Kinematic Measures of Bimanual Performance are Associated With Callosum White Matter Change in People With Chronic Stroke

Daniel H. Lench, BS a, Scott Hutchinson, MS, OTR/L b, Michelle L. Woodbury, PhD, OTR/L b, Colleen A. Hanlon, PhD a,b,c

Departments of Psychiatry and Neurosciences, College of Medicine, Medical University of South Carolina, Charleston, SC
Department of Health Research, College of Health Professions, Medical University of South Carolina, Charleston, SC
Department of Cancer Biology, College of Medicine, Wake Forest Health Sciences, Winston-Salem, NC

Keywords
Diffusion; Motor Activity; Pyramidal Tracts; Rehabilitation; Stroke

Abstract
Objectives: To investigate the relationship between bimanual performance deficits measured using kinematics and callosum (CC) white matter changes that occur in people with chronic stroke.

Design: Cross-sectional, observational study of participants with chronic stroke and age-matched controls.

Setting: Recruitment and assessments occurred at a stroke recovery research center. Behavioral assessments were performed in a controlled laboratory setting. Magnetic resonance imaging scans were performed at the Center for Biomedical Imaging.

Participants: Individuals were enrolled and completed the study (N = 39; 21 participants with chronic stroke; 18 age-matched controls with at least 2 stroke risk factors).

Main Outcome Measures: Diffusion imaging metrics were obtained for each individual’s CC and corticospinal tract (CST), including mean kurtosis (MK) and fractional anisotropy (FA).
Upper-extremity (UE) hemiparesis and motor deficits during the chronic phases of stroke affect a survivor’s quality of life and ability to be independent. The majority of studies related to UE motor recovery after stroke have focused on rehabilitating the patient’s ability to perform unimanual tasks with the paretic limb. However, the elderly often rely on the use of both hands, and bimanual skills facilitate functional independence after stroke.

Differences in bimanual and unimanual movements can be observed from both behavioral and neurobiological perspectives. Although unimanual tasks predominantly engage the use of the dominant hand, bimanual motor skills require the coordination of both hands. This can be seen during in-phase bimanual reach-to-grasp movements in which the 2 limbs exhibit synchronous temporal and spatial coordination. In both human and non-human primate studies, greater activation of the supplementary motor area (SMA) is elicited during bimanual tasks. The corpus callosum (CC) in particular plays a central role in the effective coordination of bimanual movements by mediating interhemispheric communication. Interhemispheric coordination is observed in non-human primates in which neural synchrony of homologous motor cortex (M1) is greatest during bimanual symmetrical movements. Changes in the cortical brain activity of people with stroke and unimanual motor deficits are well characterized. These changes in activity often reflect the need to compensate for damage to the corticospinal tract (CST), the major descending motor pathway, and are a powerful predictor of composite UE motor scores (e.g., Fugl-Meyer Assessment [FMA], Action Research Arm Test [ARAT]). Integrity of other white matter tracts, including the CC, appears to contribute to UE motor scores, but to a lesser extent. One limitation of these studies is the use of composite scores (e.g., FMA), which lack sensitivity to complex movements including bimanual coordination and compensation during symmetrical movement. To date, few studies have directly assessed the neurobiological basis for bimanual deficits after stroke. However, studies in healthy adults highlight the importance of interhemispheric connections between the SMA and M1.

Diffusion imaging is used to quantitatively measure the structural qualities of white matter. Fractional anisotropy (FA) is one such metric and is derived from diffusion tensor imaging (DTI), a method that can detect changes in white matter integrity after stroke. Despite DTI’s widespread use, it has limitations that may restrict its sensitivity to microstructure changes. Diffusion kurtosis imaging (DKI) overcomes one of these limitations by taking into account the non-gaussian distribution of diffusion in a biological system such as the brain and, thus, may provide more sensitive information to pathologic changes in tissue after stroke.

