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Long-term effects of contralesional rTMS in severe stroke: Safety, cortical excitability, and relationship with transcallosal motor fibers

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Abstract.

BACKGROUND: Contralesional hemispheric repetitive transcranial magnetic stimulation (rTMS) may improve motor function in mild to moderate stroke and effects are considered to be mediated through transcallosal motor fibers.

OBJECTIVE: This study aimed to investigate the safety of contralesional rTMS in a selected group of severe chronic stroke patients.

METHODS: Ten sessions of 1 Hz rTMS were applied to contralesional primary motor cortex (M1) using neuronavigated stimulation and changes in motor impairment were evaluated before, during and after rTMS applications and at 4-weeks follow-up. Neurophysiological response to stimulation was assessed through cortical excitability evaluations. The relationship between functional and neurophysiological response to rTMS and microstructural integrity of transcallosal motor fibers were searched using diffusion tensor imaging (DTI) based fractional anisotropy (FA).

RESULTS: rTMS was well-tolerated with high compliance and no dropouts; no seizures or motor worsening occurred. Transcallosal FA values revealed a positive linear relationship with the mild motor improvement detected after rTMS while higher FA values were observed in subjects with better motor outcome. Cortical excitability showed a significant change in contralesional short-interval intracortical inhibition indicating altered plasticity following rTMS.

CONCLUSIONS: Our results suggest that noninvasive neuromodulation of the contralesional hemisphere may present a possibility to assist adaptive neuroplastic changes in severe chronic stroke. Implementation of DTI-derived measures of transcallosal microstructural integrity may allow for individually-tailored interventions to guide processes of interhemispheric neuroplasticity. Further research is warranted to establish the clinical value of these findings in neurorehabilitation settings for subjects with chronic severe stroke.

Keywords: Severe stroke, cerebrovascular disease, repetitive transcranial magnetic stimulation (rTMS), diffusion tensor imaging (DTI), neurorehabilitation, cortical excitability

1. Introduction

Motor stroke with severe functional deficits is often associated with limited motor recovery and its rehabilitation remains a great challenge. It is, however, still possible to obtain significant improvements in a group of these subjects. Some of the potentially encourag-

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ing interventions for severe stroke rely on approaches exploring modulation of interhemispheric neuroplasticity (Boggio et al., 2006; Mally & Dinya, 2008; Sterr et al. 2010). In this context, diffusion tensor imaging (DTI) can be a useful tool to investigate the transcallosal motor fibers and guide rehabilitation interventions that act through interhemispheric neuroplasticity in severe stroke. DTI-guided evaluation of corticospinal tract integrity recently proved to be a promising predictor of response to neurorehabilitation in mild to moderate stroke, however, this method mostly reveals no detectable corticospinal fibers in severe stroke limiting its predictability for this patient population (Stinear et al., 2007; Jang, 2010; Lindenberg et al., 2010).

Owing to its potential to induce lasting and relatively focal effects on neuroplasticity, repetitive transcranial magnetic stimulation (rTMS) is being explored as a tool to enhance motor recovery following mild to moderate stroke. One rTMS approach that has been shown to have significant effects in motor function includes suppression of the disinhibited contralesional motor cortex (M1) as to increase excitability in the lesioned M1 via low frequency rTMS (Mansur et al., 2005; Fregni et al., 2006). This approach is based on the concept of imbalanced interhemispheric inhibition between the motor cortices and the effects are considered to be mediated through transcallosal projections from the contralesional to the lesional motor cortex (Murase et al., 2004; Takeuchi et al., 2005). Available data on the use of this approach in severe acute (Conforto et al., 2012) and chronic stroke (Boggio et al., 2006; Mally & Dinya, 2008) is, however, very limited. Because the compensatory mechanisms following severe stroke differ from mild to moderate stroke and may include recruitment of the ipsilateral corticospinal tract (Jang, 2009), some concerns should arise when implementing this method to stroke survivors with severe motor deficits, even with carefully tailored approaches.

