



# Fronto-parietal involvement in chronic stroke motor performance when corticospinal tract integrity is compromised

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## ABSTRACT

**Background:** Preserved integrity of the corticospinal tract (CST) is a marker of good upper-limb behavior and recovery following stroke. However, there is less understanding of neural mechanisms that might help facilitate upper-limb motor recovery in stroke survivors with extensive CST damage.

**Objective:** The purpose of this study was to investigate resting state functional connectivity in chronic stroke survivors with different levels of CST damage and to explore neural correlates of greater upper-limb motor performance in stroke survivors with compromised ipsilesional CST integrity.

**Methods:** Thirty chronic stroke survivors (24 males, aged  $64.7 \pm 10.8$  years) participated in this study. Three experimental sessions were conducted to: 1) obtain anatomical (T1, T2) structural (diffusion) and functional (resting state) MRI sequences, 2) determine CST integrity with transcranial magnetic stimulation (TMS) and conduct assessments of upper-limb behavior, and 3) reconfirm CST integrity status. Participants were divided into groups according to the extent of CST damage. Those in the extensive CST damage group did not show TMS evoked responses and had significantly lower ipsilesional fractional anisotropy.

**Results:** Of the 30 chronic stroke survivors, 12 were categorized as having extensive CST damage. Stroke survivors with extensive CST damage had weaker functional connectivity in the ipsilesional sensorimotor network and greater functional connectivity in the ipsilesional fronto-parietal network compared to those with preserved CST integrity. For participants with extensive CST damage, improved motor performance was associated with greater functional connectivity of the ipsilesional fronto-parietal network and higher fractional anisotropy of the ipsilesional rostral superior longitudinal fasciculus.

**Conclusions:** Stroke survivors with extensive CST damage have greater resting state functional connectivity of an ipsilesional fronto-parietal network that appears to be a behaviorally relevant neural mechanism that improves upper-limb motor performance.

## 1. Introduction

Stroke is a global leading cause of chronic disability, with an estimated 116 million disability adjusted life years lost annually (Johnson et al., 2019). Many of the 80 million global chronic stroke survivors experience ongoing disability that affects quality of life (Johnson et al.,

2019). Greater understanding of stroke recovery, particularly for those with severe impairment, is required to improve outcomes and reduced disability.

Assessing correlates between motor behavior and both neuroimaging and neurophysiological assessments in chronic stages following stroke might help identify potential mechanisms of motor recovery. For upper-

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limb motor recovery, integrity of the ipsilesional corticospinal tract (CST) has been associated with motor system recruitment and motor behavior (Hordacre et al., 2020; Lotze et al., 2012; Stinear et al., 2007; Ward et al., 2006). These cross-sectional investigations led to CST integrity being confirmed as an important biomarker of stroke recovery (Boyd et al., 2017; Stinear et al., 2012, 2017). CST integrity can be determined by observing motor evoked potentials (MEPs) following transcranial magnetic stimulation (TMS) to the ipsilesional motor cortex. By stimulating the motor cortex and recording a response in a peripheral muscle, MEP status provides an indication of descending integrity along the CST. The presence of a MEP (MEP+) provides a functional measure of CST integrity, while absence (MEP-) suggests integrity is compromised. However, TMS usually assesses only MEPs from a single target muscle. In contrast, diffusion weighted imaging reflects white matter integrity of pathways passing through a region of interest such as the posterior limb of the internal capsule or cerebral peduncle. These pathways include tracts from the motor cortex as well as more anterior frontal regions and parietal regions (Marshall et al., 2000). Similarly, structural imaging can be used to determine the overlap between the lesion and the CST (Zhu et al., 2010). Given this level of evidence, the International Stroke Recovery and Rehabilitation Roundtable recommended that measures of CST integrity are ready for use in clinical trials to guide stratification into subgroups and/or to predict outcome (Boyd et al., 2017).

However, when CST integrity is significantly compromised (e.g. MEP-), it is unclear whether recovery is possible, to what extent and by what mechanism. While recovery may be slower, it is interesting to note that several studies documenting CST damage at either autopsy (Aguilar, 1969) or imaging (Fries et al., 1993; Marshall et al., 2000) have reported recovery from severe hemiparesis to near-normal behavior. This recovery might occur from extensive, and potentially bilateral, reorganization of motor networks. Previous studies have reported increased activity of secondary motor networks in both the ipsilesional and contralesional hemispheres in stroke survivors with more severe stroke or greater CST damage (Rehme et al., 2011; Ward et al., 2006). Along similar lines, non-invasive brain stimulation to disrupt activity of secondary motor networks, including the contralesional motor cortex and ipsilesional dorsal premotor cortex, was detrimental for upper-limb behavior in stroke survivors with greater CST damage (Bradnam et al., 2012; Fridman et al., 2004). This suggests secondary motor networks have an important role in facilitating motor performance and recovery for stroke survivors where CST integrity is compromised.

Investigating neural mechanisms of motor behavior in more severely impaired stroke survivors can be challenging, particularly as many available techniques, such as task fMRI, require performance of a motor task. Resting state fMRI is an alternative that has been proposed as a promising imaging modality to identify biomarkers of impairment and recovery following stroke (Boyd et al., 2017; Lindow et al., 2016; Rehme and Grefkes, 2013). A commonly derived metric in resting state fMRI analysis is functional connectivity, which is the level of correlation in spontaneous blood oxygen level-dependent (BOLD) signal between two brain areas in the absence of any task. BOLD signals across the brain also cluster into several known, and distinct, neural networks, similar to those reported during a task (Fox and Raichle, 2007; Smith et al., 2009; Tavor et al., 2016). Several studies have reported decreased inter-hemispheric resting state connectivity between motor cortices is associated with reduced upper-limb behavior (Carter et al., 2010, 2011; Chen and Schlaug, 2013; Golestani et al., 2012; Park et al., 2011; Rehme et al., 2014; Urbin et al., 2014). In addition, it has also been reported that the ipsilesional resting state fronto-parietal network is disrupted in sub-acute and chronic stroke, suggesting an additional network that may contribute to motor control deficits following stroke (Inman et al., 2012). Although it is not clear how CST damage modulated the relationship between resting state network activity and stroke recovery in these previous studies, it may be that interhemispheric sensorimotor or ipsilesional fronto-parietal networks underpin compensatory neural

change to facilitate motor behavior.

The purpose of this prospective observational study was to investigate resting state functional connectivity in chronic stroke survivors with different levels of CST damage and to explore neural correlates of greater upper-limb motor performance in stroke survivors with compromised ipsilesional CST integrity. This was achieved by investigating upper limb motor performance, MEP status, diffusion weighted imaging and resting state functional networks. Initially we compared behavioral and imaging measures between MEP+ and MEP- people with stroke to gain insight into recovery when the CST is damaged. We then conducted an exploratory analysis to identify structural and functional neural correlates associated with greater upper-limb motor behavior in patients who are MEP-, suggesting they have experienced significant CST damage. Investigating the role of functional networks in motor behavior for stroke survivors with significant CST damage could lead to new treatment strategies and targets to support recovery in people who experience severe motor impairment.

