way ANCOVAs were computed to find the interaction between age (pediatric vs. adult) and group (hemiplegia vs. control), again using age as a covariate. In addition to examining white matter microstructure with FA, the cross-sectional areas of each region were also calculated and statistically compared in the same manner to detect thinning of the corpus callosum.

To evaluate if age could contribute to differences in FA or cross-sectional area in the pediatric participants, correlations were completed for the pediatric control group between age and the FA and area results for each region.
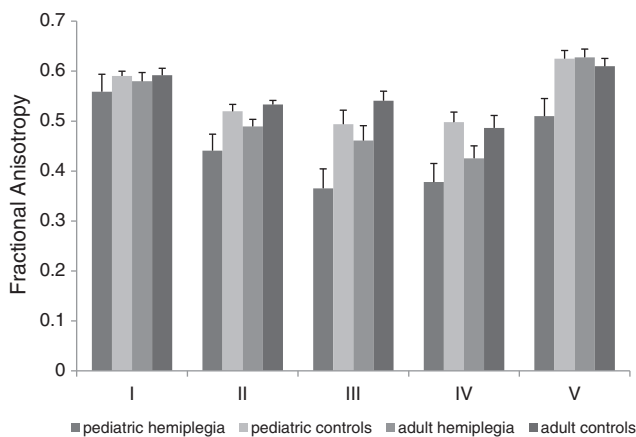
A subset of the pediatric hemiplegia (n = 6, age range 7.7–11.6 yrs, average 9.67 ± 1.34 yrs) and pediatric control (n = 3, age range 7.8–14.4 yrs, average 11.0 ± 3.30 yrs) groups underwent a quantitative assessment of mirror movements. These participants are indicated by an asterisk in Table 1. Detailed methods for this portion of the study were previously published (Sukal-Moulton et al., 2013). In brief, isokinetic efforts were completed by the non-paretic arm at 100, 50, and 25% of maximal voluntary elbow flexion torques with instruction to relax the paretic upper limb. The involuntary elbow flexion torques generated by the paretic arm were measured by a six degree-of-freedom load cell and normalized as percentage of maximum elbow flexion torque of the paretic upper limb. Correlations were also calculated for the FA and volume of each region with the amplitude of involuntary torque measured.

Statistical analysis was completed using SPSS (version 21, SPSS, Inc.), with a p value < 0.05 considered to be statistically significant for all tests.

## 3. Results

Representative color maps indicating diffusion direction are shown in Fig. 1. Significant differences in FA between groups were found for all regions of the corpus callosum except for the prefrontal region (I: F = 1.623, p = 0.201; II: F = 5.087, p = 0.005; III: F = 7.423, p = 0.001; IV: F = 5.200, p = 0.004; V: F = 5.442, p = 0.003), as shown in Fig. 2. Pediatric control subjects and pediatric hemiplegia subjects differed significantly for regions II (p = 0.049), IV (p = 0.036), and V (p = 0.025). Comparisons between adult control subjects and adult hemiplegia subjects were different for region V only (p = 0.027). The interaction effect between age (pediatric vs. adult) and group (hemiplegia



**Fig. 2.** Fractional anisotropy by region. Regions II, IV, and V show reduced fractional anisotropy values for pediatric hemiplegia relative to pediatric control subjects. Significant differences between adult stroke and age-matched controls were only found in region V.



**Fig. 3.** Cross-sectional area by region. Cross-sectional area was reduced in all regions for pediatric hemiplegia compared to pediatric control subjects. Cross-sectional area was only affected in region IV for adult hemiplegia.
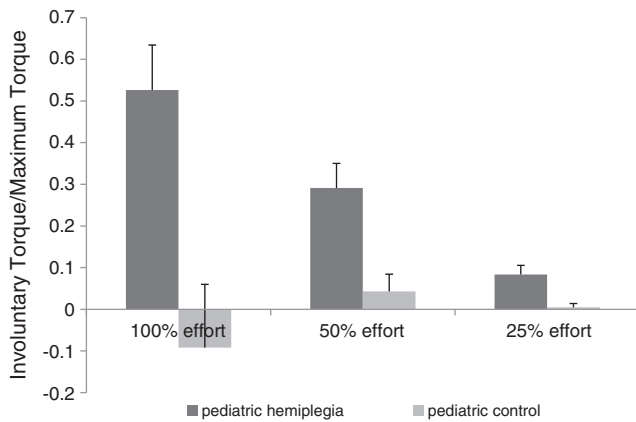
Fig. 4. Involuntary torque in the paretic arm. The paretic arm of the pediatric hemiplegia group displayed involuntary elbow flexion torque during isokinetic elbow flexion of the non-paretic arm at 100, 50, and 25% of maximal torque generated. This pattern was not observed in pediatric control participants.