The aim of this study was to extend our understanding of bimanual performance after stroke by examining its relationship to DKI and DTI metrics of 2 white matter tracts important for motor control, namely the CST and the CC. Owing to its importance in interhemispheric communication, we hypothesized that CC integrity would be associated with kinematic measures of bimanual performance.

Methods

Participants

A cohort of 21 participants with unilateral chronic stroke (>6mo) and 18 age-matched controls were recruited through the Medical University of South Carolina’s Stroke Recovery Center and the Charleston community and completed this cross-sectional study (supplemental fig S1, available online only at http://www.archives-pmr.org/). Participants were informed of study procedures and provided consent, and the study was approved by the Medical University of South Carolina Institutional Review Board. Inclusion criteria for participants with stroke included unilateral hemiparesis, ability to flex the affected elbow and shoulder from 10% to 75% of the normal range, and ability to open and close the affected hand to perform grasping tasks. Inclusion criteria for controls included right-hand dominance, at least 2 risk factors for stroke (e.g., smoking history, high blood pressure or cholesterol, diabetes, obesity, family history of stroke, and age older than 55 years).
years for men and older than 65 years for women). Exclusion criteria for both groups included history of seizure, neurologic disorders other than stroke, scalp lesion, bone defect or hemimeanecotomy, and typical contraindications for magnetic resonance imaging (MRI). Controls were right-hand dominant (as measured by the Edinburgh Handedness Inventory), and all but 3 participants with stroke were right-hand dominant before the stroke event.

Behavioral assessments

A battery of reliable, widely used research motor assessments were administered by an occupational therapist, including the Wolf Motor Function Test (WMFT), the ARAT, and a Rasch modified Fugl-Meyer Assessment of the Upper Extremity (FMA-UE). Kinematic measures were collected from a subset of 15 participants with stroke and 15 controls using a motion capture system with 49 active markers and 10 cameras. The bimanual performance tasks included reaching with both hands to pick up a box while seated on a bench, reaching with both arms to grasp and pick up 2 water bottles simultaneously. For all tasks, the start position was with the hands flat on the table surface, elbows flexed at 90 degrees, and the shoulder at 0 degrees flexion and abduction. We measured the subject’s arm length from acromion to the tip of the middle finger and used that to normalize the position of the target (water bottles or box). We then marked a location on the intersection between the table surface and sagittal plane at a distance of 80% arm length from the subject’s jugular notch. For the box reach task, the box was placed above that mark. For the simultaneous task using the 2 bottles, the bottles were placed at a fixed distance from one another (12 inches) and were centered on that mark. Participants were asked to grasp and raise the box or 2 bottles above the surface of the table. A custom inverse kinematics routine based on the Levenberg-Marquardt algorithm was used to calculate the pose of a 35 degrees of freedom model including pelvis, thorax, neck, head, clavicles, humeri, forearms, and hands. Segment orientations and joint rotations were defined following ISB recommendations. The primary kinematic measures of interest included the asymmetry of hand position and trunk displacement. Every task was repeated twice, and metrics were averaged across trials. Asymmetry of hand position was calculated by determining the distance of each hand from the target and taking the absolute difference in position between both hands. Trunk displacement was calculated using overall distance of trunk displacement (total of anterior/posterior and medial/lateral) from the participant’s starting position.

Brain imaging

High-resolution T1-weighted structural scans were acquired on a 3T MRI scanner (repetition time, 1900ms; echo time, 2.26ms; 192 slices; 1.0×1.0×1.0 mm resolution). Diffusion-weighted images were obtained using a twice-refocused echo-planar sequence with 3 diffusion weightings (b = 0, 1000, 2000 s/mm²) along 30 diffusion encoding directions (50 slices; 0% distance factor; field of view, 222×222; 74×74 matrix; repetition time, 6400ms; echo time, 96ms; slice thickness, 2.7 mm; partial Fourier encoding, 6/8; resolution, 2.7×2.7×2.7 mm).