## 2. Methods

### 2.1. Participants

Thirty people with chronic stroke were prospectively recruited from the community via advertisement in hospitals, stroke support websites, social media and newspapers. Inclusion criteria were a first ever ischemic stroke or intracerebral hemorrhage (ICH) with any level of upper-limb impairment (Fugl-Meyer < 66), at least 6 months post ictus, ≥18 years of age, and had no contraindications for MRI or TMS (Rossi et al., 2011). Exclusion criteria were language or cognitive impairments preventing full participation. A subset of participants included in this study have been reported in our previous work investigating electroencephalography measures of brain function (Hordacre et al., 2020). Participants provided written informed consent. Ethical approval was provided by the University of South Australia Human Research Ethics Committee (ID 36781).

### 2.2. Experimental protocol

Three experimental sessions were conducted at a similar time of day (morning). At the first session, anatomical (T1, T2), structural (diffusion) and functional (resting state) MRI sequences were performed. The second session was performed within 5 days of the first (median 3.5 (range 2–5) days) and involved neurophysiological testing to determine MEP status followed by upper-limb behavioral assessments. The third session was conducted 14 days later (median 14 (range 13–15) days), consisting of repeat neurophysiological testing to confirm MEP status.

### 2.3. Behavioral measures

The action research arm test (ARAT), Fugl-Meyer upper extremity (FM-UE) and grip strength assessments were performed to assess paretic upper-limb motor behavior. Behavioral measures were assessed by an experienced therapist blinded to MEP status and neuroimaging assessments. The ARAT is a valid and reliable measure of upper-limb activity, with higher scores indicative of greater activity (range 0–57) (Lyle, 1981; Pike et al., 2018). The FM-UE is a valid and reliable measure of upper-limb sensorimotor impairment, with higher scores indicating less impairment (range 0–66) (Brunnstrom, 1966; Gladstone et al., 2002). Finally, grip strength of the paretic hand was assessed as the maximal grip response from three attempts (SH5001 Saehan Hydraulic Hand Dynamometer). To obtain a comprehensive upper-limb measure of activity and impairment, a single combined behavioral measure was determined using a principal component analysis. Briefly, a principal component analysis is a multivariate statistical technique that reduces data dimensionality while preserving maximal variance of the original data. In this case, the ARAT, FM-UE and grip strength were combined to

produce a single behavioral measure that reflected variance of the original upper-limb outcome measures.

#### 2.4. Electromyography

Two Ag-AgCl surface electrodes (Ambu, Ballerup, Denmark) were positioned over the first dorsal interosseous (FDI) muscle of the paretic hand with a ground strap around the wrist. Skin was prepared by cleaning with alcohol and lightly abrading with NuPrep paste. Signals were sampled at 5 kHz (CED 1401, Cambridge, UK), amplified 1000X (CED 1902, Cambridge, UK), filtered (20–1000 Hz) and stored for offline analysis (Signal v4.09, Cambridge Electronic Design, Cambridge, UK).

#### 2.5. Transcranial magnetic stimulation

Monophasic TMS pulses were applied to the ipsilesional motor cortex at a frequency of  $0.2 \text{ Hz} \pm 10\%$  to determine MEP status. TMS was applied with a figure-of-eight coil (internal wing diameter 70 mm) connected to a Magstim 200 stimulator (Magstim, Whitland, Dyfed, UK). The coil was positioned tangentially over the scalp with the handle pointing  $45^\circ$  posterolaterally to induce a posterior-anterior current across the hand motor area. Stimulation intensity was incrementally increased, the coil position was systematically moved anterior-posterior and medial-lateral in small increments, and the coil handle was rotated to attempt to evoke a consistent MEP in the FDI and identify the ‘motor hotspot’. For MEP+ a participant needed to have at least five out of ten MEPs of any amplitude within a window of 15–40 ms after the TMS pulse. Where a MEP could not be found, even at 100% of maximal stimulator output, participants were asked (where possible) to perform an active contraction to confirm a consistent MEP could not be obtained. If this did not result in a consistent MEP, the participant was deemed MEP-. For all participants, MEP status was confirmed at session three.

Corticospinal excitability was determined at session two for MEP+ participants. The coil location for the ‘motor hotspot’ was marked on the scalp using a water-soluble felt tip marker for consistent coil placement. Resting motor threshold (RMT) was defined as the minimum intensity required to evoke a MEP with peak-to-peak amplitude  $\geq 50 \mu\text{V}$  in at least five out of ten consecutive trials in the relaxed FDI. Corticospinal excitability was determined as the peak-to-peak amplitude of 30 MEPs at 120% RMT (Goldsworthy et al., 2016).

#### 2.6. Magnetic resonance imaging

Magnetic resonance imaging was performed using a Siemens 3T MAGNETOM Skyra scanner (Siemens, Erlangen, Germany) with a 64-channel head coil. The scan protocol was: T1-weighted image MPRAGE (voxel  $1 \text{ mm} \times 1 \text{ mm} \times 1 \text{ mm}$ , repetition time (TR) = 2300 ms, echo time (TE) = 2.98 ms, flip angle =  $9^\circ$ ); T2-weighted fluid-attenuated inversion recovery (FLAIR; voxel  $1 \text{ mm} \times 0.5 \text{ mm} \times 0.5 \text{ mm}$ , TR = 5000 ms, TE = 393 ms); diffusion-weighted spin echo pulse sequence with diffusion gradients along 64 directions (voxel  $2 \text{ mm} \times 2 \text{ mm} \times 2 \text{ mm}$ , TR = 4200 ms, b-value =  $2000 \text{ s/mm}^2$ , 10 volumes without diffusion weighting b-value =  $0 \text{ s/mm}^2$ , GRAPPA acceleration factor 2 and SMS acceleration factor 3); and resting state fMRI (voxel  $2.4 \text{ mm} \times 2.4 \text{ mm} \times 2.4 \text{ mm}$ , TR = 735 ms, TE = 36 ms, SMS acceleration factor 8, 2 repeats of 6 min duration, 490 volumes for each, total of 980 volumes).

#### 2.7. Magnetic resonance imaging pre-processing and statistical analysis

Image processing was carried out using FSL (FMRIB Software Library, Oxford, UK) (Jenkinson et al., 2012; Smith et al., 2004). For T1- and T2-weighted images, non-brain tissue was removed using BET. T1-weighted images were registered to the T2-weighted images using FLIRT and lesion masks manually drawn to determine lesion location and volume.