The present study aimed to investigate whether suppression of the contralesional hemisphere using low frequency rTMS would be a safe and feasible methodology to augment motor performance in chronic stroke patients with severe motor impairment. We chose a population of severe stroke as [1] this is the subgroup of patients that would benefit most from potential novel therapeutic approaches, [2] contralesional rTMS has not been methodically tested for severe chronic stroke, and [3] there are currently no available indicators of response to rehabilitation for this patient population. Consequently, as a secondary aim, we searched for the mechanistic evidences related to this technique, which might influence response to rehabilitation in this patient population. Specifically, we investigated the microstructure of transcallosal motor fibers using estimates of fractional anisotropy (FA) and hypothesized that clinical and neurophysiological responses to successive sessions of contralesional inhibitory rTMS would relate to DTI-based transcallosal motor fiber integrity.

2. Methods

2.1. Subjects

This single-center study conducted at the Beth Israel Deaconess Medical Center (BIDMC) included adult subjects with single ischemic or hemorrhagic stroke provided that they had very severe upper extremity impairment as defined by a Fugl Meyer score of $\leq$16 (out of 66); single supratentorial lesion with intact corpus callosum; stroke onset >1 year prior to study enrollment and failure to evoke a motor evoked potential (MEP) in the affected extremity following stimulation of motor areas of both hemispheres using maximum output of the stimulator. The latter criteria was specifically included to enable enrollment of patients with no available electrophysiological evidence indicating corticospinal integrity or compensatory functional recruitment from the contralesional motor areas. Exclusion criteria included the absolute contraindications to TMS or MRI; history of a seizure; prior neurosurgery; Beck Depression Inventory score >16; Mini-Mental State Examination (MMSE) score <25; coexistent neurological/psychiatric disease; pregnancy or lactation. The study cohort included ten patients meeting these criteria; details of patient demographics are listed in Table 1. The study was approved by the Institutional Review Board and Scientific Advisory Committee of the Harvard-Thorndike Clinical Research Center (CRC) of BIDMC, and was performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to the study.

2.2. Safety and motor outcome measures

Patients were admitted to CRC unit of BIDMC for the duration of the study in order to maximize observation of potential adverse effects. Safety measures included recording of basic vital signs (i.e. blood pressure and heart rate) at the CRC unit, Mini Mental State Examination (MMSE) and side effects questionnaires

Table 1
Patient characteristics

N	Sex	Age	Lesion age	MMSE	BDI	Barthel index	FM	Lesion etiology	Lesion hemisphere	Lesion location	MEP
1	F	66	61	30	3	17	10	I	R	BG, CR, IC	–
2	F	67	14	30	3	14	10	I	R	MCA territory	–
3	F	60	34	30	4	14	7	H	R	IC, thalamus	–
4	M	75	110	30	3	19	12	I	L	BG, CR, IC	–
5	F	40	29	30	11	17	16	I	R	MCA territory	–
6	M	56	35	30	6	18	11	I	R	MCA territory	–
7	F	60	78	29	9	13	5	I	L	MCA territory	–
8	M	43	29	30	4	19	15	H	L	BG, IC, thalamus	–
9	M	69	82	29	9	16	10	I	L	MCA territory	–
10	F	59	16	30	4	19	13	H	L	Frontal lobe	–
Mean		59.5	48.8	29.8	5.6	16.6	10.9				–
SD		11	32.2	0.4	3	2.3	3.3				–
Max		75	110	30	11	19	16				–
Min		40	14	29	3	13	5				–

Abbreviations: Lesion age (months). MMSE: mini mental state examination, BDI: Beck depression inventory, Barthel Index (maximum 20), FM: arm motor Fugl-Meyer score (maximum 66), I: ischemic, H: hemorrhagic, R: right, L: left, BG: basal ganglia, CR: corona radiata, IC: internal capsule, MCA: large middle cerebral artery infarction, MEP: motor evoked potential from the affected limb, following stimulation of both motor cortices using maximum output of the stimulator.

(including headache, neck pain, discomfort at the stimulation site, seizure, syncope, dizziness, hearing impairment, impaired cognition, motor worsening, fatigue, trouble concentrating, acute mood change and occurrence of new symptoms) completed following every session. In regards to motor safety, grip strength measurements were performed before and after every session to detect a possible motor worsening as soon as possible. Further, a detailed battery of motor outcome measures was performed before TMS, upon completion of 10 sessions and at the one-month follow-up period. This battery included the Fugl-Meyer assesment of upper limb, Graded Wolf Motor Function Test, hand grip strength and Modified Ashworth Scale.

