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Role of corpus callosum integrity in arm function differs based on motor severity after stroke

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A B S T R A C T

While the corpus callosum (CC) is important to normal sensorimotor function, its role in motor function after stroke is less well understood. This study examined the relationship between structural integrity of the motor and sensory sections of the CC, as reflected by fractional anisotropy (FA), and motor function in individuals with a range of motor impairment level due to stroke. Fifty-five individuals with chronic stroke (Fugl-Meyer motor score range 14 to 61) and 18 healthy controls underwent diffusion tensor imaging and a set of motor behavior tests. Mean FA from the motor and sensory regions of the CC and from corticospinal tract (CST) were extracted and relationships with behavioral measures evaluated. Across all participants, FA in both CC regions was significantly decreased after stroke ($p < 0.001$) and showed a significant, positive correlation with level of motor function. However, these relationships varied based on degree of motor impairment: in individuals with relatively less motor impairment (Fugl-Meyer motor score > 39), motor status correlated with FA in the CC but not the CST, while in individuals with relatively greater motor impairment (Fugl-Meyer motor score ≤ 39), motor status correlated with FA in the CST but not the CC. The role interhemispheric motor connections play in motor function after stroke may differ based on level of motor impairment. These findings emphasize the heterogeneity of stroke, and suggest that biomarkers and treatment approaches targeting separate subgroups may be warranted.

1. Introduction

Persistent deficits in arm function are a significant contributor to reduced quality of life after stroke (Nichols-Larsen et al., 2005). Rehabilitation interventions can improve arm function, however, response to treatment varies (Prabhakaran et al., 2008; Stinear, 2010). While several behavioral and imaging measures have been shown to predict treatment response (Burke Quinlan et al., 2015; Chen and Winstein, 2009; Riley et al., 2011; Stinear and Byblow, 2014; Wu et al., 2015), it is currently not fully known why some individuals benefit from a period of motor training more than others. An improved understanding of brain structure-motor behavior relationships is needed to help develop possible predictors of response to or potential targets of rehabilitation interventions.

The corticospinal tract (CST) is an important neural correlate of arm and hand function after stroke. In chronic stroke, CST structural integrity often correlates with baseline arm function (Burke et al., 2014; Lindenberg et al., 2010a; Park et al., 2013), however, this factor generally leaves a significant amount of variance unaccounted for, suggesting additional factors play a role. The corpus callosum (CC) serves as the structural connection between homologous sensorimotor cortices and plays a role in the control of skilled movement (Fling and Seidler, 2012; Fling et al., 2011). Some studies have suggested that the integrity of sensorimotor regions of the CC correlates with motor function after stroke (Li et al., 2015; Lindenberg et al., 2012; Wang et al., 2012), however, these studies have been small and conflicting results have been reported (Borich et al., 2012a; Mang et al., 2015). Additionally, most previous studies investigating the CC integrity after stroke have primarily included individuals with mild to moderate motor impairment (Li et al., 2015; Liu et al., 2015; Wang et al., 2012). Level of motor impairment may be an important factor in determining the role of functional interhemispheric connections after stroke (Bradnam et al., 2012), however, no studies to date have examined whether the relationship between CC structural integrity and motor function differs based on motor severity.

The current study examined the effect of stroke on the integrity of the motor and sensory regions of the CC in individuals with a range of motor impairment level. We predicted that CC integrity would be

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decreased after stroke compared to controls and that lower structural integrity would be related to poorer motor function. Additionally, given that the role of interhemispheric functional connections differs based on motor severity, we expected that this structure-function relationship would differ based on degree of motor impairment.

2. Materials and methods

2.1. Participants

Data from 55 individuals post-stroke who were participants in three separate research studies (Burke Quinlan et al., 2015; Stewart et al., 2016; Wu et al., 2015) and 18 older, nondisabled controls were included in the current analysis. Data presented here were collected prior to any intervention and includes all available data from the three studies. Eligibility criteria varied between studies but all participants with stroke were required to be at least 18 years of age, have a confirmed diagnosis of stroke at least 3 months prior to enrollment, present with some residual arm motor deficit, and have no contraindication to magnetic resonance imaging (MRI) (Kleim et al., 2007). All participants provided written informed consent prior to study participation through a protocol approved by the University of California, Irvine Institutional Review Board.

