TOPICS IN STROKE REHABILITATION
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Corpus Callosal Microstructure Predicts Bimanual Motor Performance in Chronic Stroke Survivors: a Preliminary Cross-Sectional Study

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ABSTRACT

Background: Microstructural changes in the corpus callosum (CC) are associated with more severe motor impairment in the paretic hand, poor recovery, and general disability. The purpose of this study was to determine if CC microstructure predicts bimanual motor performance in chronic stroke survivors.

Methods: We examined the relationship between the fractional anisotropy (FA) across the CC, in both the sensorimotor and non-sensorimotor regions, and movement times for two self-initiated and self-paced bimanual tasks in 41 chronic stroke survivors. Using publicly available control datasets (n = 52), matched closely for imaging acquisition parameters, we also explored the effect of stroke and age on callosal microstructure.

Results: In mild-to-moderate chronic stroke survivors with relatively localized lesions to the motor areas, lower callosal FA values, suggestive of a more disorganized microstructure, were associated with slower bimanual performance. Associations were strongest for the primary motor fibers ($b = -2.19 \pm 1.03$, $p = .035$), followed closely by premotor/supplementary motor ($b = -2.07 \pm 1.07$, $p = .041$) and prefrontal ($b = -1.92 \pm 0.97$, $p = .05$) fibers of the callosum. Secondary analysis revealed that compared to neurologically age-similar adults, chronic stroke survivors exhibited significantly lower mean FA in all regions of the CC, except the splenium.

Conclusion: Remote widespread changes in the callosal genu and body are associated with slower performance on cooperative bimanual tasks that require precise and interdependent coordination of the hands. Measures of callosal microstructure may prove to be a useful predictor of real-world bimanual performance in chronic stroke survivors.

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Diffusion tensor imaging; stroke; corpus callosum; bimanual; recovery; behavior

Introduction

Focal ischemic injury to the central nervous system can result in changes remote from the site of injury (*diaschisis*[1]) One such case is *transcallosal* diaschisis in which the ischemic event in the lesioned cortex triggers structural and functional alterations in its contralateral homolog through the corpus callosum (CC). In recent years, noninvasive imaging of the CC microstructure, e.g. using diffusion tensor imaging-derived metrics like the fractional anisotropy (FA) index, has proven useful in predicting motor recovery after stroke[2–5] as well as response to physical and occupational therapy.[6,7]

These studies have revealed important insights regarding the status and evolution of microstructural changes in the CC following a stroke. For example, recently, Pinter and colleagues showed that callosal microstructure can be expected to change as early as 72 hours post-stroke, not only in the primary sensorimotor regions but also the non-primary sensorimotor regions.[8] These changes, particularly disorganization of fibers in the anterior callosum or genu, indexed by lower FA, were found to be associated with general disability and predicted motor recovery at 3 months.[8] Persistence of lower FA in the callosum in the chronic phase has also been correlated with paretic hand motor impairment and function.[9]

However, these studies were limited by small sample sizes and an almost exclusive focus on traditional clinical measures of unilateral (paretic) motor impairment or disability, which may only weakly correspond to changes in CC microstructure, particularly its non-

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sensorimotor regions.[10] Conversely, based on the long-established evidence for the role of CC in inter-limb coordination,[11,12] lower FA in the non-sensorimotor CC regions might be better reflected in the performance of *bimanual* tasks that preferentially engage bi-hemispheric circuits.

To address these limitations, the primary purpose of this study was to determine if CC microstructure predicts bimanual motor performance in chronic stroke survivors by examining fibers connecting both the sensorimotor and non-sensorimotor regions. Two candidate regions of the callosal genu that were of special interest for the control of bimanual skills were the prefrontal region (CC1), involved in higher order planning and response selection,[13] and, the premotor and supplementary motor regions (CC2), involved in spatiotemporal coordination.[14,15] We hypothesized that lower FA in not only the primary sensorimotor but also CC1 and CC2 would correspond with poor performance on the bimanual task.