2.3. Transcranial magnetic stimulation

2.3.1. Measurement of cortical excitability

Electromyography (EMG) was recorded from the first dorsal interosseous (FDI) muscle using standard Ag/AgCl electrodes and a ground electrode positioned on the wrist. Muscle activity was monitored to ensure complete relaxation. EMG signals were amplified with a band pass filter of 10Hz-2kHz. The signals were sampled at a rate of 5 kHz, digitized using PowerLab 4/25T device and stored on a computer using Scope software (version 4.0.8) software for offline analysis.

Because subjects enrolled in this study had no detectable MEP in the lesional hemisphere, cortical excitability measurements included motor threshold, motor evoked potential (MEP), short intracortical inhibition (SICI) and intracortical facilitation (ICF) evaluations of the contralesional hemisphere and transcallosal inhibition (TCI) from lesional to contralesional hemisphere. In order to ascertain the resting motor threshold (RMT), TMS was administered via a commercially available figure-of-8 coil (each wing measuring 70 mm diameter, peak magnetic field 2.2 T, held 45° tangentially to the scalp) using 2 Magstim 200 stimulators that were coordinated using a Bistim device (Magstim Company, Dyfed, UK). RMT was established following the guidelines of the International Federation for Clinical Neurophysiology and estimated the minumum TMS intensity capable of producing at least five MEPs of 50 μV amplitude in 10 consecutive stimuli (Groppa et al., 2012). Subsequently, TMS intensity was adjusted to achieve an MEP of 1 mV peak-to-peak amplitude in the FDI muscle and ten consecutive MEPs were recorded. In order to evaluate the intracortical inhibition (SICI) and facilitation (ICF) changes in the contralesional hemisphere, we carried out a paired-pulse paradigm employing a subthreshold 'conditioning' stimulus at an intensity of 90% of RMT, followed by a suprathreshold 'test' stimulus delivered at variable interstimulus intervals (ISI) and 120% of RMT intensity. The tested ISIs included 1,2,3,5,7,10,12 milliseconds and overall comprised ten trials for each ISI, which were delivered in random order and intermixed with control stimulation (where the test stimulus was given alone). Among the applied conditions, ISI 2 and 3 were studied to provide information on SICI whereas ISI 10 and 12 were used to evaluate the ICF. Due to the absence of MEPs in the lesional hemisphere, the investigation of transcallosal inhibition (TCI) from the

contralesional to the lesional hemisphere using paired pulse TMS was not possible. TCI from lesional to contralesional hemisphere was examined using ten trials of a paired-pulse sequence delivering stimulation to both motor cortices: two suprathreshold stimuli were applied to the lesional and contralesional motor cortices respectively with an ISI of 10 milliseconds, and the MEP was recorded from the unaffected motor cortex. Cortical excitability measurements were performed twice, before and upon completion of 10 sessions of rTMS.

2.3.2. Repetitive TMS

Subjects underwent 10 daily sessions of rTMS over ten consequent weekdays. Each stimulation comprised 1600 pulses of 1 Hz rTMS applied at 100% RMT via a figure-of-8 coil and Magstim super rapid stimulator (Magstim, Dyfed, UK). The hand motor cortex over the precentral gyrus of contralesional hemisphere was targeted using a frameless stereotaxic system (Brainsight, Rogue Research, Montreal) (Yousry et al., 1997). Localization was also confirmed functionally using single pulse TMS.

2.4. DTI acquisition and analysis

All scans were performed on a 3 Tesla Philips Intera MRI scanner (Philips Medical Systems, Best, The Netherlands). A high resolution T_1-weighted anatomical data set (3D-T_1-TFE, TR/TE = 7.4/3.4 ms, resolution $0.9 \times 0.9 \times 1.5\ mm^3$) was followed by three DTI scans, acquired with the following parameters: resolution: $1.8 \times 1.8 \times 2.0$ mm, 15 non-collinear directions with b values of 1069 s/mm^2 and 0 s/mm^2, 73 axial slices with 2-mm thickness with no gap. The three DTI acquisitions were motion corrected, coregistered and averaged within and between acquisitions using Philips software (Philips Medical Systems, Cleveland, Ohio).

