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Sensorimotor function and sensorimotor tracts after hemispherectomy

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Abstract

Hemispherectomy is currently the only effective treatment for relieving constant seizures in children with severe or progressive unilateral cortical disease. Although early hemispherectomy has been advocated to avoid general dysfunction due to continued seizures, it remains unclear whether age at surgery affects specific sensorimotor functions. Little is know about the anatomical status of sensorimotor pathways after hemispherectomy and how it might relate to sensorimotor function. Here we measured motor function and sensory thresholds of the upper and lower limbs in 12 hemispherectomized patients. Diffusion tensor imaging (DTI) was used to determine status of brainstem corticospinal tracts and medial lemniscus. Hemispherectomy subjects showed remarkable recovery in both sensory and motor function. Many patients showed normal sensory vibration thresholds. Within the smaller Rasmussen's subgroup, we saw a relationship between age at surgery and sensorimotor function recovery (i.e. earlier was better). Anatomically, we found marked asymmetry in brainstem corticospinal tracts but preserved symmetry in the medial lemniscus, which may relate to robust sensory recovery. Age at surgery predicted anatomical status of brainstem sensorimotor tracts. In sum, we found that age at surgery influences anatomical changes in brainstem motor pathways, and may also relate to sensorimotor recovery patterns.

Keywords

diffusion tensor imaging; corticospinal tract; dorsal column medial lemniscal tract; vibration sensation; Fugl-Meyer assessment

Introduction

Hemispherectomy, surgical removal of an entire cerebral hemisphere, has been performed for several decades to treat intractable unihemispheric epilepsy. The timing of surgery depends on etiology, burden of seizures and general dysfunction in patients. Most children with

Rasmussen's syndrome will have progressive worsening of seizures, progressive intellectual deterioration, and progressive hemiparesis (Vining, et al., 1997). Early surgery has been advocated to relieve the burden of constant seizures, allowing the child to return to a more normal life (Freeman, 2005; Jonas, et al., 2004; Vining, et al., 1997). However, it remains unclear whether early surgery is beneficial in terms of sensory and motor function.

In children with hemiplegia, there is rarely a complete lost of sensation and motor function in the limbs contra-lateral to hemisperectomy (de Bode, Firestine, Mathern, & Dobkin, 2005; Dijkerman, Vargha-Khadem, Polkey, & Weiskrantz, 2008; French & Johnson, 1955a, 1955b; Muller, Kunesch, Binkofski, & Freund, 1991; van Empelen, Jennekens-Schinkel, Buskens, Helders, & van Nieuwenhuizen, 2004). It has been speculated that reinforcement of the ipsilateral uncrossed corticospinal tract and bilateral cortico-reticulospinal pathways may be responsible for residual motor functions. This hypothesis is supported by studies showing that transcranial magnetic stimulation (TMS) of the motor cortex results in ipsilateral motor evoked potentials in patients after hemispherectomy (Benecke, Meyer, & Freund, 1991; Kastrup, Leonhardt, Kurthen, & Hufnagel, 2000; Rutten, Ramsey, van Rijen, Franssen, & van Veelen, 2002). In contrast, ipsilateral responses are absent in healthy children after the age of 10 and healthy adults (Muller, Kassiliyya, & Reitz, 1997). Several functional MRI (fMRI) studies have also demonstrated ipsilateral cortical activation in hemispherectomy patients using vibration, touch or painful stimulus (Bittar, Ptito, & Reutens, 2000; Graveline, Mikulis, Crawley, & Hwang, 1998; Holloway, et al., 2000; Olausson, et al., 2001; Rutten, et al., 2002), suggesting that cerebral reorganization may contribute to residual sensory function. Previous studies examined how such brain reorganization may be influenced by age at injury and nature of the insult (Benecke, et al., 1991; de Bode, et al., 2005; Holloway, et al., 2000). TMS induced ipsilateral muscle activation showed different latencies for patients with congenital and acquired diseases, suggesting differences in the underlying mechanisms (Benecke, et al., 1991). On the other hand, fMRI studies found no effects of etiology during passive hand movements (Holloway, et al., 2000), but some differences during passive ankle movements in children with prenatal stroke and Rasmussen's (de Bode, et al., 2005).

Here we investigated clinical predictors and anatomical correlates of sensorimotor function after hemispherectomy. We measured vibration sensation and motor function in twelve hemispherectomy subjects, and used diffusion tensor imaging (DTI) to reveal axonal organization in brainstem sensorimotor pathways. To our knowledge, no other study has looked at diffusion properties along the medial lemniscus and how it might relate to sensation. In this study, we found that both etiology and age at surgery predicted sensorimotor function, while age at surgery predicted anatomical status of sensorimotor tracts.

Methods

Subjects

Twelve subjects who had undergone heimspherectomy were included in this study (Table 1). Eleven subjects had hemidecortication, a procedure in which potentially epileptogenic, unihemispheric, cortical gray matter is removed while the underlying white matter and ventricles are left intact (Kossoff, et al., 2003). In most cases, the basal ganglia and thalamus were partially preserved. Subject H10 had functional hemispherectomy, where the cerebrum was partially removed and leaving behind the disconnected frontal cortex. Patients were excluded if they could not lie still in the scanner for 15 minutes bouts. We included normative DTI data for twelve age-matched controls (age range: 8–25 yrs; median age: 15 yrs; 9 female, 3 male) obtained from our pediatric and adult database (cmrm.med.jhmi.edu). Informed consent was obtained from the parents of subjects under 18 years old. Subjects over 18 years old gave informed consent prior to participating. The Johns Hopkins Institutional Review Board approved the protocol.