In a secondary exploratory analysis, we assessed the presence of FA reductions across the CC by comparing our own data in chronic stroke survivors (n = 41) to a publicly available dataset of neurologically intact, age-similar (n = 24), and younger (n = 28) control adults. This control dataset allowed us to more cleanly isolate the effects of stroke from the more general effects of age, establishing a baseline from which the stroke effects can be compared. Based on Pinter et al and Hayward et al., we hypothesized that compared to age-similar controls, FA would be significantly reduced, beyond the general reductions from aging, in all regions of the CC, including the non-sensorimotor regions.

Methods

Participants

Diffusion tensor imaging data for 41 chronic stroke survivors were acquired for a Phase 2B randomized controlled trial (Dose Optimization for Stroke Evaluation, ClinicalTrials.gov ID: NCT01749358) and were available for analysis.[16] Only baseline data from the DOSE study were included in this analysis. These data were collected between 2012 and 2015 on the Health Sciences Campus of the University of Southern California (USC). Additionally, stroke lesion volume and lesion overlap with the corpus callosum were quantified (see Supplement S1).

For our exploratory analysis examining differences in the microstructural status of the CC in chronic stroke survivors versus healthy controls, we used publicly available diffusion datasets acquired in 24 age-similar older adults and 28 younger adults, matched closely for acquisition parameters, including sequence, diffusion gradient strength and number of directions (OpenNeuro.org ID: ds001242). These data were collected between 2016 and 2018 on the University Park Campus of USC. Details of MRI acquisition protocol, and parameters for all three groups are provided in Supplement S2.

All individuals gave informed consent to participate in the two studies in accordance with the 1964 Declaration of Helsinki and the guidelines of the Institutional Review Boards of the respective campuses of USC where the data were collected.

Assessment of Callosal Microstructure

Pre-processing and analysis followed a standard pipeline using the FMRI Software Library, FSL depicted in Figure 1. A detailed description of the pipeline is provided in Supplement S3. The corpus callosum (CC) was defined as the primary region of interest. To assess microstructural status of the CC, we analyzed diffusion images in the standard space, and used the JHU white matter atlas to mask the CC (JHU ICBM-DTI-81 White-Matter Labels). The CC was then segmented geometrically on the midsagittal plane into five regions according to the Hofer-Frahm parcellation scheme.[17] Each of these segments correspond to fibers connecting homotopic regions of the prefrontal (I), premotor and supplementary motor (II), primary motor (III), primary somatosensory (IV), and parietal, temporo-occipital (V) cortices. Mask templates are available in the first author's OSF repository: osf.io/7j9xe.

Microstructural status was quantified as the fractional anisotropy (FA) index. The FA index is a composite measure reflecting the three-dimensional directional characteristics of diffusion in each voxel, serving as a proxy for fiber

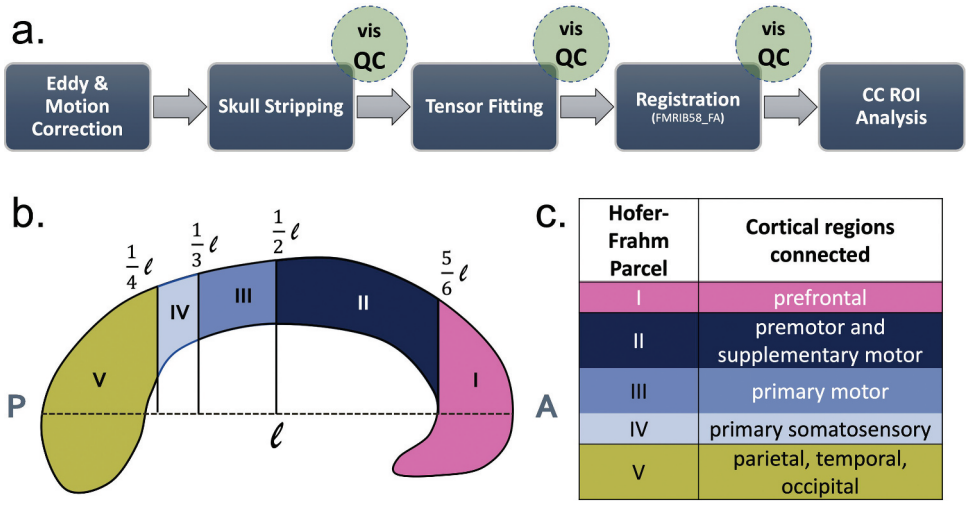

Figure 1. (a) Diffusion pipeline including preprocessing, co-registration and identifying region of interest (i.e. corpus callosum). (b) Parcellation (from posterior to anterior) of the corpus callosum using the geometric scheme proposed by Hofer & Frahm (2006). (c) Table showing cortical regions connected by the fibers running through each of the five CC segments.