Preprocessing of resting state functional data was performed in FEAT

and included motion correction using MCFLIRT, B0 unwarping with a dual echo-time gradient echo fieldmap, brain extraction, high-pass temporal filtering (cut-off 150 s), no slice timing correction, no intensity normalization and no spatial smoothing. For each subject, the two preprocessed 4D acquisitions were temporally concatenated and denoised using Multivariate Linear Optimised Decomposition into Independent Components (MELODIC) with automatic dimensionality estimation. Components that were clearly non-neuronal were manually removed. The de-noised 4D acquisition was non-linearly transformed to standard space, using a combined transformation from the results of: (i) motion correction; (ii) registration of the fMRI volume used as the motion correction reference, to the T1-weighted image using boundary-based registration; and (iii) the registration of the T1-weighted image to the MNI template using FNIRT. Functional data for each subject were then concatenated across subjects to create a single 4D dataset. For group analysis, subjects with left hemispheric lesions were flipped in the x-axis so that all lesions were displayed on the right hemisphere.

Resting state networks were identified by decomposing data using MELODIC into 30 components. Resting state networks were confirmed visually in comparison to previously defined maps (Beckmann et al., 2005). The selected networks of interest were the sensorimotor network and ipsilesional fronto-parietal network which were generated by the group MELODIC. Between-group analyses were carried out using dual regression to obtain subject specific time courses and spatial maps. A design matrix compared resting state networks of interest between 1) MEP+ and MEP- participants with two contrasts (MEP+ > MEP- and MEP- > MEP+) and 2) MEP- participants with high and low motor performance with two contrasts (high > low motor performance and low > high motor performance, high and low motor performance determined by median split of the combined behavioral measure). Analysis was carried out using FSL randomise non-parametric permutation testing with 5000 permutations for each independent component. Threshold-free cluster enhancement was used to control for multiple comparisons across voxels. Level of significance was adjusted for multiple comparisons, as there were two networks of interest and two-tailed testing (adjusted  $p < 0.013$ ).

To further explore resting state functional connectivity in the MEP- group a seed-based analysis was conducted, and high and low motor performance groups compared. A seed mask was obtained for the lesioned motor cortex from the group MELODIC sensorimotor network. Dual regression was used to obtain subject specific time courses and determine seed-based connectivity maps for each subject. A design matrix compared MEP- participants with high and low motor performance with two contrasts (high > low and low > high motor performance). Analysis was performed with FSL randomise (5000 permutations) and threshold-free cluster enhancement controlled for multiple comparisons across voxels.

Diffusion-weighted imaging data were analyzed using FMRIB’s Diffusion Toolbox (FDT). Pre-processing steps included B0-inhomogeneity distortion correction using two images with opposing phase encoding and FSL’s Topup function. Head motion and eddy current distortions were corrected using FSL’s Eddy function. A diffusion tensor was fitted at each voxel using DTIFIT which was subsequently used to estimate fractional anisotropy (FA). As a marker of CST integrity, FA within two regions of interest was determined; the posterior limb of the internal capsule (PLIC) and the cerebral peduncle. Similar to previous studies, the left and right PLICs and cerebral peduncles were delineated with reference to individual colorized FA images and the JHU white-matter tractography atlas available within FSL (Feldman et al., 2018; Hordacre et al., 2020). For the cerebral peduncles, we ensured the regions of interest did not extend into the substantia nigra (Burke et al., 2014). Mean FA values were calculated for each PLIC and cerebral peduncle (range 0 (isotropic diffusion) to 1 (anisotropic diffusion)). An FA asymmetry index was calculated as  $FA_{AI} = (FA_C - FA_I) / (FA_C + FA_I)$  where  $FA_C$  was the mean FA value of the contralesional PLIC/cerebral peduncle and  $FA_I$  was the mean FA value of the ipsilesional PLIC/

cerebral peduncle. Values for  $FA_{AI}$  ranged between  $-1$  and  $1$ , with a zero-value indicating symmetrical FA, negative values indicating reduced contralesional FA and positive values indicating reduced ipsilesional FA.

To further investigate the neurophysiology of stroke motor performance in the MEP- group, a voxelwise statistical analysis of FA was carried out using tract-based spatial statistics (TBSS). First, FA images were normalised to a standard template (FMRIB58\_FA) using a nonlinear registration. Subjects with left hemispheric lesions were flipped in the x-axis so that all lesions were displayed on the right hemisphere. A mean subject FA image was then created and used to generate an FA skeleton (threshold  $FA > 0.2$ ). Each subject's FA map was projected onto the FA skeleton for statistical analysis. Voxelwise, permutation-based (5000 permutations), non-parametric testing was performed to test for differences in white matter structure between two groups (high and low motor performance). Results were FWE-corrected to control for multiple comparisons across voxels using threshold-free cluster enhancement. To determine whether TBSS findings were driven by lesion distributions, overlap between the significant voxels identified in the TBSS analysis and lesion masks were compared between groups (independent  $t$ -test).

### 2.8. Statistical analysis of demographics, clinical and behavioral data

Statistical analysis was performed in SPSS (IBM Corp., Released 2016, IBM SPSS for Windows, Version 24.0, NY, USA) with level of significance set at  $p < 0.05$  (unless otherwise stated). Normality of data was checked, and where required, non-parametric tests were applied. Participant demographics and clinical characteristics were first compared between MEP+ and MEP- stroke participants. Age and grip strength were compared using independent  $t$ -tests. Time since stroke, lesion volume, ARAT, FM-UE, the combined behavioral measure and  $FA_{AI}$  of the CST were compared with Mann-Whitney U tests as assumptions of normality were violated. Gender and pathology (ischemic or ICH) were compared between groups using Fisher's exact test.  $FA_{AI}$  of the CST was correlated with the combined behavioral measure (Spearman rank). Variance in the combined behavioral measure was analyzed with Levene's test. MEP- stroke were split into high and low motor performance groups based on a median split of the combined behavioral measure. Age, time since stroke, lesion volume, the combined behavioral measure and  $FA_{AI}$  of the CST were compared between high and low motor performance groups using independent  $t$ -tests. Gender and pathology were compared between high and low motor performance groups using Fisher's exact tests.

## 3. Results

### 3.1. Participant characteristics

Thirty stroke survivors (24 males, aged  $64.7 \pm 10.8$  years and  $4.1 \pm 3.2$  years (range 0.5 to 14.1 years) post stroke) completed the study. Eighteen stroke survivors were MEP+ and twelve were MEP-. MEP status assessment repeated 14 days later confirmed the same categorization of MEP+ and MEP- for each participant. Of those who were MEP+, average RMT was  $59.4 \pm 11.7\%$  of maximal stimulator output and average MEP amplitude was  $0.33 \pm 0.22$  mV. Demographics and clinical characteristics for MEP groups are reported in Table 1. The combined behavioral measure accounted for 88% variance in the FM-UE, ARAT and grip strength assessments. Participant lesion maps are provided in Fig. 1 and individual participant data are reported in supplementary Table 1.

### 3.2. Measures of CST integrity are associated with post stroke behavior

As expected,  $FA_{AI}$  of the CST was larger in the MEP- group (PLIC: MEP- group,  $0.27 \pm 0.21$ ; MEP+ group,  $0.04 \pm 0.05$ ;  $U = 11.0$ ,  $p <$

**Table 1**

Participant demographics and clinical characteristics for MEP+ and MEP- stroke survivors.

