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Hemispheric asymmetry in myelin after stroke is related to motor impairment and function

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ABSTRACT

The relationships between impairment, function, arm use and underlying brain structure following stroke remain unclear. Although diffusion weighted imaging is useful in broadly assessing white matter structure, it has limited utility in identifying specific underlying neurobiological components, such as myelin. The purpose of the present study was to explore relationships between myelination and impairment, function and activity in individuals with chronic stroke. Assessments of paretic upper-extremity impairment and function were administered, and 72-hour accelerometer based activity monitoring was conducted on 19 individuals with chronic stroke. Participants completed a magnetic resonance imaging protocol that included a high resolution T_1 anatomical scan and a multi-component T_2 relaxation imaging scan to quantify myelin water fraction (MWF). MWF was automatically parcellated from pre- and post-central subcortical regions of interest and quantified as an asymmetry ratio (contralesional/ipsilesional). Cluster analysis was used to group more and less impaired individuals based on Fugl-Meyer upper extremity scores. A significantly higher precentral MWF asymmetry ratio was found in the more impaired group compared to the less impaired group ($p < 0.001$). There were no relationships between MWF asymmetry ratio and upper-limb use. Stepwise multiple linear regression identified precentral MWF asymmetry as the only variable to significantly predict impairment and motor function in the upper extremity (UE). These results suggest that asymmetric myelination in a motor specific brain area is a significant predictor of upper-extremity impairment and function in individuals with chronic stroke. As such, myelination may be utilized as a more specific marker of the neurobiological changes that predict long term impairment and recovery from stroke.

1. Introduction

Improved medical management of stroke has resulted in decreasing mortality rates (Grefkes and Ward, 2014). As a result, the number of individuals living with long-term disability as a result of stroke is rising (Krueger et al., 2015). Due to the heterogeneity of clinical presentation following stroke, it is imperative to identify biomarkers that may predict long-term impairment and function in order to appropriately individualize clinical rehabilitation goals and objectives (Bernhardt et al., 2016). With advances in diagnostic and prognostic tools, it is necessary to isolate modalities that can predict long-term outcomes for individuals with

stroke, and to understand the underlying neurobiology that contributes to the predictive value of those measures.

Neuroimaging can be utilized to aid in the identification of biomarkers that may predict recovery status in individuals with stroke. White matter imaging is often used as a predictor of stroke recovery (Feng et al., 2015; Stinear et al., 2012). Diffusion tensor imaging (DTI) can be performed within 10 days post stroke to quantify initial post stroke structural degeneration (Werring, 2000). Such indices have been found to strongly predict upper-extremity motor function at both 3- and 6-months post stroke (Puig et al., 2010; Stinear et al., 2012). The combination of acute corticomotor function, derived from DTI and motor evoked potentials, using transcranial magnetic stimulation, has also been demonstrated to strongly predict recovery from upper-extremity impairment after stroke (Byblow et al., 2015). Although these modalities are predictive of long-term upper-extremity impairment, the underlying neurobiological bases driving the relationship between white matter microstructure and motor capacity remains unclear. While relationships between white matter integrity, quantified with DTI, and motor impairment have been established after stroke, it is

important to note that DTI measures are not a specific marker for myelination (Arshad et al., 2016). While DTI can grossly identify water movement, it is unable to differentiate between individual white matter substrates, which may produce the observed signal. Multiple structural features can be individually or collectively responsible for the observed changes in DTI measures, including: 1) axonal membrane status, 2) myelin sheath thickness, 3) number of intracellular neurofilaments and microtubules, and 4) axonal packing density (Alexander et al., 2007; Beaulieu, 2002). To understand the neurobiological components contributing to the change in motor outcome observed there is a need to adopt neuroimaging techniques that can quantify these structural features.

Myelin formation has been identified as a specific target for therapeutic intervention following stroke, as recovery of axonal fibres is not complete without adequate myelination (Mifsud et al., 2014). Oligodendrocytes are responsible for initiating a cascade of events that result in the formation of myelin. Acute cerebral ischemia, such as that caused by a stroke, causes a rapid breakdown of oligodendrocytes and demyelination (Tekkök and Goldberg, 2001), which greatly limits overall axonal integrity in the lesioned area (Saab and Nave, 2016). Although animal work has underlined the importance of active myelination on motor recovery after stroke (Chida et al., 2011; McKenzie et al., 2014), it is unclear how these findings transfer to humans.

Until recently, technical limitations prevented the imaging of myelin in vivo. Myelin water fraction (MWF) can be derived in humans non-invasively in vivo from multi-component T2-relaxation imaging (Alonso-Ortiz et al., 2014; Prasloski et al., 2012b). Formalin-fixed human brains yield T_2 distributions similar to those found in vivo, and histopathological studies show strong correlations between MWF and staining for myelin (Laule et al., 2004; Moore et al., 2000). With the development of non-invasive imaging techniques, myelin can be quantified in the human brain (Prasloski et al., 2012b), both cross-sectionally and longitudinally (Lakhani et al., 2016) Work from the Human Connectome Project and others have identified that the primary motor and sensory regions are among the most densely myelinated and most easily delineated in the human brain, allowing for more reliable automatic identification and parcellation of myelinated regions (Glasser et al., 2016; Glasser and Van Essen, 2011; Nieuwenhuys and Broere, 2016). In addition, myelination of corticospinal projections from these regions may vary based on the length of the tract and the size the axon. As such, quantification of corticospinal tract (CST) myelin using in vivo neuroimaging has not been validated to date (Glasser and Van Essen, 2011). Previous work from our group did not reveal a relationship between ipsi- and contralesional CST MWF, measured from the posterior limb of the internal capsule, and motor function or impairment (Borich et al., 2013). In order to limit variability arising from CST tract heterogeneity between individuals with stroke, the current study focused on the most well defined, myelinated regions of interest, located in precentral and postcentral areas.

