Compensation or Pre-stroke Advantage? An Investigation of the Relationships Between Structural and Diffusion MRI Measures in the Right Hemisphere and Language and Cognitive Abilities in Left-hemisphere Stroke Survivors

by

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ABSTRACT

Previous work indicates that structural changes in the right hemisphere following left hemisphere stroke may be related to language abilities. However, the mechanisms behind this relationship remain unclear, particularly regarding the relative contributions of gray and white matter. The present study examined how structural and diffusion measures in the right hemisphere differ between chronic left hemisphere stroke survivors and matched control subjects, and the relationships between language and cognition measures and these right hemisphere measures. T1-weighted MRI, diffusion tensor images (DTI), and a battery of cognitive tests were obtained from 27 chronic left hemisphere stroke survivors and 44 neurologically intact matched control participants. Cortical and volumetric measures of gray and white matter in regions of interest were obtained from the T1 images and compared between groups, and correlated with behavioral measures. Tract-Based Spatial Statistics and tractography methods from the DTI were examined in a similar manner. The T1 MRI-based analyses revealed that the stroke survivors did not differ from the control group in any of the gray or white matter volume measurements. The cortical thickness and mean curvature analyses identified right lateral frontal and insular ROIs exhibiting thinner and greater curvature (an indication of atrophy) in the left hemisphere stroke survivors compared to controls. The DTI-based results showed that the stroke survivors had lower fractional anisotropy and fewer reconstructed fibers in the right language ventral-stream tracts. Regarding correlations between the right hemisphere measures and behavioral performance, there were no significant results within the DTI data, and only one significant result in the gray matter analyses: faster processing speed was correlated with greater cortical thickness in the right frontal cortex in chronic left hemisphere stroke survivors. Overall, the present study provides support for the idea that the right hemisphere exhibits post-stroke

changes, particularly in right dorsal stream gray matter and the ventral stream's white matter, and that these differences are not captured by T1-imaging alone; in fact, the DTI tract-specific analyses were perhaps the most revealing. Future studies are needed, perhaps incorporating functional neuroimaging, to elucidate how these right hemisphere differences in left hemisphere stroke survivors is related to language recovery.

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CHAPTER 1

INTRODUCTION

Damage to the left hemisphere due to stroke can lead to aphasia, which may include a variety of language production and comprehension impairments. Individuals with aphasia also are known to present with impairments in cognitive performance (Murray, 2012). The dual-stream model of speech processing (Hickok & Poeppel, 2007) hypothesizes that there are dorsal and ventral neural pathways in the brain that each support language in distinct ways. The left dominant neural dorsal pathway supports speech production, articulation and integration of sensory and motor information. The dorsal stream involves left hemisphere frontal regions including inferior frontal gyrus, premotor, insula, and parietal-temporal regions. In contrast, the ventral stream supporting speech comprehension and lexical access is more bilaterally distributed. The ventral stream involves the left and right hemisphere's superior temporal gyrus, middle temporal gyrus and inferior temporal gyrus. Therefore, damage to different regions within the dual streams might result in different kinds of language impairments in left hemisphere stroke survivors. Language abilities also highly interact with other cognitive functions such as verbal working memory and processing speed. However, how cognitive resources are related to the bilateral speech pathways remains unclear.

The recruitment of intact right hemisphere regions is thought to be a potential factor supporting language performance in left hemisphere stroke survivors, in addition to residual involvement of the lesioned left hemisphere (Turkeltaub, 2019). Although the characteristics of the lesion in the left hemisphere such as location and size are crucial factors predicting post-stroke language abilities (Meier et al., 2019), there is evidence that structural and functional differences in the right hemisphere may play a role in post-stroke language recovery (e.g., Forkel et al., 2014; Meier et al., 2019; Xing et al., 2016).

However, the contributions by the right hemisphere are not clear. It could be due to either adaptation in response to the contralateral stroke, or due to pre-existing individual differences in the right hemisphere. Based on the dual-stream model of speech processing (Hickok & Poeppel, 2007), damage to the regions/pathways that support left-dominant functions such as speech production might result in greater compensation effects in the right hemisphere than damage to the regions/pathways that support more bilateral functions (i.e. speech comprehension). Specifically, the right hemisphere homologues of the left inferior frontal gyrus, insula, and temporoparietal regions supporting language production may be compensating to support speech fluency when the left dominant dorsal pathway is damaged. In contrast, the right middle temporal and superior temporal regions that support language comprehension may not change much post-stroke since the ventral language pathway is already more bilaterally organized in most individuals.

While the mechanisms of right hemisphere involvement in language recovery in left hemisphere stroke survivors remain unclear, language production outcomes at the chronic stage of stroke have been shown to be predicted by some measures of gray matter in the right hemisphere measures, at least in some specific regions: Xing et al. (2016) found that the structural gray matter volume in right temporoparietal cortex (e.g., supramarginal and superior temporal cortex) was positively associated with language production outcomes. Furthermore, stroke survivors with aphasia exhibited greater gray matter in the right temporoparietal cortex compared to controls and stroke survivors without aphasia. Xing et al. suggested that this finding might reflect structural plasticity in the intact right hemisphere in response to damage to left hemisphere language resources. Hope et al. (2017) examined the relationship between right hemisphere structural changes and language speaking and writing skills. They found that greater

language production abilities were associated with greater gray matter changes in a right middle temporal region; they also found that poorer language production performance was associated with lower gray matter measurements in right temporal and right precentral regions. Thus, gray matter volume in right temporal regions may be an important factor in language production skills after stroke.

White matter measurements in both the left and right hemispheres might also be the significant predictors of language outcomes after a left hemisphere stroke. Lee et al. (2018) investigated both gray matter and white matter volume and fractional anisotropy (FA) in stroke survivors with severe and mild aphasia. They found that stroke survivors with severe aphasia exhibited lower FA in the bilateral inferior frontal gyrus (IFG), angular & supramarginal gyrus (SMG), and superior longitudinal fasciculus (SLF) than the control group. Stroke survivors with severe aphasia exhibited lower FA in right superior longitudinal fasciculus (SLF) than stroke survivors with mild aphasia. However, they found no significant differences in gray matter or white matter volume between the stroke and control groups. Their study also showed that stroke survivors with severe aphasia exhibited reduced FA in both intact and lesioned hemisphere white matter, but they did not differ in white matter volume. This suggests that FA, a reflection of white matter integrity, might be a better potential index for the recovery of language abilities compared to white matter volume measures. However, Meier et al. (2019) found that the relationships between language production abilities and major left hemisphere white matter tracts (i.e., arcuate fasciculus, inferior frontal-occipital fasciculus, inferior longitudinal fasciculus, uncinate fasciculus) disappeared after taking lesion volume into consideration. Furthermore, they found no significant relationship between right white matter FA values and post-stroke language abilities. This study suggests that lesion volume and gray matter in the left hemisphere are sufficient predictors of language

performance in left hemisphere stroke survivors. Ivanova et al. (2016) investigated the relationships between seven major bilateral white matter pathways and language processing in stroke survivors with aphasia. Not surprisingly, they found several white matter tracts in the left hemisphere whose integrity were positively correlated with greater language performance. However, they found no significant relationships between white matter tracts in the right hemisphere and language processes. But, other studies do implicate the right hemisphere's white matter measurements in language abilities post-stroke: Pani et al. (2016) found that greater speech fluency was associated with higher FA in right white matter regions (i.e., middle temporal gyrus, precentral gyrus, posterior inferior frontal gyrus and corpus callosum) that are homologous to left hemisphere regions known for supporting language production. Overall, these somewhat conflicting results imply that white matter properties may predict language outcomes, but the role of right hemisphere white matter in post-stroke language recovery remains unclear.

Many previous studies have focused on the right arcuate fasciculus (AF), which is a homologous pathway that connects posterior inferior frontal regions (in the left hemisphere, classical Broca's area) and posterior superior temporal regions (in the left hemisphere, Wernicke's area), and was long assumed to be the major pathway in the left hemisphere supporting language processing. Forkel et al. (2014) found that the volume in the right arcuate fasciculus (AF) at the acute stage of stroke predicted language recovery at the chronic stage. Their findings suggested that the pre-existing individual differences in right arcuate fasciculus (AF) volume might be important to support the later functional compensation needed for maintaining language abilities post-stroke. Schlaug et al. (2009) found an increased number of fibers in right arcuate fasciculus (AF) after 75–80 daily speech therapy. However, the changes in the number of fibers in right arcuate fasciculus (AF) did not relate to the language outcomes. Furthermore, Geva

et al. (2015) found no differences in FA values between stroke survivors and control subjects using tract-based spatial statistics (TBSS) and no evidence for mean FA or tract volume of the right arcuate fasciculus (AF) predicting language abilities in chronic stroke survivors. Interestingly, a recent diffusion tensor imaging (DTI) study of both acute and chronic stroke (Keser et al., 2020) found a deleterious effect of right white matter pathway integrity on language production recovery after left hemisphere stroke. Their results showed that increased FA in the right arcuate fasciculus (AF), but not in the right frontal aslant tract (FAT), was associated with poorer naming recovery. In summary, there are inconsistent findings about the right arcuate fasciculus (AF)'s contributions to language recovery after left hemisphere stroke.

Other major white matter tracts might be potential factors in language recovery after stroke (Agosta et al., 2013; Dick et al., 2014; Tremblay & Dick, 2016). The more anterior and superior white matter tracts such as the uncinate fasciculus (UF), superior longitudinal fasciculus (SLF), anterior portions of arcuate fasciculus (AF) and inferior frontal-occipital fasciculus (IFOF) might also support the dorsal neural pathway of language production. The more posterior and inferior white matter tracts such as the inferior longitudinal fasciculus (ILF) and the more posterior portions of arcuate fasciculus (AF) and inferior frontal-occipital fasciculus (IFOF) might support the ventral neural pathway of language comprehension (Agosta et al., 2013; Rizio & Diaz, 2016). However, the contributions of these white matter tracts to language recovery after stroke, particularly in the right hemisphere, have not been fully studied.

To summarize the state of the literature described above, there is a mix of findings in previous studies regarding the role of the non-lesioned right hemisphere in language abilities in stroke survivors with aphasia. There are some studies that found differences in right gray matter and white matter measures between stroke survivors and

normal control subjects (Hope et al., 2017; Pani et al., 2016; Schlaug et al., 2009; Xing et al., 2016). There is one study that found that poorer language production recovery was related to greater integrity of right arcuate fasciculus (AF) (Keser et al., 2020). Some other studies suggested that there are pre-existing differences in structural measures of the right hemisphere that may be advantageous to language recovery (Forkel et al., 2014; Pani et al., 2016), while other studies showed that right hemisphere structural measures are not significant predictors of post-stroke language abilities (Geva et al., 2015; Ivanova et al., 2016; Meier et al., 2019). Furthermore, there is debate as to whether the structural changes in the right hemisphere result from pre-existing individual differences, or from adaptation after stroke, perhaps due to the recruitment of additional or different cognitive resources. Therefore, single subject approaches (Crawford & Garthwaite, 2007) may be needed to shed light on the individual differences in right hemisphere measures in stroke survivors that relate to language performance.