2.2. Clinical measures of motor function

The upper extremity Fugl-Meyer (UE FM) motor score (See et al., 2013), Box & Blocks test (BBT) (Mathiowetz et al., 1985), and the hand domain of the Stroke Impact Scale (SIS) (Duncan et al., 1999) were used to measure arm motor impairment, motor function, and health related quality of life, respectively. For all measures, a higher score indicates greater function. All clinical measures were completed by a licensed physical therapist.

2.3. Measures of white matter integrity

All participants underwent a single MRI session on a 3T Achieva scanner (Phillips Medical System, Best, Netherlands). A high resolution structural MPRAGE image was acquired (TR = 8.4 ms, TE = 3.9 ms) which included 150, 1 mm thick slices with no interslice gap (acquisition voxel size 1 mm^3). A T2-FLAIR image was also acquired (TR = 11.000 ms, TE = 125 ms) and included 31, 5 mm thick slices (acquisition voxel size 0.58 mm × 0.58 mm × 5 mm). Diffusion tensor images (DTI) were acquired using echo planar imaging (TR = 11.190 ms, TE = 69 ms) and included 60, 2 mm axial slices with no interslice gap, 32 directions, and a b value of 800 s/mm^2 (acquisition voxel size 1.75 mm × 1.75 mm × 2 mm).

Structural integrity of the CC and CST was quantified by mean fractional anisotropy (FA) from the DTI images in selected regions of interest (ROI) using the FMRIB Software Library (FSL; FMRIB Center, Oxford, UK). FA is a measure of the structural integrity of white matter with values ranging between 0 (isotropic) and 1 (anisotropic). Higher FA values indicate greater white matter structural integrity along a primary direction. Diffusion images were corrected for eddy currents and head motion followed by removal of the skull and dura (Smith, 2002). A voxelwise map of FA was then created using DTIFit. Masks were manually drawn on the motor and sensory sections of the CC and the CST in each participant's native space. The accuracy of all masks was confirmed by a second investigator (JCS). Mean FA was extracted from each ROI using a threshold of FA > 0.2.

The motor and sensory sections of the CC were defined as sections III and IV as described by Hofer and Frahm (Hofer and Frahm, 2006) (Supplemental Fig. 1). Both masks included the center slice and four adjacent slices. To determine the integrity of the CST, an ROI was drawn on the axial slice that showed the largest cross-sectional area of the cerebral peduncle (Schaechter et al., 2008). The cerebral peduncle was chosen for this measure as it contains descending CST motor fibers and was remote from the stroke lesion in this study cohort. CST FA ratio was calculated ($FA_{lesioned}/FA_{nonlesioned}$) to determine CST integrity in the lesioned hemisphere for each individual. An ROI approach to determining FA and FA ratio in the CST of the lesioned hemisphere has been shown to have good intra- and inter-rater reliability (Borich et al., 2012b).

2.4. Stroke lesion location

The stroke lesion was outlined manually on the T1 structural image in MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricon) using the T2-FLAIR image as a guide in each participant's native space. All areas of injured tissue including the lesion core and surrounding diffuse injury were included in the mask. All lesion masks were confirmed by a second investigator (JCS). A previous analysis in our laboratory found good intra- and inter-rater reliability with this approach to lesion mask drawing (Burke et al., 2014). Stroke lesions were then classified as to whether transcallosal fibers were lesioned or not. First, a model was created using data from the control participants. Tracts were drawn in native space using each CC mask as a seed region using probabilistic tractography in FSL (Behrens et al., 2007). Each tract was thresholded (1% of total streamlines), binarized, and transformed to MNI space in FSL. A sum mask of all tracts across participants was created and thresholded at $N \geq 3$ (voxels where at least three control participants had a tract). Next, each stroke lesion (transformed to MNI space) was categorized as overlapping the sum mask (above CC) or not overlapping the sum mask (below CC).