Recent work has demonstrated that oligodendrocyte precursor cell proliferation and myelin structure are associated with motor learning in rodent models (Gibson et al., 2014; Xiao et al., 2016). In particular, this work emphasized the possibility that functional motor activity may influence myelination of redundant neural pathways and improve conduction velocity via more efficient neural synchrony (Fields, 2015). The current study will extend previous lines of inquiry by exploring the relationship between real-world activity in the upper-extremity to myelination in humans. The ability to use the stroke-affected upper-limb in 'everyday tasks' is cited as a primary goal for individuals living with stroke (Barker and Brauer, 2005; Barker et al., 2007). Monitoring upper-extremity usage after stroke using accelerometers is a low-cost, non-invasive way to measure functional activity and to quantify overall real-world activity (Hayward et al., 2015). Use of the stroke affected upper-limb correlates with long-term motor impairment as greater activity generally results in reduced impairment (Gebruers et al., 2014; Lang et al., 2007; Shim et al., 2014). Identifying relationships between

accelerometer based measures of activity and myelination will inform future investigations about the potential specificity of myelin as predictive biomarker for understanding what people can do, via measurement of impairment and function, versus what people actually do in the real-world.

Given the important relationships between white matter, activity and post-stroke impairment as well as the recent advances in imagining techniques, it is imperative to consider the contribution of myelination to post-stroke impairment, function and activity in humans. In order to identify potential differences in myelination based on the level of impairment after stroke, the current study identified 'more impaired (M)' and 'less impaired (L)' groups of participants. Therefore, the primary objective of the current investigation is to understand whether MWF in sensorimotor regions of interest is a biomarker of long term impairment, function or arm use in a population of individuals living with chronic stroke. Furthermore, we sought to identify if there were differences in MWF in sensorimotor regions of interest between individuals classified as 'more impaired' versus those who were 'less impaired'.

2. Methods

2.1. Participants

Twenty-two participants were enrolled in this study. Participants were included if they were between the ages of 45 and 85, had been clinically-diagnosed with a first time, ischemic infarct at least six months (chronic) prior to their enrollment in the study (Table 1). Participants completed a magnetic resonance (MR) screening form and were excluded if they had any strict contraindications to MR scanning. Consent from each participant was obtained according to the declaration of Helsinki; the clinical ethics boards at the University of British Columbia approved all aspects of the study.

2.2. Clinical testing

Upper-extremity motor impairment was quantified using the UE portion of the Fugl-Meyer (FM-UE; Fugl-Meyer et al., 1975) scale (0–66, where higher scores indicate less impairment). Hemiparetic motor function was assessed using the Wolf Motor Function Test (WMFT; Wolf et al., 2001) which consisted of 15 timed movement tasks. For each task, the task rate (repetitions/60 s) was calculated using Eq. (1) in order to be more sensitive to individuals with moderate to severe functional impairment (Hodics et al., 2012). If an individual was not able to complete one repetition of a task within 120 s, then a task rate of zero was recorded.

$$\text{Task rate} = \frac{60(s)}{\text{Performance Rate}} \qquad (1)$$

2.3. Activity monitoring

Activity monitoring was conducted using Actical Accelerometers (Philips, Amsterdam, Netherlands). Actical accelerometers have been shown to be reliable indicators of day-to-day activity in individuals with chronic stroke (Rand et al., 2009). A device was placed on each upper-extremity at the wrist crease. Activity monitors were worn continuously for three consecutive days (72 h) following the initial assessment. Data was sampled at 32 Hz and was time-locked into 15 s epochs. For each 15 s epoch, data was rectified and integrated within the Actical Software package and stored as an activity count (AC) which represents the intensity of the activity performed during that interval (Rand et al., 2009, 2010). Activity counts were averaged over the three days. In order to accommodate for the variability of day-to-day activity, an activity count asymmetry ratio (activity-AR) was calculated (Eq. (2)), where an index >1 indicated greater activity of the ipsilesional limb compared

Table 1
Participant demographics and clinical testing scores, classified by impairment grouping (L = Less impaired group, M = More impaired group). FM-UE = Fugl-Meyer Upper Extremity; WMFT = Wolf Motor Function Test; *denotes participants for which Freesurfer was unable to segment anatomical T1 scans.