orientation.[18,19,20] It is computed as a normalized fraction of the eigenvalues derived directly from voxel-wise fitted tensors, and ranges from 0 (isotropic diffusion, spherical in shape) to 1 (anisotropic diffusion, ellipsoidal in shape). The FA composite measure works particularly well for directionally homogenous, well-aligned fibers such as those of the CC, especially after thresholding for edge effects. In a random subset of stroke survivors (n = 20), we validated the FA index generated in the standard-space CC mask with those in the native FA maps and found no difference in mean FA between the two spaces. Results from these comparisons and bootstrap analyses are provided in Supplement S4.

In stroke survivors only, we also computed tissue volume as an index of CC macrostructure. To do this, individual CC masks were drawn in the native space of each participant's structural T1 image using ITK-SNAP (v. 3.8). We normalized CC volumes to express them as a percentage of total white matter volume. To compute total white matter volume, we performed tissue segmentation using FSL's FAST routine with visual quality checking to ensure that all viable white matter tissue, sparing the lesion, was identified in the segmentation procedure.

Bimanual Motor Performance

In conjunction with diffusion imaging, behavioral data for 33 of the 41 right-handed stroke survivors were available for analysis (see Supplement S5 for a full description of all 41 participants). The behavioral paradigm has been described in detail previously.[21] Briefly, participants were covertly observed as they performed the letter-envelope task of the Actual Amount of Use Test. The letter-envelope task consisted of two components: folding the letter then inserting the letter into the envelope.

Data were captured on video and analyzed offline to quantify whether participants chose a unimanual or bimanual strategy and the time taken to complete the task at self-selected speed, i.e. movement time. Start times were defined as the frame when initial contact was made with the letter or envelope, and end times were defined as the frame when the goal was accomplished, i.e. when the last fold was completed, or letter was fully inserted into the envelope. Movement time (MT) was defined as the time elapsed between the start and end time points and was determined for each component of the composite task.

Given that the strategy was self-selected, the speed was self-paced, and the testing itself was conducted unbeknownst to the participants, performance on this task was largely unconstrained, serving as a proxy for interlimb coordination in

those who chose a bimanual strategy, as if it were in the real world, even if qualitatively variable between individuals.

Statistical Analysis

All analyses were conducted using the R statistical computing package (version 4.0.2).[22] The main models used to test our hypotheses are described in the sections below. Estimates of marginal trends and marginal means from the main models were obtained using the *emmeans* package,[23] and were adjusted for multiple comparisons using the Tukey's HSD method. Significance was set at $p = .05$.

All continuous variables, age, chronicity, Upper Extremity Fugl-Meyer scores (UEFM), and movement time, were assessed for normality. A one-way ANOVA was used to compare age among the three groups (i.e. younger controls, older controls, and stroke survivors) followed by pairwise comparisons using Tukey's HSD. Kruskal-Wallis test was used to compare the proportion of females and males among the three groups.

Distributions for chronicity and movement time were positively skewed and so they were log-transformed. Assumptions for generalized linear models, including linearity, equality of variance, independence and normality of errors were met and model diagnostics, including leverage and multicollinearity of independent variables, were tested when appropriate.

Relationship between callosal microstructure and bimanual performance in chronic stroke survivors

First, in chronic stroke survivors only, to determine if mean callosal FA can be used to predict MT, we used linear mixed effects regression of the form below:

$$\begin{aligned}\log(MT)\tilde{M}eanFA + Strategy + MeanFA : Strategy \\ + MeanFA : CCregion + \log(Chronicity) \\ + CCvolume + (1|CCregion : subject)\end{aligned} \quad (1)$$

To confirm that the above hypothesized relationship between mean CC FA and MT is in fact due to the coordinative elements of bimanual performance rather than an epiphenomenon emerging from weakness of one limb, we needed to rule out such a relationship between CC FA and unimanual performance. To do this, we tested for a moderating effect of strategy on the relationship between FA and MT (mean FA x strategy, where strategy was coded as 0: bimanual, or 1: unimanual). A significant relationship in those who chose a unimanual strategy would suggest that performance on this task is not compromised due to transcallosal diaschisis alone but at least in part due to the motor capacity of the affected hand.