Clinical assessment

Motor function on the paretic limbs was assessed using the Fugl-Meyer scale, which measures reflexes, ability to move in and out of synergy, and movement coordination (Fugl-Meyer, Jääskö, Leyman, Olsson, & Steglind, 1975). We chose the Fugl-Meyer scale because it has been shown to be valid, reliable and sensitive for assessing impairment throughout different recovery stages in hemiparetic subjects (Lin, et al., 2009). Vibration sensation was quantified using Vibratron II (Physitemp Instruments Inc, Clifton, NJ) to measure vibration thresholds of the great toes and index fingers. On each trial, the tested finger or toe contacted two rods sequentially, where only one rod vibrated. Subjects were asked to identify the vibrating rod using a forced choice procedure. Testing began at amplitude detectable on 100% of trials, and continued with decreasing amplitude until the subject could only identify the vibrating rod on 50% of trials (level predicted by chance alone). The vibration threshold was calculated using the method described previously (Arezzo, Schaumburg, & Laudadio, 1985). Vibration amplitude in microns is equivalent to 0.5 × vibratron unit^2. Touch sensation was tested using Semmes Winstein graded monofilaments on the great toes and index fingers. Each finger or toe was tested separately, where threshold was determined as the lowest gram filament that could be correctly detected on 4 out of 5 trials. The Behavioural Inattention Test (BIT) Star Cancellation was used to measure visuospatial neglect (Wilson, Cockburn, & Halligan, 1987).

Magnetic Resonance Imaging

Diffusion tensor images were acquired using a 1.5T scanner (Philips Medical Systems, Best, Netherlands) with SENSE head coil. Each DTI dataset was acquired with a multislice, single-shot echo-planar imaging (SENSE factor = 2.5) spin echo sequence. Transverse slices (parallel to the line connecting the anterior and posterior commissures) covering the whole brain were acquired with no slice gap and 2.5 mm nominal isotropic resolution (FOV = 240 × 240, data matrix size = 96 × 96, reconstructed to 256 × 256). Diffusion weighting was applied along 32 directions with a diffusion *b*-factor of 700 s/mm^2. Five minimally weighted images ($b \approx 33$ s/mm^2) were also acquired as part of each DTI dataset. To improve the signal to noise ratio, three DTI datasets were acquired and averaged after co-registration. The complete scan session took less than 15 minutes.

Data processing

Images were first realigned using the AIR program (Woods, Grafton, Holmes, Cherry, & Mazziotta, 1998) to remove any potential small bulk motions that occurred during the scans. Subsequently, diffusion weighted images were processed using DTI Studio (H. Jiang & S. Mori, Johns Hopkins University). The diffusion tensor was calculated for each voxel and converted to three pairs of eigenvectors ($\mathbf{v}_1$, $\mathbf{v}_2$ and $\mathbf{v}_3$) and eigenvalues (λ_1, λ_2,λ_3), which defined the shape and orientation of the diffusion ellipsoid, respectively (Basser, Mattiello, & Lebihan, 1994). Diffusion anisotropy was measured using fractional anisotropy (FA), scaled from 0 (isotropic) to 1 (anisotropic) and defined as:

$$FA = \sqrt{\frac{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}{2(\lambda_1 + \lambda_2 + \lambda_3)}}.$$

Region of interest (ROI) analysis

The corticospinal tract (CST) and medial lemniscus (ML) were identified on color-coded FA maps (Pajevic & Pierpaoli, 1999) based on the DTI atlas of white matter tracts (see www.dtiatlas.org, Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004). In the color maps, red indicate fibers running along the right-left direction, green inferior-superior, and blue

anterior-posterior (Fig. 2). We defined anatomical ROI for each tract manually using ROIEditor (www.mristudio.org), which automatically selects pixels within a set angular threshold (0.6) and FA threshold (> 0.1) that surround a user-defined seed pixel. ROIs were specified on axial slices at all pons level where the CST (anterior pair of blue fibers, 5–6 slices) and ML (posterior pair of blue fibers, 3–4 slices) can be identified. Slice-by-slice mean FA and size (i.e. number of pixels) were calculated for each tract. For inter-subject averaging, the tract length was linearly interpolated to 5 slices for CST and 3 slices for ML.

Average FA and size across slices was calculated for each tract. Symmetry in average FA and size between ipsi- and contra-lesion CST and ML was determined by calculating the laterality index = (ipsi – contra)/(ipsi + contra). Negative values indicated a smaller parameter on the ipsi-lesional tract, and a value of 0 indicated equal parameter on both sides. Reproducibility was assessed by calculating intra-rater correlations (Shrout & Fleiss, 1979), where the protocol was repeated two times by J.C.. The first and second assessment showed high agreement for CST size (ICC > 0.94) and FA (ICC > 0.97), and agreement for ML size (ICC > 0.88) and FA (ICC > 0.70).

Statistics

Mann-Whitney test was used to compare Fugl-Meyer scores and vibration thresholds between subgroups with Rasmussen's ($N = 5$) and stroke ($N = 5$), but not the smaller subgroup with cortical dysplasia ($N = 2$). Spearman's rank correlation coefficients were calculated between age at surgery and clinical scores (Fugl-Meyer, vibration threshold). A group (hemispherectomy *vs.* control) × side (ipsi- *vs.* contra-lateral) × slice (3 ML or 5 CST) repeated measures analysis of variance was used to test differences between means in size and FA. *Post hoc* analyses were performed using the Tukey's significant different test. We determined the correlation between age at surgery and symmetry in size and FA for the CST and ML. Stepwise multiple linear regression analyses were performed using Statistica (StatSoft, Tulsa, OK) to determine which MRI or demographic variables best predicted sensorimotor scores.