2.5. Statistical analysis

Statistical analysis was performed using JMP (version 8.0.2, SAS Institute, Inc., Cary, NC). Mean FA was compared between groups (stroke, control) with an independent t-test and within group with a paired t-test (2-tailed $\alpha = 0.05$). The relationship between mean FA and each

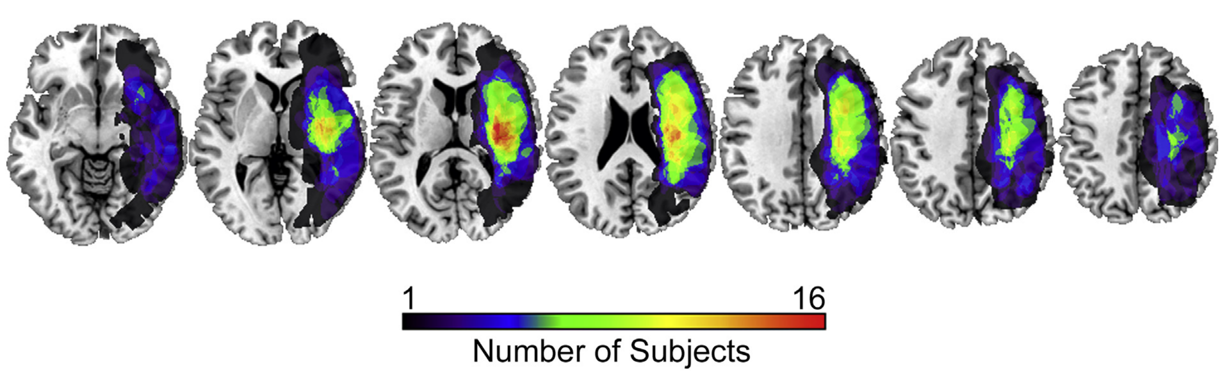

Fig. 1. Summary mask of stroke lesions. Color represents number of participants with a lesion in that voxel. All stroke lesions were flipped to the right side for data presentation.

clinical measure was determined using correlation analysis. To determine if correlations differed based on motor severity, the stroke group was split into a lower FM group (UE FM ≤ 39) and a higher FM group (UE FM > 39) based on the group mean; this mean score is similar to group means reported in previous large, multi-site clinical trials (Winstein et al., 2016; Wolf et al., 2006) and a suggested score to delineate mild motor impairment from moderate to severe motor impairment in studies of neural repair (Dobkin and Carmichael, 2016). The relationship between white matter integrity and motor status was examined for the entire stroke population and individually for each subgroup (Low FM, High FM). Pearson's r is reported unless data was not normally distributed or data could not be converted to achieve normality; in such instances, Spearman's ρ is reported. For all correlations, a p-value corrected for the number of brain regions ($p < 0.0167$) was used to determine significance.

Step-wise linear regression modeling was conducted to examine whether multiple variables combined to predict motor function in each subgroup (Low FM, High FM). Possible predictors included white matter integrity (CST, motor CC, sensory CC), age, months post-stroke, and lesion volume. Lesion location (above CC/below CC) was entered as a possible predictor in all models. All possible predictors that had a bivariate correlation ($p < 0.1$) with the dependent variable (UE FM, SIS Hand) were advanced to a forward stepwise multivariate model ($p < 0.05$ to enter, $p > 0.1$ to leave).

3. Results

3.1. Participants

On average, participants with stroke presented with moderate motor impairment, minimal sensory impairment, decreased arm and hand function, and reported moderate to significant difficulty in using the paretic hand to perform functional activities (Table 1). Stroke lesions were both cortical and subcortical (Fig. 1) and were equally distributed between the right and left hemispheres. No participant had stroke injury to any of the ROIs used in the analysis.