To test our a-priori hypothesis that lower FA in not only the primary sensorimotor but also non-sensorimotor regions (CC1, prefrontal & CC2, premotor and supplementary motor) would correspond with poor performance, we included a term to test the moderating effect of CC region on the relationship between mean FA and MT. CC region was a categorical variable with 5 levels to code for the segments of the CC, with CC3 (motor) set as the reference level. Because a single value for MT per subject was repeated over five CC regions, there was no reason to suspect MT to change as a function of CC region. There may be, for instance, an additive shift in the random variance associated with subject and regional differences in intercepts, e.g. mean FA value for CC5 could be higher than CC3 in subj#1 but lower in subj#5. Thus, to estimate variance from this additive shift, we modeled the random effects as an interaction between subject and CC region.

To arrive at the final model (eq. 1) we used a combined – forward then backwards – stepwise approach, in which we tested for the confounding effects of age, sex, chronicity, side of lesion, UEFM score, and normalized total CC volume by adding them to the base model that consisted only of mean FA, strategy, and CC region. Then, from the combined model, we removed predictors that were not significant ($p < .05$). Based on this selection process, only log-transformed chronicity and normalized total CC volume were included in the above final model. Notably, by including normalized total CC volume, we were able to consider the likely loss in CC tissue volume.

Comparing callosal microstructure between chronic stroke survivors and neurologically intact adults

Second, to explore the effect of stroke on mean callosal FA, we used linear mixed effects regression of the following form:

$$\begin{aligned} Mean\ FA \sim & Group + CCregion \\ & + Group : CCregion + (1|subj) \\ & + (1|scanner : subj) \end{aligned} \quad (2)$$

Our hypothesis was that mean FA would be lower in stroke survivors compared to age-similar adults. We suspected that while group effects would be largest for CC3 (motor) directly adjacent regions (e.g. CC2, premotor) would also show significant reductions in FA. Given that our data were obtained from two different scanners, random effects were estimated as random intercepts for both subject- and scanner-related variances.

Here again, we arrived at the final model (eq. 2) through the same process described above, testing for the confounding effects of age and sex; neither met a cutoff $p = .05$, so were removed from the above final model. Note that age was in fact partially embedded within the grouping factor itself. However, because testing for age-related effects on FA was not the primary purpose of this study, we only preserved age as a categorical variable. A supplementary analysis of the relationship between age and FA is provided for the interested reader (Supplement S6).

This manuscript conforms to STROBE Guidelines.

Results

Table 1 provides demographic information. Chronic stroke survivors consisted of 22 individuals with left hemisphere stroke and 19 with right hemisphere stroke. There was no significant difference in age ($p = .196$), sex ($p = .529$), chronicity ($p = .409$), or UEFM ($p = .633$) between the two stroke groups. Additionally, the difference in UEFM score (Δ median = 1.5 points) between the groups did not meet the minimal clinically important difference.[24] Lesion volume was slightly larger in those with right hemisphere strokes but not statistically significant (Δ mean = 1945.4 cc, $p = .054$).

Table 1. Participant characteristics.

	CONTROLS		
	Younger (N = 28)	Older (N = 24)	STROKE (N = 41)
Age (years)			
Mean (SD)	24.4 (5.07)	67.0 (5.55)	59.1 (13.1)
Sex			
Female	9 (32.1%)	9 (37.5%)	11 (26.8%)
Male	19 (67.9%)	15 (62.5%)	30 (73.2%)
Chronicity (years)			
Median [Min, Max]	NA	NA	1.90 [0.474, 14.4]
UE Fugl-Meyer (/66)			
Median [Min, Max]	NA	NA	43.0 [19.0, 58.0]
Lesion Volume (cc)			
Median [Min, Max]	NA	NA	6.05 [0.0160, 121]

On average across all stroke survivors, the lesion constituted < 0.05% (~11 voxels) of the total CC volume, whereas voxels of the CC constituted < 0.2% (~2 voxels) of the total lesion volume, confirming a very minor degree of direct injury to the CC. Supplement S1 shows lesion overlap among 41 chronic stroke survivors. Individual descriptions of lesion locations are provided in Supplement S5.