Results

Sensorimotor function

All subjects had some degree of sensory and motor function on the paretic limbs. Clinical assessment for the hemispherectomized subjects is shown in Table 1. Group average Fugl-Meyer scores were calculated for subjects with cortical dysplasia (D, triangles), Rasmussen's syndrome (R, circles) and congenital stroke (S, diamonds) (Fig. 1A). The maximum Fugl-Meyer score for lower and upper extremity are represented by horizontal red and blue lines, respectively. Motor function on the paretic leg showed a 29% mean impairment, and there was no difference between the Rasmussen and stroke subgroups (Mann-Whitney $U = 8.5$, $P = 0.3$). The paretic arm was 55% impaired overall, with the Rasmussen's performing significantly worse than the stroke subgroup (Mann-Whitney $U = 1.0$, $P = 0.02$). Lower extremity motor score was not correlated with age at surgery (Fig. 1B; Spearman's $\rho = -0.16$, $P = 0.2$), while upper extremity score declined with age at surgery (Fig. 1C; $\rho = -0.65$; $P = 0.02$). Note that this upper extremity correlation depended in large part on the two subjects who had surgery during adolescence (age 13), whereas the lower extremity score was not affected by these two subjects.

Average vibration sensation was calculated for each etiology group (Fig. 1D). All subjects were able to feel vibration on the great toe and index finger bilaterally, and some subjects were within normal limits. Vibration sensation is considered significantly impaired if the threshold is greater than 3.35 vu on the great toe, and greater than 2.30 vu on the index finger (Arezzo, et al., 1985;Zackowski, et al., 2006). Average vibration threshold for the great toe on the paretic

leg (3.1 ± 1.5 vu) was typically within normal range, and there was no difference between the Rasmussen and stroke subgroups (Mann-Whitney U = 11.0, $P \geq 0.5$). Vibration sensation on the paretic index finger (3.2 ± 1.7 vu) was mildly impaired, and there was no difference between etiology groups (Mann-Whitney U = 11.0, $P \geq 0.5$). Vibration thresholds on paretic great toe (Fig. 1E; Spearman's $\rho = 0.40$, $P = 0.2$) and paretic index finger (Fig. 1F; $\rho = 0.0$, $P = 0.4$) were not correlated with age at surgery. Vibration threshold on the non-paretic index finger (0.9 ± 0.3 vu) and non-paretic great toe (1.8 ± 0.6 vu) were also within normal ranges.

Anatomy of sensorimotor tracts

Diffusion tensor imaging data from one hemispherectomy subject (H1) is displayed in color-coded FA maps (Fig. 2A–C), where red indicates white matter fibers running along the right-left direction, green inferior-superior, and blue anterior-posterior. The pons (in red) is clearly visible on a mid-sagittal slice (Fig. 2B). The CST (anterior pair of blue) and ML (posterior pair of blue) are visible on axial slices at pons level (Fig. 2C). Note that FA value is an indirect indicator of white matter density, under the assumption that there is a single fiber orientation within a pixel. If there is more than one population of tracts with different orientations within a pixel, then the pixel will also tend to have lower FA. We only placed ROIs on anatomically well-documented tracts, where they are relatively isolated (Wakana, et al., 2004). Therefore, we interpret changes in FA to indicate changes in the number of fibers. However, it is possible that there are unknown tracts localized in the same region, which could affect our interpretation of FA.

Hemispherectomized subjects clearly had asymmetric CST with the 'ipsi-lesional CST' being much smaller. The presence of ipsi-lesional CST was seen on colored FA maps of ten hemispherectomy subjects, and was not visible in two subjects (H5 and H6). As the entire ipsi-lesional cerebral cortex is removed, it is impossible that the 'ipsi-lesional CST' originated from the ipsi-lesional motor cortex. Possible origins of these fibers will be discussed below. We will refer to these fibers as the 'ipsi-lesional CST' only because they reside in the location where the CST should be. In contrast to the CST, ML appears symmetric in all hemispherectomy subjects.

Slice-by-slice CST size for each subject group (Fig. 2D) are shown for all pons level where the tract is visible. Repeated measures analysis of variance showed that the ipsilesional CST was smaller in hemispherectomy compared to controls (group effect: $F(1,44) = 101.74$, $P < 0.001$; group × side interaction: $F(1,44) = 53.47$, $P < 0.001$). *Post hoc* analysis indicated that left and right CST sizes were the same in healthy controls (Tukey's, $P \geq 0.5$), the contra-lesion CST size was comparable to controls ($P = 0.2$), and the ipsi-lesional CST was smaller compared to controls ($P < 0.001$). Figure 2E shows mean FA in CST across slices. Mean FA for the ipsi-lesional CST was lower in hemispherectomy compared to control subjects (group: $F(1,44) = 86.40$, $P < 0.001$; group × side: $F(1,44) = 120.45$, $P < 0.001$). *Post hoc* analysis indicated that mean FA for the left and right CST was the same in healthy controls (Tukey's, $P \geq 0.5$), the contra-lesion CST was comparable to controls in FA ($P = 0.6$), and the ipsi-lesional CST had lower FA ($P < 0.001$).

Figure 2F shows the slice-by-slice ML size for each group. Overall, ML was smaller in hemispherectomy compared to control subjects (group effect: $F(1,44) = 32.75$, $P < 0.001$). The effect of group was not different between sides (group × side interaction: $F(1,44) = 0.14$, $P = 0.7$). *Post hoc* analysis revealed that ipsi- and contra-lesion ML were the same size in hemispherectomy subjects (Tukey's, $P \geq 0.5$), but both were smaller compared to controls (Ps < 0.01). The left and right ML were equal size in control subjects ($P \geq 0.5$). Mean FA for ML was the same between hemispherectomy and control groups (Fig. 2G). There was no evidence of group effect ($F(1,44) = 0.08$, $P \geq 0.5$) or interaction effect between group and side ($F(1,44) = 0.59$, $P \geq 0.5$) in mean FA.