The present study aims to investigate the ability of right hemisphere structural and diffusion measures to predict language and related cognitive abilities in chronic left hemisphere stroke survivors. Therefore, in the present study, we examined T1-weighted images and DTI images of twenty-seven left hemisphere chronic stroke survivors and forty-four matched control subjects. Behavioral cognitive and language performance measures were obtained through standard assessments including the Wechsler Adult Intelligence Scale-IV (WAIS-IV) and Boston Diagnostic Aphasia Exam (BDAE). There are four main hypotheses:

1. In the stroke survivors, speech fluency will be correlated with larger or more intact measures of the right hemisphere homologues of the left-lateralized dorsal stream. In particular, gray matter measures, such as volume, thickness, and curvature, in the right fronto-parietal and insula regions, and white matter

measures, such as volume and FA value in the right arcuate fasciculus (AF), frontal aslant tract (FAT), and superior longitudinal fasciculus (SLF) will be correlated with greater speech fluency.

2. In the stroke survivors, better auditory comprehension will be associated with greater gray and white matter measures in the right temporoparietal regions and their supporting white matter tracts (i.e. the right uncinate fasciculus (UF), inferior and middle longitudinal fasciculus (ILF and MdLF), and inferior fronto-occipital fasciculus (IFOF)) that constitute the right hemisphere portions of the ventral speech processing stream.
3. In the stroke survivors, cognitive performance on measures such as working memory and processing speed will be correlated with gray and white matter measurements of right fronto-parietal regions known to support these cognitive processes, and in some studies to be correlated with post-stroke language recovery.
4. If the stroke survivors do in fact exhibit correlations between right hemisphere brain measures and cognitive and language performance, then I predict that this is due to post-stroke compensation, not pre-stroke individual differences. Thus, I expect that the same brain measures that predict behavioral performance will also exhibit a significant difference between the stroke survivor and control groups. If my hypothesis is incorrect, and these correlations are due to pre-existing structural differences within the stroke group, then there will be no between-group differences on these brain measures.

CHAPTER 2

METHODS

2.1. Participants

2.1.1. Stroke group

Twenty-seven left hemisphere stroke survivors were included with the following inclusion criteria: native English speakers, at least 6 months post-stroke, right-handed pre-stroke, and no history of neurological or psychological disease other than the stroke. See Table 1 for characteristics of the group.

2.1.2. Healthy control subjects

Forty-four neurologically intact control subjects that were matched to the stroke survivors on age ($p > .05$) and gender ($p > .05$) included in the study (Table 1). The stroke survivors had lower education level than the control subjects ($p < .01$).

Table 1

Demographic data of stroke survivors and health control subjects

Demographic Variables	Stroke Survivors ($N = 27$)	Control Subjects ($N = 44$)
Age (years)		
M	56.7	56.3
SD	13.6	18.6
Range	28-80	25-80
Gender, *n*		
Female	14	28
Male	13	16
Education Level (years)		
M	15.5	17.5
SD	2.7	3.0
Range	12-24	12-24
NA, *n*	0	6

2.2. Cognitive Behavioral Measures

Stroke survivors were given the Boston Diagnostic Aphasia Exam (BDAE), which includes subtests of auditory single word comprehension and a speech sample via a picture description task. Cognitive functions were measured by the Wechsler Adult Intelligence Scale-IV (WAIS-IV)'s Working Memory Index, which includes subtests of Arithmetic and Digit Span; and the WAIS-IV's Processing Speed Index, which includes subtests of Coding and Symbol Search.

2.3. MRI Data Acquisition

MRI data were acquired using a 3.0 T Philips Ingenia scanner located at The Keller Center for Imaging Innovation at Barrow Neurological Institute. For N=10 stroke survivors, a high-resolution structural T1-weighted MPRAGE MRI sequence of the whole brain was acquired with following parameters: Repetition Time (TR) = 8.1 ms; Echo Time (TE) = 3.70 ms; flip angle = 8°; Field of View (FOV) = 256×256mm^2, voxel size = 1×1×1 mm; 208 coronal slices, slice thickness = 1 mm. For each of the remaining subjects (N =26 stroke survivors, and all control subjects), a T1-weighted MPRAGE MRI sequence was acquired with following parameters: Repetition Time (TR) = 6.74 ms; Echo Time (TE) = 3.10 ms; flip angle = 9°; FOV = 256×256 mm^2; voxel size = 1.2×1.1×1.1 mm; 170 sagittal slices, slice thickness = 1.2 mm.

Diffusion MRI data was collected for N = 27 stroke survivors and N = 24 control subjects with the following parameters: TR = 7.06 ms; TE = 118.85 ms; flip angle = 90°; FOV = 192×192 mm^2; voxel size = 1.4×1.4×3.0 mm; 48 coronal slices, slice thickness = 3.0 mm; 33 diffusion-weighted directions; b = 2500 s/mm^2; 1 non-diffusion-weighted reference image.

2.4. Image Data Preprocessing and Processing

2.4.1. T1-weighted data processing

T1-weighted images were converted from DICOMS to NIfTI format using dcm2niiX in MRIcron. Cortical reconstruction and volumetric segmentation on the raw T1-weighted images were performed using Freesurfer 6.0.0 software (http://surfer.nmr.mgh.harvard.edu/, Dale et al., 1999) with automated procedures. One subject (AZ1045) was processed using Freesurfer 7.1.1 version. T1-weighted images were first corrected for magnetic field inhomogeneities and normalized. Automated Talairach transformation was applied. After the intensity normalization, the non-brain tissues were removed. The normalized and skull-stripped images were then segmented into gray matter structures and the subcortical white matter. The automated region of interest labels were used (Desikan et al., 2006). For the present study, we focused on sixteen right hemisphere cortical regions of interest (ROIs) related to language production and comprehension were included (see Table 2). For each ROI in each subject, estimations on gray matter volume, cortical thickness, mean curvature, white matter volume, and white matter intensity were extracted using default Freesurfer procedures. Specifically, cortical thickness (mm) is defined as the shortest distance between the white matter and pial surfaces at each vertex in the ROI (Fischl & Dale, 2000). Gray matter (mm^3) volume was estimated by the cortical thickness times the average surface area of the triangles that are adjacent to the vertex. Mean curvature (mm^{-1}) was measured by average of the two principal curvatures which are the maximum and minimum of the normal curvature at a given point on a cortical surface. Estimated total intracranial volume (eTIV, mm^3) for each subject was also obtained. The volume measures were normalized by eTIV for each subject since the volume measures of brain structures are correlated to the head

size. In contrast, thickness and curvature measures of brain structures are not known to be affected by head size.

2.4.2. Lesion identification and size calculations

The lesion maps were processed on the T1-weighted images in MRIcron. The lesion maps were smoothed with a 3 mm full-width half maximum Gaussian kernel to remove jagged edges associated with manual drawing. The lesion maps were then binarized with a 50% probability threshold. The lesion size of each stroke survivor was then calculated by the number of non-zero voxels in each lesion map.

Table 2

Right hemisphere ROIs in Freesurfer used in the present study.

ROI name	Stream-related
Caudal Middle Frontal	Dorsal
Inferior Parietal	Dorsal, Ventral
Insula	Dorsal
Medial Orbitofrontal	Dorsal
Middle Temporal	Ventral
Pars Opercularis	Dorsal
Pars Orbitalis	Dorsal
Pars Triangularis	Dorsal
Precuneus	Dorsal, Ventral
Rostral Anterior Cingulate	Dorsal
Rostral Middle Frontal	Dorsal
Superior Frontal	Dorsal
Superior Parietal	Dorsal
Superior Temporal	Ventral
Supramarginal	Dorsal, Ventral
Transverse Temporal	Ventral

2.4.3. Diffusion tensor images (DTI) data preprocessing

DTI data were converted from DICOM images to NIfTI format using dcm2niiX in MRIcron. Preprocessing of the DTI data for each subject was performed using FMRIB's Diffusion Tool (FDT) 5.0, part of FSL 6.0.4 software (Smith et al., 2004). Following the

eddy correction using eddy_correct, the non-brain tissues were removed using the Brain Extraction Tool v2.1 (BET2) (Smith, 2002) with a threshold set to 0.2. FA maps and mean diffusivity (MD) maps were obtained after reconstructing the diffusion tensors at each voxel using DTIFIT. FA is a diffusion measure for the white matter integrity which reflects directionality of the fibers in white matter with higher values usually associated with better behavioral performance. MD is a diffusion measure that reflects water diffusion in the white matter with higher values indicating damage to that region.

2.4.4. Tract-Based Spatial Statistics (TBSS) processing

To examine the diffusion MRI data, voxel-wise statistical analysis for whole brain FA and MD values were performed using TBSS ("Tract-Based Spatial Statistics," 2006), part of FSL. First, the FA images were preprocessed to remove the artifacts from diffusion tensor fitting (i.e., DTIFIT in the DTI preprocessing). Second, the FA images were aligned to a standard space, the FMRIB58_FA template, using nonlinear registration tool FNIRT (Andersson et al., 2007a, 2007b), which used a b-spline representation of the registration warp field (Rueckert et al., 1999). Third, the mean FA image from all the subjects was generated and skeletonized. Fourth, each subject's FA data was then projected onto the mean FA skeletonized image with a threshold set to 0.2. The MD images were processed using tbss_non_FA scripts, which applied the original nonlinear registration to the MD images and projected the registered images onto the original mean FA skeleton. The right hemisphere of the registered and skeletonized FA and MD images were then used for further statistical analyses.

2.4.5. Tractography

Probabilistic fiber tracking was performed to reconstruct the white matter tracts for each subject using FMRIB's Diffusion Toolbox (FDT), part of FSL. First, the estimations of fiber orientations in each voxel were determined using BEDPOSTX (Behrens et al., 2003, 2007). The tracts were then reconstructed for each subject using PROBTRACKX2 (Behrens et al., 2003, 2007). Nine tracts of interests related to language processing in the right hemisphere were included (see Table 3). Specifically, this study included five tracts related to the dorsal stream: arcuate fasciculus (AF), frontal aslant tract (FAT), three branches of superior longitudinal fasciculus (SLF1, 2, 3) and four tracts related to the ventral stream: uncinate fasciculus (UF), inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), middle longitudinal fasciculus (MdLF). The seed masks, target masks, termination masks, and stop masks in MNI space were extracted using XTRACT (Warrington et al., 2020). A set of default criteria for constraining the fiber tracking were used: number of samples: 5000, curvature threshold: 0.2, loopcheck, maximum number of steps: 2000, step length: 0.5 mm, subsidiary fiber volume fraction threshold: 0.01. Additionally, a logical OR-function was added for the three branches of superior longitudinal fasciculus (SLF1, 2, 3) so that the streamlines that pass through one or both target masks would be counted in each given tract. The valid streamlines refer to the samples generated from the seed mask that reach the target mask and were not rejected by the exclusion mask. The estimated number of reconstructed fibers were estimated by the number of the streamlines after each tract' reconstruction. Then, after fiber tracking, to obtain the ROI mask for each tract for each subject, the density path map (fdt_path.nii.gz) in standard space was binarized at a threshold value of 2%. The tract masks were then applied to the registered FA and MD maps to calculate the mean scalar indices for each subject for each tract.