There were two main findings: First, callosal microstructure was significantly associated with bimanual performance in chronic stroke survivors. Notably, a significant relationship was observed not only with the primary sensorimotor regions, but also regions of the premotor/supplementary motor and prefrontal regions. Second, chronic stroke survivors showed significantly lower mean fractional anisotropy, compared to neurologically intact adults. These results are further described below.

Result 1: Lower callosal FA is associated with slower bimanual but not unimanual performance in chronic stroke survivors

After accounting for chronicity and total normalized CC volume, mean callosal FA was significantly associated with movement time in chronic stroke survivors who selected a bimanual strategy. That is, a more disorganized microstructure of the CC predicted slower movement times. Table 2 provides model estimates from mixed-effects regression. To interpret values in Table 2, please note again that the reference level for strategy was 'bimanual' whereas that for CC region it was 'CC3' (motor).

Post-hoc tests of marginal trends revealed that slope was significantly different from 0 for those who chose a bimanual strategy ($b = -3.34 \pm 0.72$, $p < .001$), but not for those who chose a unimanual strategy ($b = -0.52 \pm 1.55$, $p = .74$). Figure 2A shows how strategy moderates the relationship between mean callosal FA and bimanual movement time.

As expected, marginal slope was largest for CC3 (motor, $b = -2.19 \pm 1.03$, $p = .035$), followed closely by CC2 (premotor, $b = -2.07 \pm 1.07$, $p = .041$) and

Table 2. Robust mixed-effects regression coefficients from model (1) to estimate relationship between movement time and mean fractional anisotropy (FA), moderated by strategy as well as the five segmented regions of the CC. Note again that CC3 (motor) was the reference level (thus the factor 'Mean FA' is the slope for CC3 and estimates for other levels are added to this estimate to derive individual slopes presented in the post-hoc marginal trends).

	log(mt)		
Predictors	Estimates	CI	p
Intercept	5.05	4.05–6.05	**<0.001**
Mean FA	-3.60	-5.15 – -2.06	**<0.001**
Strategy	-1.87	-3.96–0.21	0.078
log(Chronicity)	0.16	0.08–0.23	**<0.001**
Total Normalized CC Volume	-0.06	-0.19–0.06	0.337
Mean FA x Strategy	2.82	0.01–5.62	**0.049**
Mean FA x CC1	0.27	-0.04–0.59	0.092
Mean FA x CC2	0.13	-0.18–0.43	0.418
Mean FA x CC4	0.33	-0.00–0.66	0.053
Mean FA x CC5	0.61	0.20–1.01	**0.003**
Random Effects			
σ^2	0.28		
$\tau_{00\ CC\_region:subjID}$	0.03		
ICC	0.10		
N_{CC_region}	5		
N_{subjID}	33		
Observations	330		
Marginal R^2/Conditional R^2	0.144/0.227		

CC1 (prefrontal, $b = -1.92 \pm 0.97$, $p = .05$). The slope for CC3 did not significantly differ from CC1 and CC2 as observed in the interaction terms, Mean FA x CC1 and Mean FA x CC2. This suggests that consistent with our hypothesis, FA of premotor and prefrontal CC were both similarly predictive of bimanual MT as the motor CC. The slopes, however, were less steep for CC4 (sensory, $b = -1.87 \pm 0.96$, $p = .053$) and CC5 (parietal, temporo-occipital, $b = -1.59 \pm 0.9$, $p = .079$) as observed in the interaction terms, Mean FA x CC4 and Mean FA x CC5. However, post-hoc comparisons of all slopes revealed that the slope of only CC5 was significantly smaller than CC3 ($t = -2.93$, $p = .031$). Figure 2B shows estimated marginal slopes for each of the 5 regions of the CC.