	MEP+	MEP-	Statistic
Age (years, mean $\pm$ SD)	66.4 $\pm$ 10.9	62.0 $\pm$ 10.4	$t_{(28)} = 1.11$ , $p = 0.28$
Gender (n, male/female)	14/4	10/2	$p = 0.55$
Time since stroke (years, mean $\pm$ SD)	3.2 $\pm$ 2.3	5.4 $\pm$ 4.0	$U = 70.0$ , $p = 0.11$
Pathology (n, ischemic/ICH)	17/1	10/2	$p = 0.35$
Lesion volume (cm <sup>3</sup> , mean $\pm$ SD)	37.1 $\pm$ 61.5	47.4 $\pm$ 44.3	$U = 76.0$ , $p = 0.19$
Combined behavioral measure (mean $\pm$ SD)	0.65 $\pm$ 0.45	-0.97 $\pm$ 0.79	$U = 13.0$ , $p < 0.001$
FM-UE (mean $\pm$ SD)	52.6 $\pm$ 7.4	27.7 $\pm$ 13.6	$U = 14.0$ , $p < 0.001$
ARAT (mean $\pm$ SD)	51.2 $\pm$ 8.4	15.8 $\pm$ 18.4	$U = 13.0$ , $p < 0.001$
Grip strength (kgf, mean $\pm$ SD)	19.5 $\pm$ 7.2	7.5 $\pm$ 5.8	$t_{(28)} = 4.88$ , $p < 0.001$

Abbreviations: ARAT, action research arm test; FM-UE, Fugl-Meyer upper extremity; ICH, intracerebral hemorrhage; kgf, kilogram-force. Note, bold indicates a statistically significant difference between MEP+ and MEP- groups.

0.001; cerebral peduncle: MEP- group,  $0.12 \pm 0.08$ ; MEP+ group,  $0.02 \pm 0.05$ ;  $U = 35.0$ ,  $p = 0.001$ ). The behavioral principal component was greater in the MEP+ group (Table 1).  $FA_{AI}$  values closer to zero were associated with better upper-limb motor performance on the combined behavioral measure (PLIC:  $\rho = -0.75$ ,  $p < 0.001$ ; cerebral peduncle:  $\rho = -0.72$ ,  $p < 0.001$ ; Fig. 2).

### 3.3. Different resting state connectivity between MEP+ and MEP- participants

Functional connectivity in two of the contrasts reached the adjusted level of significance ( $p < 0.013$ ), indicating a difference between MEP+ and MEP- stroke survivors. Firstly, a cluster of 89 voxels was found to have greater functional connectivity with the ipsilesional sensorimotor network in stroke participants that were MEP+ compared to those who were MEP- (peak z-statistic 4.21, MNI coordinates 64 0 30, Fig. 3). Secondly, two clusters were found to have greater functional connectivity with the ipsilesional fronto-parietal network in stroke participants that were MEP- compared to those who were MEP+ (cluster 1, 303 voxels, peak z-statistic 5.38, MNI coordinates 54 30 32; cluster 2, 54 voxels, peak z-statistic 4.79, MNI coordinates 60 -52 26, Fig. 3). No other contrasts were significant.

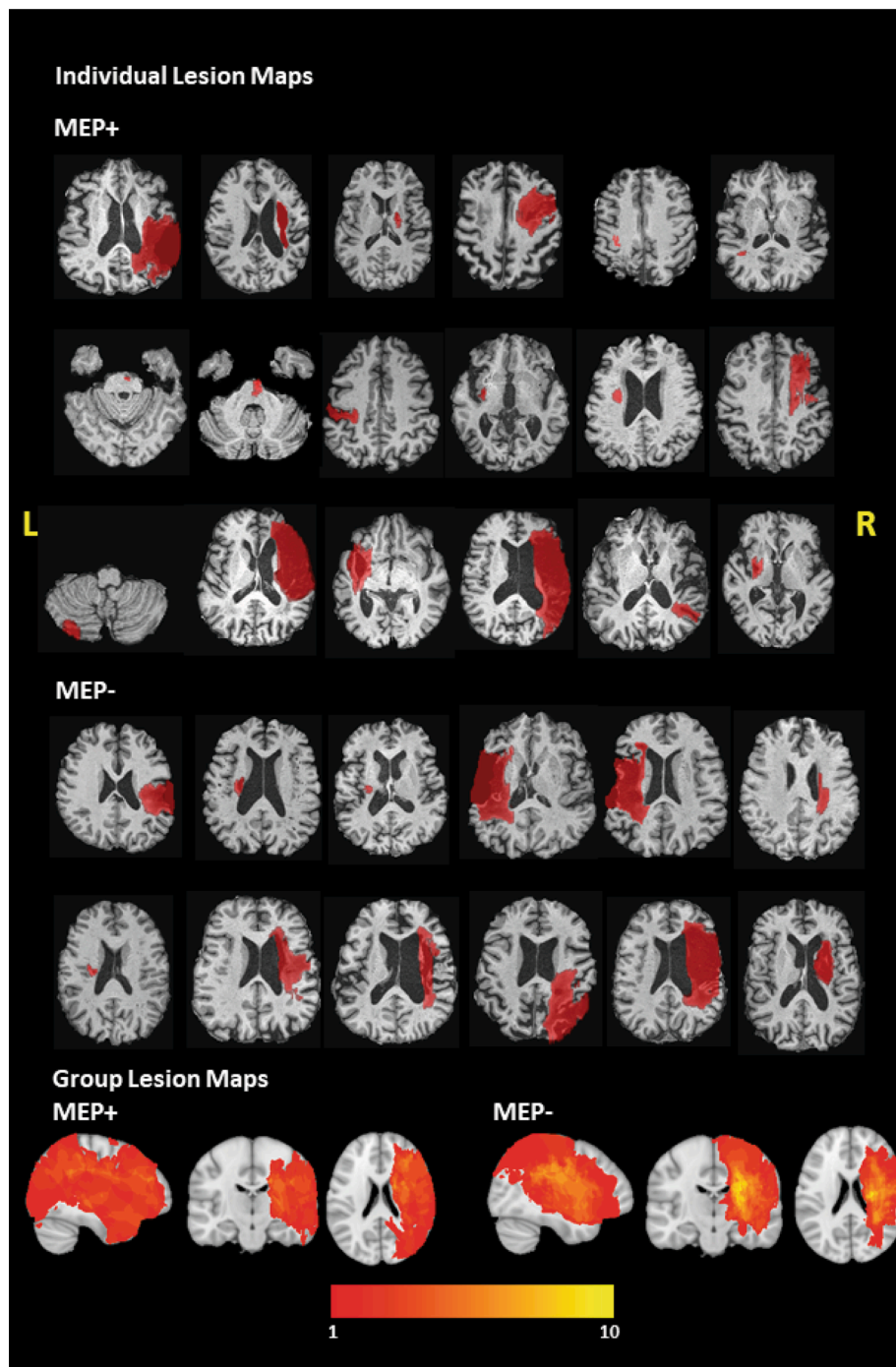
### 3.4. Upper-Limb behavior for MEP- stroke survivors

There was significantly more variance in the behavioral principal component for the MEP- group ( $F = 3.51$ ,  $p = 0.04$ ), suggesting a wide range of upper-limb motor performance scores for MEP- stroke survivors. This is emphasized by the range of individual behavioral scores within MEP- stroke survivors (ARAT range 0-56, FM-UE range 4-53, grip strength range 0-18 kg force; Fig. 4). To gain some insight into the neural correlates of upper-limb motor performance in MEP- stroke survivors, the group was split into high and low motor performance. Participant characteristics for each group are reported in Table 2.