Tract volume (mm^3) was computed by the number of nonzero voxels in each tract multiplied by the voxel size. In addition, both the measures of volume and number of streamlines were corrected by the estimated total intracranial volume (eTIV, mm^3) for each subject since these brain structures are related to the head size. In contrast, the diffusion metrics such as mean FA and mean MD should not be affected by head size.

Table 3

Right hemisphere ROIs in FSL

Tract Name	Stream-related	Connections
Arcuate Fasciculus	Dorsal	Inferior PMC to STG
Frontal Aslant Tract	Dorsal	IFG to SFG
Superior Longitudinal Fasciculus I	Dorsal	IFG to superior parietal
Superior Longitudinal Fasciculus II	Dorsal	MFG to angular gyrus
Superior Longitudinal Fasciculus III	Dorsal	posterior IFG to SMG
Uncinate Fasciculus	Ventral	Frontal to anterior temporal
Inferior Longitudinal Fasciculus	Ventral	MTG, ITG – occipital lobe
Middle Longitudinal Fasciculus	Ventral	anterior STG - parietal - occipital lobe
Inferior Fronto-Occipital Fasciculus	Ventral	Frontal – temporal - occipital

Note. IFG: inferior frontal gyrus, MFG: middle frontal gyrus,SFG: superior frontal gyrus,SMG: supramarginal gyrus,PMC: premotor cortex, STG: superior temporal gyrus, MTG: middle temporal gyrus.

2.5. Statistical Analysis

Two main branches of analyses, one for the structural MRI measures, and one for the diffusion MRI measures, were included in this study. For the structural T1-weighted MRI data set, three types of statistical analyses were performed: ROI-based between-group analyses, ROI-based correlation analyses, and ROI-based single-subject analyses. For the diffusion DTI data set, four types of statistical analyses were performed: voxel-

wise between-group analyses, ROI-based between-group analyses, voxel-wise correlation analyses, and ROI-based correlation analyses. Each is described in detail below.

2.5.1. ROI-based between-group analysis: Group comparisons of the gray and white matter structural measures from T1 images.

To determine whether there is a compensation effect or pre-existing effect on the right hemisphere after stroke, independent t-tests of brain measures (i.e., gray matter volume, cortical thickness, mean curvature, white matter volume, and white matter intensity) for each ROI between the group of stroke survivors and the group of normal control subjects were performed. These analyses were conducted in R (R Core Team, 2017). The Benjamini-Hochberg false discovery rate correction was used to adjust p-values for multiple comparisons (Benjamini & Hochberg, 1995).

2.5.2. ROI-based within-group correlation analysis: Partial correlation analysis between structural measures from T1 images and behavioral measures within stroke survivors.

To determine the relationships between the structural brain measures for each right hemisphere ROI and performance on the cognitive and language measures of interest (i.e., working memory, processing speed, auditory single word comprehension, and picture description task), partial Pearson correlation analyses between brain measures for each ROI and cognitive behavioral measures in stroke survivors, controlling for their age and corrected lesion size, were performed. The partial Pearson correlation analyses were calculated using the ppcor package (Kim, 2015) in R. The Benjamini-Hochberg false discovery rate correction was used to adjust p-values for multiple comparisons.

2.5.3. ROI-based individual-level analysis: Bayesian single-subject analysis for each stroke survivor in relation to the control group.

To identify which (if any) of the stroke survivors exhibit significantly different structural compensation in right hemisphere structural measures than the control group, Bayesian single-subject analyses were performed (Crawford & Garthwaite, 2007; Dubois, 2008). For each ROI for each stroke survivor, each of the brain measures were compared to the control group. That is, in a given ROI, the proportion of the control sample that has a value of brain measure that is significantly greater or less than a stroke survivor's value was identified. If a stroke survivor has a significantly greater measurement in an ROI than the control group, this may suggest that post-stroke compensation may be a possibility. Bayesian single-subject analyses were performed in R using the singlecase package (Dubois, 2008).

2.5.4. Voxel-wise between-group analysis: TBSS (Tract-Based Spatial Statistics) of group comparisons of the white matter diffusion measures.

To determine the locations of diffusivity differences between the stroke and control groups in the right hemisphere, voxel-wise comparisons of FA and MD in the right hemisphere were performed using randomise in FSL (Winkler et al., 2014) with 5000 permutations, demeaning the data, and with age as a nuisance covariate. TBSS results were adjusted for the family-wise error (FWE) rate using threshold-free cluster enhancement (TFCE) in randomise.

2.5.5. Voxel-wise within-group analysis: TBSS correlation analysis between the white matter diffusion measures and behavioral measures within stroke survivors.

To determine the relationships between the spatial diffusion brain measures and the behavioral performance, a linear correlation analysis between the FA and MD images and behavioral measures of interest (i.e., working memory, processing speed, auditory single word comprehension, and picture description task), for stroke survivors were performed with 5000 permutations, demeaning the data, and with age and corrected lesion size as nuisance covariates. TBSS results were adjusted for the FWE rate using TFCE in randomise.

2.5.6. ROI-based between-group analysis: Group comparisons of the tracts' diffusion and structural measures from DTI images.

In addition to voxel-wise analyses for the diffusion data, to further characterize the right white matter tracts, a ROI-based between-group analysis also was conducted. Independent t-tests of mean scalar indices (for FA and MD), corrected tract volume, and corrected number of the reconstructed streamlines for each ROI between the stroke survivors and control subjects were performed. These analyses were conducted in R. The Benjamini-Hochberg false discovery rate correction was used to adjust p-values for multiple comparisons.

2.5.7. ROI-based within-group correlation analysis: Partial correlation analysis between tracts diffusion and structural measures from DTI images and behavioral measures within stroke survivors.

To determine the relationships between the measures for each right hemisphere tract and behavioral performance on our measures of interest (i.e., working memory, processing speed, auditory single word comprehension, and picture description task), partial Pearson correlation analyses within the stroke survivors, controlling for age and corrected lesion size, were performed. The partial Pearson correlation analyses were calculated using the ppcor package in R. The Benjamini-Hochberg false discovery rate correction was used to adjust p-values for multiple comparisons.

CHAPTER 3

RESULTS

3.1. T1-weighted images

3.1.1. T1-weighted images: Between-group differences.

The comparison between stroke survivors and control subjects revealed no significant difference on the corrected gray matter volume or corrected white matter volume in the 16 ROIs ($p > .05$ for all ROIs). See Table 4 and Figures 1A and 1D. However, the cortical thickness comparison showed that the stroke survivors had significantly thinner cortical thickness in the right insula cortex (adjusted $p = .03$, $t = -2.83$), precuneus cortex (adjusted $p = .02$, $t = -3.11$), rostral anterior cingulate (adjusted $p = .001$, $t = -4.10$), and superior frontal cortex (adjusted $p = .001$, $t = -4.02$), compared to the control subjects. See Table 4 and Figure 1B. The curvature comparison showed that the stroke survivors had significantly greater mean curvature in the insula cortex (adjusted $p = .004$, $t = 3.93$), than the control subjects (see Table 4 and Figure 1C). The white matter intensity comparison showed that the stroke survivors had significantly lower white matter intensity in the caudal middle frontal (adjusted $p = .045$, $t = -2.81$), pars opercularis (adjusted $p = .03$, $t = -3.07$), and superior frontal ROIs (adjusted $p = .03$, $t = -3.30$). See Table 4 and Figure 1E.

Table 4

Cortical measures in the right hemisphere from T1-weighted images.

ROI	GM Volume [x 10^{-3}]		GM Thickness (mm)		Mean Curvature (mm^{-1})	
	Stroke	Control	Stroke	Control	Stroke	Control
Caudal Middle Frontal	3.54	3.47	2.37	2.44	0.12	0.11
Inferior Parietal	8.73	8.67	2.34	2.39	0.13	0.13
Insula	4.59	4.46	2.89*	3.05	0.12*	0.12
Medial Orbitofrontal	3.38	3.26	2.36	2.44	0.13	0.13
Middle Temporal	7.36	6.80	2.78	2.73	0.13	0.13
Pars Opercularis	2.37	2.33	2.39	2.50	0.12	0.12
Pars Orbitalis	1.80	1.62	2.55	2.56	0.15	0.15
Pars Triangularis	2.49	2.50	2.31	2.34	0.13	0.13
Precuneus	6.23	6.04	2.27*	2.39	0.13	0.13
Rostral Anterior Cingulate	1.17	1.26	2.74*	2.97	0.13	0.13
Rostral Middle Frontal	9.11	9.09	2.23	2.28	0.14	0.14
Superior Frontal	12.84	13.04	2.52*	2.70	0.13	0.12
Superior Parietal	7.86	7.52	2.04	2.11	0.12	0.12
Superior Temporal	7.16	6.90	2.66	2.70	0.11	0.11
Supramarginal	6.31	5.80	2.39	2.46	0.13	0.13
Transverse Temporal	0.55	0.55	2.28	2.34	0.11	0.11

Note. GM: gray matter.
*Corrected for multiple comparisons p value < .05. The comparison on the cortical measure in a given ROI between the stroke survivors and the control subjects.

Table 4 (cont.)

White matter measures in the right hemisphere from T1-weighted images.

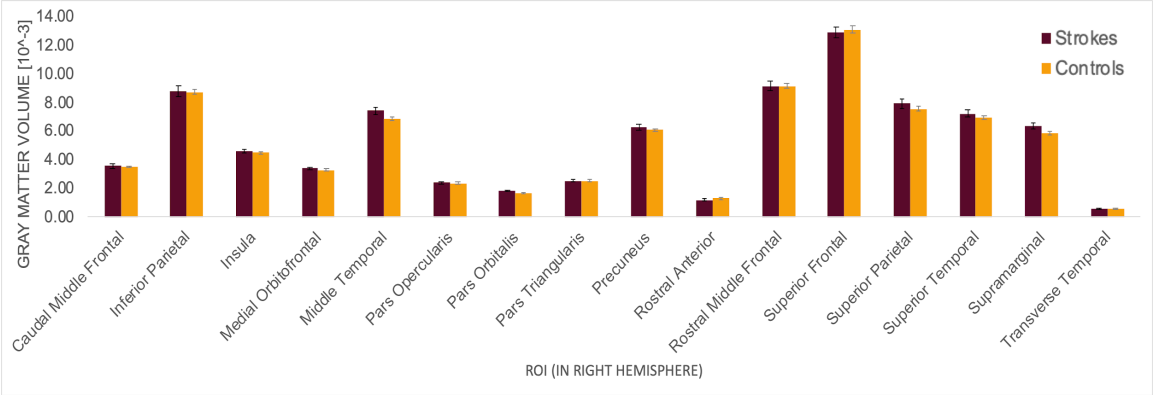
ROI	WM Volume [x 10^{-3}]		WM Intensity	
	Stroke	Control	Stroke	Control
Caudal Middle Frontal	3.93	3.88	95.5*	96.9
Inferior Parietal	7.41	7.34	95.3	96.6
Insula	6.57	6.39	95.6	95.7
Medial Orbitofrontal	2.58	2.55	97.8	98.8
Middle Temporal	4.15	3.87	89.2	90.7
Pars Opercularis	2.12	2.11	95.6*	97.5
Pars Orbitalis	0.88	0.84	88.9	90.5
Pars Triangularis	2.17	2.17	94.2	95.9
Precuneus	6.53	6.39	99.9	99.9
Rostral Anterior Cingulate	1.24	1.19	103.6	103.1
Rostral Middle Frontal	8.43	8.48	95.7	96.6
Superior Frontal	11.79	11.59	93.7*	94.9
Superior Parietal	7.97	7.84	96.5	96.6
Superior Temporal	4.58	4.41	91.8	93.1
Supramarginal	5.95	5.51	97.5	99.0
Transverse Temporal	0.43	0.42	97.5	97.9

Note. WM: white matter.