	Participant ID	Age (years)	Time since stroke (months)	Stroke hemisphere	FM-UE (/66)	WMFT rate more affected UE (reps/min)	Activity asymmetry ratio	Lesion volume (mL)	MNI lesion centroid coordinates (x,y,z)	Ipsilesional precentral ROI lesion overlap (mL|%ROI)		Ipsilesional postcentral ROI lesion overlap (mL|%ROI)	
Less Impaired group (N = 13)	L1	66	119	R	56	46.88	2.01	55.10	14,−22,41	1.13	9.42	0.27	3.84
	L2	68	28	R	62	55.65	1.93	0.79	9,−6,6	0.00	0.00	0.00	0.00
	L3	78	108	L	60	57.58	2.87	0.05	−6,−16,−33	0.00	0.00	0.00	0.00
	L4	58	96	L	59	78.35	1.12	0.14	−5,−20,−44	0.00	0.00	0.00	0.00
	L5	72	49	R	50	38.70	3.07	0.36	29,−14,9	0.00	0.00	0.00	0.00
	L6	71	112	R	59	62.95	2.34	0.10	20,−16,16	0.00	0.00	0.00	0.00
	L7	67	85	R	43	46.95	4.70	108.33	39,−9,24	8.57	56.53	2.77	45.19
	L8	68	42	L	65	62.10	0.67	35.37	−30,−62,−23	0.00	0.00	0.00	0.00
	L9	77	33	L	58	44.97	0.70	0.50	−5,−20,−32	0.00	0.00	0.00	0.00
	L10	70	76	R	64	48.74	0.34	0.16	20,−15,24	0.00	0.00	0.00	0.00
	L11	64	189	L	59	37.94	0.62	77.95	−27,−69,−21	0.00	0.00	0.00	0.00
	L12	73	60	L	54	38.39	2.60	0.38	−19,−22,12	0.00	0.00	0.00	0.00
	L13	73	30	L	57	34.56	3.03	43.55	−25,−54,0	0.00	0.00	0.00	0.00
	Mean	**69.62**	**79.07**	**6R, 7L**	**57.38**	**50.29**	**2.00**	**25.35**	**–**	**0.75**	**5.07**	**0.23**	**3.77**
More Impaired group (N = 9)	M1	57	162	R	32	11.91	18.00	0.97	23,26,41	0.00	0.00	0.00	0.00
	M2*	64	159	R	16	8.07	4.06	352.48	37,−4,16	N/A	N/A	N/A	N/A
	M3	72	45	R	13	0.00	13.68	61.88	34,−6,21	4.50	46.83	2.03	35.68
	M4*	62	171	L	19	0.40	5.76	71.71	−34,−18,21	N/A	N/A	N/A	N/A
	M5	56	74	R	38	39.45	2.16	5.63	25,−13,28	0.31	2.46	0.07	0.90
	M6	51	45	R	27	22.31	4.86	65.33	38,8,3	0.17	1.75	0.02	0.33
	M7*	48	35	R	10	5.04	16.24	203.57	36,4,28	N/A	N/A	N/A	N/A
	M8*	65	46	L	33	21.99	5.19	253.09	−40,−18,25	N/A	N/A	N/A	N/A
	M9	60	57.00	R	31	20.95	3.96	134.61	38,−29,40	0.81	8.58	0.74	8.55
	Mean	**60.98**	**78.30**	**7R, 2L**	**33.36**	**21.38**	**8.21**	**101.00**	**–**	**1.55**	**17.30**	**0.79**	**11.84**

to the contralesional limb, and an index <1 indicated greater activity of the contralesional limb activity compared to the ipsilesional limb.

$$\text{Activity Count Asymmetry Ratio} = \frac{\text{Ipsilesional Limb Activity Count}}{\text{Contralesional Limb Activity Count}} \quad (2)$$

2.4. MRI acquisition

Magnetic resonance data were acquired at the University of British Columbia MRI Research Centre on a Philips Achieva 3.0T whole body MRI scanner (Phillips Healthcare, Best, NL) using an eight-channel sensitivity encoding head coil and parallel imaging. The following scans were collected: (1) 3D T1 turbo field echo scan (TR = 7.4 ms, TE = 3.7 ms, flip angle θ = 6°, FOV = 256 × 256 mm, 160 slices, 1 mm slice thickness, scan time = 6.0 min) and (2) whole-cerebrum 32-echo three-dimensional gradient- and spin-echo (3D GRASE) for T2 measurement (TR = 1000 ms, echo times = 10, 20, 30, …, 320 ms, 20 slices acquired at 5 mm slice thickness, 40 slices reconstructed at 2.5 mm slice thickness (i.e. zero filled interpolation), slice oversampling factor = 1.3 (i.e. 26 slices were actually acquired but only the central 20 were reconstructed), in-plane voxel size = 1 × 1 mm, SENSE = 2, 232 × 192 matrix, receiver bandwidth = 188 kHz, axial orientation, acquisition time = 14.4 min (Prasloski et al., 2012b).

2.5. MWF map generation

T_2 relaxation analysis used a non-negative least-squares approach (Whittall and MacKay, 1989) with the extended phase graph algorithm (Prasloski et al., 2012a) to partition the T2 signal using an unbiased approach based on signal characteristics. Partitions included short (15–40 ms), intermediate (40–200 ms) and long (>1500 ms) components using in-house software code (MATLAB R2013b, The MathWorks, Inc.) developed at the University of British Columbia. MWF was defined as the sum of the amplitudes within the short T_2 component (15–40 ms) divided by the sum of the amplitudes for total T_2 distribution. Voxel-based MWF maps were produced for each participant. The FAST toolbox in the FMRIB Software Library (FSL; Smith et al., 2004) was used to automatically segment images into gray matter, white matter and cerebrospinal fluid (Zhang et al., 2001). The white matter segmentation mask was eroded by one voxel to remove any brain edge artifacts or subcortical gray matter tissue. Successful erosion was visually confirmed for each mask.

2.6. Cortical reconstruction

Cortical reconstructions and volumetric segmentation were generated with Freesurfer image analysis suite V5.3, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 2001; Reuter et al., 2010, 2012; Ségonne et al., 2004). Briefly, this processing included motion correction, removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Ségonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles; (Fischl et al., 2002, 2004), intensity normalization (Sled et al., 1998), tessellation of the gray matter white matter boundary, automated topology correction (Fischl et al., 2001; Ségonne et al., 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to another tissue class (Dale et al., 1999; Fischl and Dale, 2000). Freesurfer morphometric procedures have good test-retest reliability across scanner manufacturers and field strengths (Han et al., 2006; Reuter et al., 2012). All Freesurfer analyses were performed on the same workstation, using the same software version (Gronenschild et al., 2012).