DTI analysis was performed with FSL (www.fmrib.ox.ac.uk/fsl). Skull stripped DTI images were registered to b = 0 images in order to correct for eddy current distortions and simple head motion. Diffusion tensors were fitted to each voxel of the diffusion-weighted images and Markov Chain Monte Carlo sampling was used to build up distributions at these voxels. The resulting DTI images were then coregistered to the T_1-weighted anatomical image. For fiber tracking, we adapted the two-step fiber tracking method described by a previous study (Wahl et al., 2007). The first step included placement of large rectangular regions of interest (ROI) in the primary motor regions of precentral gyri (M1) of both hemispheres. Following the tracking step, a second ROI on the corpus callosum was added where the fibers from the first tracking emerged, and a second tracking was performed. Finally, two neurologists independently located the fibers projecting to the anatomical landmark of the hand motor region (Yousry et al., 1997). The two-step tracking method was reported to show superior sensitivity compared to one-step method and allowed tracking of more fibers (Wahl et al., 2007). After obtaining the DTI data, FA values of the entire transcallosal motor tracts were determined. FA is the most extensively studied diffusivity parameter compared to the other diffusivity measures (i.e. mean diffusivity, parallel and axial diffusivity) and has been reported to successfully and reliably measure directionally-restricted water diffusion and damage to microstructural architecture of white matter in stroke (Stinear et al., 2007; Lindenberg et al., 2010). A standard threshold FA value of 0.15 was performed; this threshold has been found to reliably isolate white matter from the rest of the brain (Jones et al., 1999).

2.5. Statistical analysis

Given the small size of the specific cohort used in this study, nonparametric statistics were employed. We initially performed nonparametric analysis of variance tests (Friedman ANOVA) to test the changes between baseline, post-TMS and follow-up evaluation scores. When appropriate, paired comparisons were conducted using Wilcoxon signed-rank test. Non-parametric pairwise correlations between DTI parameters and motor outcome changes were calculated using Spearman's rank correlation coefficient with Bonferroni correction. Statistical significance was set at <0.05.

3. Results

3.1. Safety outcome measures

In a total of 100 sessions, no adverse events were witnessed; no seizures or syncope occured. The patients tolerated rTMS well with high compliance and no dropouts. Basic vital signs measurements throughout the study did not reveal any significant changes concerning safety ($p = 0.61$ for systolic, $p = 0.37$ for diastolic pressures and $p = 0.69$ for heart rate). Side effects were minor and included discomfort at the stimulation site and mild headache responsive to acetaminophen. Daily handgrip measures examined

before and after TMS did not show any decrement compared to the baseline (Fig. 1A). Motor outcome measures did not worsen; on the contrary, mild improvements were detected (explained in detail below).

3.2. Behavioural outcome measures

Fugl Meyer Scale (FM) showed a significant change between baseline, post-TMS and follow-up conditions ($X_2 = 7.4$, $p = 0.02$). Paired comparisons revealed significant differences between baseline vs. post-TMS ($p = 0.02$) and follow-up ($p < 0.01$) (Fig. 1B). There was a significant effect of rTMS on affected hand *grip strength* ($X_2 = 10, p < 0.01$). *Grip strength* was found to be significantly increased, as compared with baseline, for the post-TMS ($p < 0.01$) and follow-up ($p < 0.01$) conditions (Fig. 1C). *Modified Ashworth Scale* showed a trend for change ($X_2 = 4.55$, $p = 0.1$) while *Graded Wolf Motor Function Test* did not significantly change ($p > 0.05$) (Fig. 1D).

3.3. Cortical excitability measures

There was no significant effect of rTMS on unconditioned contralesional MEP amplitudes ($p > 0.05$). ISI measures revealed a significant change for ISI 2 condition only, pointing to a decreased SICI, suggesting therefore a change in plasticity following rTMS ($p = 0.01$) (Fig. 2A). We did not detect a significant change in the transcallosal inhibition from lesional to contralesional hemisphere ($p > 0.05$). Upon completion of the rTMS sessions, no MEPs appeared in the affected extremity following stimulation of motor areas of both hemispheres using maximum output of the stimulator.