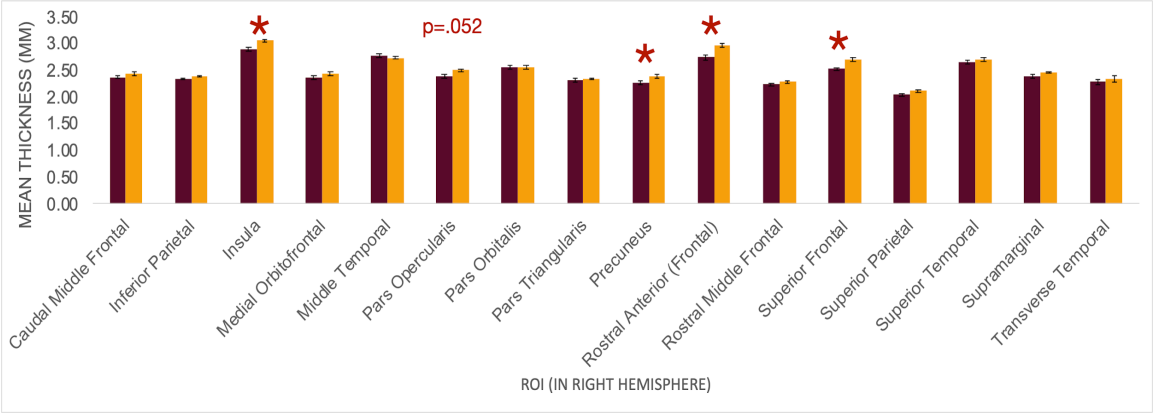
Figure 1

Group comparisons in the measures from T1-weighted images between stroke survivors and control subjects.

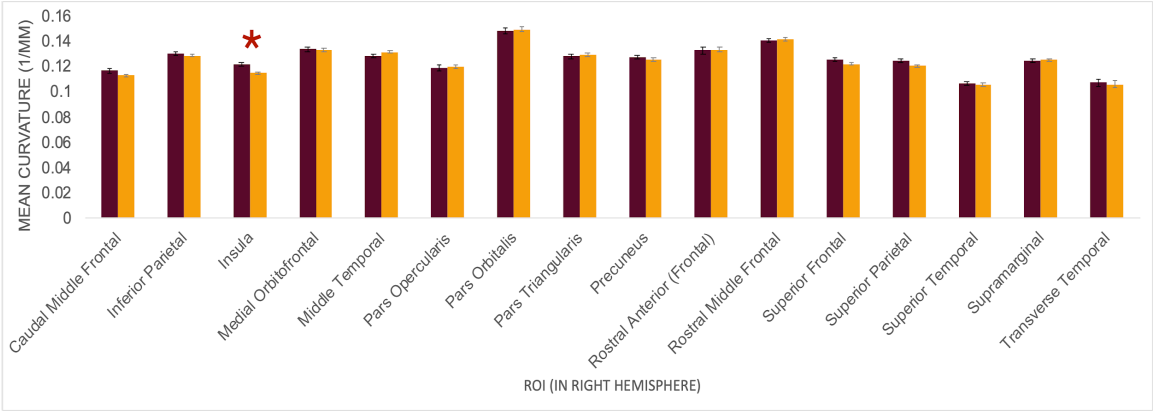
A. Gray matter volume [x 10^{-3}].



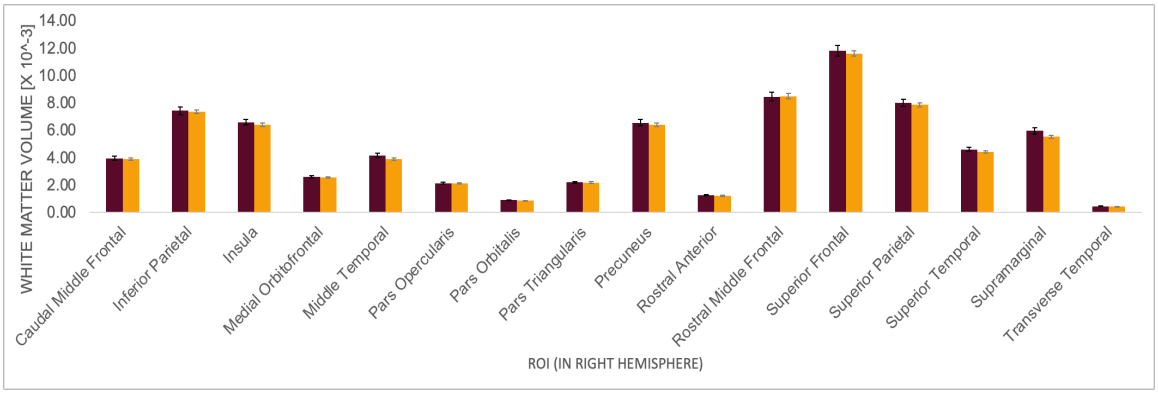
B. Cortical thickness (mm).



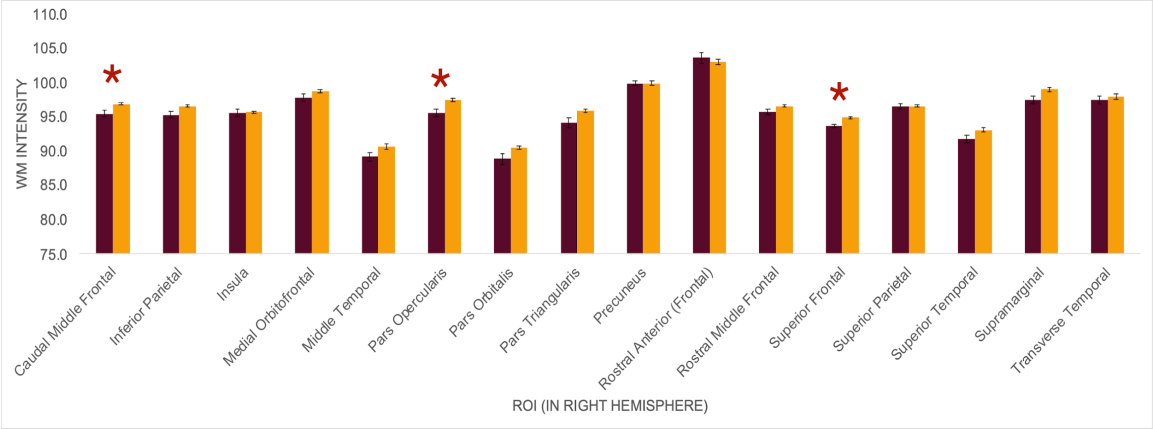
C. Mean cortical curvature (mm^{-1}).



D. White matter volume [x 10^{-3}].



E. White matter intensity.



3.1.2. T1-weighted images: Within-group correlation analysis.

The partial Pearson correlation analyses showed that greater cortical thickness in the right caudal middle (r = .66, p = .02) and superior frontal (r = .66, p = .02) ROIs were significantly correlated with better (i.e., faster) processing speed while controlling for effects of age and corrected lesion size. There is no significant correlation between the other structural measures and the behavioral measures. See Table 5.

Table 5

Correlation coefficients between brain measures in the right hemisphere from T1-weighted images and behavioral measures.

A. Gray matter volume.

ROI	WMI	PSI	ACT	PDT
Caudal Middle Frontal	0.29	0.13	0.28	0.24
Inferior Parietal	0.18	0.35	0.38	0.37
Insula	0.39	0.10	0.26	0.16
Medial Orbitofrontal	0.08	-0.07	-0.04	0.29
Middle Temporal	0.27	0.20	0.33	0.27
Pars Opercularis	0.11	0.05	0.24	0.39
Pars Orbitalis	0.01	0.17	0.19	0.10
Pars Triangularis	0.26	0.35	0.16	0.34
Precuneus	0.06	0.16	0.37	0.24
Rostral Anterior Cingulate	0.01	0.22	0.12	0.37
Rostral Middle Frontal	0.10	0.24	0.29	0.17
Superior Frontal	0.22	0.20	0.37	0.35
Superior Parietal	0.07	0.32	0.31	0.33
Superior Temporal	-0.02	0.05	0.17	0.31
Supramarginal	0.06	0.07	0.15	0.34
Transverse Temporal	0.18	-0.02	0.20	0.34

Note. WMI: working memory index; PSI: processing speed index; ACT: Auditory comprehension task; PDT: picture description task.

B. Cortical thickness.

ROI	WMI	PSI	ACT	PDT
Caudal Middle Frontal	0.25	0.66*	0.32	0.46
Inferior Parietal	0.07	0.43	0.10	0.36
Insula	0.07	0.15	0.06	0.37
Medial Orbitofrontal	0.05	0.21	-0.06	-0.07
Middle Temporal	-0.09	0.05	-0.11	-0.05
Pars Opercularis	-0.10	0.09	-0.03	0.37
Pars Orbitalis	0.15	0.28	0.33	0.11
Pars Triangularis	0.01	0.57	0.06	0.35
Precuneus	-0.05	0.35	0.38	0.09
Rostral Anterior Cingulate	-0.04	0.12	-0.03	0.09
Rostral Middle Frontal	-0.07	0.53	0.14	0.32
Superior Frontal	0.20	0.66*	0.31	0.41
Superior Parietal	0.08	0.41	0.34	0.29
Superior Temporal	0.00	-0.10	0.19	0.30
Supramarginal	0.03	0.30	0.23	0.27
Transverse Temporal	0.36	0.17	0.26	0.04

*Corrected for multiple comparisons p value < .05. The partial correlation coefficients between thickness and processing speed index were controlling for age and corrected lesion size.

