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The Assessment of Inter-Hemispheric Imbalance using Imaging and Non-Invasive Brain Stimulation in Patients with Chronic Stroke

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Abstract

OBJECTIVE—To determine how inter-hemispheric balance in stroke, measured using transcranial magnetic stimulation (TMS), relates to balance defined using neuroimaging (functional magnetic resonance (fMRI) and diffusion tensor imaging (DTI)), and how these metrics of balance are associated with clinical measures of upper limb function and disability.

DESIGN—Cross-Sectional

SETTING—Clinical Research Laboratory

PARTICIPANTS—Ten chronic stroke patients (63±9 years) in a population based sample with unilateral upper-limb paresis.

INTERVENTION—Not applicable

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MAIN OUTCOME MEASURES—Inter-hemispheric balance was measured with TMS, fMRI and DTI. TMS defined inter-hemispheric differences in recruitment of corticospinal output, the size of the corticomotor output maps and the degree of mutual transcallosal inhibition they exerted upon one another. fMRI studied whether cortical activation during the movement of the paretic hand was lateralized to the ipsilesional or to the contralesional primary motor (M1), premotor (PMC) and supplementary motor cortices (SMA). DTI was used to define inter-hemispheric differences in the integrity of the corticospinal tracts projecting from M1. Clinical outcomes tested function (upper-extremity Fugl-Meyer (UEFM) and the perceived disability in the use of the paretic hand [Motor Activity Log (MAL)].

RESULTS—Inter-hemispheric balance assessed with TMS relates differently to fMRI and DTI. Patients with high fMRI lateralization to the ipsilesional hemisphere possessed stronger ipsilesional corticomotor output maps [M1 (r=.831, p=.006), PMC (r=.797, p=.01)], and better balance of mutual transcallosal inhibition (r=.810, p=.015). Conversely, we have found that patients with less integrity of the corticospinal tracts in the ipsilesional hemisphere show greater corticospinal output of homologous tracts in the contralesional hemisphere (r=.850, p=.004). However, neither an imbalance in their integrity nor an imbalance of their output relates to transcallosal inhibition. Clinically, while patients with less integrity of corticospinal tracts from the ipsilesional hemisphere showed worse impairments (UEFM) (r = −.768, p=.016), those with low fMRI lateralization to the ipsilesional hemisphere had greater perception of disability (MAL) [M1 (r=.883, p=.006), PMC (r=.817, p=.007) and SMA (r=.633, p=.062).

CONCLUSIONS—In patients with chronic motor deficits of the upper limb, fMRI may serve to mark perceived disability as well as transcallosal influence between hemispheres. DTI-based integrity of corticospinal tracts, however, may be useful in categorizing the range of functional impairments of the upper-limb. Further, in patients with extensive corticospinal damage, DTI may help infer the role of the contralesional hemisphere in recovery.

Keywords

Diffusion tensor imaging (DTI); Functional magnetic resonance imaging (fMRI); Transcranial magnetic stimulation (TMS); Inter-hemispheric imbalance; transcallosal inhibition; Stroke; Motor cortex

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In chronic stroke it is believed that hand deficits persist because of an imbalance between the ipsilesional and the contralesional hemisphere activity.[1–3] Neurophysiologically, this inter-hemispheric imbalance is thought to arise from altered transcallosal inhibition (TCI), where inhibition exerted from the ipsilesional hemisphere (lesioned) upon the contralesional hemisphere (intact) is weaker than inhibition exerted from the contralesional hemisphere upon the ipsilesional hemisphere.[4–6] The inter-hemispheric imbalance in chronic stroke has been examined using many different modalities; however, it has yet to be determined whether these modalities truly reflect TCI.

Transcranial magnetic stimulation (TMS) is one the most popular noninvasive methods used to define inter-hemispheric imbalance. It can study activity of motor cortices via electromagnetic induction. The action of passing a brief and strong current through an insulated coiled wire placed on the scalp induces a perpendicular magnetic field that can

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pass unimpeded through the skull and induce weak current flow in an area of the brain. This causes depolarization and triggers action potentials or post-synaptic potentials in neurons of the targeted cortex.[7] TMS has been used to describe inter-hemispheric imbalance in a couple different ways. First, TMS can denote inter-hemispheric differences in corticospinal output.[3] When single pulses of TMS are delivered at incrementally greater intensities, the responses evoked in the contralateral muscle (hemisphere opposite of the target limb) can be plotted as a recruitment curve. Second, with single pulses of TMS applied over multiple scalp sites, one can study the entire representation of the corticomotor output for the contralateral muscle- also known as a corticomotor output map.[3,8]

Functional magnetic resonance imaging (fMRI) captures inter-hemispheric imbalance during movement of the paretic hand. It records regions showing higher changes in blood flow during voluntary movement than during rest. Comparison of activation in the ipsilesional versus the contralesional motor cortex yields a metric called laterality index signifying inter-hemispheric imbalance with regard to cortical control in the movement of the paretic hand.[2]