2.7. MWF map cortical registration and ROI generation

Linear co-registration was conducted using tools from the Freesurfer image analysis suite for each participant between MWF map and Freesurfer parcellated T1 anatomy, similar to (Deoni et al., 2015). Specifically, this process involved; 1) registration of the first echo of the T2 weighted scan to the MWF map, 2) registration of the first echo of the T2 weighted scan to the Freesurfer parcellated T1 anatomy, and 3) registration of the MWF map to the Freesurfer parcellated anatomy. The Freesurfer generated white matter parcellation map (Salat et al., 2009) was then used to extract mean MWF from the apriori identified regions of interest for each hemisphere. In order exclude lesioned tissue in the calculation of MWF, only non-zero voxels were included in the calculation of mean MWF from each region of interest. Intensity normalization was conducted for each participant and refers to a global signal intensity adjustment required by Freesurfer in order to provide for more accurate registration when the intensity scaling of volumes are very different (Sled et al., 1998). The intensity of the MWF scan is temporarily scaled up by a constant to allow for registration of volumes, and later divided by that constant to normalize values back to % MWF.

MWF asymmetry ratios (MWF-AR) were calculated for two apriori sensorimotor regions of interest (Fig. 1a) using Eq. (3). Ratios were utilized instead of an absolute MWF value to normalize MWF values so that comparisons could be made between individuals. As this is the first investigation that has looked at MWF from these regions in individuals with chronic stroke, normative values for MWF are not available. As such, this method was adopted to minimize the potential MWF variability between individuals of varying lesion locations and ages. Regions of interest were: 1) precentral gyrus and 2) postcentral gyrus.

$$\text{MWF Asymmetry Ratio} = \frac{\text{MWF Contralesional Hemisphere}}{\text{MWF Ipsilesional Hemisphere}} \quad (3)$$

2.8. Lesion mapping

Lesion analysis was conducted on each participant using a semi-automatic method. Lesions were mapped using the Lesion Identification with Neighbourhood Data Analysis (LINDA) pipeline (Pustina et al., 2016). LINDA successfully identified the lesion in 16 out of 22 participants. All automatic lesion identifications were visually inspected and edited using MRIcron (Rorden and Brett, 2000), if necessary. Lesions in the remaining 6 participants were identified manually using T1 anatomical MRI scans and masked using MRIcron. All participant lesions are presented in Fig. 2 and lesion volume, lesion centroid MNI co-ordinates and overlap with MWF ROIs are presented in Table 1.

2.9. Statistical analysis

We performed a two-group k-means cluster analysis to delineate high and low functioning participants based on FM-UE score. Bivariate correlations were conducted between demographics (age, time since stroke, lesion volume) and primary outcome measures (pre/postcentral MWF-AR, FM-UE score, WMFT rate and activity-AR) to determine which demographic variables to control for when conducting analyses of covariance ($p < 0.05$). A between-group multivariate analysis of covariance (MANCOVA) and a single univariate ANCOVA were used to assess differences between more impaired and less impaired participants, with statistically significant demographic variables determined from the bivariate correlation analysis ($p < 0.05$) included as covariates to control for observed relationships to FM-UE score. The MANCOVA tested the differences in MWF-AR from sensorimotor regions of interest (precentral gyrus, postcentral gyrus) between more impaired and less impaired groups. The univariate ANCOVA assessed differences in the activity-AR between the two groups. Separate one-way repeated measures ANOVAs were conducted on the absolute MWF between hemispheres (repeated factor) and groups (more affected/less affected) for each region of interest (precentral/postcentral). Pairwise post-hoc comparisons were made if a significant interaction was found, with a Bonferroni correction applied.

Simple linear regression was performed to evaluate the relationship between demographics (age, time since stroke, lesion volume) and brain structure (MWF-AR), with function (WMFT-rate), impairment (FM-UE score) and arm use (activity-AR), separately. Each variable was entered into each simple regression independently to identify significant relationships between predictor variables and outcomes measures. Significance level for simple regressions were set at $p < 0.05$. Statistically significant results from the simple regression analysis were used to inform variables entered into the subsequent stepwise linear regression analyses with WMFT-rate, FM-UE scores and activity-AR as the dependent variables. Variables were included in the final model of the stepwise linear regression if they added statistically significantly to the prediction, $p < 0.05$.

3. Results

All participants completed the assessment protocol with no adverse events. Cluster centres based on FM-UE score were FM-UE = 28 (n = 9; More Impaired Group) and FM-UE = 57 (n = 13; Less Impaired Group), with a mean cut-off of FM-UE = 42.5. MWF data was unavailable for four participants in the more impaired group because of complications during cortical reconstruction with Freesurfer due to lesion size and location (Li et al., 2015). As a result, statistical analyses involving comparisons of MWF are limited to 18 participants (5 More Impaired; 13 Less Impaired).

3.1. Relationships between demographics and structure, impairment, function or arm-use

There were no statistically significant correlations between age or time since stroke with any of the primary outcome measures (FM-UE, WMFT-rate, pre/postcentral MWF-AR or activity-AR). Lesion volume
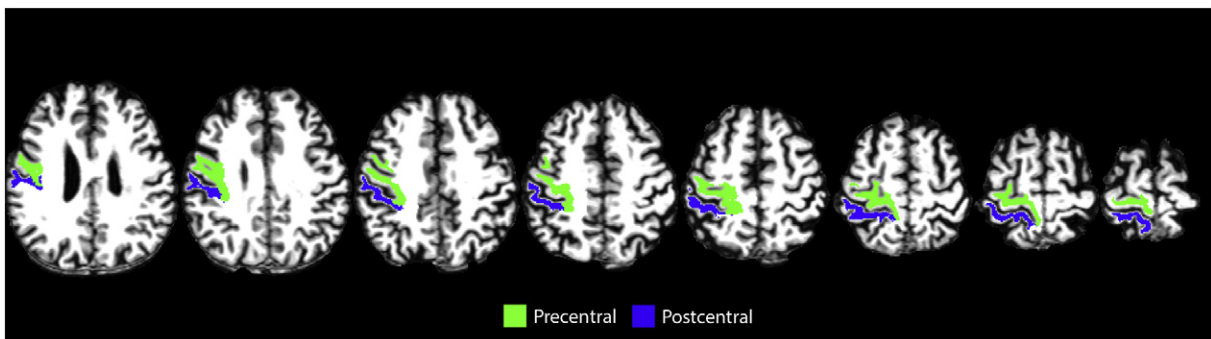