C. Cortical mean curvature.

ROI	WMI	PSI	ACT	PDT
Caudal Middle Frontal	0.16	0.05	-0.07	-0.55
Inferior Parietal	0.06	-0.31	0.17	-0.33
Insula	0.26	0.08	-0.11	0.37
Medial Orbitofrontal	-0.09	0.06	0.10	-0.25
Middle Temporal	0.27	-0.13	0.23	0.05
Pars Opercularis	-0.01	-0.12	0.08	0.00
Pars Orbitalis	0.12	0.33	0.04	-0.23
Pars Triangularis	0.00	-0.01	-0.10	-0.09
Precuneus	0.39	0.04	0.06	0.06
Rostral Anterior Cingulate	-0.03	0.21	0.08	0.11
Rostral Middle Frontal	0.19	-0.01	0.07	0.05
Superior Frontal	0.16	0.00	-0.21	-0.16
Superior Parietal	0.14	0.20	0.14	0.01
Superior Temporal	-0.05	-0.17	-0.08	0.01
Supramarginal	-0.06	-0.29	-0.13	-0.34
Transverse Temporal	-0.11	-0.07	-0.30	0.12

D. White matter volume.

ROI	WMI	PSI	ACT	PDT
Caudal Middle Frontal	0.12	-0.05	0.00	0.16
Inferior Parietal	0.19	0.24	0.25	0.37
Insula	0.18	-0.03	0.23	0.15
Medial Orbitofrontal	-0.13	-0.11	-0.02	0.35
Middle Temporal	0.24	0.14	0.30	0.19
Pars Opercularis	0.14	0.01	0.16	0.32
Pars Orbitalis	0.21	0.17	0.13	0.28
Pars Triangularis	0.26	0.07	0.05	0.23
Precuneus	0.06	0.04	0.22	0.22
Rostral Anterior Cingulate	0.16	-0.20	-0.16	0.05
Rostral Middle Frontal	0.20	0.13	0.21	0.18
Superior Frontal	0.04	-0.01	0.06	0.29
Superior Parietal	0.15	0.24	0.25	0.31
Superior Temporal	-0.03	0.07	-0.11	0.26
Supramarginal	-0.03	-0.04	-0.09	0.22
Transverse Temporal	0.03	0.15	-0.41	-0.02

E. White matter intensity.

ROI	WMI	PSI	ACT	PDT
Caudal Middle Frontal	-0.02	0.20	-0.08	0.44
Inferior Parietal	0.00	0.10	-0.14	0.47
Insula	0.13	0.09	-0.02	0.05
Medial Orbitofrontal	-0.23	0.15	-0.02	0.08
Middle Temporal	0.19	0.30	0.05	0.29
Pars Opercularis	0.20	0.22	0.01	0.28
Pars Orbitalis	0.15	0.13	-0.34	0.25
Pars Triangularis	0.11	0.11	-0.22	0.33
Precuneus	-0.31	-0.22	-0.26	-0.33
Rostral Anterior Cingulate	-0.07	-0.40	0.06	-0.19
Rostral Middle Frontal	0.21	0.21	-0.06	0.54
Superior Frontal	-0.16	-0.03	0.18	0.48
Superior Parietal	0.02	0.06	-0.18	0.34
Superior Temporal	0.18	0.32	0.02	0.44
Supramarginal	-0.03	0.19	0.06	0.41
Transverse Temporal	0.14	0.32	0.02	0.00

3.1.3. T1-weighted images: Single subject analyses.

The numbers of stroke survivors with greater gray matter volume, thickness, curvature, white matter volume, and intensity than the 95% of controls in each of the right hemisphere ROIs are indicated in Table 6.

Among the 16 ROIs, four ROIs had at least six stroke survivors that had greater values than the 95% of the matched control group on at least one of the measures. There are eight stroke survivors that had greater gray matter volume, four stroke survivors had greater thickness, six stroke survivors had greater white matter volume, and two stroke survivors had lower curvature in the right middle temporal cortex than 95% of the matched control subjects. There are six stroke survivors that had greater gray matter volume, four stroke survivors had greater white matter volume, and two stroke survivors had lower curvature in the right caudal middle frontal cortex than 95% of the matched control subjects. There are four stroke survivors that had greater gray matter volume, six stroke survivors had greater white matter volume and one stroke survivor had lower

curvature in the right superior frontal cortex than 95% of the matched control subjects. Lastly, there are six stroke survivors that had greater gray matter volume, six stroke survivors had greater white matter volume and one stroke survivor had greater curvature in the right supramarginal cortex than 95% of the matched control subjects.

Table 6

Summary of the number of stroke survivors have greater values than 95% of matched control subjects from Bayesian single subject analysis. (N = 27)

ROI	GM Measures			WM Measures	
	Volume	Thickness	Curvature	Volume	Intensity
Caudal Middle Frontal	6*	0	2	4	3
Inferior Parietal	4	0	0	4	2
Insula	2	0	0	3	4
Medial Orbitofrontal	4	0	0	3	1
Middle Temporal	8*	4	2	6*	1
Pars Opercularis	4	1	2	4	1
Pars Orbitalis	5	0	1	4	4
Pars Triangularis	4	1	2	1	3
Precuneus	5	0	0	3	1
Rostral Anterior Cingulate	0	0	4	3	4
Rostral Middle Frontal	4	0	1	3	2
Superior Frontal	4	0	1	6*	0
Superior Parietal	5	0	1	2	1
Superior Temporal	4	1	0	4	0
Supramarginal	6*	0	1	6*	2
Transverse Temporal	1	0	2	3	1

Note. GM: gray matter; WM: white matter.
*At least six stroke survivors had greater values than the 95% of the matched control group.

3.2. DTI analyses

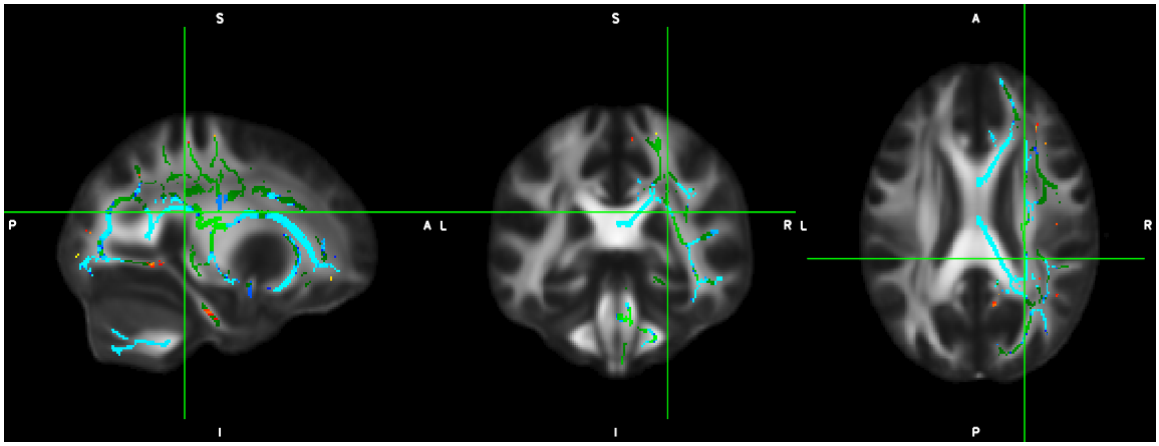
3.2.1. DTI TBSS: Between-group differences.

The control subjects had significantly higher FA in the right ventral stream's white matter tracts than the stroke survivors, with age as a nuisance covariate ($p < .05$, TFCE corrected). See Figure 2. Although the stroke survivors had numerically higher FA

in the right dorsal stream than the control subjects ($p > .05$, TFCE corrected), that finding was not significant. No significant difference in MD in the right white matter tracts between the stroke survivors and the controls were presented.

Figure 2

TBSS results in the right hemisphere that control subjects had higher FA than stroke survivors.



Note. Green lines represent the skeletonized tracts in the right hemisphere. Yellow/red lines represent the differences between stroke survivors and control subjects. Blue lines represent the significant differences between groups.

3.2.2. DTI TBSS: Within-group correlation analysis.

There were no significant correlations found between any of the diffusion metrics (i.e., FA and MD) in the right white matter tracts and the behavioral measures (i.e., WMI, PSI, accuracy in the auditory single word comprehension, and total number of words generated in the picture description task) within the stroke survivors with age and corrected lesion size as nuisance covariates.

3.2.3. DTI Tractography: Between-group differences.

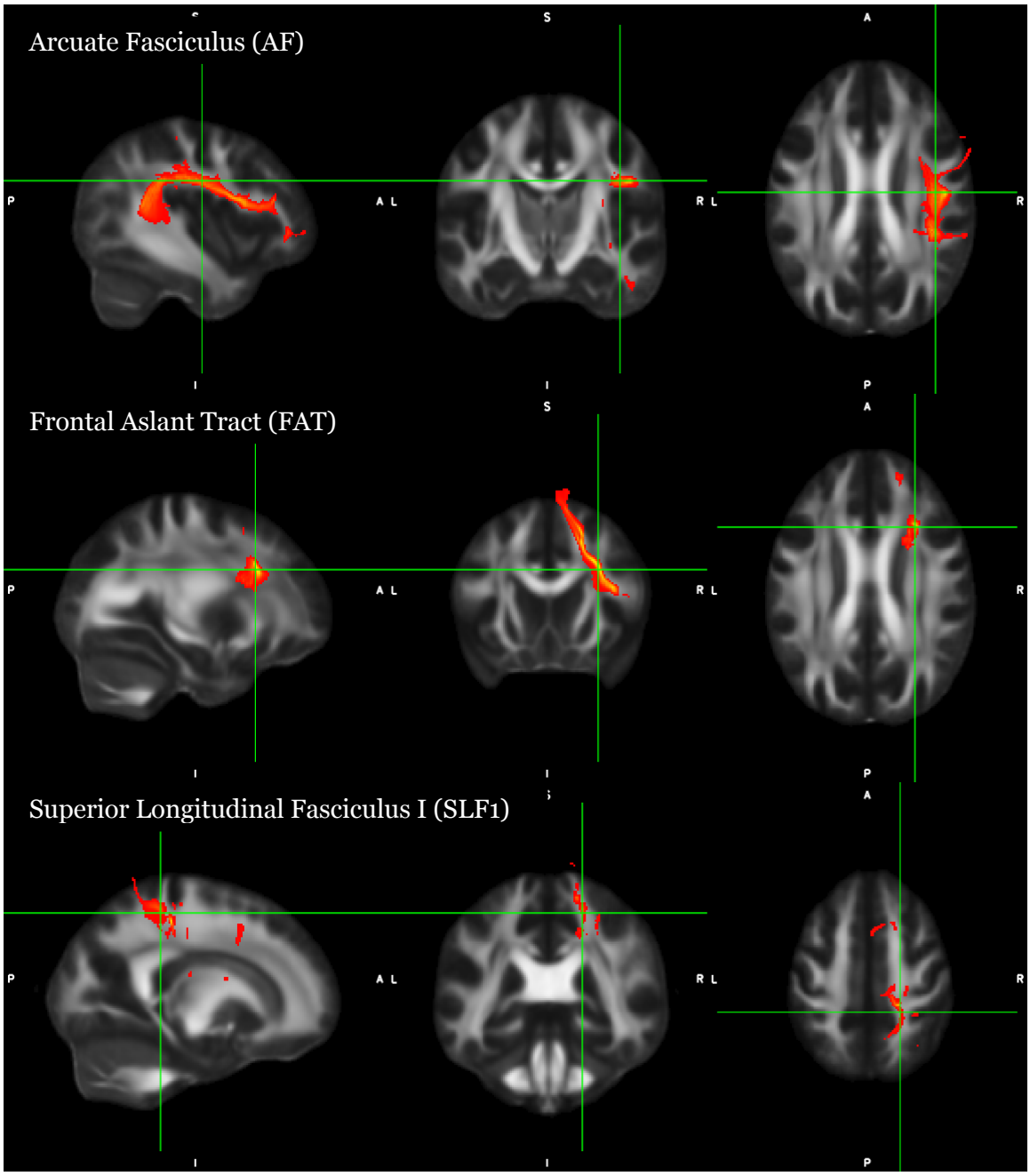
Two stroke survivors were excluded from the following analysis because their fiber tracking failed (AZ1008 and AZ1016) - a known difficulty for some subjects (Geva et al., 2015). A sample result of successful tractography is in Figure 3.