3.2. Corpus callosum and corticospinal tract integrity – All participants

Mean FA for the motor and sensory sections of the CC is shown in Fig. 2. FA was significantly lower in the stroke group compared to the control group in both the motor and sensory ($p < 0.001$) sections of the corpus callosum. As expected, mean FA was significantly lower in the

Table 1
Participant demographics.

	Stroke	Control
N	55	18
Age	59.4 (21–86)	65.0 (48–81)
Gender	18F/37M	13F/5M
Hand dominance	53R/2L	18R
Box & blocks paretic/left	16.2 (0–56)*	58.3 (46–75)
Box & blocks non-paretic/right	52.3 (26–73)	60.1 (46–75)
Months post-stroke	11.7 (3–85)	
Side of stroke lesion	33L/22R	
Lesion type	88%I/12%H	
Lesion volume (cc)	27.8 (0.2–178.4)	
Diabetes mellitus[ǂ]	28%Y	
Hypertension[ǂ]	51%Y	
Hypercholesterolemia[ǂ]	49%Y	
Received tPA[ǂ]	11%Y	
NIH Stroke Scale	3.8 (0 − 11)	
UE FM motor score (max 66)	38.5 (14–61)	
SIS hand domain (max 5)	2.3 (1.0–4.6)	
Nottingham sensory score (N = 44; max 17)	14.0 (4–17)	

Values represent group mean (range). Y = Yes; I = Ischemic; H = Hemorrhagic; tPA = Tissue plasminogen activator. [ǂ]Data available for some participants. *$p < 0.05$ for difference between paretic and non-paretic arms.

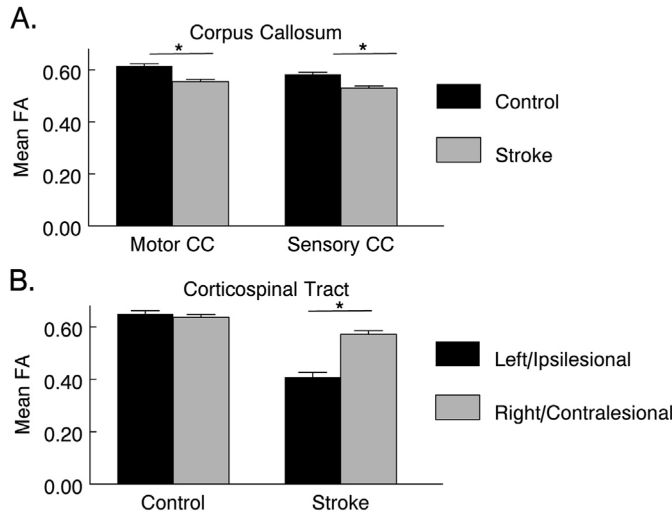

Fig. 2. Mean FA in each group for the motor and sensory regions of the corpus callosum (A) and the corticospinal tract (B). Each bar represents the group mean with standard error bars. *$p < 0.05$ for differences between groups/sides.

ipsilesional CST compared to the contralesional CST ($p < 0.001$) leading to a mean CST FA ratio of 0.71 ± 0.19 (compared to a ratio of 0.98 ± 0.07 in controls). Within the stroke group, CST FA ratio positively correlated with FA in the motor ($r = 0.306$, $p = 0.008$) and sensory ($r = 0.273$, $p = 0.019$) sections of the CC such that individuals with greater CST integrity (higher ratio) had higher integrity in the CC.

3.3. Relationship between white matter integrity and motor function – All participants

Overall, FA in both the motor section of the CC and the CST showed a positive correlation with motor function (Supplemental Table 1). Individuals with greater white matter integrity (higher FA) in these regions tended to have less motor impairment (higher UE FM score), move more blocks on the BBT, and report less difficulty using the hand in everyday activities (higher SIS hand score). The sensory section of the CC showed a positive relationship with SIS hand score only.