Precentral   Postcentral

Fig. 1. Axial multi-slice representation of sensorimotor MWF regions of interest parcellated automatically with Freesurfer in a representative participant overlaid on a T1-anatomical scan.
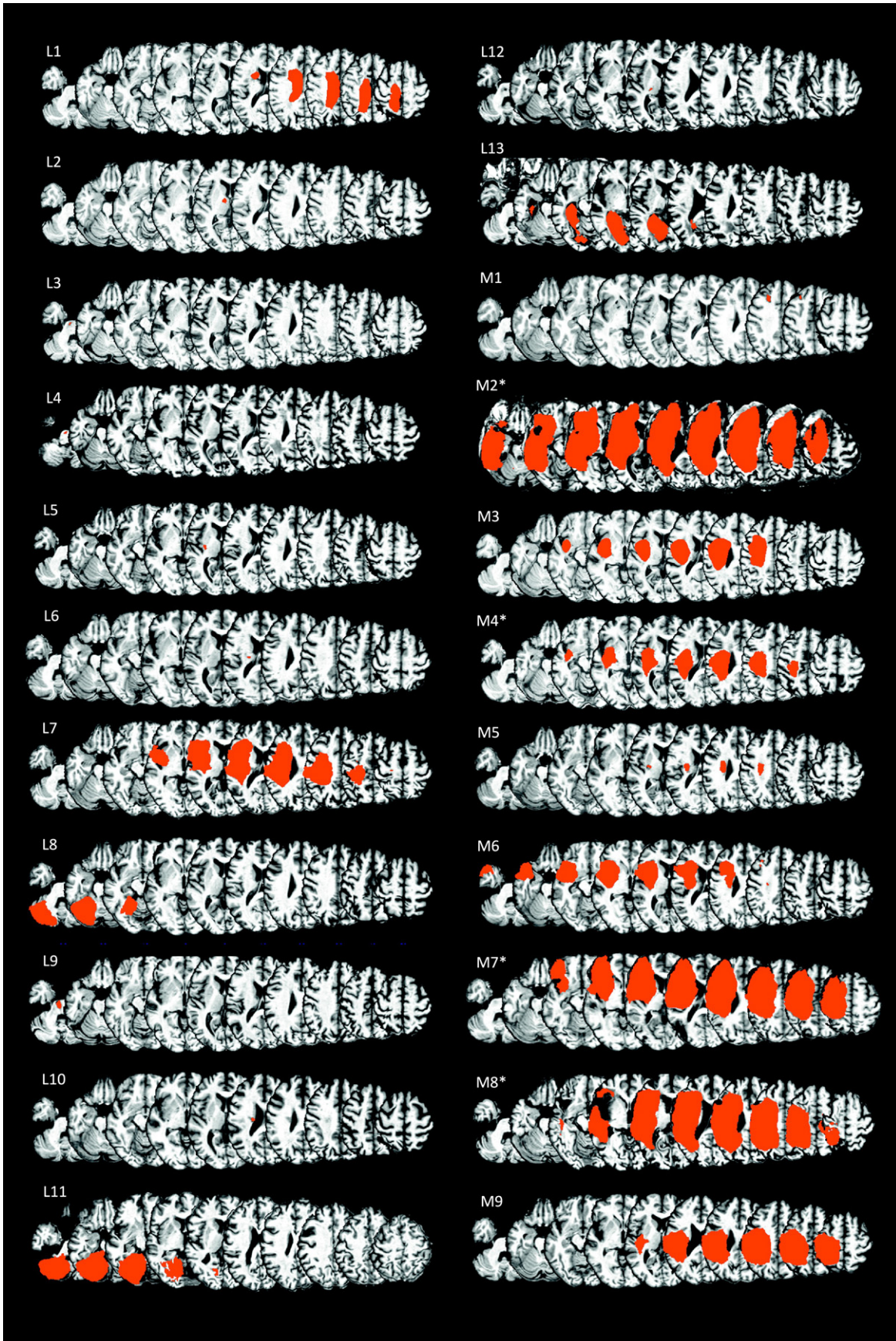
Fig. 2. Lesion volumes for each participant in the axial plane (L = Less impaired group, M = More impaired group). Lesion volumes are displayed in red and all lesions have been presented in the left hemisphere. *Denotes participants for which Freesurfer was unable to segment anatomical T1 scans.

was significantly negatively correlated with FM-UE (R = −0.490, p = 0.039). As a result, lesion volume was included as a covariate in the subsequent ANCOVAs.