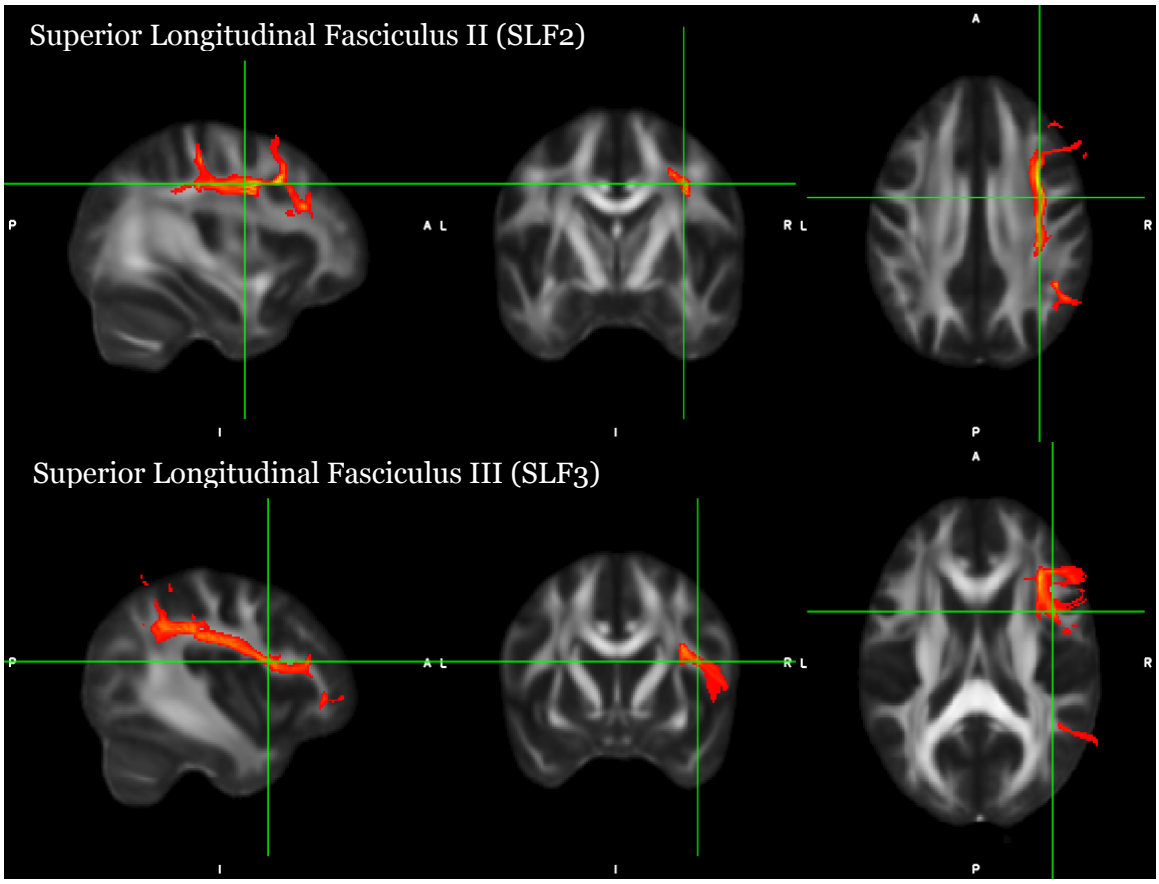
The stroke survivors had significantly lower mean FA in the AF (adjusted p = .045, t = -2.87) and uncinate fasciculus (UF) (adjusted p = .045, t = -2.69). The group comparison between stroke survivors and control subjects revealed no significant differences in MD in all of the right hemisphere tracts (p > .05 for all the ROIs). See Table 7 and Figure 4A and 4B. The corrected tract volume comparison showed that the stroke survivors had significantly smaller volume in all the right hemisphere tracts (p < .05 for all the ROIs) compared to the control subjects. See Table 7 and Figure 4C. The corrected number of the reconstructed streamlines comparison between stroke survivors and control subjects showed that there is no significant difference in any of the right hemisphere dorsal stream tracts (i.e., AF, FAT, SLF1, SLF2, SLF3) (p > .05 for all the ROIs), but the stroke survivors had significantly fewer reconstructed streamlines than control subjects in all of the right hemisphere ventral stream of tracts (i.e., UF, ILF, IFOF, MdLF) (p < .05 for all the ROIs). See Table 7 and Figure 4D.

Figure 3

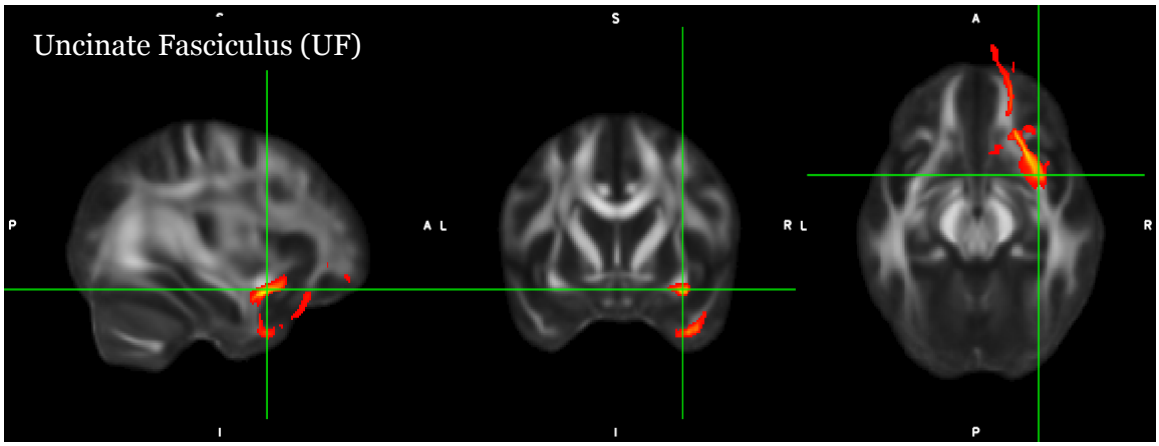
A sample result of AZ1003 from tractography.

Dorsal streams





Ventral streams



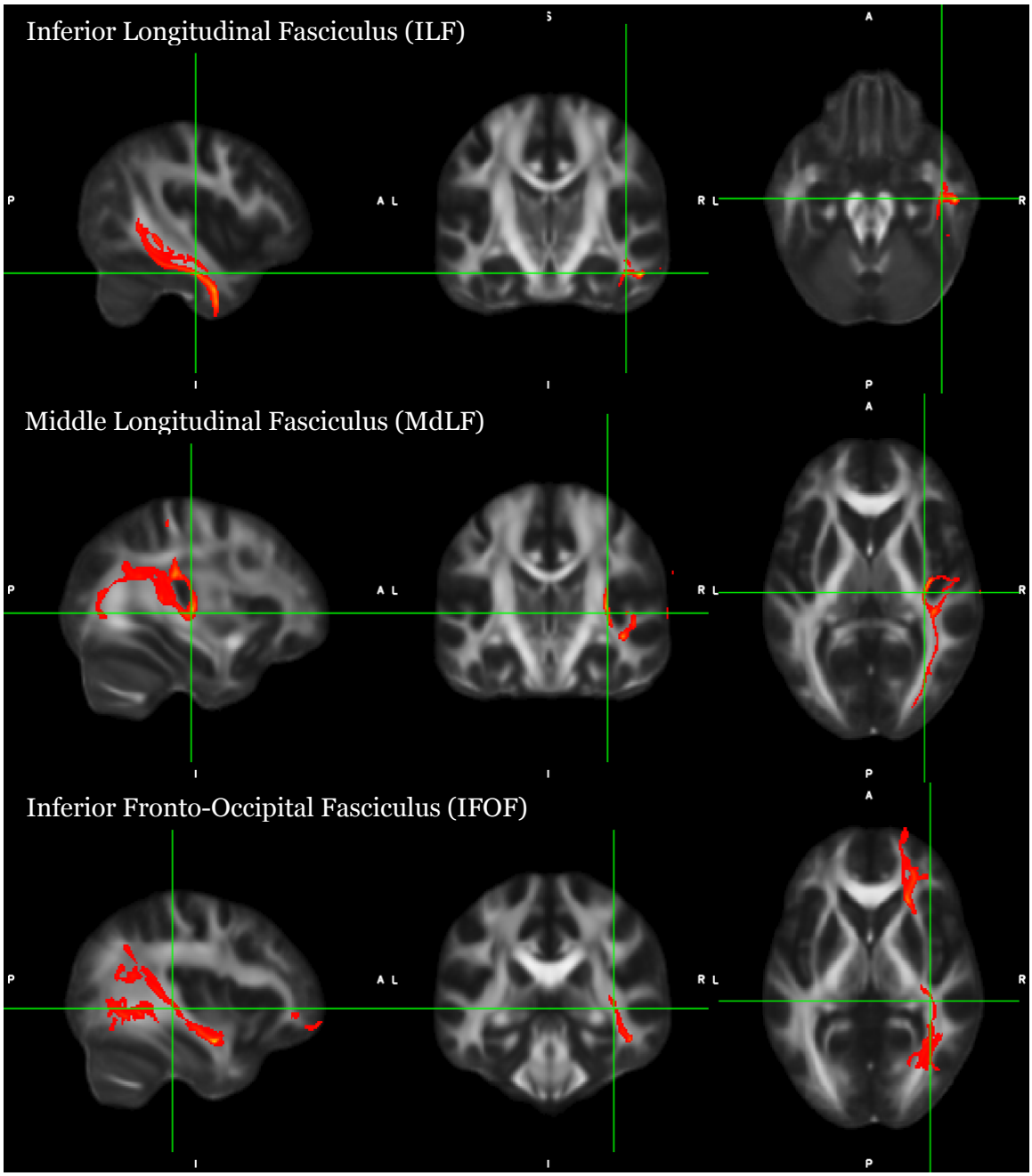

Inferior Longitudinal Fasciculus (ILF)
Middle Longitudinal Fasciculus (MdLF)
Inferior Fronto-Occipital Fasciculus (IFOF)

Table 7

Diffusion and structural measures in the right hemisphere from DTI images.