3.4. Relationship between white matter integrity and motor function – Participants grouped by level of motor impairment

The stroke group was divided into a Low FM group ($n = 29$) and a High FM group ($n = 26$). These two subgroups did not significantly differ in age or months post-stroke but did differ in lesion volume and in measures of motor function (Table 2, Supplemental Fig. 2). The Low FM group had significantly lower FA than the High FM group in the CST (CST FA ratio) and the motor section of the CC; FA in the sensory section of the CC was also lower but this difference did not quite reach statistical significance ($p = 0.07$). Mask volume (CST, motor CC, sensory CC) did not significantly differ between the two subgroups ($p > 0.108$ across comparisons).

The relationship between white matter structural integrity and motor function was examined for each subgroup individually (Table 3, Fig.3). In the Low FM group, CST FA ratio but not FA in the motor section of the CC correlated with UE FM motor score; a similar trend was seen for number of blocks moved on the BBT ($\rho = 0.407$, $p = 0.029$). In the High FM group, motor function correlated with structural integrity as well, but in the CC and not the CST. Mean FA in the motor section of the CC but not CST FA ratio correlated with SIS Hand domain; a similar trend was found between the motor CC and UE FM motor score ($p = 0.058$).

Based on the results of the bivariate correlation analysis, the dependent variable used for regression analyses were the UE FM for the Low

Table 2
Clinical measures and white matter integrity by subgroup.

	Low FM group	High FM group
N	29	26
Age	59.6 ± 14.9	59.1 ± 13.6
Months post-stroke	6.4 ± 6.9	17.7 ± 25.1
Side of stroke lesion	15R/14L	7R/19L
Lesion volume (cc)	40.8 ± 52.7	11.1 ± 16.3*
Lesion location (above CC/below CC)	13/16	6/20
UE FM motor score (max 66)	26.6 ± 8.0	51.9 ± 6.0
SIS hand domain (max 5)	1.5 ± 0.7	3.1 ± 0.9*
Box & blocks paretic (# blocks moved)	3.6 ± 5.1	30.3 ± 14.1*
Box & blocks non-paretic (# blocks moved)	51.3 ± 12.5	53.3 ± 8.7
Nottingham sensory score (max 17)	12.7 ± 4.8	15.5 ± 2.5
Ipsilesional CST mask volume (mm^3)	130.1 ± 23.8	140.2 ± 28.9
Motor CC mask volume (mm^3)	606.0 ± 142.0	596.2 ± 107.2
Sensory CC mask volume (mm^3)	243.5 ± 64.6	274.8 ± 77.4
CST FA ratio	0.64 ± 0.19	0.79 ± 0.16*
Motor CC mean FA	0.54 ± 0.07	0.58 ± 0.05*
Sensory CC mean FA	0.52 ± 0.07	0.55 ± 0.06

Values represent group mean ± standard deviation. *$p < 0.05$ for difference between groups.

FM group and the SIS hand domain for the High FM group. In the Low FM group, only CST ratio showed a bivariate correlation with UE FM motor score. CST ratio was a significant predictor of UE FM motor score ($F = 9.017$, $p = 0.006$, $R^2 = 0.223$); adding lesion location (above CC/below CC) did not significantly increase ($p = 0.732$) the variance in UE FM motor score explained. In the High FM group, motor CC FA, sensory CC FA, months post-stroke ($r = 0.422$, $p = 0.032$), and lesion volume ($r = -0.357$, $p = -0.073$) showed a bivariate correlation with SIS hand domain. Motor CC FA and months post-stroke remained in the final model for prediction of SIS hand domain ($F = 7.091$, $p = 0.004$, $R^2 = 0.328$); adding lesion location did not significantly increase ($p > 0.732$) the variance in SIS hand domain score explained.

4. Discussion

This study examined CC and CST structural integrity in individuals with chronic stroke and whether brain-behavior relationships differed according to level of motor impairment. Both the motor and sensory sections of the CC and the CST showed significantly less integrity after stroke compared to a group of older nondisabled adults. Across all stroke participants, variability in the structural integrity of these regions between individuals correlated with variability in motor impairment and function. However, the relationship between brain structure and motor function differed based on level of motor impairment. The integrity of structural connections contained in the motor section of the CC correlated with motor status in individuals with less motor impairment but not in individuals with more motor impairment. Instead, in individuals with greater motor impairment, motor status showed a significant correlation with CST integrity only. Differences in brain structure-motor function relationships based on level of motor impairment may have implications for the development and assessment of intervention protocols aimed at optimizing arm function after stroke.