Average FA and size symmetry across slices were calculated for etiology groups (Fig. 3A) to assess anatomical status of ipsi-lesional tracts ("affected") normalized to contralesion ("unaffected") side. A laterality index of 0 indicates left-right symmetry, and the purple shaded region is the normal range in age-matched controls. The CST was asymmetric (laterality index $\neq 0$) in both FA ($t(11) = 16.0$, $P < 0.001$) and size ($t(11) = 33.8$, $P < 0.001$) across etiology groups. CST FA asymmetry increased with age at surgery (Fig. 3B; Spearman's $\rho = -0.68$, $P = 0.02$), while there was no correlation between age at surgery and CST size symmetry (Fig. 3C; $\rho = 0.04$, $P \geq 0.5$). In contrast to the CST, ML was symmetric (laterality index = 0) in both FA ($t(11) = 0.57$, $P \geq 0.5$) and size ($t(11) = 1.91$, $P \geq 0.5$) across etiology groups (Fig. 3D). There was no correlation between age at surgery and ML FA symmetry (Fig. 3E; $\rho = 0.46$, $P = 0.4$) or ML size symmetry (Fig. 3F; $\rho = 0.50$, $P = 0.3$).

Clinical and anatomical predictors of sensorimotor function

We used a stepwise multiple regression to determine whether clinical history and anatomical properties of the CST predicted motor function. The diagnosis of Rasmussen's predicted combined upper and lower extremity Fugl-Meyer score ($R^2 = 0.65$, $P = 0.007$). The prediction did not improve significantly by adding age ($P \geq 0.5$), age at surgery ($P = 0.3$), time since surgery ($P = 0.3$), FA symmetry ($P = 0.4$) or size symmetry ($P \geq 0.5$). When patients with Rasmussen's syndrome were analyzed separately, age at surgery predicted total Fugl-Meyer score ($R^2 = 0.8$, $P = 0.04$). Figure 4A shows that early surgery correlated with better (higher) motor scores in Rasmussen's subgroup. This relationship could not be more accurately modeled with an exponential function for the Rasmussen's subgroup ($R^2 = 0.8$, $P = 0.03$) or all twelve patients ($R^2 = 0.5$, $P = 0.02$).

Clinical history and anatomical status of the ML did not predict individual sensory function. When subjects with Rasmussen's syndrome were analyzed separately, vibration threshold on the great toe (but not index finger) was predicted by age at surgery ($R^2 = 0.61$, $P = 0.05$). Early surgery correlated with better (lower) vibration threshold in the Rasmussen's subgroup (Fig. 4B).

Reliability of results

We verified our results by having another author (A.B.) identify the regions of interests for the CST and ML in all hemispherectomy subjects. Statistical analyses on both sets of measurements revealed significant asymmetry in CST FA and size, and significant correlation between age at surgery and CST FA asymmetry (Table 2). Statistical tests on both measurement sets consistently indicated no correlation between age at surgery and CST size asymmetry, no asymmetry in ML FA and size, and no correlation between age at surgery and ML FA and size asymmetry.

Discussion

Consistent with previous studies (de Bode, et al., 2005), we found that motor function is less impaired on the lower limbs than upper limbs. Several previous studies have suggested that there is an etiology-specific difference in motor recovery (de Bode, et al., 2005; Holloway, et al., 2000). Our findings also indicate that the Rasmussen group has worse motor function compared to subjects with congenital stroke. In addition, we showed evidence that motor function declines with older age at surgery. However, since patients with late surgery tend to have Rasmussen's syndrome, it is unclear whether patients with other etiologies (i.e. stroke, dysplasia) would also have decreased motor function with late surgery. Further, there were only two subjects who had surgery in adolescence (age 13). What is evident is that within the Rasmussen group, age at surgery predicted motor function.

Differences in motor recovery could depend on plasticity in the remaining cerebral hemisphere. Activity from the intact hemisphere may control ipsilateral muscles via the direct uncrossed corticospinal tract or indirect cortio-reticulospinal pathways. A recent imaging study showed that white matter properties of the contra-lesion corticospinal tract are unchanged in the brain and brainstem (Wakamoto, Eluvathingal, Makki, Juhasz, & Chugani, 2006), which suggests that motor recovery may rely less on structural changes in the direct uncrossed CST and possibly more on use of the indirect cortio-reticulospinal pathways. In the current study, we found that late surgery is associated with both decreased motor function and decreased FA in 'ipsi-lesional CST'. It is unclear whether the 'ipsi-lesional CST' represents remnants (non-functional) of the pathway that had originated from the exercised motor cortex, or other fibers that reside in the location where CST should be. The former is unlikely because the degeneration of axons and myelin should progress (Vargas & Barres, 2007); however, we did not find such a relationship between time since surgery and size or FA. We hypothesize that the 'ipsilesional CST' may represent functional fibers that originate from the pontomedullary reticular formation, which normally receives input from both CST pathways and then descend via the reticulospinal pathways targeting motoneurons bilaterally. This would suggest that motor recovery after surgery might be facilitated by improved use of the indirect cortio-reticulospinal pathways.

While there is no evidence of etiology differences in sensory recovery, we found that vibration sensitivity declined with age at surgery in the Rasmussen subgroup. One recent study has reported impairments on the non-paretic limbs (Dijkerman, et al., 2008); temperature and pressure sensitivity was decreased, but passive joint movement sense was normal. Here we found that vibration sensation on the non-paretic arm and leg was normal in all hemispherectomy subjects. Differences between sensory modalities suggest that the medial lemniscus, which carries proprioceptive and fine touch information, and the spinothalamic tract, for temperature and pain, may have different reorganization after hemispherectomy.