Image analysis

Spatial quantification of the lesion

Lesions were manually drawn in MRICron (https://www.nitrc.org/projects/mricron) using each participant’s T1-weighted structural scan and checked by a second rater to ensure consistency. Using enantiomorphic normalization, the lesion and structural image were normalized into the MNI space. An overlap map of normalized lesions was created by summing the binary lesion masks. The inverse transformation created during normalization was used in later processing steps (Clinical Toolbox, SPM12). Diffusion-weighted imaging preprocessing

Multishell diffusion-weighted images were imported into MRtrix3 (http://www.mrtrix.org) for preprocessing including denoising, Gibbs ringing artifact removal, and eddy current correction (FSL, version 5.0). Slice dropout was accounted for using outlier detection and replacement.

Constrained spherical deconvolution tractography

Multishell, multitissue constrained spherical deconvolution was performed to determine white matter fiber orientations. The algorithm proposed by Dhillander et al was selected to estimate the response function for constrained spherical deconvolution. The iFOD2 tracking algorithm was used to perform probabilistic streamline tractography. The 3 CC tracts were defined by their homologous cortical connections (left and right SMA, pre-SMA, M1) as inclusion regions of interest (ROI) and a manually defined midsagittal section of CC as the seed. CSTs were tracked by placing a seed in M1 and a manually drawn end region in the pons. Cortical ROIs were attained from the human motor area template. ROIs were transformed from the MNI space into subject-specific diffusion space. Two thousand streamlines were selected for each section with a step size of 0.2 mm. To reduce the contribution of low probability streamlines, fsilmaths was used to remove voxels less than 5% of the robust maximum of the streamline distribution.

Fractional anisotropy and mean kurtosis

Diffusion tensor metrics and kurtosis parameter calculations were performed using Matlab scripts from the DESIGNER pipeline. Fractional anisotropy (FA) and mean kurtosis (MK) values were extracted from the left and right CST and each of 3 CC segments. The mean tract FA and MK values from parameter estimate maps were calculated as a weighted mean of streamline probability. Figure 1 shows the CC and CST tracts from an individual with chronic stroke.

Statistical analysis

Normality of variables tested were assessed using the Shapiro-Wilk test (P>.05) in SPSS (version 24). Variables
that did not meet normality criteria were log transformed. Graphs are displayed with raw rather than log transformed data for interpretability. Within- and between-group differences in demographic variables and motor performance were evaluated using independent and paired $t$ tests as appropriate. A $2 \times 3$ mixed design analysis of variance (ANOVA) was used to compare FA and MK values across the 3 CC ROIs between the stroke and control groups. Post hoc $t$ tests were performed when a significant interaction was detected. $t$ tests comparing the between-group FA and MK were corrected for multiple comparisons of CSTs (left/right, affected/non-affected), wherein a $P$ value less than .025 was considered significant, or CC segments (M1, SMA, pre-SMA), wherein a $P$ value less than .0167 was considered statistically significant. A $2 \times 2$ mixed design ANOVA was used to compare CST FA and MK values between the stroke and control groups. For tracts in which there was a significant reduction in FA or MK compared with controls, partial correlations were used to determine the relationship of motor scores or kinematic variables and diffusion metrics. A subset of 15 participants with stroke received kinematic assessments. All partial correlations (2-tailed, significant at $P < .05$) were controlled for participant age at the time of participation and total lesion volume (cc).

Results

Participants and motor performance

Demographics and motor performance are listed in table 1. UE motor impairment severity was moderate (37.82±11.61) based on the Rasch modified FMA-UE score. The mean lesion volume was 44.3±55.9 cc (range, 0.68-211.44 cc), and the mean time since stroke ranged from 6.0 to 187.6 months. Figure 2 shows a lesion overlap map. Grip strength for the affected hand of participants with stroke was lower than the grip strength in the left ($t=5.1702$, $df=37$, $P<.001$) and right ($t=6.78$, $df=37$, $P<.001$) hands of the controls. As expected, the time to complete the WMFT was slower ($t=3.65$, $df=37$, $P<.001$) and ARAT scores were lower ($t=6.015$, $df=37$, $P<.001$) in participants with stroke. Trunk displacement during the box reach assessment ($t=5.66$, $df=27$, $P<.001$) and simultaneous grasp assessment ($t=5.07$, $df=27$, $P<.001$) was greater in participants with stroke. Difference in hand position relative to target was greater during simultaneous grasping ($t=3.27$, $df=28$, $P<.01$).