Lastly, diffusion tensor imaging (DTI) is a relatively new MRI modality that is being used to characterize inter-hemispheric imbalance.[9] DTI assesses integrity of the white matter tracts based on the principle of water diffusion, where white matter normally has anisotropic diffusion.[10] The magnitude and directionality of anisotropic diffusion yields DTI metrics of tract integrity such as fractional anisotropy (FA).[11] In stroke, DTI measures inter-hemispheric imbalance by comparing the mean FA of the corticospinal tracts within the ipsilesional and the contralesional hemisphere, termed $FA_{asymmetry}$.[9,12,13]

The varying metrics that are used to define inter-hemispheric imbalance are often used interchangeably. Also, these metrics are presumed to reflect altered TCI in patients, but this has never been confirmed.[12,14] Further, it is unclear which metric of imbalance represents upper-limb functional impairments and disability. Therefore, the purpose of the present study was three-fold: 1) examine if the various metrics of imbalance can be used interchangeably by finding their mutual relationships; 2) confirm if they are an accurate representation of TCI by examining relationships between fMRI laterality, and DTI asymmetry to a commonly used TCI metric, ipsilateral silent period i.e the suppression of ongoing voluntary motor output due to a supra-threshold TMS pulse delivered to the ipsilateral hemisphere; [15–17] and 3) examine the relation of metrics to two widely used clinical measures- upper-extremity Fugl-Meyer (UEFM)[18] and Motor Activity Log (MAL). Our study aimed to better understand if multiple metrics of inter-hemispheric imbalance are able to relate to the degree of impairment and disability of the paretic hand in chronic stroke.[19]

Our report is significant because TMS, fMRI and DTI remain investigational and none of the techniques are currently FDA approved as a clinical diagnostic tool for stroke. They are time-, resource- and cost-intensive. Knowing their similarities (objective 1 and 2), as well as their unique clinical strengths (objective 3) would help future studies eliminate redundancies or harness their potentially complementary features. In addition, our preliminary study allows us to understand which modality/modalities relate to impairments as well as

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perceived use of the extremity, so that future studies may be able to identify which one(s) could define functional recovery along the course of treatment. These steps are critical to justify their use as diagnostic tools in future clinical practice.

1. METHODS

Participants

The local research ethics board reviewed and approved this study. In a cross-sectional design, data from 10 patients with stroke (63 ± 9 years) have been included. Location and side of stroke are presented in Table 1. Our inclusion criteria were: age ≥ 21 years, chronic phase of recovery (> 6 months) after first-ever (ischemic or hemorrhagic) stroke, trace ability to extend fingers or thumb or wrist ≥10° and chief complaint of inadequate ability to use the paretic hand in daily life. The exclusionary criteria related to contraindications of TMS[20, 21] and imaging.[22,23] Briefly, these include cardiac pacemaker, metallic implant in the head, seizure disorder and use of any neuro- or psycho-active medications as published in recommendations.[20]

Assessments and Procedures

TMS—We used TMS to examine how TCI was exerted mutually between both hemispheres, and compared the corticomotor output devoted to the paretic vs. non-paretic muscles using recruitment curves and corticomotor output maps for both hemispheres. Patients were seated comfortably in a chair with both arms and forearms supported and hands resting on a flat surface. Single pulse TMS[a] was delivered using a figure-of-eight coil (diameter 70mm). Patients' fMRI activation (see below) was used to stereotactically guide TMS [BRAINSIGHT software (Rogue Research, Montreal, Canada)] to M1. TMS-evoked responses in the contralateral muscle, called motor evoked potentials, were recorded in the first dorsal interosseous (FDI) muscle using surface electromyography[b] via bipolar electrodes (silver-silver chloride, 8 mm diameter) positioned over the muscle belly. A reference electrode was placed over the lateral epicondyle.

TMS was performed on both hemispheres. First, we found the scalp site that was able to elicit a motor evoked potential with the lowest stimulator output i.e resting motor threshold (≥50μV in at least 3/5 trials), termed motor hot spot. At the motor hotspot, we then created a recruitment curve by increasing the stimulator intensity by increments of 10% of the resting motor threshold (from 90%–150%) (10 trials each). Next, we defined the corticomotor map for the FDI muscle. This was achieved by delivering single pulses of TMS (5 pulses each, @ 110% of resting motor threshold, randomized) to sites on a 7×5 grid (10 mm spatial resolution) centered on the motor hotspot. Finally, to signify TCI, we examined the ipsilateral silent period (iSP).[15,17] Patients were asked to volitionally contract their FDI muscle at 50% of their maximum voluntary contraction. They were provided visual feedback[c] so they could accurately maintain the designated level of force. We delivered

[a]Magstim 200[2], The Magstim Company Limited, Sprinf Gardens, Whitland Carmarthenshire, SA 0HR, UK
[b]BRAINSIGHT software, Rogue Research Inc., 206-4398 boul. St – Laurent, Montreal Quebec, H2W 1Z5
[c]Powerlab 4/25T and LabChart, ADInstruments Inc., 2205 Executive Circle, Colorado Springs CO 80906, USA

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supra-threshold TMS (150% motor threshold, 15 stimulations) ipsilateral to the contracting muscle.

fMRI—We recorded movement related changes in blood flow using the blood oxygen level-dependent (BOLD) fMRI signal, using a Siemens Trio 3T[d] scanner.[24–26] For anatomically based images, 176 axial slices with a thickness of 1mm and field of view (FOV) = 256×256 mm were collected. An inversion time/echo time (TE)/repetition time (TR) and flip angle of 1900 msec/1.71 msec/900 msec and 8 degrees was used. BOLD Echo-planar imaging (EPI) was acquired with 160 repetitions of 31-4-mm thick axial slices. Imaging parameters consisted of TE= 29ms, TR= 2.8s, flip angle= 80°, matrix = 128×128 and field of view = 256×256 mm^2 providing an in-plane resolution of 2×2 mm^2.