3.2. Differences in brain structure between more impaired and less impaired groups

The overall results of the first MANCOVA demonstrated a statistically significant difference in MWF-AR based on impairment level (more impaired vs. less impaired; $F_{2,14}$ = 13.224, p = 0.001; Wilk's λ = 0.346, partial η^2 = 0.654). Individuals in the more impaired group had significantly greater MWF-AR in the precentral region (Fig. 3; more impaired = 1.41 ± 0.05, less impaired = 1.08 ± 0.03; $F_{1,15}$ = 28.112, p < 0.001) owing to the higher myelin water signal in the less-affected hemisphere in individuals in the more impaired group. There was no significant difference in MWF-AR in the postcentral region between groups ($F_{1,15}$ = 0.938, p = 0.348). The repeated measures ANOVA (Fig. 4) revealed a significant interaction between group and hemisphere on absolute MWF in the precentral region ($F_{1,16}$ = 34.028, p < 0.001). Post-hoc pairwise tests revealed significantly increased MWF in the contralesional hemisphere compared to the ipsilesional hemisphere in the more impaired group (p < 0.0001). In the postcentral region, there was a significant main effect of hemisphere on absolute MWF (ipsilesional: 0.093 ± 0.005; contralesional: 0.113 ± 0.005; $F_{1,16}$ = 6.465, p = 0.022). There was no statistically significant main effect of group and no statistically significant interaction between group and hemisphere for the postcentral region. The univariate ANCOVA revealed a significant difference between the two groups on the activity-AR from the upper-extremity (More Impaired = 8.88 ± 1.74, Less Impaired = 1.87 ± 1.05; $F_{3,15}$ = 5.851, p = 0.013; partial η^2 = 0.438).

3.3. Simple linear regression

Full results from the simple linear regressions are presented in Table 2 and correlations are displayed in Fig. 5.

3.3.1. Demographics
Lesion volume accounted for a significant amount of variance in the FM-UE score ($F_{1,16}$ = 5.067, R^2 = 0.241, p = 0.039). Age and time since
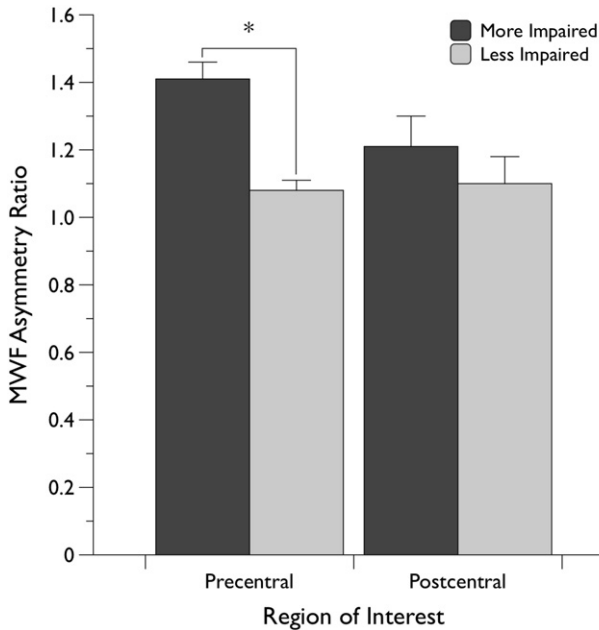

Fig. 3. Mean (+ SEM) MWF-AR between more impaired (dark gray) and less impaired (light gray) groups measured subcortically from the precentral and postcentral regions of interest.
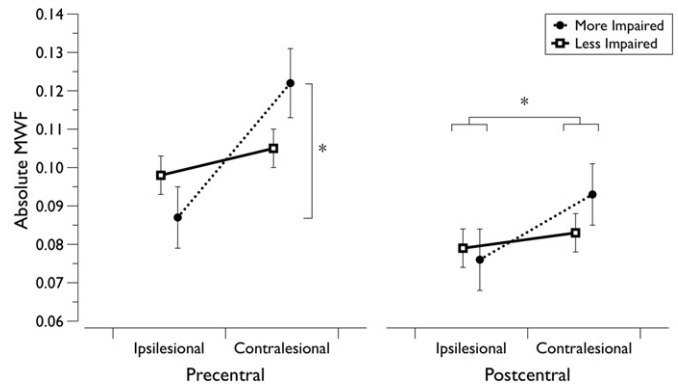

Fig. 4. Differences in mean (+ SEM) absolute MWF between groups (Less Impaired/More Impaired) and hemisphere (ipsilesional/contralesional) for each region of interest (precentral/postcentral). Significant differences (p < 0.05) are denoted with *.

stroke did not account for a significant amount of variance for the FM-UE score, affected WMFT-rate or activity-AR.

3.3.2. Structure
Precentral MWF-AR accounted for a significant amount of variance in the FM-UE score ($F_{1,16}$ = 18.128, R^2 = 0.531, p = 0.001) and the WMFT-rate ($F_{1,16}$ = 18.066, R^2 = 0.530, p = 0.001), but not the activity-AR. Postcentral MWF-AR did not account for a significant amount of variance for the FM-UE score, affected WMFT-rate or activity-AR.

3.4. Stepwise linear regression

3.4.1. Impairment (FM-UE)
Lesion volume and precentral MWF-AR were input into the stepwise regression for predicting the FM-UE score. A final model that included only precentral MWF-AR significantly predicted FM-UE score (R^2 = 0.531, $F_{1,16}$ = 18.128, p = 0.001).

3.4.2. Function (WMFT-rate)
Only precentral MWF-AR was entered into the stepwise regression for affected WMFT-rate and was identified as a significant predictor of WMFT-rate (R^2 = 0.530, $F_{1,16}$ = 18.066, p = 0.001).

3.4.3. Activity
Stepwise linear regression was not run on activity-AR because none of the variables from the simple linear regression analysis significantly predicted activity-AR.

4. Discussion

The primary objective of this investigation was to reveal neurobiological markers that may predict motor function, impairment and upper-extremity activity in individuals with chronic stroke. Specifically, we sought to understand the contribution of MWF in sensorimotor brain regions to previously observed relationships between white matter integrity and upper-extremity activity with post-stroke impairment and function. In the current study, participants were clustered into one of two groups based on FM-UE impairment scores using k-means clustering. Individuals in the more impaired group demonstrated significantly greater MWF-AR between hemispheres in the precentral region, with greater MWF in the contralesional hemisphere. In addition, linear regression analysis revealed that precentral gyrus MWF-AR accounted for a significant amount of variance in both the FM-UE scores and the WMFT-rate.