FA: CC and CST

Regarding CC FA, a 2-way mixed ANOVA revealed a main effect of group ($F=15.47$, $P=.00036$) but no interaction between group and CC segment. The M1 (S=0.436±0.036, C=0.481±0.026), SMA segment (S=0.451±0.033, C=0.493±0.034), and pre-SMA (S=0.428±0.040, C=0.464±0.032) of the CC had greater FA in the control than the stroke group. Regarding CST FA, a 2-way mixed design ANOVA revealed a main effect of group ($F=25.59$, $P=.00013$) and interaction of group $\times$ hemisphere ($F=21.745$, $P=.000042$). Among participants with stroke, the mean FA was lower in the lesioned hemisphere’s CST (0.435±0.046) compared with the non-lesioned hemisphere’s CST (0.492±0.0313; $P<.00022$). FA in the lesioned hemisphere of participants with stroke was reduced compared with FA in the right hemisphere of the controls ($P=1 \times 10^{-6}$). The FA on the non-lesioned hemisphere was reduced when compared with FA on the left CST in controls ($P=.0402$). However, this was not
MK: CC and CST

Regarding CC MK, a 2-way mixed ANOVA revealed a main effect of group (F = 8.549, \(P = .006\)) but no interaction between group and CC segment. The M1 (S = 0.910 ± 0.100, C = 1.017 ± 0.085), SMA (S = 0.894 ± 0.103, C = 0.966 ± 0.075) segments of the CC had greater MK in the control group than the stroke group (see Fig 3B). Regarding CST MK, a 2-way mixed design ANOVA revealed a significant effect of group (F = 14.087, \(P = .00061\)) and interaction of group x hemisphere (F=20.966, \(P = .00005\)).

Among participants with stroke, the MK was lower in the lesioned hemisphere’s CST (0.934 ± 0.108) compared with the non-lesioned hemisphere’s CST (1.061 ± 0.090; \(P = .00015\)). MK in the lesioned hemisphere of participants with stroke was reduced compared with MK in the right hemisphere of controls (\(P=1 \times 10^{-5}\)).

Relationship of FA and MK to motor impairment in the affected UE

FA and MK partial correlations with motor performance measures are shown (corrected for age and lesion) in Table 2. Supplemental Figures S2 and S3 (available online only at http://www.archives-pmr.org/) display scatterplots for each correlation.

Relationship of FA and MK to kinematic measures of bimanual movement

FA and MK partial correlations with hand asymmetry and trunk displacement are shown (corrected for age and lesion) in Table 3. Figure 4 shows a 3-dimensional representation of the correlations. Supplemental Figures S4 and S5 (available online only at http://www.archives-pmr.org/) display scatterplots for each correlation.

Discussion

Bimanual motor control after stroke is an often overlooked yet critical component of stroke recovery. The aim of this study was to investigate the relationship between CC and CST white matter integrity and kinematics during bimanual motor control. We found that both DTI and DKI metrics from the CC correlate with hand asymmetry and trunk compensation during bimanual motor tasks in participants with chronic stroke. This supports and extends our knowledge of CC structural integrity in chronic stroke and its role in the performance of bimanual movements. To our knowledge, this is the first study in participants with stroke to directly implicate the role of CC white matter structure (as measured by DTI and DKI) in kinematic measures during a bimanual task.
Role of CC and bimanual movement