3.4. Relationship between rTMS-induced motor improvement and fractional anisotropy of transcallosal fibers

Spearman's rank correlation coefficient indicated a statistically significant linear relationship between the transcallosal FA values and the change in the FM score during the follow-up ($r_s = 0.82$, $p < 0.05$) (Fig. 2B). Further, Spearman's rank correlation analyses revealed no significant correlation between the FA values and patient demographic data, FM score or other motor function scores at baseline, suggesting this relationship between improvement in motor impairment and transcallosal fiber integrity is not confounded by other factors ($p > 0.05$). There was no significant relationship between the cortical excitability changes and the FA values ($p > 0.05$). The probabilistic tracking of transcallosal motor fibers in a stroke patient with severe motor dysfunction is depicted in Fig. 2.

4. Discussion

The present study evaluated the safety of successive sessions of inhibitory rTMS over the contralesional motor cortex in a selected group of patients with chronic severe stroke. Our results demonstrate that the procedure was well-tolerated without any concerns regarding safety, cognition or motor function. The microstructural properties of the transcallosal motor fibers and functional motor gains following rTMS modulation of contralesional motor cortex showed a linear relationship highlighting the critical role of transcallosal fiber integrity and interhemispheric communication in this process. Further, we detected a decrease in the intracortical inhibition of the contralesional hemisphere following stimulation, which may shed light on the core plasticity mechanisms related to this rTMS approach in severe stroke.

Our major concern in this study was the possibility of worsening in motor function because reports regarding the role of unaffected hemisphere in the rehabilitation of severe stroke are rather contradictory. While the interhemispheric imbalance has been reported to attenuate the affected hemisphere function more prominently in more impaired individuals (Murase et al., 2004), there are several reports supporting the recruitment of ipsilateral corticospinal pathways to the affected extremity in the acute and chronic term of severe stroke (Fisher, 1992; Caramia et al., 2000; Stinear et al., 2007). Here, we performed detailed motor assessments in a specific group of patients, in whom TMS failed to produce MEPs in the affected hand, and detected no motor worsening throughout the study. On the contrary, our results suggested mild improvements, which will need to be tested in future randomized-controlled studies. Because TMS-provoked seizures have been reported in patients with chronic stroke (Hömberg & Netz, 1989, Fauth et al., 1992), another critical concern was the possibility of inducing a seizure associated with rTMS applications. In this study, we excluded patients with a history of a seizure and performed 1 Hz rTMS over the contralesional motor cortex using standard stimulation parameters within the currently recommended safety guidelines. We found a total of 100 contralesional inhibitory rTMS sessions to be well-tolerated with no seizures and only minor side effects.

An important finding of this study is the significant change in the intracortical excitability of the unaf-