For the movement related paradigm, patients were asked to perform self-paced flexion-extension of fingers of the paretic hand in a block design (each block lasting 45 seconds). fMRI preprocessing included head motion correction and EPI alignment to the high resolution T1 image. Head motion correction was performed using a voxel-specific motion regression following the method of Bullmore et al. 1999[27] to reduce artifactual effects of motion at each voxel. EPI data was smoothed with a 3-mm full width at half maximum Gaussian kernel. The difference in magnetic resonance signals between rest and movement period was analyzed using 3dDeconvolve with Analysis of Functional Neuroimages (AFNI) software[e]. Voxels (volume) that showed significantly greater BOLD signal during finger movements versus rest were considered active at a corrected threshold of $P < 5\times10^{-6}$ (determined through AlphaSim with a single voxel threshold of $P < .01$ and a cluster size > 13 voxels).[28] All images were transformed to Talairach space and activation was examined in M1, PMC, and SMA. These regions were defined for each subject based on guidelines published in our previous work and of others.[22,29]

DTI—With DTI, we examined the inter-hemispheric imbalance in integrity of corticospinal tracts. We acquired a High Angular Resolution Diffusion Imaging dataset with 71 diffusion-weighting gradients (b = 1000 s/mm2) and 7 b=0 s/mm2 image volumes, whole- brain coverage and 2mm isotropic voxels (field of view 256×256mm, image matrix 128×128, 52 2-mm thick slices). All data were corrected for eddy currents and head motion. On FA maps, regions-of-interest were drawn at the level of the posterior limb of internal capsule, M1, PMC and SMA. For the posterior limb of internal capsule, an axial image was chosen at an approximate level where the foramen of monroe was visible. M1, PMC and SMA were drawn on single axial images using similar method to that of fMRI. Corticospinal fiber tracts were reconstructed (virtually) using probabilistic tractography from the internal capsule to each of the regions separately.[12, 30]

Clinical Assessment of function—UEFM is an impairment-based test rated on an ordinal scale (0 to 2) by an investigator.[18] We focused on the distal portion of the UEFM, which evaluates wrist, hand and coordination for a maximum score of 30.[12] We have chosen

[d]Siemens Trio 3T scanner, Wittelsbacherplatz 2, 80333 Munich, Germany
[e]Analysis of Functional Neuroimages (AFNI) software., http://afni.nimh.nih.gov/afni/

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UEFM because it is a commonly-used clinical test with acceptable inter-rater reliability (0.97)[31] and concurrent validity.[32]

MAL is a semi-structured interview assessing the patient's perceived use of the paretic hand in 14 different activities of daily living. Here, we employed the portion of MAL that records the *Amount of Use*.[19] Ratings vary from 0 (absence of use or inability to use) to 5 (as frequent as in pre-morbid state). The test has strong validity,[33] internal consistency and stability in chronic stroke.[34]

Data Analysis: TMS

iSP for measurement of TCI—Onset of iSP was defined when EMG of the contracting muscle was suppressed below 1 standard deviation of the pre-stimulus EMG for 5ms. Offset was defined when EMG of the contracting muscle returned to within 1SD of the pre-stimulus value for 5 ms[16] (Fig. 1). We computed the level of TCI as the percentage decrease in mean EMG during iSP as a proportion of pre-stimulus EMG (equation 1).

$$Ipsilateral\ Silent\ Period\ (\%\,TCI) = 1 - \frac{Mean\ pre\ stimlus\ EMG - iSP\ EMG}{Mean\ pre\ stimlus\ EMG} \times 100 \quad \text{Equation 1}$$

Ultimately, we computed a ratio of iSP exerted from contralesional hemisphere upon the paretic muscle and from ipsilesional hemisphere upon the non-paretic muscle. A balanced ratio (~1) would indicate a balanced level of TCI exerted between both hemispheres, whereas an iSP ratio <1 indicates greater inhibition exerted from the ipsilesional upon contralesional hemisphere, and >1 indicates greater inhibition from the contralesional upon ipsilesional hemisphere.[35]

Recruitment Curve—At the hotspot, the stimulator intensity was increased from 90% to 150% of the resting motor threshold in a randomized order, at 10% increments while amplitude of corresponding MEPs was plotted as a recruitment curve.[36] Similar to Talelli et al 2007[37], recruitment curves were variable among patients. This made it difficult to fit the curves to a single model. Instead, we measured area under the curve (AUC) to define the corticospinal output of the M1 from the ipsilesional and the contralesional hemisphere.

Corticomotor Output Maps—Scalp sites consistently eliciting motor evoked potentials > 30μV were analyzed (3 of 5 pulses/trials). The size of the map was defined as the number of sites that met the motor evoked potential criteria.