### 3.5. Connectivity and upper-limb motor performance in stroke survivors with compromised CST integrity

The high and low motor performance group in stroke survivors who were MEP- showed differences in functional connectivity for the ipsilesional fronto-parietal network, but not the interhemispheric sensorimotor network. Specifically, two clusters were found to have greater functional connectivity with the ipsilesional fronto-parietal network in the high motor performance group (Fig. 4). One cluster contained 36





**Fig. 1.** Individual and group lesion maps. Images for individual lesion maps are shown in the axial plane at the level of the largest cross-sectional area of the lesion. Lesion tracings for each participant are shown in red. Lesion tracings for MEP+ stroke survivors are shown in the top three rows and MEP- stroke survivors are shown in the following two rows. Group lesion maps are shown for MEP+ and MEP- participants. Data is shown in standard space and for the group maps and all image analysis, data was flipped about the midline so that all lesions appear in the right hemisphere ( $X = 40, Y = -18, Z = 21$ ). The color bar shows number of participants with a lesion that includes the location. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

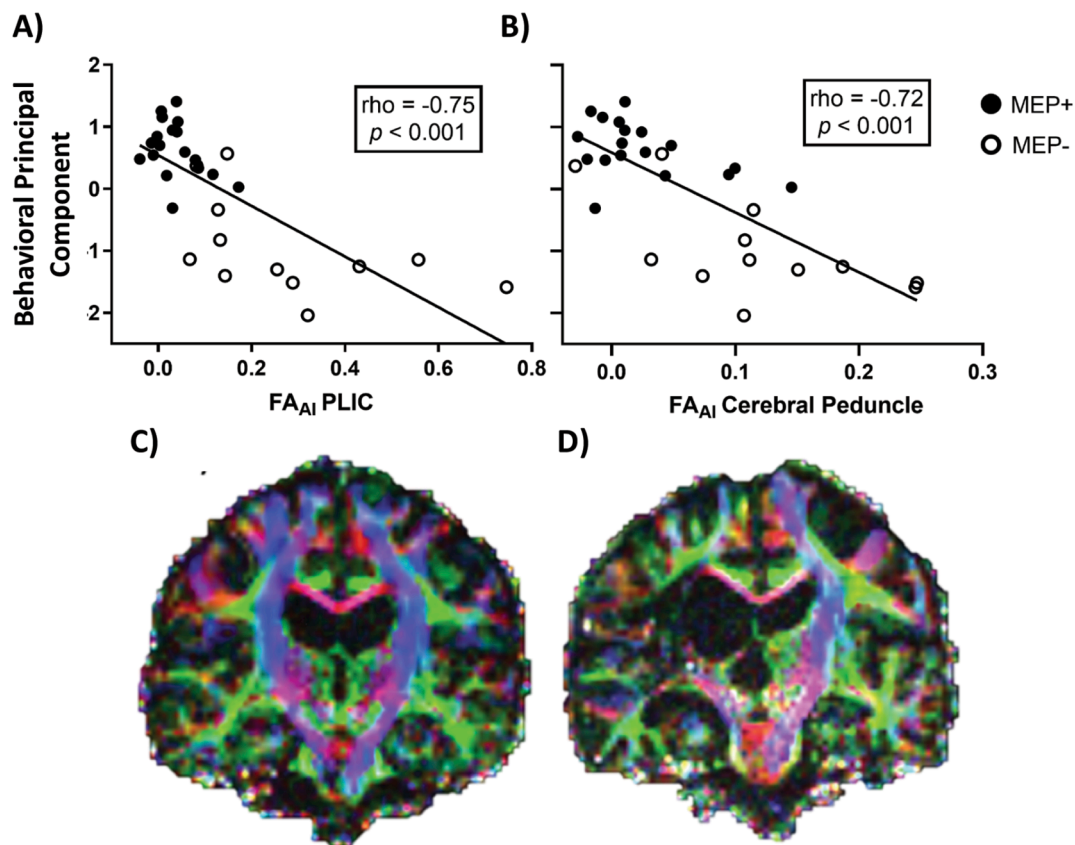
voxels, with a peak z-statistic of 9.33 (MNI coordinates 52 -58 34) and the second cluster contained 27 voxels, with a peak z-statistic of 5.02 (MNI coordinates 50 14 34). In addition, resting state analysis with a seed in the lesioned motor cortex found greater functional connectivity for voxels within the sensorimotor region (Fig. 4). The cluster contained 1011 voxels, with peak z-statistic of 2.19 (MNI coordinates 58 -6 32).

There were no statistical differences between groups for  $FA_{AI}$  of the PLIC (high motor performance  $0.19 \pm 0.18$ , low motor performance  $0.36 \pm 0.21$ ,  $t_{(10)} = -1.56$ ,  $p = 0.15$ ). However, there was a difference between groups for  $FA_{AI}$  of the cerebral peduncle (high motor performance  $0.06 \pm 0.05$ , low motor performance  $0.16 \pm 0.06$ ,  $t_{(10)} = -2.90$ ,  $p = 0.02$ ). For the whole brain TBSS analysis there was a cluster of voxels where FA was significantly different between groups, with those in the

high motor performance group showing greater FA in ipsilesional frontal pathways (Fig. 4). The cluster contained 177 voxels, with a peak z-statistic of 4.31 (MNI coordinates 20 16 41). This group difference did not appear to be driven by lesion distributions between groups. Only two participants from each group had lesions that overlapped voxels identified in the TBSS analysis and there was no statistical difference in overlap volume between groups ( $t_{(10)} = 0.56$ ,  $p = 0.59$ ).