Table 3
Correlation between white matter integrity and motor function based on level of motor impairment.

	CC motor FA	CC sensory FA	CST FA ratio
High FM group			
UE FM total	0.377	0.119	0.227
Box & blocks	0.317	0.169	0.075
SIS hand domain	**0.508***	0.352	0.070
Low FM group			
UE FM total	-0.036	0.239	**0.500***
Box & blocks+	-0.126	0.086	0.407
SIS hand domain+	-0.059	0.127	0.319

*$p < 0.0167$; + Spearman's ρ reported, all other values are Pearson's r.

Most previous studies investigating the CC integrity after stroke have focused on individuals with a narrow range of deficits (mild to moderate motor impairment) and a narrow range of injury topography (subcortical stroke below the level of the CC) (Li et al., 2015; Lindenberg et al., 2012; Liu et al., 2015; Wang et al., 2012), choices in study design that might limit the extent to which results generalize. The current study, however, included individuals with a wide range of motor impairment and lesion locations. Overall, FA in the motor and sensory sections of the CC was significantly lower in the stroke group compared to controls and this decrease correlated with level of motor function. Lower FA values are thought to be indicative of axon damage or reduced myelin integrity that result in changes in diffusivity in either the axial or radial directions (Song et al., 2003; Zhang et al., 2009). There are several possible explanations for the observed reduction in CC integrity. Since our study population included stroke lesions above the level of the CC, a decrease in CC integrity may have been due to the stroke injuring the target cortical regions of axons contained in the CC (Bonilha et al., 2014). It is also possible that changes in CC integrity were due to a general decrease in movement and physical activity (Gow et al., 2012). Finally, an increase in leukoaraiosis in the stroke group may have theoretically contributed to the decrease in CC integrity. Given that leukoaraiosis primarily presents in periventricular white matter (Etherton et al., 2016), we do not expect this to have directly affected the white matter in our CC ROIs; however, such white matter changes could affect the overall integrity of the tract. Overall, the structural integrity of the CC after stroke may have implications for functional connections between motor and sensory brain regions in the two hemispheres (Liu et al., 2015) and the effectiveness of interventions that target interhemispheric interactions.

The results of the current study support the role of the CST in motor function after stroke. However, our results suggest that above a critical level of motor capability, neural resources other than the CST may also play an important role in motor function. In individuals with relatively greater motor impairment (UE FM ≤ 39), motor function correlated with integrity of the CST but not integrity of the motor section of the CC, suggesting that the role of these interhemispheric connections in supporting movement may be limited in this subgroup. In individuals with relatively less impairment (UE FM > 39), higher FA in the CST did not correspond to greater motor function. Instead, higher FA in the motor section of the CC related to better motor function, supporting the idea that connectivity between the two motor cortices may show compensatory changes to support movement (Liu et al., 2015). It is possible that FA is not a sensitive measure of CST integrity in more mildly impaired individuals with chronic stroke (Stinear et al., 2007); other measures of integrity, such as functional integrity measured with transcranial magnetic stimulation, may better reflect the status of the CST in this subgroup. Overall, these differences in the structural correlates of motor function based on level of motor impairment support the idea that biomarkers of motor recovery vary based on the characteristics of the stroke group (Burke and Cramer, 2013) and should be considered in future studies that investigate predictors of motor function.