We know of no other study assessing white matter properties in the medial leminscus after hemispherectomy. We were surprised to find that the medial leminscus remains symmetric after surgery, since sensation is markedly more impaired on the paretic limbs. We also found that the medial leminscus is smaller on both sides in the hemispherectomy subjects, which may explain some ipsilesional sensory impairments reported previously (Dijkerman, et al., 2008). The ipsi-lesional medial leminscus may be preserved because the thalamus was partially left intact. Previous studies on stroke patients with ventroposterior thalamic lesions have shown that disruption of this somatosensory relay does not necessarily impair contralateral vibration sensation or somatosensory cortex activation (Remy, et al., 1999; Staines, Black, Graham, & Mcilroy, 2002). This is consistent with the observation that hemispherectomy subjects usually have well-preserved tactile detection, but not for more complex tactile functions such as directional sensibility (Backlund, Morin, Ptito, Bushnell, & Olausson, 2005). Taken together, these previous findings and our current results suggest that vibration sensation does not require the integrity of the well-defined medial lemniscus-thalamocortical circuitry, and may involve more parallel systems. Instead of acting as a simple relay structure, the thalamus may have a more important role in sensory gaiting required for more complex sensory processing (Staines, et al., 2002).

It is important to note that our DTI data provide averaged water diffusion property within a pixel, which is an indirect indicator of white matter tracts. A decrease in FA does not necessarily mean a reduction in number of fibers. If there were multiple fiber populations with different orientations, then their contributions would be averaged within a pixel lowering the FA. Our interpretation of reduced brainstem sensorimotor pathways is reasonable given the lack of a cerebral hemisphere; however we cannot definitively say that some of these anatomical tracts are missing.

We are aware of the heterogeneity in our study population and the limited number of patients in each age and etiology subgroup. We also acknowledge that many developmental changes occur during childhood and adolescence, and a future longitudinal study could provide a clearer picture of the interactions between development and recovery. Therefore, we do not attempt to draw definitive interpretations about the effects of etiology and age at surgery. Nonetheless, our data suggests that earlier surgery is related to better sensory and motor function outcome. The reduction of medial lemniscus bilaterally is a new finding from this study. Observation that some subjects recover normal vibration thresholds after hemispherectomy suggests a role in reorganization of thalamic or cerebral circuits upstream.

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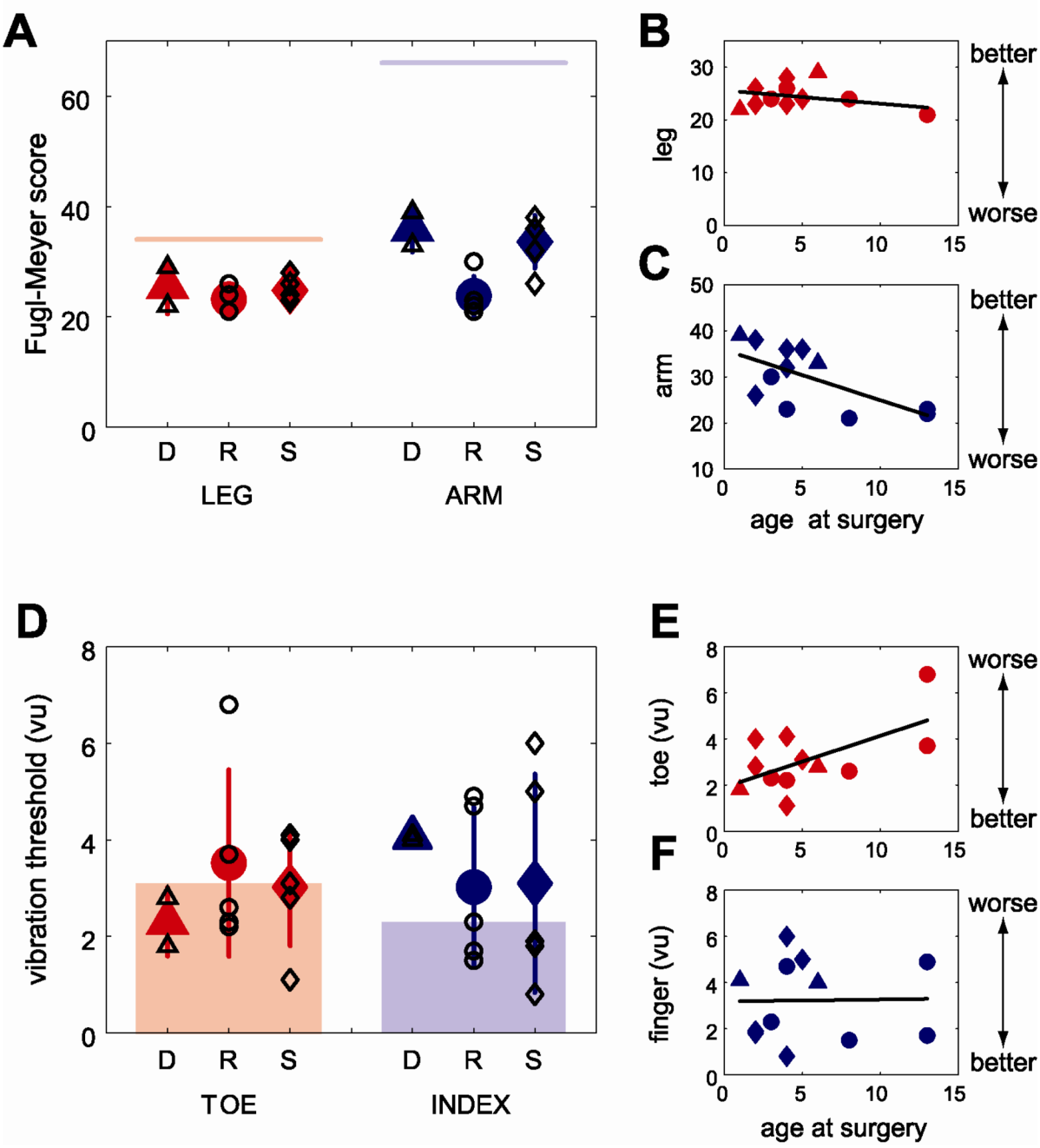

Figure 1.