#### 4. Discussion

Motor recovery following stroke involves a complex interaction between several determinants including structural integrity of white matter pathways and network level reorganization to compensate for

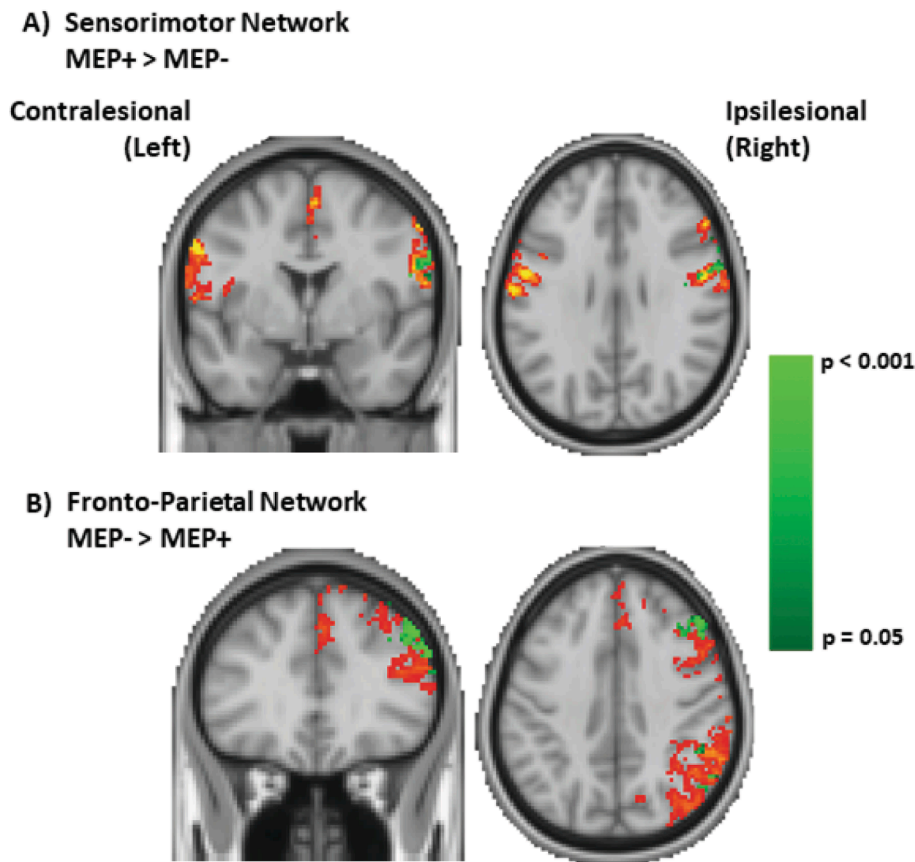


**Fig. 2.** Structural measure of corticospinal tract integrity correlated with upper-limb behavior. For both the PLIC (A) and cerebral peduncle (B), balanced FA between contralesional and ipsilesional CST (FA<sub>Ai</sub> values close to 0) was associated with greater upper-limb behavior. Lower FA of the ipsilesional compared to contralesional CST (positive FA<sub>Ai</sub> values) was associated with poor upper-limb behavior. C) Representative example of balanced FA between contralesional and ipsilesional CST (FA<sub>Ai</sub> values close to 0). D) Representative example of lower FA of the ipsilesional compared to contralesional CST (positive FA<sub>Ai</sub> value). For (C) and (D), red, green and blue represent the x, y, z diffusion directions respectively. Higher signal intensity (brightness) reflects higher FA such that brighter areas are more anisotropic than darker areas. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

neural damage and facilitate behavioral restoration (Hordacre et al., 2020; Lotze et al., 2012; Stinear et al., 2007; Ward et al., 2003, 2006). There is good evidence that residual integrity of the CST, as measured with MEP status, is a marker of stroke outcome and recovery of the upper-limb (Stinear et al., 2012, 2007). However, it is less clear if, or how, improvement of motor performance can be achieved in those who are MEP- and have more extensive CST damage. Using resting state fMRI, we found stroke survivors without MEPs exhibited greater functional connectivity of the ipsilesional fronto-parietal network compared to stroke survivors in whom a MEP could be elicited. Furthermore, in an exploratory sub-analysis, we observed that MEP- stroke survivors with higher levels of upper-limb behavior had greater resting state functional connectivity compared to those with poorer behavior. Greater connectivity was observed for the ipsilesional fronto-parietal network and between an ipsilesional motor cortex seed and the sensorimotor network. These findings are important for stroke rehabilitation as they provide insight into neural correlates of better motor performance in stroke survivors that have greater damage of the CST (MEP-).

The fronto-parietal network is, in part, thought to facilitate higher order cognitive motor function such as movement planning, decision making, sensory integration, spatial attention and awareness (Andersen and Cui, 2009; Binkofski et al., 1999). This suggests that the fronto-parietal network is implicated in both top-down and bottom-up attentional processes. In support, previous studies have suggested that stroke-related motor control deficits may arise due to disconnection with higher order motor areas such as the fronto-parietal network (Inman et al., 2012). Furthermore, electroencephalography studies have demonstrated motor and fronto-parietal network connectivity increases

with improvements in motor performance (Bönstrup et al., 2018; Wu et al., 2015), suggesting neuroplastic changes within this network may be important for stroke recovery. Our results extend this previous work, as we observed greater fronto-parietal resting state connectivity for MEP- compared to MEP+ stroke survivors. Greater fronto-parietal connectivity appeared to be behaviorally beneficial for stroke patients who were MEP-, suggesting this is likely to be an adaptive network response. Although we did not observe increased connectivity between a motor cortex seed and the fronto-parietal network, our results do suggest greater ipsilesional connectivity in the high motor performance group. As such, this result could indicate that increased reliance on higher order motor control networks is a neural compensation strategy when structural reserve is depleted in individuals with more severe stroke-related damage. In support, previous fMRI work indicates that functional connectivity of both the primary motor cortex and ventral premotor cortex was implicated in motor recovery for extremely impaired stroke survivors (Lee et al., 2017). Similarly, structural integrity of motor-ventral premotor pathway appears to increase specifically in patients with significant damage to the CST, likely indicating structural compensation to support motor output (Schulz et al., 2017). Along similar lines, we also observed greater microstructural integrity of white matter pathways likely reflecting the ipsilesional rostral superior longitudinal fasciculus in MEP- stroke survivors with better upper-limb behavior. This white matter pathway provides a structural connection between frontal and parietal brain regions which are associated with upper-limb behavior in chronic stroke (Schulz et al., 2015). However, given the cross-sectional nature of this study, we of course cannot know if greater fronto-parietal connectivity emerges as a result of stroke or other unknown factors.