Functional connectivity between the ipsilesional and contralesional sensorimotor cortices has been shown to correlate with level of arm function (Carter et al., 2010; Grefkes et al., 2008; Murase et al., 2004). However, the precise role of the contralesional hemisphere in arm function after stroke remains controversial, with some studies reporting a supportive role in motor function (Lotze et al., 2006) and others interference (Murase et al., 2004). Level of motor impairment may be a factor in determining the role of the contralesional hemisphere in movement (Bradnam et al., 2012). Our findings suggest that the interhemispheric structural connections contained in the CC may play a different role in arm and hand function based on level of motor impairment. Motor severity should be considered in future studies investigating the role of the contralesional hemisphere in motor function after stroke.

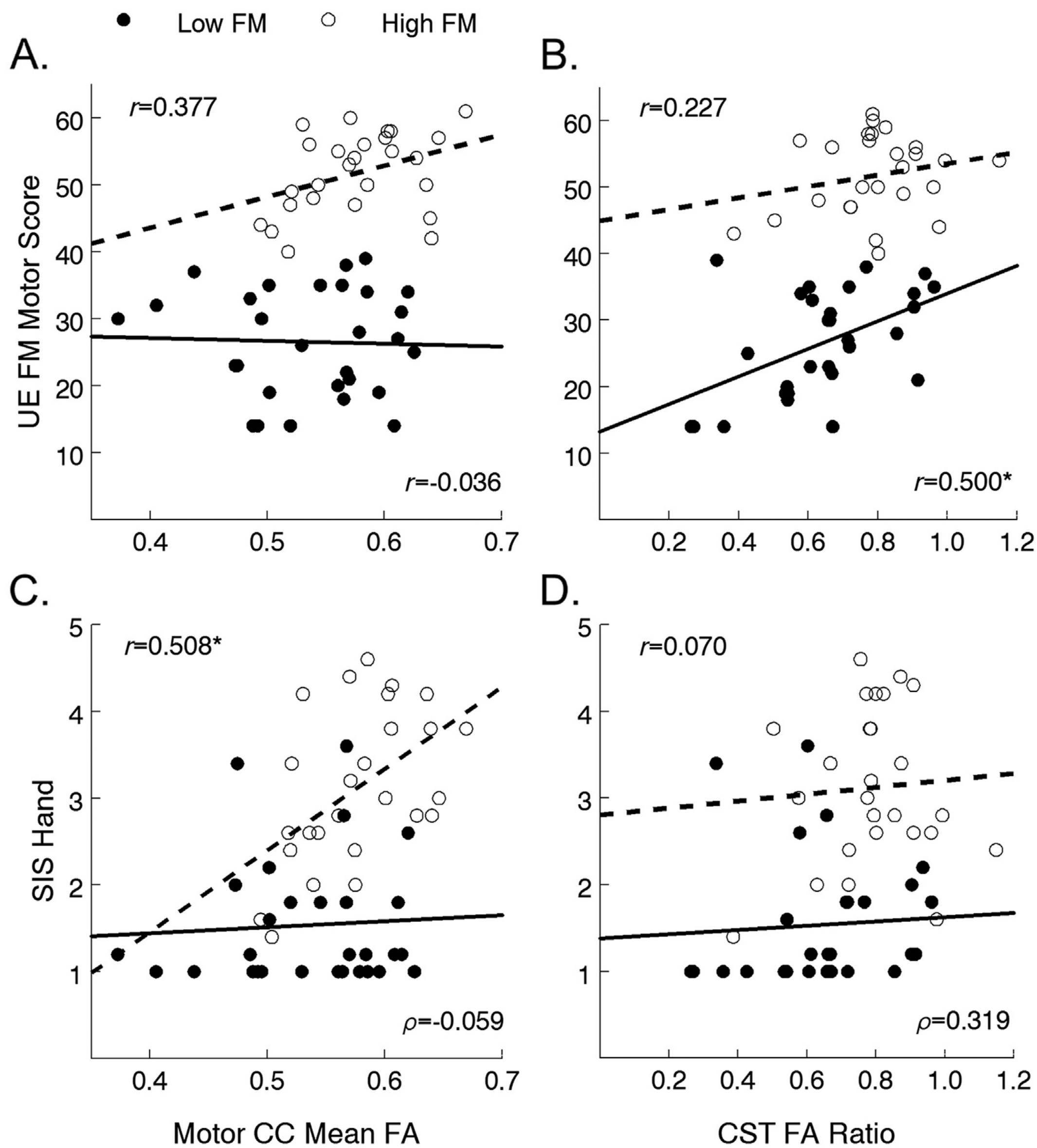

Fig. 3. Relationship between UE FM Motor Score (A and B) and SIS Hand Domain Score (C and D) and mean FA in the motor section of the CC and CST FA ratio based on level of motor impairment. Each data point represents an individual participant. Regression line (Low FM group = solid line; High FM group = dashed line) and correlation coefficient (Low FM group = lower right corner; High FM group = upper left corner) shown separately for each group. *$p < 0.0167$ for significant correlation.

The High FM group and Low FM group differed in the structural integrity of CST and motor CC; individuals with less motor function (Low FM group) showed overall lower integrity in these pathways. These same individuals also had significantly larger lesion volume and were less months post-stroke, although all participants were in the chronic phase of stroke recovery. Therefore, we cannot fully determine if group differences in FA were due to differences in level of motor function or these other variables (lesion volume, months post-stroke). We did include these variables as possible predictors of motor status in the regression model analyses conducted in each subgroup. Only months post-stoke remained as a significant predictor for the High FM group; neither variable was a predictor for the Low FM group. Variability in months post-stroke was greater in the High FM compared to the Low FM group and may partially explain this finding. Future work should include time post-stroke in addition to white matter pathway integrity as a possible predictor of motor status after stroke.

The findings of this study may have implications for the development and implementation of rehabilitation techniques aimed at improving arm function in chronic stroke. The effectiveness of interventions that rely on interhemispheric connections (e.g. bimanual priming (Stinear et al., 2014) or noninvasive stimulation of the nonlesioned hemisphere (Lindenberg et al., 2010b)) may be particularly affected by the structural integrity of the CC and level of motor impairment; individuals with mild