Sensorimotor function in hemispherectomy subjects. (**A**) Lower and upper extremity Fugl-Meyer scores are plotted for subjects with cortical dysplasia (D, triangles), Rasmussen's syndrome (R, circles) and congenital stroke (S, diamonds). Colored symbols represent group average; black symbols represent individual subjects. Black symbols represent individual subjects. The maximum Fugl-Meyer score for lower and upper extremity are represented by horizontal red and blue lines, respectively. (**B, C**) Fugl-Meyer scores for the lower extremity (**B**) and upper extremity (**C**) are plotted against age at surgery with the best linear fit (solid line). (**D**) Vibration threshold in vibratron units (vu) on the paretic great toe and index fingers are plotted for etiology groups. The normal threshold range in the toe and finger are represented

by red and blue bars, respectively. (**E, F**) Vibration threshold on the paretic great toe (E) and index finger (F) are plotted against age at surgery with the best linear fit (solid line).

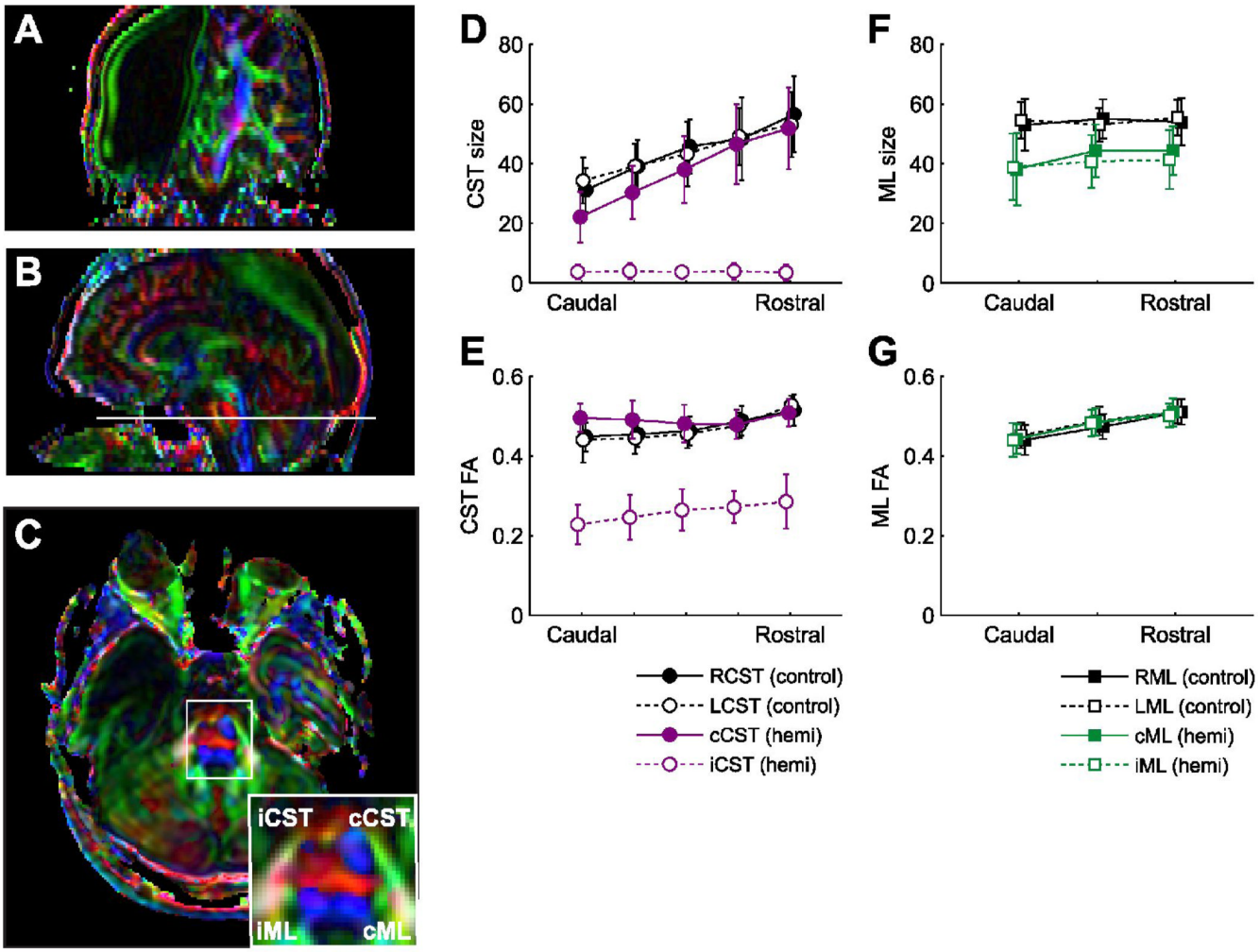

Figure 2.

(**A–C**) Color-coded FA maps and identification of white matter tracts. Coronal (**A**), sagittal (**B**) and axial (**C**) images from a hemispherectomy subject (H1). Red indicates fibers running along the right-left direction, green inferior-superior, and blue anterior-posterior. The pons (in red) is clearly visible on the mid-sagittal slice. The axial slice is taken at mid-pons level (white horizontal line), where the corticospinal tracts (anterior pair of blue) and medial lemniscus (posterior pair of blue) are visible. Locations of ROIs are labeled on the enlarged axial image of the pons (white box). (**D–G**) Slice-by-slice tract size and mean FA in hemispherectomy subjects and age-matched controls. (**D, F**) Size determined as the number of pixels for the CST (**D**) and ML (**F**) are plotted along the rostral-caudal axis within pons level. (**E, G**) Mean FA values for the CST (**E**) and ML (**G**) are plotted. Error bars represent ± SD. Abbreviations: iCST, ipsilesional corticospinal tract; cCST, contra-lesion corticospinal tract; iML, ipsi-lesional medial lemniscus; cML contra-lesion medial lemniscus; RCST, right corticospinal tract; LCST, left corticospinal tract; RML, right medial lemniscus; LML left medial lemniscus.