**Fig. 3.** Resting state network differences between MEP+ and MEP- stroke survivors. A) MELODIC independent component (IC) for the sensorimotor network show in red-yellow and voxels that reached significance for the MEP+>MEP- contrast shown in green. Functional connectivity between the significant voxels and the whole ipsilesional sensorimotor network was greater for MEP+ stroke survivors compared to MEP- stroke survivors. B) MELODIC IC for the ipsilesional fronto-parietal network show in red-yellow and voxels that reached significance for the MEP->MEP+ contrast shown in green. Functional connectivity between the significant voxels and the whole ipsilesional fronto-parietal network was greater for MEP- stroke survivors compared to MEP+ stroke survivors. P-values have been corrected for multiple comparisons. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

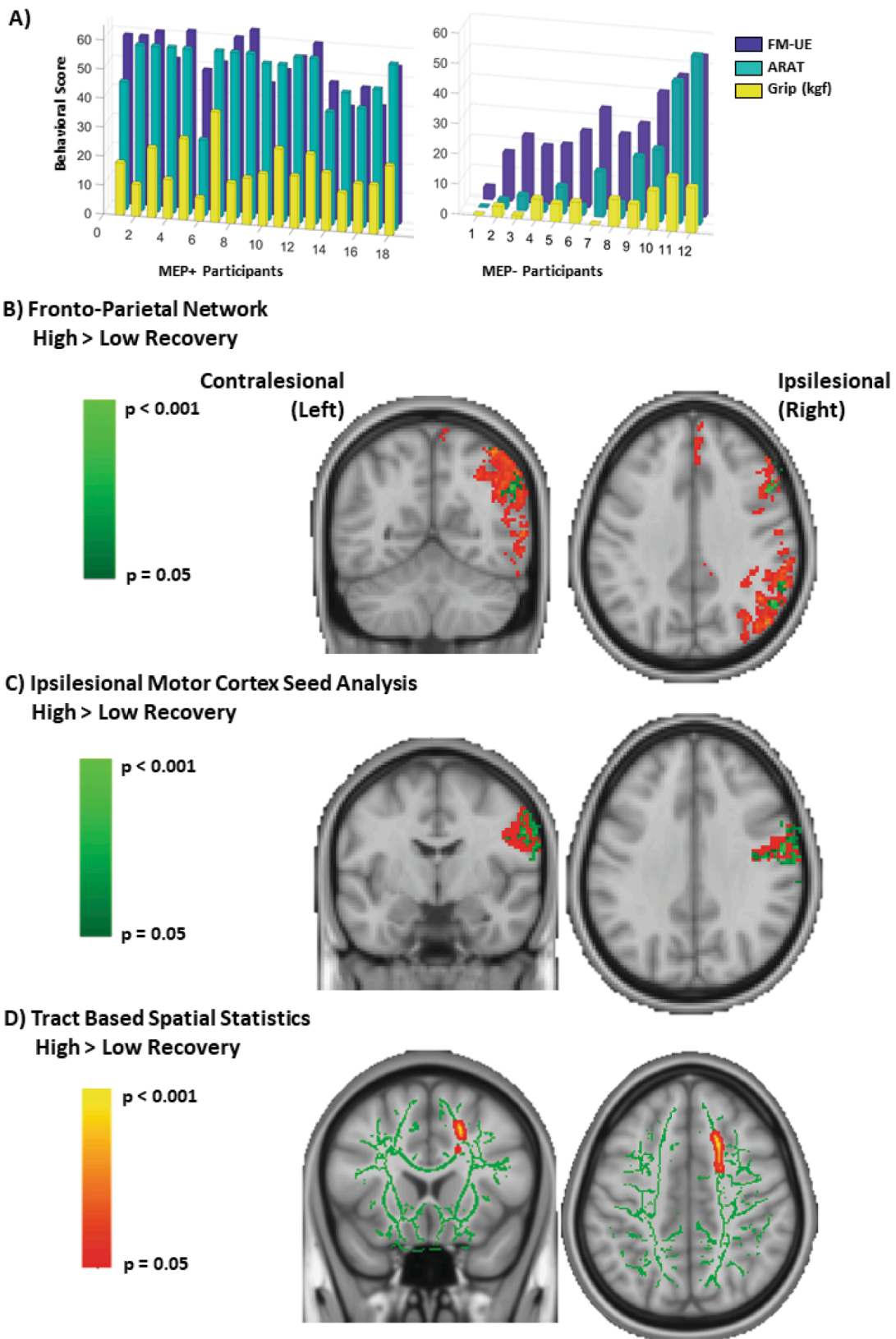
Similarly, we cannot discount the possibility that differences in this network are a consequence, rather than cause, of behavioral improvements. Further studies are required to investigate temporal characteristics of the changes in the fronto-parietal network and its relationship with upper-limb behavior.

How could an ipsilesional network support better motor performance in stroke survivors that are MEP-? As a MEP could not be observed, it is likely that descending motor pathways were significantly damaged, limiting potential for ipsilesional networks to drive motor output via these tracts. It is conceivable that some level of motor output is achieved via descending white matter tracts from premotor and supplementary motor regions which can influence motor output and response to therapy after stroke (Newton et al., 2006; Potter-Baker et al., 2016; Riley et al., 2011). While we systematically moved the TMS coil position anterior-posterior and medial-lateral in order to provide every opportunity to evoke a MEP, even from more anterior cortical regions, it remains possible that motor output could descend via white matter tracts from premotor and supplementary motor regions and that the fronto-parietal network may be modulating motor output through these pathways. In addition, we suggest there are two further explanations for this finding. First, there is some limitation to the use of MEPs as a marker of CST integrity. For example, similar to many previous studies, surface electromyography to record MEPs was positioned over a distal hand muscle (Hordacre et al., 2019; Lai et al., 2015; Stinear et al., 2017). While this method is likely to provide a reasonable surrogate of CST integrity, it may miss data on the corticospinal integrity for more proximal muscles. It is noteworthy that the Fugl-Meyer and ARAT assess multiple segments of the paretic limb, while the MEP was specific to a single distal hand muscle. Furthermore, microstructural integrity of the ipsilesional CST appeared to differ between high and low motor performance groups, but only reached statistical significance at the cerebral peduncle. The reason for this difference between the two groups of

interest is not clear, but has been noted in previous studies with motor function showing a stronger correlation with lower segments of the CST (Feldman et al., 2018). This may suggest a very limited residual capacity of the ipsilesional CST, enabling ipsilesional cortical regions to provide descending control of the paretic limb. In support, increased activation of the dorsal and ventral premotor cortex, supplementary motor area and inferior parietal cortex are associated with an improved motor performance, suggesting these may be neural resources to support motor recovery (Johansen-Berg et al., 2002a, 2002b; Loubinoux et al., 2003, 2007). Alternatively, there is some indication that premotor networks can contribute to motor output in the opposite hemisphere (Boudrias et al., 2012). This might enable the contralesional motor cortex to support upper-limb behavior through ipsilateral motor pathways. Although ipsilateral MEPs from the contralesional hemisphere were not investigated in this study, there did not appear to be differences in microstructure of white matter pathways in the contralesional hemisphere. Therefore, we favor an explanation that there may be a minor, but important, residual capacity of the ipsilesional CST to convey descending motor commands in those that are MEP-.