In the healthy brain, transcallosal fibers of CC connect homologous cortical regions, allowing for information to be integrated across hemispheres. In healthy individuals, this is supported by the CC’s relationship to bimanual skill performance. Consistent with our findings, bimanual coordination is particularly correlated with the portion of CC connecting the left and right SMA. In diseases in which myelination of CC is degraded (eg, multiple sclerosis and amyotrophic lateral sclerosis), a reduction in white matter integrity is correlated with reduced bimanual coordination. Our results support evidence that participants with stroke and impaired reach performance tend to have...
Table 2 Correlation of diffusion metrics and motor performance

| Tract     | FA      | ARAT (n=21) | WMFT (n=21) |
|-----------|---------|-------------|-------------|
| CST (more affected hemisphere) | $r = 0.230, P = .344$ | $r = 0.502, P = .029^*$ | $r = -0.485, P = .035^*$ |
| M1 CC segment | $r = .424, P = .070$ | $r = 0.512, P = .025^*$ | $r = -0.503, P = .028^*$ |
| SMA CC segment | $r = .436, P = .062$ | $r = .440, P = .060$ | $r = .437, P = .061$ |
| Pre-SMA segment | $r = .166, P = .498$ | $r = .239, P = .324$ | $r = -.279, P = .248$ |
| CST (more affected hemisphere) | $r = .628, P = .004^*$ | $r = .517, P = .023^*$ | $r = -0.595, P = .007^*$ |
| M1 CC segment | $r = .444, P = .051$ | $r = .226, P = .353$ | $r = -.329, P = .169$ |
| SMA CC segment | $r = .453, P = .052$ | $r = .267, P = .269$ | $r = -.310 P = .197$ |
| Pre-SMA segment | $r = .232, P = .340$ | $r = .110, P = .654$ | $r = -.176, P = .470$ |

* $P < .05$.

Table 3 Correlation of diffusion metrics and bimanual kinematics

| Bimanual Kinematics | Box Reach Task (n=15) | Simultaneous Grasp Task (n=15) |
|---------------------|-----------------------|--------------------------------|
| Hand Asymmetry      | FA        | MK        | FA        | MK        |
| CST (more affected hemisphere) | $r = .455, P = .137$ | $r = -.281, P = .376$ | $r = -.294, P = .354$ | $r = -.765, P = .004$ |
| M1 CC segment       | $r = -.682, P = .010$ | $r = -.572, P = .041$ | $r = -.548, P = .052$ | $r = -.557, P = .048$ |
| SMA CC segment      | $r = -.704, P = .007$ | $r = -.557, P = .048$ | $r = -.626, P = .022$ | $r = -.577, P = .039$ |
| Pre-SMA CC segment  | $r = -.620, P = .024$ | $r = -.664, P = .013$ | $r = -.457, P = .116$ | $r = -.573, P = .041$ |
| Trunk Displacement  | FA        | MK        | FA        | MK        |
| CST (more affected hemisphere) | $r = -.274, P = .390$ | $r = -.720, P = .008$ | $r = -.245, P = .442$ | $r = -.717, P = .009$ |
| M1 CC segment       | $r = -.548, P = .065$ | $r = -.375, P = .230$ | $r = -.229, P = .475$ | $r = -.373, P = .233$ |
| SMA CC segment      | $r = -.620, P = .031$ | $r = -.355, P = .258$ | $r = -.502, P = .096$ | $r = -.398, P = .200$ |
| Pre-SMA CC segment  | $r = -.686, P = .014$ | $r = -.386, P = .258$ | $r = -.472, P = .122$ | $r = -.343, P = .275$ |

lower CC integrity as well. Consistent with these studies, we found that white matter integrity was reduced within the CC of participants with stroke compared with age-matched controls, possibly the result of Wallerian degeneration.

Unlike previous studies there was a relatively weak relationship between CC structural integrity and overall motor impairment. Other studies have indicated that this relationship may differ depending on the severity of impairment. Thus, the lack of association observed in our sample may be the result of a wide distribution of motor impairment severity. In agreement with previous kine- matic studies in participants with stroke, there was a disruption of cooperative coordination of both hands relative to age-matched controls. Our findings suggest that CC integrity after stroke is associated with this disruption of bimanual coordination rather than with unimanual skills or overall motor severity.