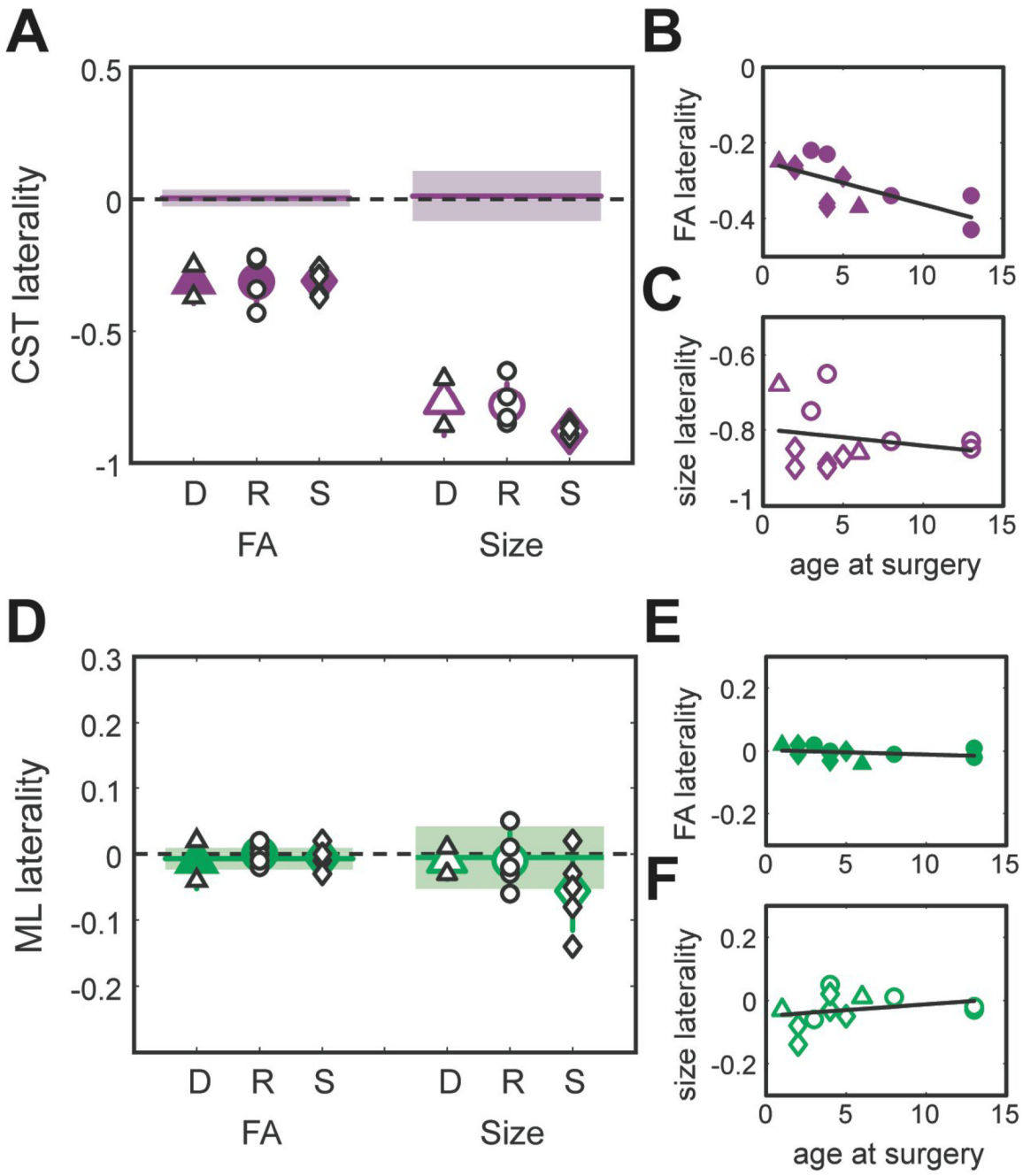

Figure 3.

Mean FA and size asymmetry plotted for the CST (**A**) and ML (**D**). Colored symbols represent group average for subjects with cortical dysplasia (D, triangles), Rasmussen's syndrome (R, circles) and congenital stroke (S, diamonds). Black symbols represent individual subjects. A laterality index of 0 (dotted line) indicates left-right symmetry. Color shaded regions indicate normal range in age-matched controls. CST FA (**B**), CST size (**C**), ML FA (**E**) and ML size asymmetry (**F**) are plotted against age at surgery with the best linear fit (solid line).