vs. control) was significant for region V (F = 8.804, p = 0.005). Age was not found to correlate with FA values in any region for the pediatric control group.

As observed in Fig. 1, the corpus callosum appears thinner in the individual with pediatric hemiplegia compared to both the adult with hemiplegia and the control subject. This observation was confirmed quantitatively, with the results displayed in Fig. 3. In comparing cross-sectional area between groups for each region, significant differences were found for all regions (I: F = 6.090, p = 0.002; II: F = 3.949, p =0.016; III: F = 13.333, p < 0.001; IV: F = 7.616, p < 0.001; V: F = 10.659, p < 0.001). Comparisons between cross-sectional area in pediatric control and pediatric hemiplegia subjects were significant for all regions (I: p = 0.007; II: 0.017; III: p < 0.001; IV: p = 0.027; V: p = 0.001). Comparisons between adult control and adult hemiplegia patients were only significant for region IV (p = 0.012). Significant interactions between age (pediatric vs. adult) and group (control vs. hemiplegia) were found for regions III–V (III: F = 13.162, p = 0.001; IV: F = 12.657, p = 0.001; V: F = 6.422, p = 0.016). Age was not found to have a significant correlation with cross-sectional area in any region for the pediatric control participants.

The pediatric hemiplegia group did exhibit greater levels of involuntary interlimb coupling in their paretic elbow when the non-paretic elbow was engaged in a task, as shown in Fig. 4. This was true for all levels of torque generated with the non-paretic elbow. When correlating the torques in the paretic elbow with the DTI results, significant correlations were found for the volume of region III with the torque in the 100% condition (p = 0.046, Pearson coefficient = −0.741) and between volume of region II with the torque in the 50% condition (p = 0.021, Pearson coefficient = −0.827).

## 4. Discussion

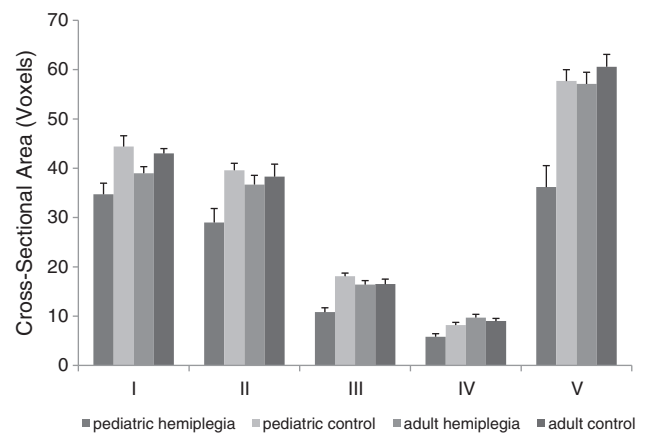Losses in transcallosal motor pathways following unilateral brain injuries can contribute to deficits with bimanual coordination, complex unilateral tasks, and locomotion. Based on our results, the corpus callosum is affected to a greater extent by unilateral injuries occurring early in life compared to adult-onset stroke. This was found both in terms of white matter microstructural properties (FA) and size (cross-sectional area) of the corpus callosum.

Differences between pediatric and adult hemiplegia may be due to the developmental state of the corpus callosum at the time of injury, as well as subsequent reorganization. Myelination of the corpus callosum begins in the splenium at 1–3 months, followed by the body, and lastly the genu at 6 months (Deoni et al., 2011; Paus et al., 2001). Continued maturation is associated with increased interhemispheric

inhibition and decreasing mirror movements, which typically vanish by age 8 for simple unimanual tasks (Koerte et al., 2009). To determine if there was any effect of age on the FA values we observed, we correlated age and FA for each region for the pediatric control group. The relationship was not significant for any region. This was to be expected, as our cohort had an average age of 12 years old, and thus large age-related changes in the corpus callosum would no longer be expected.