A testable hypothesis raised by findings from this study is to determine whether upregulation of the ipsilesional fronto-parietal network facilitates greater upper-limb behavior in stroke survivors with significant damage of the CST. While therapies to upregulate ipsilesional fronto-parietal connectivity are unlikely to restore motor performance to levels equivalent of MEP+ stroke survivors, such approaches could enable greater recovery than currently achieved and are therefore worth investigating. In support, a previous review raised the idea that targeting higher order areas, such as fronto-parietal networks, with non-invasive brain stimulation may be a better therapeutic strategy in stroke survivors with greater impairments compared to stimulation targeting the motor cortex directly (Plow et al., 2015). Based on the current study, we hypothesize increased fronto-parietal network connectivity in MEP-





(caption on next page)



**Fig. 4.** MEP– stroke survivors exhibit variable levels of upper-limb behavior, with those achieving greater motor performance exhibiting areas of increased functional connectivity with the fronto-parietal resting state network, greater connectivity between a motor cortex seed and the sensorimotor network and greater fractional anisotropy within an ipsilesional frontal white matter pathway. A) Individual behavioral outcomes for MEP+ and MEP– stroke survivors. Note that some MEP– stroke participants were able to achieve comparable upper-limb motor performance to those in the MEP+ group. MEP– stroke participants 1 to 6 were the low motor performance group and participants 7 to 12 were the high motor performance group. B) MELODIC IC for the ipsilesional fronto-parietal network show in red-yellow and voxels that reached significance for the high > low recovery contrast in dual regression shown in green. C) Ipsilesional motor cortex seed analysis, with the seed mask shown in red and voxels that reached significance for the high > low contrast shown in green. D) Tract based spatial statistics (TBSS) comparing FA in high and low motor performance groups for MEP– stroke patients. Binarized mean FA skeleton shown in green and voxels that reached significance for the high > low motor performance contrast shown in red-yellow. For B) and C) high and low motor performance groups were determined by a median split of the combined behavioral measure. P-values have been corrected for multiple comparisons. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

**Table 2**

Participant demographics and clinical characteristics for MEP– stroke survivors separated by high and low recovery.

	High Recovery	Low Recovery	Statistic
Age (years, mean $\pm$ SD)	57.7 $\pm$ 11.3	66.3 $\pm$ 8.1	$t_{(10)} = -1.52$ , $p = 0.16$
Gender (n, male/female)	4/2	6/0	$p = 0.46$
Time since stroke (years, mean $\pm$ SD)	5.3 $\pm$ 2.6	5.5 $\pm$ 5.4	$t_{(10)} = -0.10$ , $p = 0.93$
Pathology (n, ischemic/ICH)	5/1	5/1	$p = 1.00$
Lesion volume (cm <sup>3</sup> , mean $\pm$ SD)	45.4 $\pm$ 37.8	49.3 $\pm$ 53.6	$t_{(10)} = -0.14$ , $p = 0.89$
Combined behavioral measure (mean $\pm$ SD)	0.69 $\pm$ 0.96	-0.69 $\pm$ 0.37	$t_{(10)} = 3.30$ , $p = 0.008$
FM-UE (mean $\pm$ SD)	37.7 $\pm$ 10.7	17.7 $\pm$ 7.4	$t_{(10)} = 3.79$ , $p = 0.004$
ARAT (mean $\pm$ SD)	28.0 $\pm$ 19.5	3.7 $\pm$ 3.1	$U = 1.5$ , $p = 0.004$
Grip strength (kgf, mean $\pm$ SD)	10.5 $\pm$ 6.3	4.1 $\pm$ 3.1	$t_{(10)} = 2.23$ , $p = 0.049$

Abbreviations: ARAT, action research arm test; FM-UE, Fugl-Meyer upper extremity; ICH, intracerebral hemorrhage; kgf, kilogram-force. Note, bold indicates a statistically significant difference between high and low recovery groups in stroke survivors that were MEP–.

stroke survivors would be behaviorally beneficial in those with some residual CST integrity, quantified with FA<sub>AI</sub> at the level of the cerebral peduncle. There is some preliminary evidence to support the hypothesis that increasing fronto-parietal network connectivity with facilitatory transcranial direct current stimulation to the ipsilesional premotor cortex could benefit motor performance (Andrade et al., 2017; Cunningham et al., 2015). If upregulation of the ipsilesional fronto-parietal network did promote greater upper-limb behavior, this could suggest a role for interventions such as non-invasive brain stimulation treatments or cognitive strategies to engage the fronto-parietal network during training (Olesen et al., 2004; Violante et al., 2017). This result would imply that neuroimaging has an important role in guiding treatment strategies.

Although this cross-sectional study provides a rich dataset, with multimodal MRI, repeated TMS assessments and comprehensive upper-limb behavioral tests, there are limitations. Most notably, we cannot draw conclusions regarding stroke recovery and the time course of changes in fronto-parietal resting state functional connectivity in MEP– stroke survivors. Furthermore, a key element of this study was differentiating stroke survivors based on MEP status. While there are other approaches to assess CST integrity, a TMS method was selected as it provides a dichotomous measure (MEP+ or MEP–) and it is part of a clinical prediction tool for stroke recovery (Stinear et al., 2017). Furthermore, diffusion weighted measures of CST integrity differed between MEP status groups, providing confidence that we appropriately stratified for CST integrity. Dichotomizing stroke survivors into MEP+ and MEP– groups could hinge on several factors including fatigue and the location of the muscle being assessed. These characteristics may be particularly important for stroke survivors with extensive CST damage and who are on the border of MEP+ and MEP– status. To mitigate these

influences, we repeated the MEP status assessment to demonstrate participants had been correctly categorized. An additional consideration is that determining MEP status from proximal upper-limb muscles in addition to the hand muscle tested here would have been advantageous. This would have helped determine if CST integrity was preserved for different muscle groups and might explain how some stroke survivors achieved higher levels of motor performance. Furthermore, we did not explore whether network activity was influenced by stroke characteristics such as an ischemic or ICH lesion. Subsequent appropriately powered studies are required to investigate the influence of stroke characteristics on post-stroke network activity. Finally, neurovascular changes following stroke may complicate interpretation of BOLD signal. While an independent component analysis was performed to de-noise the data, it remains possible that vascular differences could play a role in the reported group differences.

In conclusion, our results demonstrate that stroke survivors with more extensive CST damage (MEP–) have greater resting state functional connectivity of an ipsilesional fronto-parietal network compared to people in whom MEPs can be observed. This network appeared behaviorally relevant as MEP– stroke survivors with better motor performance exhibited greater ipsilesional fronto-parietal resting state functional connectivity. It may be this ipsilesional network can increase descending drive to the paretic upper-limb to improve motor performance. These findings suggest neuroimaging has a valuable role in understanding motor behavior in those with more severe stroke impairment. In stroke survivors with limited residual integrity of the ipsilesional CST, fronto-parietal networks may be a therapeutic target worthy of consideration.

#### CRediT authorship contribution statement

**Brenton Hordacre:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Funding acquisition. **Martin Lotze:** Conceptualization, Methodology, Formal analysis, Writing - review & editing. **Mark Jenkinson:** Formal analysis, Writing - review & editing. **Alberto Lazari:** Formal analysis, Writing - review & editing. **Christen D. Barras:** Formal analysis, Writing - review & editing. **Lara Boyd:** Conceptualization, Formal analysis, Writing - review & editing. **Susan Hillier:** Conceptualization, Formal analysis, Writing - review & editing, Funding acquisition.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2021.102558>.

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