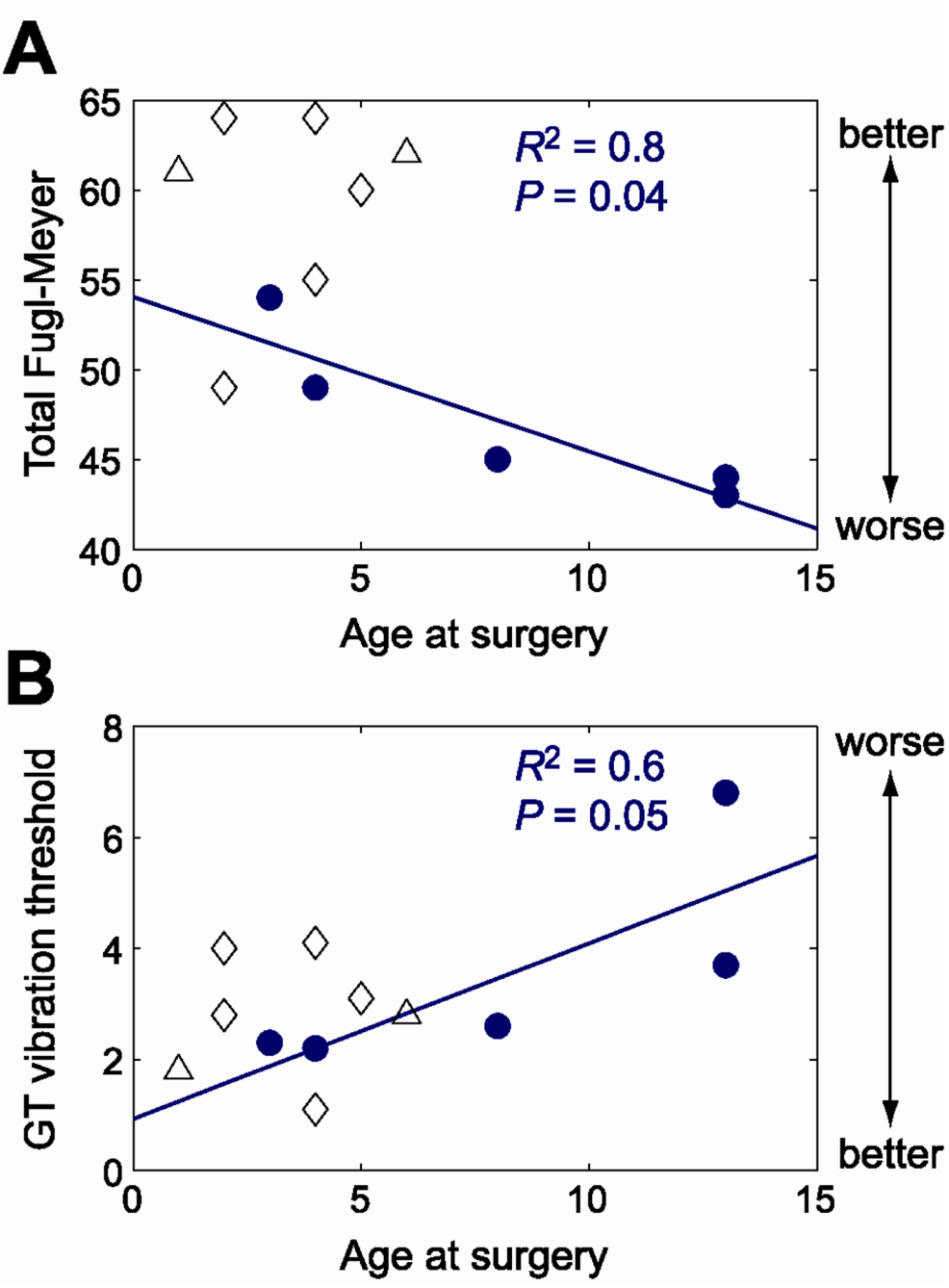

Figure 4.

Relationship between age at surgery and total Fugl-Meyer score (**A**) and vibration threshold on the paretic great-toe (**B**). Surgery in older children is associated with lower motor scores and higher vibration thresholds in subjects with Rasmussen's syndrome (blue circles). Best linear fit (blue line) is shown for the Rasmussen group. Data for subjects with congenital stroke (white diamonds) or cortical dysplasia (while triangles) are overlaid for comparison.

Table 1

Subject characteristics and clinical assessment

Subject	Age	Sex	Diagnosis[+]	Age at surgery (months)	Time since surgery (months)	Lower FM score (/66)	Upper FM score (/34)	GT vibration threshold[a] (vu)	IF vibration threshold[b] (vu)	GT touch threshold[c] (g)	IF touch threshold[d] (g)
H1	18	F	R Rasmussen	119	100	24	21	2.6	1.5	3.61	4.31
H2	13	M	R Stroke	28	141	23	26	2.8	1.8	6.65	6.56
H3	08	M	L Dysplasia	21	87	22	39	1.8	4.1	3.61	6.65
H4	15	F	R Rasmussen	163	25	21	22	6.8	4.9	6.65	6.65
H5	08	F	L Stroke	50	58	23	32	1.1	0.8	6.65	4.56
H6	15	F	R Rasmussen	46	137	24	30	2.3	2.3	3.61	3.61
H7	20	F	R Stroke	30	217	26	38	4	1.9	6.65	6.65
H8	12	F	R Rasmussen	49	98	26	23	2.2	4.7	4.31	6.56
H9	25	F	R Rasmussen	156	145	21	23	3.7	1.7	3.61	2.83
H10[*]	20	F	R Stroke	53	193	28	36	4.1	6	6.65	6.65
H11	11	F	R Dysplasia	84	54	29	33	2.8	4	6.65	4.56
H12	14	F	R Stroke	69	106	24	36	3.1	5	3.61	3.61

Abbreviations: FM, Fugl-Meyer; GT, great toe; IF, index finger.

[*] Subject H10 had functional hemispherectomy; all other subjects had hemidecortication.

[+] Rasmussen's syndrome occurs primarily in younger children. It is characterized by intractable seizures and a slowly progressive hemiparesis. Cortical dysplasia refers to a heterogeneous group with congenital malformations of cortical development.

[a] normal ≤ 2.39 vibratron units (vu); mild ≤ 3.35 vu; moderate ≤ 4.31 vu

[b] normal ≤ 1.58 vu; mild ≤ 2.30 vu; moderate ≤ 3.02 vu

[c] normal ≤ 3.61g

[d] normal ≤ 2.83g

Table 2

Summary of statistical analyses on DTI measurements

Test result	Rater 1 (J.C.)	Rater 2 (A.B.)
Asymmetry in CST FA (laterality index ≠ 0)	$t(11) = 16.0$, $P < 0.001$*	$t(11) = 14.8$, $P < 0.001$*
Correlation between age at surgery and CST FA asymmetry	$\rho = -.0.74$, $P = 0.006$*	$\rho = -0.70$, $P = 0.01$*
Asymmetry in CST size (laterality index ≠ 0)	$t(11) = 33.8$, $P < 0.001$*	$t(11) = 35.6$, $P < 0.001$*

*Significant, $P < 0.05$.