Table 2
Simple regression results.

Predictor	FM-UE score			Affected WMFT rate			Upper extremity activity-AR		
	F	p	R^2	F	p	R^2	F	p	R^2
Age	4.016	0.062	0.201	0.716	0.410	0.043	0.855	0.369	0.051
Time since stroke	0.106	0.748	0.007	0.022	0.884	0.001	0.669	0.425	0.040
Lesion volume	5.067	0.039*	0.241	3.698	0.072	0.188	0.205	0.657	0.013
Precentral MWF-AR	18.128	0.001*	0.531	18.066	0.001*	0.530	3.244	0.091	0.169
Postcentral MWF-AR	0.129	0.724	0.008	1.529	0.234	0.087	0.626	0.440	0.038

* $p < 0.05$.

4.1. Increased interhemispheric MWF asymmetry in more impaired individuals

In the current study, we observed significantly greater MWF-AR in the more impaired group in the precentral region. This observed asymmetry is being driven by increased MWF in the contralesional hemisphere, relative to the ipsilesional hemisphere. Although stabilization of the ipsilesional hemisphere may begin to occur three months post-stroke, the ipsilesional hemisphere does not recover in isolation. Rather, the contralesional hemisphere demonstrates a number of neurophysiological adaptations from the acute through to the chronic phase (Carmichael, 2003). This shift in activity towards the contralesional hemisphere has been identified as a marker of mal-adaptive plasticity, where greater asymmetry in motor cortical network activation is related to poorer recovery potential (Calautti et al., 2001). While there is not yet direct evidence using measures of myelination to further determine these relationships, other measures of brain physiology may provide some context.

Asymmetric cortical excitability has been assessed using transcranial magnetic stimulation and been found to attribute to compensatory activity of the contralesional hemisphere (Di Lazzaro et al., 2010). Specifically, a reduction of interhemispheric inhibition from the ipsilesional to the contralesional hemisphere has been associated with poorer motor outcomes in individuals with chronic stroke (Volz et al., 2014). The degree of asymmetry between interhemispheric corticospinal systems measured with electroencephalogram coherence has also been implicated as a strong predictor for overall motor function, where increased impairment results in reduced functional recovery (Graziadio et al., 2012). Although there is substantial evidence that cortical compensatory activity of the contralesional hemisphere following stroke may limit the recovery of long-term motor function, there is not currently enough direct support from literature in humans that these changes may mediated by changes in myelination.

Recent work on myelin plasticity in animal models may help to inform some the observed findings in the current study. In rodents,
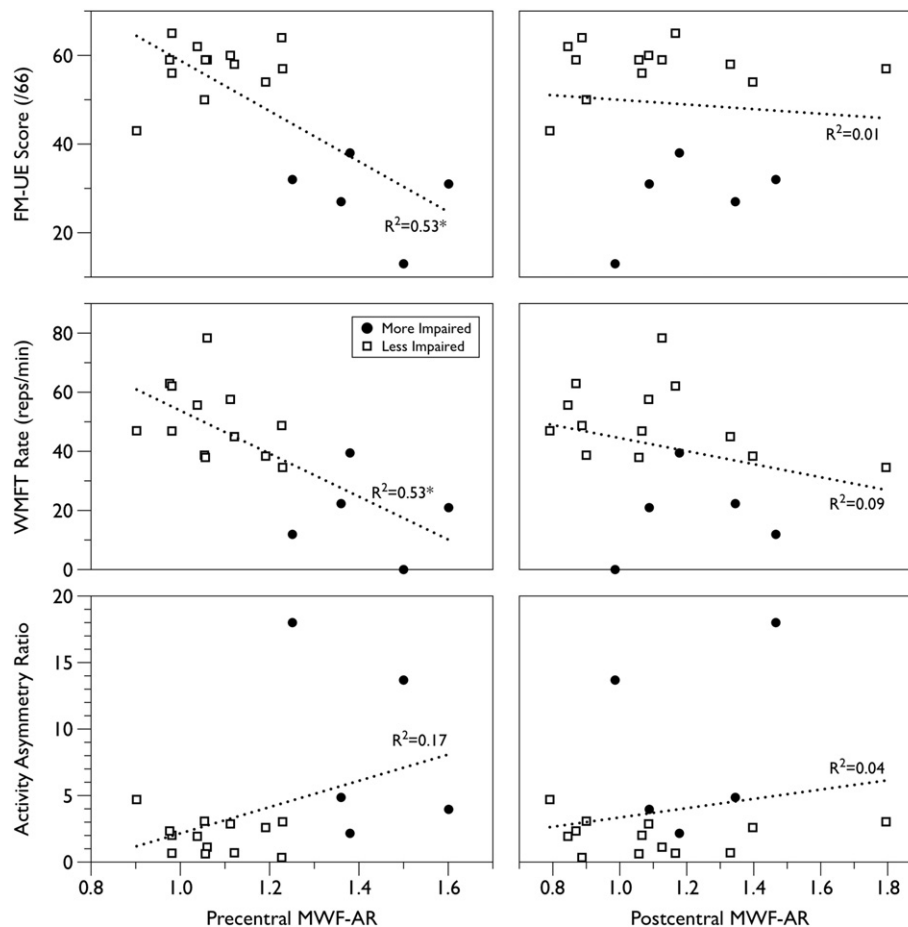