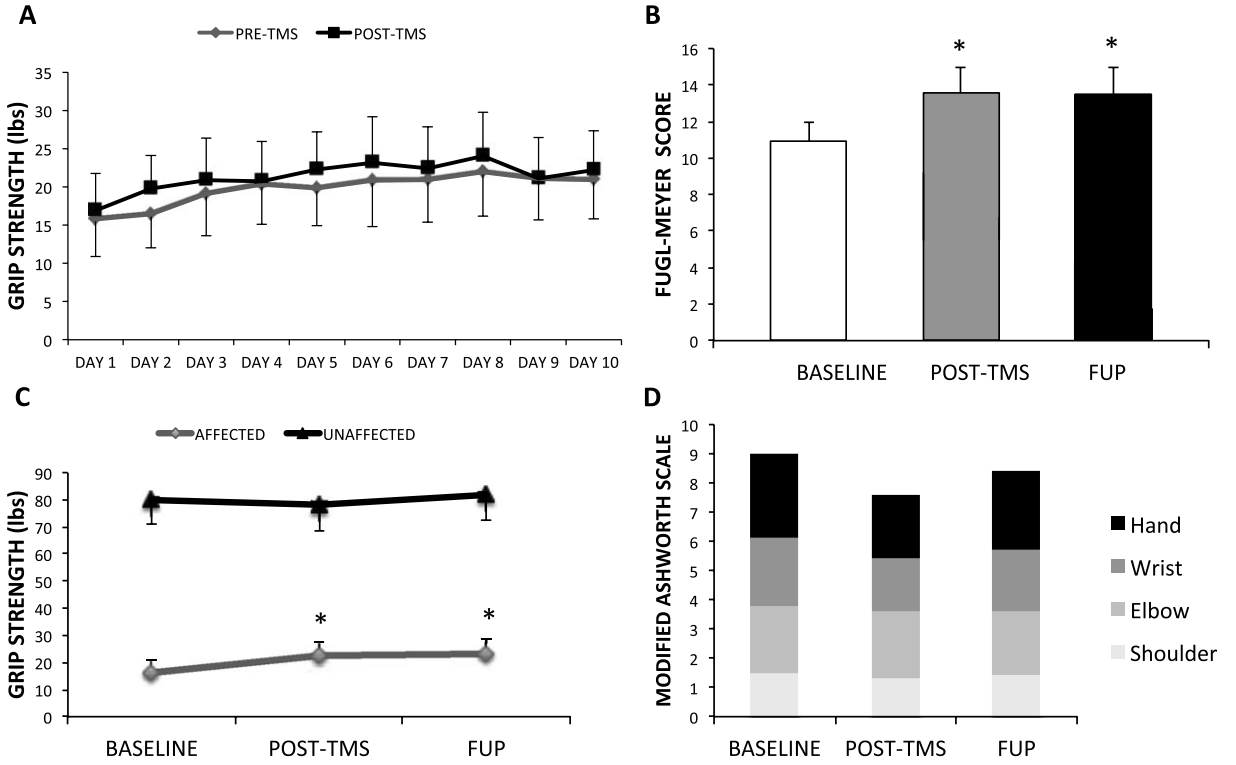

Fig. 1. (A) Grip strength measurements performed immediately before and after rTMS sessions during ten days of stimulation. (B) Fugl-Meyer score, (C) Grip Strength and (D) Modified Ashworth Scale values during baseline, after ten days of rTMS and at the 1-month follow-up. Asterisk indicates $p < 0.05$.

fected contralesional hemisphere, as characterized by a decrease in SICI following successive sessions of rTMS whereas there was no significant change in the intracortical facilitation. It has been documented that ICI and ICF are discrete phenomena (Ziemann et al., 1996; Liepert et al., 1998) and this finding suggests that the release of the intracortical inhibition may be more critical for rTMS-induced plasticity than the intracortical excitatory changes. Post-stroke excitability changes in the contralesional hemisphere are not well-documented and our search revealed no other reports that investigated the cortical excitability changes in the contralesional hemisphere following repeated applications of rTMS. First, reduced SICI of the contralesional hemisphere does not necessarily induce an increase in interhemispheric inhibition to the lesional hemisphere but may rather be representative of neural reorganization supporting motor recovery (Bütefisch et al., 2008; Huynh et al., 2013). SICI is mediated by $GABA_A$ receptors (Di Lazzaro et al., 2006), and hence, this finding likely points to a down regulation of the $GABA_A$ ergic inhibitory inputs following stimulation. Available evidence suggests that the reduction in $GABA_A$ dependent inhibition facilitates the induction of LTP/LTD (Jacobs & Donoghue, 1991; Hess & Donoghue, 1994), which may result in enhanced synaptic plasticity through unmasking of preexisting connections, disinhibition of neuronal networks and changes in synaptic processes (Hess & Donoghue, 1994). As a result, the transcallosal influence of contralesional hemisphere may asist the adaptive plastic changes and compensatory processes in ipsilesional M1, possibly through the weak excitatory connections established between homologous M1s (Ugawa et al., 1993; Werhahn et al., 2002). Potential differences in the role of callosal fibers during recovery period may depend on the severity of lesions and functional deficits, and probably plasticity-inducing interventions. Given the favorable changes in our patients' motor impairment, this significant change in cortical excitability may be a neurophysiological indicator of adaptive plasticity triggered by rTMS.