motor impairment and greater structural integrity may be expected to respond better. Interventions that target maximizing use of the remaining CST fibers may be more appropriate in individuals with relatively more severe motor impairment. While the current study is cross-sectional, the results highlight the critical value of stratification in studies of the motor system after stroke (Cramer, 2010) and suggest that future work could investigate whether the structural integrity each motor pathway (CST, CC) predicts response to a period of motor training differently based on baseline level of motor impairment.

This study has a few limitations that should be considered in interpreting the results. This study investigated motor behavior-brain structure relationships in individuals with chronic stroke. The relationship between DTI derived measures of white matter pathway integrity and motor function may be different in the acute or sub-acute phase of stroke recovery; these measures may not capture the effects of stroke early in the recovery process (Doughty et al., 2016). No measures of functional connectivity or integrity of other motor pathways such as the rubrospinal tract (Ruber et al., 2012) were included in the current study. Future work could examine additional brain structure-brain function relationships and their role in motor function in a similarly diverse sample of individuals. This study provided a cross-sectional look at current functional status. Additional research could investigate whether these relationships change over time or predict response to a specific intervention. We used an ROI approach to quantify FA in the CC and CST similar to procedures used in other stroke studies. Whether this ROI approach or a tractography approach (e.g. tracts drawn between two motor cortices or tracts descending from motor cortex) is best to define white matter integrity after stroke is not fully known. Finally, we used a data driven approach to separate individuals into a lower and higher FM groups. The optimal approach for classification of individuals post-stroke for understanding brain-motor behavior relationships is not currently known. Future work could investigate these relationships using different classification approaches or other outcome measures.

5. Conclusions

The interhemispheric structural connections between the primary motor and sensory cortices contained in the CC play an important role in motor function after stroke. The relationship between CC structural integrity and motor function was stronger in individuals with less motor impairment suggesting these callosal connections may be more important in individuals with greater movement capacity. Interventions that target communication between the two hemispheres after stroke may be impacted by the integrity of CC fibers and measurement of their status warrant consideration in future studies.

Disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2017.02.023.

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