Data Analysis: fMR

Laterality Index—To examine inter-hemispheric imbalance during movement of the paretic hand, we calculated a laterality index,[2,22] which expresses whether activation during movement of the paretic hand is mainly ipsilesional or contralesional. Laterality index varies from −1 to 1, with 1 indicating purely ipsilesional and −1 indicating purely contralesional activation (equation 2).

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$$Laterality\ Index = \frac{Volume_{ipsilesional} - Volume_{contralesional}}{Volume_{ipsilesional} + Volume_{contralesional}} \quad \text{Equation 2}$$

Data Analysis: DTI

Asymmetry Index—Structural integrity of the corticospinal tracts was compared between the two hemispheres using asymmetry index. Mean FA along the tracks were compared between the ipsilesional and contralesional sides.[12] These asymmetry indices for M1, PMC and SMA were given by (equation 3):

$$FA_{asymmetry} = \frac{FA_{Contralesional} - FA_{ipsilesional}}{FA_{contralesional} + FA_{ipsilesional}} \quad \text{Equation 3}$$

0 indicates perfect symmetry between both sides, while positive values signify reduced tract integrity in the ipsilesional hemisphere.

Statistics

Statistical analysis was performed using Statistical Package for the Social Sciences (v18, SPSS Inc., Chicago, IL). We defined the bivariate relation between TCI and Laterality index, TCI and $FA_{asymmetry}$, map count and Laterality index, AUC and $FA_{asymmetry}$, and map count and $FA_{asymmetry}$. To identify metrics that are associated with function, we computed correlations between UEFM and each of the physiologic and imaging metrics (TCI, map count, AUC, Laterality index and $FA_{asymmetry}$) and between MAL and each of the parameters. All relationships were assessed using non-parametric Spearman's correlation test at alpha value of significance set at 0.05.

2. RESULTS

All patients were able to maintain volitional contraction of the paretic muscle for the iSP measurement; however one patient was excluded due to technical issues. All but one patient could elicit motor evoked potentials in the paretic muscle with TMS pulses applied to the ipsilesional hemisphere and all patients were able to perform the self-paced finger flexion-extension task with fMRI. Due to excessive head motion within the scanner, one subject had to be excluded from fMRI calculations (laterality index) and one patient had to be excluded from the DTI calculations ($FA_{asymmetry}$). The same patient was excluded for the DTI and iSP metric and an additional patient was excluded for the fMRI metric.

fMRI and TMS: Laterality versus TCI, recruitment curve and corticomotor output map

We first examined the relationship between TCI (iSP) ratio and laterality index. We found that patients with greater fMRI laterality to the ipsilesional M1 also had a more balanced TCI (ratio closer to 1) (Fig. 2a; r = .810, p = .015). Next, we examined relationships between fMRI laterality index and corticomotor output maps devoted to the paretic muscle. We found that patients with greater ipsilesional fMRI laterality in the M1 and PMC also had

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larger ipsilesional corticomotor output maps measured with TMS (Fig. 2b & 2c; r = .831 p =.006 & r =.797 p=.01).

DTI and TMS: $FA_{asymmetry}$ versus TCI, corticomotor output map, recruitment curve

$FA_{asymmetry}$ of corticospinal tracts was not related to TCI or corticomotor output maps (not shown), but it shared a positive relation with the recruitment curve of the contralesional hemisphere. Patients with less corticospinal tract integrity from the ipsilesional M1 (greater $FA_{asymmetry}$) also showed greater corticospinal output from the contralesional hemisphere measured as the recruitment curve (Fig. 3; r = .850 p = .004).

Metrics of Inter-hemispheric imbalance and Clinical Assessment of Function

When relating fMRI, DTI and TMS measures of inter-hemispheric balance to outcomes of function, we have found different types of association with clinical measures. Patients with greater UEFM scores (better function) showed favorable value of $FA_{asymmetry}$ of the corticospinal tracts originating from M1 (Fig. 4a; r = −.768 p = .016). UEFM was not correlated with TMS (data not shown). MAL on the other hand was not correlated with measures of TMS or DTI, but patients with greater MAL scores (perceived use of the paretic hand) showed greater fMRI lateralization, favoring ipsilesional M1 and PMC (Fig 4b & 4c; r = .883 & r = .817; p < .05) and showed a similar trend with the laterality of SMA (Fig. 4d; r = .633 p = .062). Figure 4e and 4f show fMRI activation maps and DTI tractography, respectively.

Discussion

We examined the associations between neurophysiologic and imaging-based metrics that characterize inter-hemispheric imbalance, and explored how they related to two widely used clinical measures of hand function- UEFM and MAL. We have found that even though metrics noted with imaging (fMRI and DTI) relate to those measured neurophysiologically (TMS), the nature of such relationship varies. Patients with higher laterality of fMRI activation in the ipsilesional motor cortices also show larger ipsilesional corticomotor output maps and favorable balance of TCI between hemispheres. However, patients with poor ipsilesional tract integrity recorded with DTI, showed greater contralesional corticospinal output. Metrics of both fMRI and DTI were related to clinical outcomes, albeit differently. fMRI was associated with MAL- patient's perceived report of their disability in using the paretic hand, while DTI was associated with the objective assessment of the patients' impairments (UEFM). Although preliminary and exploratory, our findings carry implications for clinical practice. Because fMRI laterality during voluntary movement relates to overall global perceived use of the paretic hand as well neurophysiologic outcomes, we propose that fMRI may serve to mark perceived disability and could be used as a surrogate measure of neurophysiologic imbalance in chronic stroke deficits. However, DTI-based integrity of the corticospinal tracts may be useful in categorizing range in the severity of the motor impairments, an outcome expressed by a number of other studies. [11, 12, 40–42] Further, DTI could be used as a tool to explore the role of the contralesional corticomotor output during recovery in patients with extensive damage.

