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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

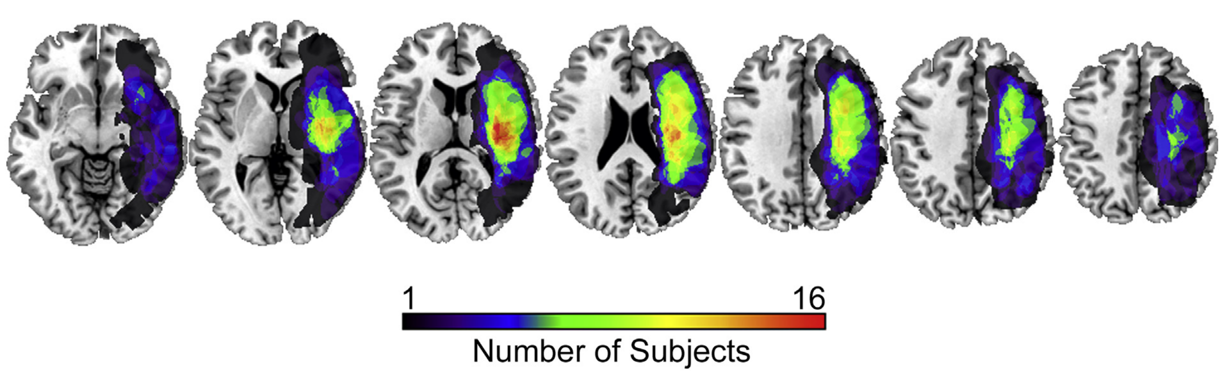

Fig. 1. Summary mask of stroke lesions. Color represents number of participants with a lesion in that voxel. All stroke lesions were flipped to the right side for data presentation.