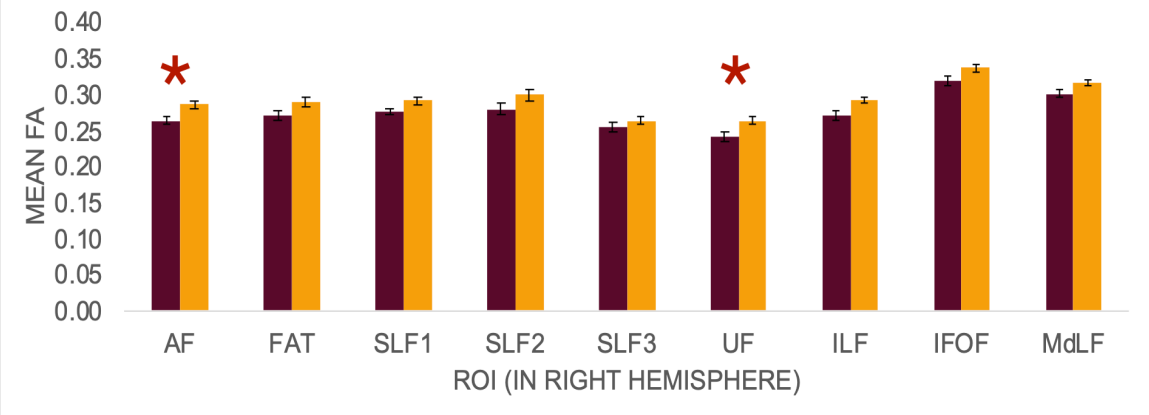
Tract	Diffusion Measures				Structural Measures			
	FA		MD [x 10^{-3} mm^2/sec]		Tract Volume		Number of Streamlines (mm^{-3})	
	Stroke	Control	Stroke	Control	Stroke	Control	Stroke	Control
AF	0.26*	0.29	0.68	0.67	0.22*	0.32	0.91	1.00
FAT	0.27	0.29	0.71	0.68	0.04*	0.05	0.11	0.13
SLF1	0.28	0.29	0.76	0.72	0.06*	0.12	0.06	0.08
SLF2	0.28	0.30	0.65	0.63	0.04*	0.09	0.17	0.27
SLF3	0.25	0.26	0.68	0.68	0.07*	0.15	0.30	0.40
UF	0.24*	0.26	0.72	0.72	0.04*	0.08	0.20*	0.33
ILF	0.27	0.29	0.66	0.66	0.09*	0.20	0.29*	0.49
IFOF	0.32	0.34	0.68	0.67	0.09*	0.20	0.20*	0.68
MdLF	0.30	0.32	0.67	0.67	0.09*	0.22	0.10*	0.27

Note. AF: Arcuate Fasciculus; FAT: Frontal Aslant Tract; SLF: Superior Longitudinal Fasciculus; UF: Uncinate Fasciculus; ILF: Inferior Longitudinal Fasciculus; IFOF: Inferior Fronto-Occipital Fasciculus; MdLF: Middle Longitudinal Fasciculus.
*Corrected for multiple comparisons p value < .05. The comparison on the white matter measure in a given ROI between the stroke survivors and the control subjects.

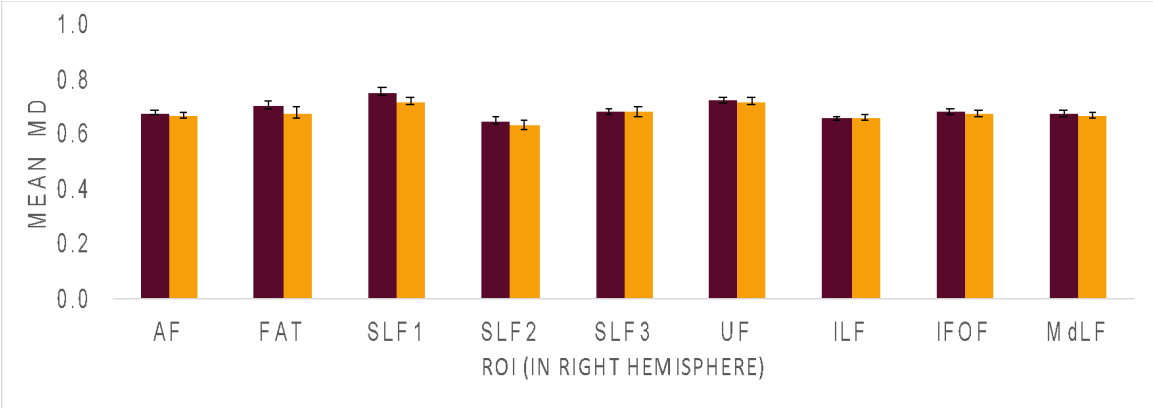
Figure 4

Group comparisons in the measures from DTI images between stroke survivors and control subjects.

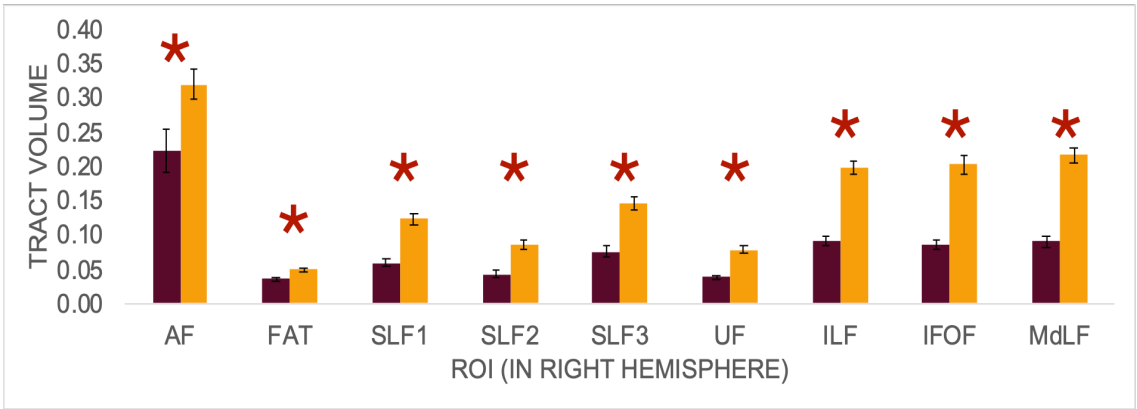
A FA.



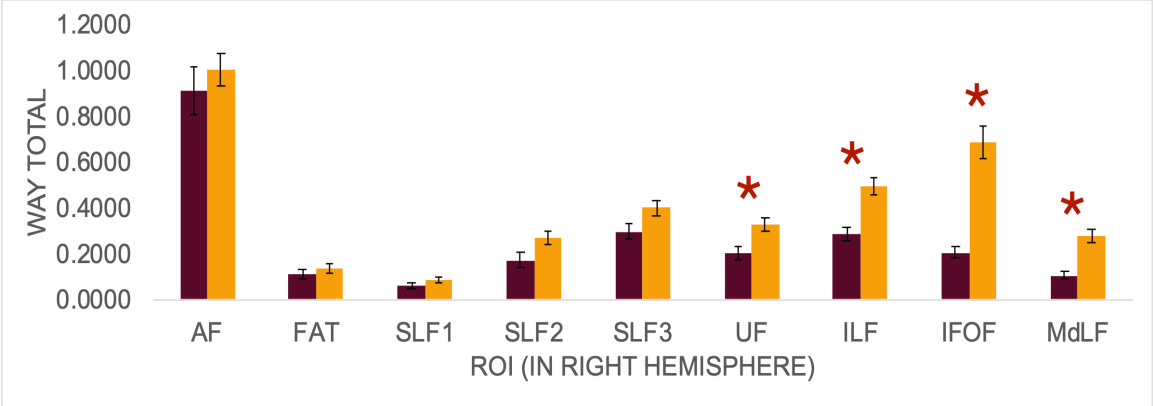
B MD (x 10^{-3}).



C Tract volume.



D Number of streamlines (mm^{-3}).



Note. AF: Arcuate Fasciculus; FAT: Frontal Aslant Tract; SLF: Superior Longitudinal Fasciculus; UF: Uncinate Fasciculus; ILF: Inferior Longitudinal Fasciculus; IFOF: Inferior Fronto-Occipital Fasciculus; MdLF: Middle Longitudinal Fasciculus.

3.2.4. DTI Tractography: Within-group correlation analysis.

The partial Pearson correlation analyses identified no significant correlations between the diffusion metrics (i.e., FA and MD) or the structural metrics (i.e., volume and streamlines) in any of the right hemisphere tracts and any of the behavioral measures after controlling for age and corrected lesion size ($p > .05$ for all the ROIs). See Table 8.

Table 8

Correlation coefficients between diffusion and structural metrics in the right hemisphere from DTI images and behavioral performance.

A FA.

Tract	WMI	PSI	ACT	PDT
AF	0.04	0.14	-0.11	0.11
FAT	-0.36	0.03	-0.24	0.12
SLF1	-0.06	-0.18	0.16	-0.11
SLF2	0.08	0.03	-0.03	-0.26
SLF3	0.02	0.24	-0.20	-0.04
UF	-0.25	-0.26	-0.03	-0.02
ILF	0.09	-0.05	-0.27	-0.13
IFOF	-0.09	-0.12	-0.12	-0.37
MdLF	-0.08	-0.19	-0.16	-0.18

Note. WMI: working memory index; PSI: processing speed index; ACT: Auditory comprehension task; PDT: picture description task.

B MD.

Tract	WMI	PSI	ACT	PDT
AF	0.13	0.10	-0.14	0.09
FAT	0.43	-0.18	0.12	-0.18
SLF1	0.24	-0.11	0.20	-0.07
SLF2	0.13	0.13	0.18	0.14
SLF3	0.15	-0.08	-0.23	0.08
UF	0.24	0.34	-0.02	0.11
ILF	0.25	-0.06	-0.08	0.26
IFOF	0.38	0.23	0.18	0.12
MdLF	0.26	0.01	0.19	0.19

C Tract volume.

Tract	WMI	PSI	ACT	PDT
AF	0.07	0.12	0.14	0.02
FAT	0.31	0.18	0.06	-0.04
SLF1	0.05	0.20	-0.17	0.02
SLF2	0.14	0.32	-0.20	0.01
SLF3	0.00	0.13	-0.05	-0.11
UF	0.09	0.21	-0.10	-0.02
ILF	0.06	0.20	0.09	-0.15
IFOF	0.05	0.11	-0.01	-0.07
MdLF	0.13	0.25	0.04	-0.03

D Number of reconstructed streamlines.