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Neurophysiologic metrics of inter-hemispheric imbalance versus fMRI laterality

fMRI laterality has been used since 1997[2] in stroke to signify changes in inter-hemispheric imbalance with volitional movements of the paretic hand. Previous studies have reported relationships between fMRI and TMS in healthy subjects. It has been shown that fMRI activation is positively related to corticomotor output maps,[38] while BOLD fMRI signal intensity of activation is related to TCI.[39, 40] With chronic stroke patients, it has been shown that reduced fMRI laterality to the ipsilesional hemisphere relates to smaller motor evoked potentials.[41] This suggests that patients with weaker corticospinal output of the ipsilesional hemisphere favor the contralesional hemisphere to a greater extent. Similarly, previous fMRI studies have reported in chronic stroke that prior to treatment[12] as well as post treatment,[2] the fMRI laterality tends to favor the contralesional hemisphere. Our study supports this work by showing evidence that greater fMRI laterality towards the ipsilesional hemisphere is associated with increased ipsilesional corticomotor maps measured with TMS (Fig 2b–c). Further, to our knowledge, this is the first study to show an association between fMRI laterality and TCI balance in chronic stroke. Because of these findings we propose that fMRI laterality may be a surrogate marker of the altered TCI in chronic stroke deficit (Fig 2a).

Neurophysiologic metrics versus $FA_{asymmetry}$

fMRI laterality has been the primary method to show that there is an increase in activation of the contralesional hemisphere following stroke.[2,12] We further expand on these findings by showing a similar phenomenon using $FA_{asymmetry}$ and TMS. We show that patients with greater ipsilesional corticospinal tract damage, indeed, had a greater corticospinal output of the contralesional hemisphere measured with TMS (Fig 3). The importance of the contralesional hemisphere is still unknown as it relates to motor recovery. One hypothesis is that the increase in contralesional excitability is a result of learned nonuse of the paretic limb- the maladaptive phenomenon where patients learn to restrict use of the paretic hand in daily activities for fear of failing.[42] Learned nonuse will result in greater use of the unaffected limb thus increasing excitability of the unaffected hemisphere. However, a more optimistic hypothesis is that the contralesional hemisphere may have a role in the recovery of the paretic limb. Previous studies have found that contralesional cortices reorganize (show greater fMRI activation) in recovery of motor skill following stroke.[43] In fact, when the contralesional hemisphere is inactivated, animals with large infarcts lose the ability to perform a reaching task,[44] and patients show poorer reaction times.[45] Here, we suggest the contralesional hemisphere as a potential substrate for recovery; future studies could explore whether ipsilateral corticospinal output or if alleviated callosal influence is critical for the role of the contralesional hemisphere.

We were unable to show any relationship between $FA_{asymmetry}$ and TCI. These results differ from that of Lindberg et al. 2007. They not only demonstrate a relationship with the slope of the recruitment curve, but they also show a relationship with the degree of TCI balance in their chronic stroke patients.[46] The differences reflect the variance in ways used to analyze outcomes. For example, DTI is a relatively new modality and studies differ from each other as to where they place the seed (e.g. anterior cerebral peduncle vs. posterior limb of the internal capsule). Further, there are differences as to whether we should analyze at a single

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slice or across the entire length of the corticospinal tract. The differences in analysis provide different, yet important results. However, because of these differences, one should be aware when interpreting results.

Neuroimaging and Neurophysiological correlates of Clinical Outcomes of function

Previous studies have shown that corticospinal tract integrity measured with DTI has high predictive value for motor function in the moderate to severely impaired patients. [11, 12, 40–42] We add to this by showing such a relation in a sample of mild to severely impaired. Stinear et al. 2007 indicated predictive value of DTI's $FA_{asymmetry}$ only in those patients who were not able to evoke a motor potential with TMS. Our study is able to demonstrate an association between UEFM and DTI even in patients that elicit motor evoked potentials. The variance may emerge from the choice of DTI analysis as previously mentioned. Here we measure integrity along the entire length of tract using a method less affected by confounds from the lesion (details [47, 48,49]). Hence, we may have been able to witness the 'detailed' degeneration of the tracts even in less impaired patients.

While DTI is critical in marking overall function of the paretic hand, we propose fMRI is important in capturing overall use of the paretic hand. It has previously been suggested that MAL scores are reflective of frontal system changes, which are involved in learned nonuse behavior following stroke.[42] Our results support this interpretation by showing that global activity of fMRI in frontal areas (M1, PMC and SMA) is positively correlated to MAL scores. Our result is supported by a previous study that showed that decreasing the use of the paretic limb related to greater fMRI activation in the contralesional PMC and M1.[50] Our results offer an important extension of the previous study by characterizing the inter-hemispheric imbalance as it relates to MAL rather than absolute activation. By showing a relationship between fMRI laterality and MAL we have found an important neuronal marker that may provide insight into the patients' perceived outlook of their disability. Future studies will determine if this translates to longitudinal treatment protocols.