Result 2: Compared to neurologically intact adults, chronic stroke survivors exhibit lower FA in all regions of the CC, except the splenium

There was a significant interaction between group and CC region (F (8, 360) = 21.01, $p < .001$). Compared to neurologically intact older adults, mean FA was lower for all CC regions, except the splenium (parietal, temporo-occipital region). Greatest decrements were seen for the primary motor region, CC3 ($\Delta FA = 0.052$, $t = 4.84$, $p < .001$), but was closely followed by the premotor and supplementary motor, CC2 ($\Delta FA = 0.050$, $t = 4.69$, $p < .001$), primary sensory, CC4 ($\Delta FA = 0.034$, $t = 3.15$, $p = .005$), and lastly prefrontal regions, CC1 ($\Delta FA = 0.029$, $t = 2.73$, $p = .02$). Figure 3 shows the interaction between CC region .

Discussion

Poor callosal microstructure was associated with slower performance on a self-initiated and self-paced cooperative bimanual task in chronic stroke

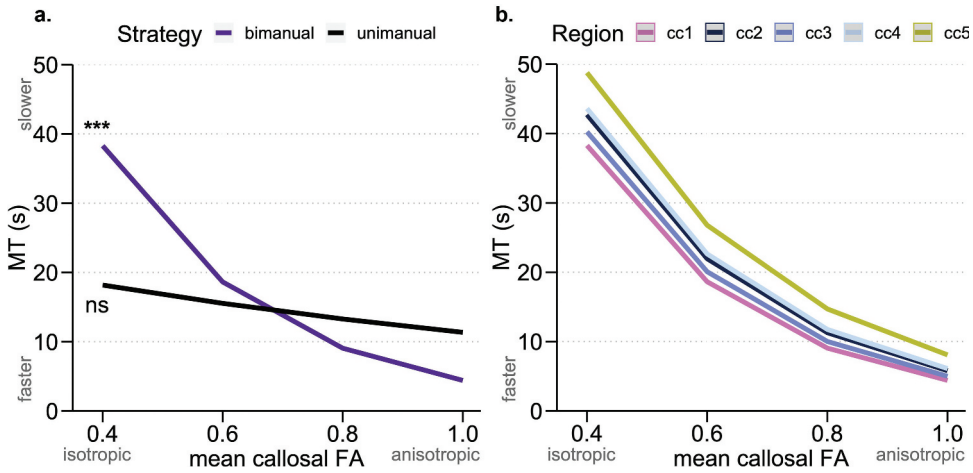

Figure 2. Movement time (MT) as a function of mean callosal FA as moderated by, A. strategy and B. callosal region. Lines are estimated marginal trends from the mixed effects model showing significant relationship between FA and MT for those who chose a bimanual but not unimanual strategy, and for the different CC regions.

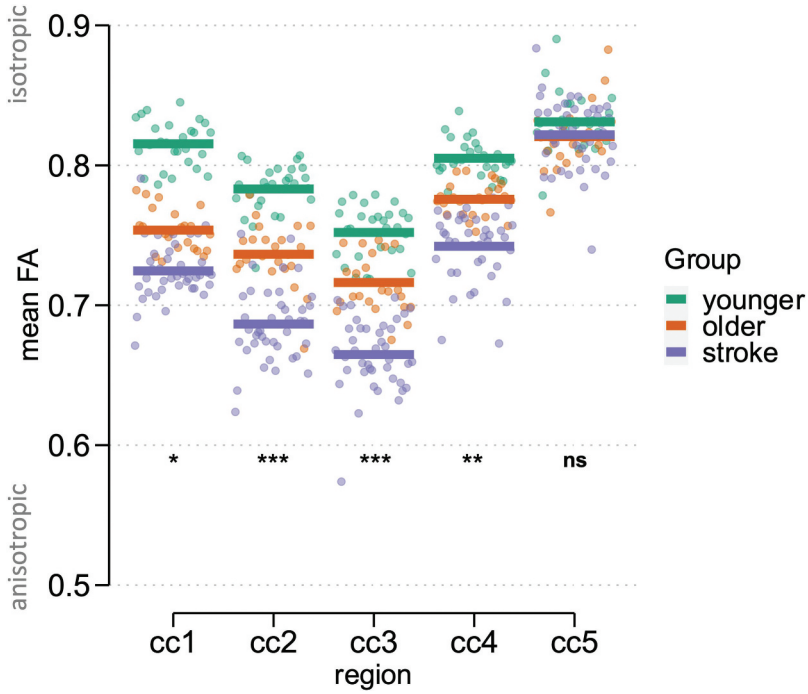

Figure 3. Model estimated marginal means for CC FA across the five regions along with individual data points. * $p < .05$, ** $p < .01$, *** $p < .001$.