Tract	WMI	PSI	ACT	PDT
AF	-0.12	-0.14	-0.14	-0.17
FAT	0.01	-0.08	-0.15	0.00
SLF1	-0.15	0.19	-0.43	0.20
SLF2	0.35	0.37	-0.16	0.50
SLF3	0.01	0.01	-0.17	0.26
UF	0.06	0.29	-0.09	-0.03
ILF	-0.13	0.02	0.12	-0.09
IFOF	-0.43	-0.11	-0.30	-0.08
MdLF	-0.10	0.07	-0.03	-0.56

CHAPTER 4

DISCUSSION

The aim of this study was to take a converging methods approach to examine the relationships between right hemisphere structures and the language and cognitive abilities in left-hemisphere stroke survivors at the chronic stage via T1-weighted structural MRI and DTI. The major findings, which will be discussed in more detail below, are: (1) white and gray matter volumes in the ROIs did not differ between the stroke survivors and the matched control subjects, but the cortical thickness in the right frontal, parietal, and insula regions were thinner in the stroke survivors compared with the control subjects, (2) cortical thickness in right frontal cortex was positively associated with processing speed, (3) FA values in the right hemisphere's ventral stream were lower in the stroke survivors compared with the controls, whereas MD values did not differ between groups, and (4) the estimated number of reconstructed fibers in the right ventral white matter tracts was lower in the stroke survivors than in the control subjects, whereas the estimated number did not differ in the right dorsal tracts. Meanwhile, the tract volumes were smaller in all the right tracts in stroke survivors compared with the control subjects.

4.1. Structural MRI Findings

The present study found no gray or white matter volume differences between groups after correcting for intracranial volume. The stroke survivors in Lee et al. (2018)'s study also did not differ in the volume of the gray and white matter from the control subjects. However, since stroke survivors might have huge individual differences in lesion characteristics and the following reorganization in the intact hemisphere, single subject analysis at the individual level were further conducted to better capture the

differences in each stroke survivor's structural brain. The greater gray matter volume in the right temporoparietal regions in stroke survivors from Bayesian single subject analysis were in line with previous studies (e.g., Sihvonen et al., 2020; Xing et al., 2016). Xing et al. (2016) found that the chronic stroke survivors had greater gray matter volumes in the right temporoparietal cortex (i.e., supramarginal, middle and superior temporal gyrus) compared with the control subjects. Sihvonen et al. (2020) found that increased gray matter volume in the right temporoparietal regions (i.e., middle and superior temporal gyrus) in stroke survivors with aphasia after music listening. The Bayesian single subject findings suggest that the structural plasticity in both the right temporoparietal and fronto-parietal regions especially the middle temporal region could be a potential compensatory mechanism in post-stroke recovery, but future studies will be needed to determine the nature of this mechanism.

The cortical thickness in the right frontal cortex (i.e., caudal middle and superior frontal ROIs) were positively associated with cognitive processing speed after controlling for the two of the main factors accounting for post-stroke language outcomes (i.e., age and corrected lesion size). The Bayesian single subject analyses indicated that none of the stroke survivors had greater cortical thickness in these right caudal middle and superior frontal regions that were positively associated with cognitive processing speed, compared with the matched control group. Furthermore, the cortical thickness in the right frontal regions (i.e., superior frontal and rostral anterior cingulate), parietal region (i.e., precuneus), and insula were thinner in the stroke survivors compared with the control subjects. These findings suggest that the better processing speed performance associated with cortical thickness in these regions might be the results of advantageous pre-existing individual differences in cortical thickness of these ROIs instead of post-stroke compensation.

Increased cortical mean curvature has been shown to indicate white matter atrophy (Deppe et al., 2014). In the current study, no significant differences in the mean curvature between the stroke survivors and the control subjects were presented in the right hemisphere ROIs except in the right insula ROI. The curvature results were generally in line with the white matter volume results that there was no sign of white matter atrophy (as measured by white matter volume) in any of the right hemisphere ROIs. Taken together, these results suggest that white matter structures in the right hemisphere did not compensate or change in chronic left hemisphere stroke survivors. Although there was no sign of white matter atrophy within stroke survivors from these curvature and volume analyses, the white matter intensity in the right lateral frontal regions (i.e., inferior, middle and superior frontal ROIs) were lower in stroke survivors compared with the control subjects. This suggests that perhaps more sensitive white matter measures, extracted from DTI data, may be needed to best characterize right hemisphere white matter differences in the stroke survivors (our DTI results are discussed below).

4.2. Diffusion MRI Findings

Diffusion and structural measurements were also obtained from the diffusion tensor MRI. FA values indicate white matter integrity, typically with higher values related to better brain health and general cognitive performance. In contrast, MD values are an indication of white matter integrity, with increased values associated with white matter damage. In this study, using a whole-brain, voxel-wise TBSS analysis, FA in right ventral stream white matter regions were significantly lower in the stroke survivors compared with the controls. Although there was a trend that the stroke survivors had higher FA values in the right dorsal stream of tracts than the control subjects, it did not

reach significance. No significant difference in MD values across the whole right hemisphere between groups was found. Furthermore, no significant correlations were found between FA or MD in the right white matter tracts and any of the behavioral performance measures, with age and corrected lesion size as nuisance covariates. These exploratory voxel-by-voxel findings suggest that the diffusivity in the white matter tracts of the right hemisphere's ventral stream is different in the stroke survivors compared to the control subjects, but these differences do not reflect better post-stroke performance on our language or cognitive measures.

An ROI-based analysis also was conducted to reconstruct nine major white matter tracts in the intact right hemisphere. The between-group comparisons of these tracts showed that mean FA was lower in the right AF and UF in the stroke survivors compared with the control subjects. As in the voxel-wise analyses, no differences in mean MD between groups were found, and none of the right tracts had significant correlations with the behavioral performance after controlling for age and corrected lesion size.

FA values across ventral right hemisphere white matter were significantly lower in the stroke survivors compared with control subjects using TBSS, and tractography located these mean FA differences to the right AF and UF. Both the FA results of TBSS and of tractography differed from similar previous studies (Geva et al., 2015; Ivanova et al., 2016; Lee et al., 2018). Lee et al. (2018) that found lower FA in the right dorsal ROIs such as superior longitudinal fasciculus (SLF) and fronto-parietal regions (i.e., IFG, supramarginal, angular) but not the right ventral ROIs such as inferior longitudinal fasciculus (ILF) and superior temporal region in stroke survivors with severe aphasia compared with controls. Conversely, Ivanova et al. (2016) actually found *higher* mean FA in two right ventral tracts (i.e., ILF and IFOF) in their stroke survivor group

compared with controls. Both of these two studies obtained the mean FA value for each ROI by applying an atlas from FSL's library onto the DTI, whereas our current study used fiber tracking to reconstruct nine tracts. Compared with the atlas-based DTI metrics extraction, the advantage of tractography is the ROIs generated from fiber tracking would be more meaningful and precise for each subject. As for previous studies using TBSS, Geva et al. (2015) found no difference in FA using voxel-wise comparisons in the whole right hemisphere between stroke survivors and controls. But Geva et al. did have a noticeably smaller sample size (n = 15) than our study.

In addition to the diffusion metrics, the present study also obtained the corrected tract volume and the estimated number of reconstructed fibers. Interestingly, the main finding in this tractography analysis was that the number of streamlines in the right ventral white matter tracts (i.e., UF, ILF, IFOF, and MdLF) were significantly lower in the stroke survivors compared with control subjects, whereas no significant differences in the number of streamlines were present for the right dorsal white matter tracts (i.e., AF, FAT, SLF1~3). Meanwhile, the corrected tract volumes were smaller in all the right tracts in stroke survivors compared with the control subjects. These results suggest that white matter in the right hemisphere experiences changes due to a left hemisphere stroke, but that the dorsal and ventral streams are affected differently. Specifically, the results suggest that there was potentially a loss in the number of fibers in the right ventral stream after left hemisphere stroke, however, the right dorsal stream may not experience fiber loss.

Our findings of smaller tract volume across the right hemisphere white matter tracts and decreased number of reconstructed fibers in the ventral stream of the chronic left-hemisphere stroke survivors compared with controls contradicted the findings of previous studies (Geva et al., 2015; Schlaug et al., 2009). For example, Geva et al. (2015)

found that there was no difference in the right AF volume between stroke survivors and their control group. However, as mentioned above, they used a relatively small sample size (n= 15 stroke survivors). Schlaug et al. (2009), with an n=6 stroke survivors, found an increased number of fibers in the right AF in all stroke survivors after speech therapy. Combined with our findings, the Schlaug et al. findings may suggest that perhaps the right AF is affected by left hemisphere damage, and is a promising target for rehabilitation. Furthermore, these studies focused on only one specific tract AF. Our findings outside of the right AF, particularly in the UF tract, suggests that all the language-related white matter tracts should be investigated in studies of right hemisphere differences in left hemisphere stroke survivors to better capture post-stroke brain changes.

4.3. Limitations and Future Directions

The following section discusses some limitations to the present study, and ideas for future studies to address these shortcomings.

One potential limitation concerning the interpretation of any tractography results, including ours, is that the results are highly influenced by how seed masks, target masks, exclusion masks, and stop masks are defined. Currently, there is no standard definition on the exact locations for each white matter tract (Dick et al., 2014). Therefore, future studies should address the consistency when defining the anatomical locations using standardized protocols or standardized ROI masks. To objectively characterize the tracts, the current study used ROI masks from XTRACT (Warrington et al., 2020) defined in standard space instead of subjectively drawing by hand for each subject. Therefore, the results in this study should have minimized the errors due to human

factors, but it is possible that some accuracy is lost as the normalization process is not 100% accurate for all brains when using a template in standard space.

Another potential neuroimaging-related limitation is that while this study included both T1-weighted structural MRI and diffusion MRI metrics, future studies should also consider including functional MRI data to provide a more complete picture of how the right hemisphere changes after a left hemisphere stroke, and how these changes may be related to cognitive and language abilities. Furthermore, including functional MRI could examine how structural plasticity is related to functional plasticity, which may be a stronger predictor of language recovery than structural measures alone.

Although the present study controlled for the effects of age and lesion size, lesion location also plays an important role in post-stroke language recovery. Future studies should investigate how lesion location within the left hemisphere affects right hemisphere changes post-stroke. Although the current study used an age- and gender-matched control group as a sort of proxy for a "pre-stroke" conditions, longitudinal studies of stroke survivors in the acute and then chronic stages of stroke recovery would provide causal evidence as to the factors leading to right hemisphere differences after left hemisphere stroke. Lastly, the age range of stroke survivors in the current study is wide, from 28 to 80. While this wide age range allows us to sample from a wide range of performance profiles, and we controlled for subjects' age in all analyses and had an age-matched control group, future studies might consider including more younger and older stroke survivors to have enough power to explore younger and older adults in separate groups.

4.4. Conclusion

In summary, this study provided evidence that the combination of structural and diffusion MRI techniques reveals gray and white matter differences in the right hemisphere of chronic left hemisphere stroke survivors compared to matched controls, particularly in the right ventral stream's cortical regions (e.g., right temporal and parietal regions) and the white matter tracts. However, none of the language or cognitive abilities examined significantly correlated with these measures, except that processing speed was significantly associated with gray matter thickness in right frontal cortex regions in the stroke survivors. Furthermore, it is notable that the underlying fiber tracts in right dorsal streams did not differ from controls, whereas right ventral stream white matter tracts exhibited fewer fibers and lower FA than the control subjects. Future studies are needed to identify the specific mechanisms of right hemisphere changes in stroke survivors with left hemisphere damage, but the present study provides strong evidence that the "intact" right hemisphere's language regions and white matter tracts exhibit decline following left hemisphere stroke.

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