Limitations and Conclusions

We acknowledge caution in interpreting our results because of its limited sample size. In addition to a small sample size, another limitation of our study is the cross-sectional design. Therefore, we can only provide preliminary evidence of correlations across metrics currently serving investigational purpose in clinical studies/trials, without suggesting their causative interactions. In order to fully understand the relationship across different modalities and their ability to prognosticate stroke recovery, larger longitudinal studies must be performed.

In summary, we have shown in a small cross-sectional study that metrics of inter-hemispheric imbalance noted with fMRI and DTI are associated with those of TMS, albeit differently. Further, we show that fMRI and DTI are related to clinical outcomes; however, correlations differ based on the nature of the clinical assessment. In demonstrating that fMRI has a real-time perspective of inter-hemispheric imbalance in movement as it relates to favorable TCI and output from the ipsilesional hemisphere, we conjecture that fMRI may be critical in capturing chronic deficits of the patient's perceived use of the paretic hand and neurophysiologic outcomes. DTI's examination of corticospinal tracts, however, may or

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may not directly infer TCI, but it may be an important metric to classify patients across levels of motor impairment severity. In a clinical setting each modality offers similar yet unique perspective, which can ultimately aid in determining what interventions may best enhance rehabilitation outcomes.

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Abbreviations

BOLD	Blood Oxygen Level-Dependent
DTI	Diffusion tensor imaging
EMG	Electromyography
EPI	Echo-planar imaging
FA	Fractional anisotropy
FDI	First Dorsal Interosseous
fMRI	Functional magnetic resonance imaging
iSP	Ipsilateral silent period
M1	Primary motor cortex
PMC	Premotor cortex
SMA	Supplementary Motor area
TMS	Transcranial magnetic stimulation
TCI	Transcallosal Inhibition

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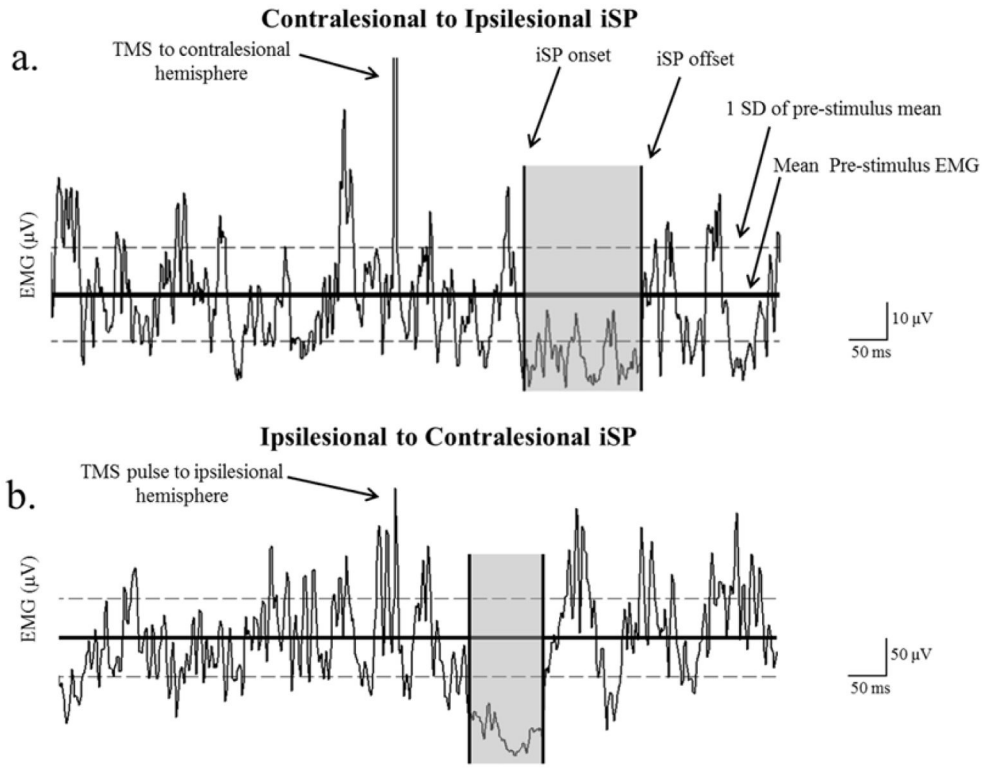

Figure 1.

Example of an ipsilateral silent period (iSP) from (a) contralesional to ipsilesional and (b) ipsilesional to contralesional hemisphere. The ISP ratio was the % EMG decrease of contralesional to ipsilesional/% EMG decrease of ipsilesional to contralesional hemisphere. ISP onset and offset were determined as the point where the EMG went below 1SD of the pre-stimulus mean and returned back within 1 SD of the pre-stimulus mean. Even though the patients maintained a contraction at 50% of the maximum voluntary contraction, it is important to notice the difference between the EMG scale of the paretic hand (a) and the non-paretic hand (b), where the paretic hand EMG reached a maximum of ~ 50 μV, and the non-paretic hand reached a maximum of ~ 400 μV. Despite the difference in EMG activity it has recently been shown that level of EMG does not influence the degree of inhibition.[51] Results are reported as ISP ratio, which is defined as the Contralesional to Ipsilesional iSP/ Ipsilesional to Contralesional iSP. The subject shown had an iSP ratio of .75.