Fig. 5. Simple regressions (correlations) between MWF and FM-UE score, WMFT-rate and activity-AR for sensorimotor regions of interest (precentral, postcentral). Significant correlations ($p < 0.05$) are denoted with *.

oligodendrocyte precursor cell proliferation may be dependent on skilled motor learning (Gibson et al., 2014; McKenzie et al., 2014) or exercise (Krityakiarana et al., 2010). Histological staining of myelin in adult rats following a 6-week paradigm of complex skill learning revealed a relationship between myelination and rate of learning, as well as an increase in FA in the contralateral hemisphere to the trained limb (Sampaio-Baptista et al., 2013). As emphasized in a recent review, myelination throughout adulthood is experience dependent and can be driven by relatively low-doses of repetitive, skilled motor training (Purger et al., 2015). Further, the disruption to ipsilesional myelin forming oligodendrocyte precursor cells caused by ischemia has been documented and identified as an important potential contributor to post-stroke white matter impairment and may account for some of the observed relationships between upper-extremity impairment and MWF-AR in the current study (Mifsud et al., 2014).

4.2. MWF-AR is a predictor of motor impairment and function, but not activity

MWF-AR in the precentral region was a significant predictor of upper-extremity impairment and motor function in individuals with chronic stroke. Due to the specific pathology of stroke, MWF asymmetry rather than absolute MWF may reveal interhemispheric adaptations that are not captured by investigating each hemisphere independently. The underlying microstructural relationship between white matter integrity and motor impairment may be explained, in part, by myelination of motor cortical white matter tracts. Although current models for stroke recovery identify the first three months following stroke as the most critical time period for spontaneous reduction of impairment (Byblow et al., 2015), biomarkers, such as subcortical primary motor MWF asymmetry, may have the potential to serve as further indictor of outcome status beyond the sub-acute phase, even when functional improvements appear to have plateaued.

Conversely, sensorimotor MWF-AR was not a significant predictor of upper-extremity activity. Activity monitoring using accelerometry has gained increasing prevalence in research due to predictive relationships between acutely measured activity counts and motor impairment three-months post-stroke (Gebruers et al., 2013). However, others have demonstrated that despite functional improvements in the upper-extremity 12 months after stroke, use of the contralesional limb does not increase in correspondence (Rand and Eng, 2015). The lack of a relationship between upper-extremity use and myelination corresponds with other investigations, which have shown limited or no associations between upper-extremity activity and motor cortical activation, measured with functional magnetic resonance imaging (Kokotilo et al., 2010), as well as ipsilesional and contralesional resting state connectivity (Urbin et al., 2014). During the chronic phase of stroke, the limited predictive value of activity monitoring observed in the current study may be related to a plateau of observed functional improvement and limited cortical plasticity, compared to acute/sub-acute phases (Kwakkel and Kollen, 2013; Meyer et al., 2015). In addition, the sensitivity of activity monitoring using accelerometry over multiple days may be limited due to individual schedules of activity that may arise from changes in the weather or day of the week (i.e. weekday vs. weekend). We did observe a significant difference in the activity-AR between the more impaired and less impaired groups, which indicates that upper-extremity activity ipsilateral to the lesioned hemisphere is more predominant in more impaired individuals. While the specific aims of the current study were to explore relationships between upper-extremity activity and MWF asymmetry, future work will benefit from using accelerometry to quantify the specific 'real-world' activities and the intensity of those activities (Bailey et al., 2015; Hayward et al., 2015). Recent advances in accelerometry analysis may allow for a more in-depth investigation of potential relationships between markers of activity asymmetry and structure, such as MWF.

4.3. Limitations

As this study used several relatively novel methodologies, there were some limitations that which could be addressed in future iterations of similar research. Firstly, this study was limited by the inability to generate cortical segmentations in four participants with stroke, primarily due to lesion volume. Three of the four segmentations that could not be completed by Freesurfer corresponded to the participants with the three largest lesion volumes. Despite this, others have determined that Freesurfer is currently the best tool available to perform cortical segmentation in individuals with stroke (Li et al., 2015). The MWF to Freesurfer registration method utilized in the current study was developed to limit errors associated with manual ROI drawing and to allow for more expansive ROI investigation, which was successful in most participants. In future investigations that utilize an ROI based MWF analysis, it may be prudent to exclude participants who have a lesion volume which covers >50% of the lesioned hemisphere. In part because of the complications with cortical segmentation in some individuals, this study was also limited by the small N in the more impaired group. Despite the limited number of participants in this group, the observed effect sizes were large enough to demonstrate important differences between the groups. Finally, the specificity of the MWF ROI analysis is limited by the thickness of the voxel (5 mm). This is a current limitation of a new scanning sequence that optimizes the practical challenge of minimizing scan length with maximizing scan resolution. We compensated for this by reconstructing at a 2.5 mm thickness using a zero-filled interpretation method. In addition, larger ROIs were selected to minimize the need for fine spatial sensitivity.

5. Conclusions

Results from this study build upon previous work to identify underlying microstructural relationships between MWF and upper extremity motor outcomes. Importantly, these results indicate that MWF asymmetry in the precentral area is a predictor of upper-extremity impairment and motor function and that simply monitoring activity asymmetry between limbs does not predict impairment or function in individuals with chronic stroke. In addition, we identified that MWF-AR is more pronounced in more impaired individuals and may be driven by increased MWF in the contralesional hemisphere. Further inquiry into MWF as a biomarker of recovery potential is required earlier post stroke using a longitudinal approach to unpack the time-course associated with the asymmetry outcome. In addition, future investigations may benefit from utilizing more sensitive accelerometry analysis techniques that will help to identify the intensity and symmetry profiles of limb use after stroke.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Acknowledgements

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