Role of CST and motor performance

The CST is a major descending pathway that is important for controlling voluntary movement of the upper and lower limbs. Residual CST integrity to predict motor outcome and impairment can be readily measured using single pulse transcranial magnetic stimulation or diffusion metrics. Consistent with previous studies, CST integrity is reduced in the more affected hemisphere and when compared with age-matched controls. Research to date has focused on motor severity and unilateral motor performance as it relates to CST integrity. As expected, we found that reduced ipsilesional integrity of the CST was associated with poor performance of the affected limb as measured by the ARAT. Contrary to the CC, the CST was not associated with bimanual kinematics, suggesting that it has a weaker influence on bimanual task performance. Although this study focused on the CST originating in M1, there are a number of secondary descending corticofugal tracts that may contribute more to bimanual motor performance.

Diffusion metrics in chronic stroke

FA is reduced in people with chronic stroke and correlates well with motor function. DKI has expanded upon measures such as FA by addressing assumptions about the diffusivity characteristics of water in the brain. Although both FA and MK metrics correlated with behavioral metrics in our sample, the strength of correlation coefficients between MK in the CST and WMFT time was stronger than with FA. This suggests that beyond FA, MK may be a valuable metric in stroke studies evaluating changes in white matter structure. Kurtosis metrics appear to be valuable in the acute and subacute phases of stroke, in which MK of the CST correlated with FMA-UE. In addition, a reduction in MK in the ipsilesional hemisphere of chronic stroke is consistent with a previous study in people with aphasia in which MK was shown to be more sensitive to microstructural changes.
changes after therapy than FA metrics. ⁵⁰ Although diffusion metrics appear to have a relationship to microstructural properties, interpretation is difficult, and conclusions should be drawn with caution.

Study limitations

The bimanual tasks performed in this study were symmetrical in nature and did not include asymmetrical movements (eg, opening a jar), which are out of phase. Thus, our results are limited in their generalizability to the variety of bimanual tasks individuals with stroke experience in everyday life. Although we found a strong relationship between FA and MK in the CC and bimanual kinematics, additional brain structures damaged by the stroke may have contributed to hand asymmetry and trunk displacement. Although not systematically assessed in this study, lesions extending beyond the motor network may influence attention and visual-spatial cognitive ability and may have contributed to bimanual motor performance. As is the case with many studies of stroke, lesion location was highly heterogeneous and lesion damage was observed bilaterally in a small subset of cases. Lateralization of lesions may have influenced our results, which may be better controlled for in studies with larger sample sizes. Finally, because participants were in the chronic phase of stroke, reductions in FA and MK may be the result of less frequent arm use to perform everyday activities.

Conclusions

Understanding how CC diffusion metrics relate to bimanual kinematics over time (from the acute to chronic stages) is likely to improve models used to predict motor recovery. Exploring DKI and DTI in a longitudinal approach will be critical for future investigations. This study provides support for the involvement of anatomic structures (eg, CC) in tasks involving simultaneous use of both hands. CC may be a useful biomarker for therapeutic strategies focused on bimanual movement training and rehabilitation. ⁵¹-⁵³

Suppliers

a. Motion Capture cameras; PhaseSpace, Inc.
b. MRI 3T Prisma; Siemens Medical.
c. MRicron; Neuromaging Tools & Resources Collaboratory.
d. Matlab 2017b; MathWorks.
e. MRtrix3; MRtrix.
f. FMRIB Software Library (FSL) V6; FMRIB Analysis Group.
g. SPSS Statistics Version 23; IBM Corp.

Corresponding author

Colleen A. Hanlon, PhD, 1 Medical Center Blvd, Wake Forest School of Medicine, Winston-Salem, NC 27157. E-mail address: chanlon@wakehealth.edu.

Acknowledgments

We thank Christopher Austelle, MD, for his help with participant recruitment and data collection, as well as Blair Dellenbach for her help with behavioral assessments.

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