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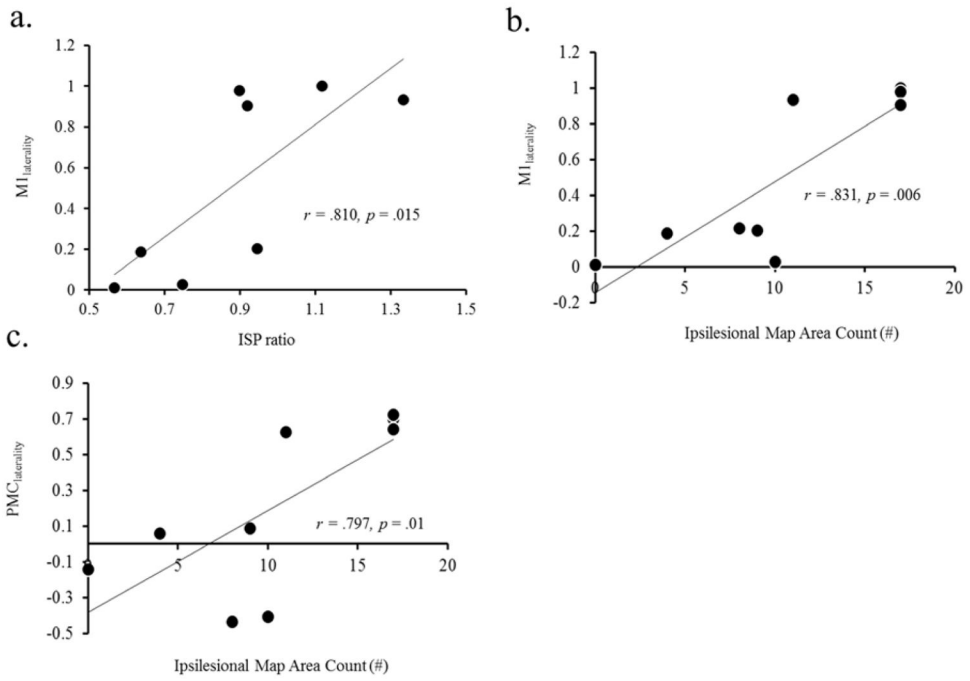

Figure 2.

Correlation between fMRI laterality index and TMS. (a) There was a positive correlation between the ratio of ISP and fMRI laterality index within the M1. (b & c) There was a significant positive correlation between fMRI laterality index within the M1 and PMC to the total ipsilesional map area count with TMS.

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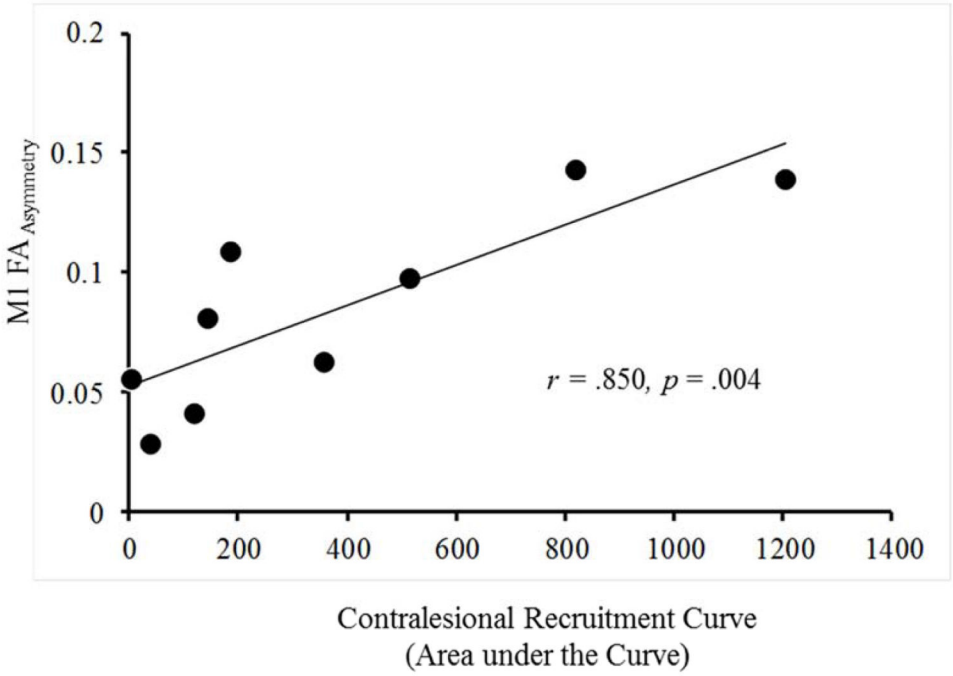

Figure 3.

Correlation between DTI and TMS. There was a significant positive correlation between $FA_{asymmetry}$ of corticospinal tracts originating from M1 and the recruitment curve of the contralesional hemisphere discerned with TMS.