survivors. This relationship was found to be significant only in those who chose a bimanual strategy and not in those who chose a unimanual strategy, lending support to the idea that callosal fiber organization is uniquely important for interhemispheric communication underlying *bimanual* performance and is not simply a reflection of unimanual weakness and disuse.

A novel observation in this study is that microstructural disorganization of fibers connecting the premotor area and SMA was associated with slower bimanual performance in stroke survivors. Self-initiated movement choices have been shown to preferentially activate the anterior midcingulate cortex and SMA.[13] Slow and imprecise initiation of bimanual movements in patients who have undergone anterior callosotomy suggests a causal involvement of these fibers for self-initiated movements.[25] One explanation for these observations is that the anterior callosum serves as a direct route for sharing motor corollary discharges across the medial wall of the frontal lobe enabling faster bimanual performance.[26] Although not as extreme as callosotomy, it stands to reason that poor microstructural status of the anterior callosum in stroke survivors may slow performance on a self-initiated bimanual task through a similar mechanism.

We extended previous findings in acute stroke survivors[8] to show that reductions in callosal FA persist in the chronic phase, in those with mild to moderate motor impairment.[5,9] Not surprisingly, greatest decrements in FA were observed in the primary motor and primary somatosensory regions of the CC and effect sizes were generally consistent with previous reports in mild-to-moderate chronic stroke survivors (ΔFA ~0.05).[5] Changes observed in the genu and rostral body of the CC were especially interesting as they suggest that transcallosal reorganization after stroke not only impacts the primary motor region, but also constituent regions of the larger sensorimotor networks, involved in the control of self-initiated bimanual motor actions that require anticipatory motor planning and sequencing.[13]

Methodological limitations of this study offer opportunities for future research. First, control imaging datasets were acquired on a different scanner. Although we accounted for this in our statistical model, future work could ensure better homogeneity

of scanner-related variance across groups. Second, the issue of fiber crossing,[20] even though less pronounced for the CC, must be taken into consideration when interpreting lower FA values. Third, bimanual tasks studied here represent a very small subset of a known large repertoire of bimanual skills, and the lack of behavioral data in neurologically intact controls leaves room for interpreting the nature of interlimb coordination. Lastly, retrospective design and a relatively small sample size, especially of those individuals who chose a unimanual strategy, warrant replication with larger samples. Whereas correlational analysis is the current standard for brain-behavior analysis using structural imaging, future work that extends to prospective multimodal imaging might reveal new insights into transcallosal diaschisis after stroke in humans.

Conclusion

In mild-to-moderate chronic stroke survivors with relatively localized lesions to the motor areas, callosal microstructure can be expected to change not only in the primary sensorimotor region, but also in the premotor, supplementary motor and prefrontal regions. Remote widespread changes in the callosal genu and body are associated with slower performance on self-initiated cooperative bimanual tasks that require precise and interdependent coordination of the hands. Callosal microstructural status may prove to be a useful predictor of real-world bimanual performance in chronic stroke survivors and should be explored in future investigations.

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Disclosure statement

Carolee J. Winstein is a member of the data safety and monitoring board for Enspire DBS (DBS is Deep Brain Stimulation) Therapy, Inc, and also for Syntactx, and she receives an honorarium for her services. She is a member of the external advisory board for MicroTransponder, Inc. and receives payment for her consulting. She is Editor of the 6th edition of Motor Control and Learning, published by Human Kinetics, Inc and receives royalty payments. She is an Editor for the 2nd Edition of Stroke Recovery and Rehabilitation, published by DemosMedical Publishers and receives royalty payments.

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Data and code availability

Data table and code for analysis are available in the first author's OSF repository: osf.io/7j9xe

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