Based on the developmental trajectory of the corpus callosum, injuries early in life are likely to affect the developmental course of the immature callosal fibers. Additionally, with early injuries, especially when occurring prenatally, both motor areas may reorganize to the intact hemisphere, thus negating the need for callosal communication between motor areas (Carr, 1996; Eyre et al., 2007; Farmer et al., 1991; Staudt et al., 2004). Our findings that the pediatric hemiplegia group compared to pediatric control subjects had reduced cross-sectional area of the corpus callosum across all regions, as well as reduced fractional anisotropy values in three of the five callosal regions, illustrate how greatly the corpus callosum can be affected by early unilateral injury. Reductions in transcallosal motor fibers would contribute to decreased interhemispheric inhibition between the two primary motor areas, and thus a greater occurrence of mirror movements in this population.

The effect of a unilateral brain injury on the corpus callosum was less widespread in the adult hemiplegia group compared with the pediatric hemiplegia group. In adult hemiplegia, only the primary sensory (region IV) cortical connections demonstrated a change in cross-sectional area, and significant differences in fractional anisotropy were only observed in the region corresponding to parietal, occipital, and temporal cortical areas (region V). This supports previous findings that callosal fibers connecting higher order motor areas are affected following stroke. While previous studies have reported other regions of the corpus callosum being affected as well (Gupta et al., 2006; Wang et al., 2011), the subjects used in this current study represented a more chronic stroke population, where more recovery and normalization of activity may have occurred.

In comparing the differential effect of age on callosal changes, the pediatric hemiplegia group had greater microstructural changes (decreased FA) in the callosal region connecting the temporal, parietal, and occipital areas. The temporoparietal junction has been implicated in predictive motor coding, with losses of connectivity postulated to affect motor performance (Wang et al., 2011). This region also demonstrated reduced area, along with the regions corresponding to primary motor and primary sensory connections. Therefore we can conclude that unilateral lesions occurring early in life have a greater effect on the corpus callosum than injuries occurring in adulthood, both in terms of the size of corpus callosum and the microstructural properties of the white matter.

In additional to maturational differences accounting for the greater losses in callosal fibers in pediatric hemiplegia compared to adult hemiplegia, the nature of the lesions must also be taken into account. While both populations had unilateral brain injuries, periventricular lesions are more typical in pediatric populations, thus there may be a greater impact on the corpus callosum directly from the lesion. However, the extent of the damage to the corpus callosum can only be truly appreciated using DTI methods, as done in this paper, and therefore the full extent of callosal damage is commonly missed with clinical studies.

Of note is that based on Upper Extremity Fugl-Meyer scores, the adult hemiplegia group is more impaired than the pediatric hemiplegia group. This can be explained by the limitations of the Fugl-Meyer scale, which focuses mainly on abnormal synergy patterns. While these patterns are characteristic in adult hemiplegia, they may not be the underlying movement impairment in the majority of children with hemiplegia. In the pediatric condition, especially with pre- and perinatally acquired injuries, it is likely that the loss of independent limb control is more affected (Sukal-Moulton et al., 2013). As the results of this study show, pediatric hemiplegia implicates the corpus callosum more

than in adult hemiplegia, the effects of which are not specifically measured by the Fugl-Meyer assessment.

The results from the subset of individuals that underwent the bilateral torque experiment clearly show that the pediatric hemiplegia group exhibits mirror movements while the control group does not. While only two regions demonstrated significant correlations, this may be due to a limited sample size. Interestingly, it was area and not fractional anisotropy that was found to be correlated.

This study offers insight into the differences in clinical presentation between children and adults following unilateral brain injuries. The reduced size and microstructural changes (as shown by fractional anisotropy) in the corpus callosum in pediatric hemiplegia compared to adult hemiplegia and control subjects supports the observation that losses of independent limb control is a greater problem in the pediatric population. This finding gives neuroanatomical support for the need for unique interventions for pediatric and adult stroke. Future work will further divide the pediatric hemiplegia group based on pre, peri, or postnatally acquired unilateral brain injuries to further explore the influence of injury timing on callosal microstructure and associated movement dysfunctions.

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## Disclosures

None.

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