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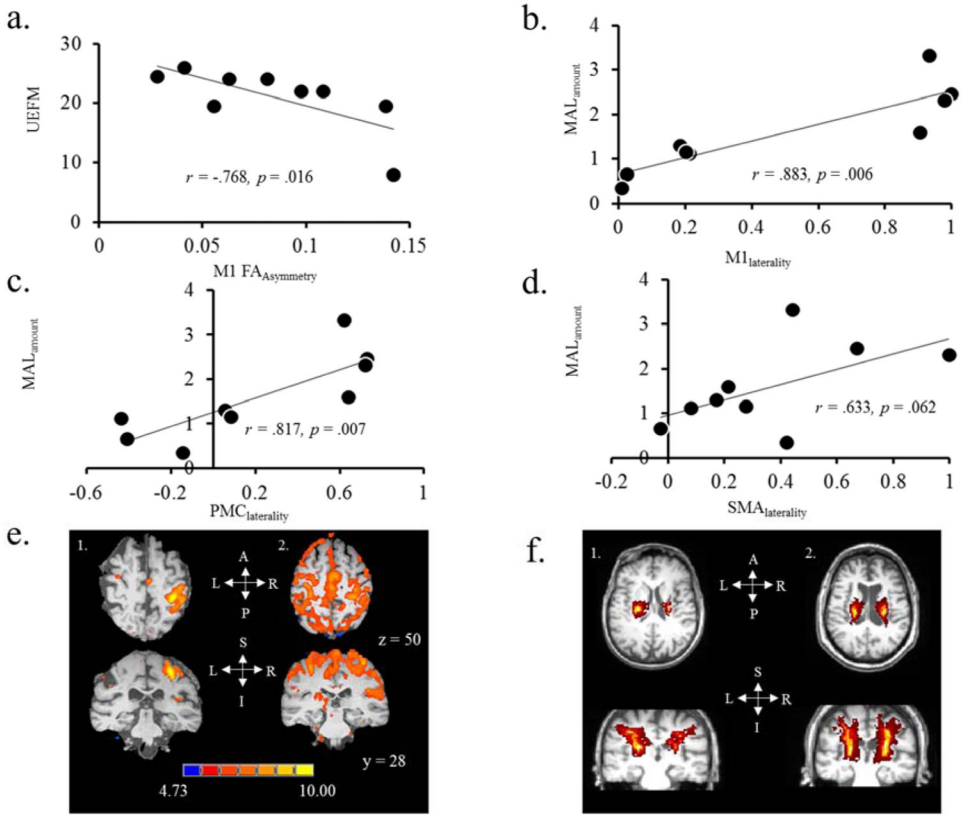

Figure 4.

Relationship between clinical assessment scores (UEFM & MAL) and neurophysiologic and neuroimaging outcomes. (a) There was a negative correlation between UEFM and M1 $FA_{asymmetry}$. (b–d) there was a positive correlation between MAL and fMRI laterality index within the M1, PMC and SMA. (e) FMRI based images in two different patients. Subject (1) shows high fMRI laterality signifying good ipsilesional hemisphere dominance during contraction of the paretic hand. Subject (2) shows low fMRI laterality signifying weaker ipsilesional hemispheric dominance during contraction of the paretic hand. Their MAL scores were 2.3 and .66, respectively, signifying that patient with higher laterality showed higher MAL. (f) DTI-based images in two different patients. Subject (1) shows poor M1 $FA_{asymmetry}$ signifying weaker integrity of corticospinal tracts originating from the ipsilesional side. Subject (2) shows good M1 $FA_{asymmetry}$ signifying similar integrity of tracts in both hemispheres. Their UEFM scores were 35 and 50, respectively, signifying that patient with higher function showed favorable integrity on ipsilesional side
S = superior, I = inferior, A = anterior, P = posterior, L = left & R = right.

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Table 1

Age (years). Gender (M = Male; F= Female). Time since stroke (months). MMI = Mini Mental Exam (Maximum 30). Hand Dominance (R = Right; L = Left). UEFM = Upper Extremity Fugl-Meyer (Maximum 30). MAL = Motor Activity Log Amount Score (Maximum 5)

Patient	Age	Gender	Time Since Stroke (mo)	Lesioned Hemisphere	Stroke Etiology	Stroke Location	MMI	Hand Dominance	UEFM	MAL
1	68	F	32	R	Ischemic	Basal Ganglia	30	R	21	1.12
2	66	M	19	R	Ischemic	Mesial Frontal Cortical	24	R	26	1.29
3	58	F	24	R	Ischemic	Basal Ganglia	30	L	24	0.66
4	69	M	23	L	Hemorrhagic	Thalamus & Putamen	28	R	24	2.45
5	54	M	29	L	Ischemic	Centrum Semi-Ovale & Basal Ganglia	29	R	22	1.16
6	72	M	84	R	Ischemic	Pontine	26	R	25	2.31
7	55	F	48	L	Hemorrhagic	Dorsal Thalamus	30	R	20	3.32
8	59	F	23	L	Ischemic	Caudate head, globus pallidus, insula, punctate cortical foci	29	R	20	1.6
9	76	M	24	R	Ischemic	Basal Ganglia and Corona Radiata	28	R	8	0.35
10	50	M	54	L	Hemorrhagic	Thalamus	30	R	22	1.03