In normal individuals, interhemispheric neural activity between the homologous motor cortices is well-balanced through opposite inhibitory influences exerted by M1s of both hemispheres (Ferbert et al., 1992). This interhemispheric inhibitory strength has been posi-

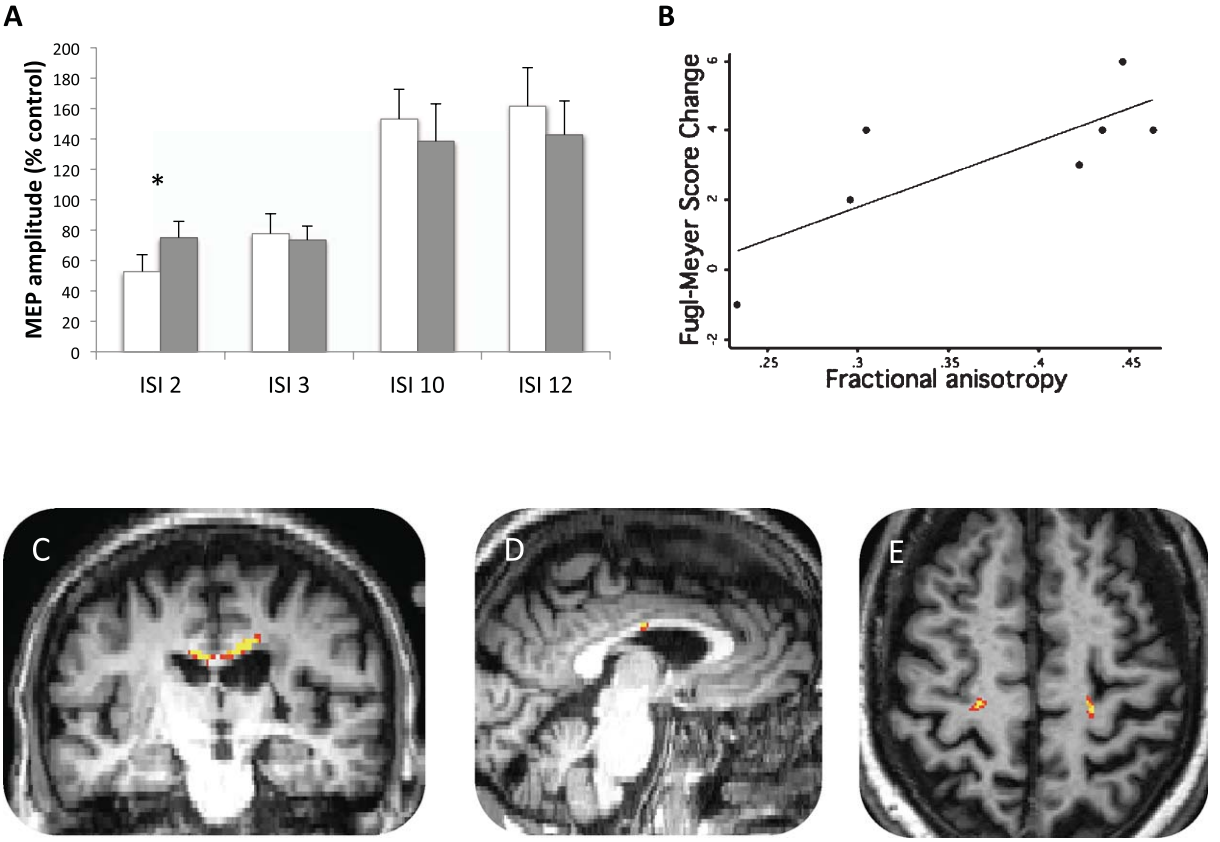

Fig. 2. (A) The change in contralesional SICI and ICF parameters after 2 weeks of contralesional rTMS over the primary motor cortex in severe stroke. White columns represent pre-TMS and gray columns represent post-TMS values. Asterisk indicates $p < 0.05$. (B) The scatterplot presenting the relationship between fractional anisotropy and Fugl-Meyer (FM) score change following repeated sessions of rTMS in a group of severe stroke patients ($r_s = 0.82$, $p < 0.05$). Note that the change in FM score is positively correlated with the fractional anisotropy of the transcallosal motor tract and higher fractional anisotropy values are associated with better motor outcome. Coronal (C), sagittal (D) and axial (E) slices illustrating the probabilistic tractography results of the transcallosal motor fibers for a single stroke patient with severe motor dysfunction. The tracking results, indicated by the yellow-red voxels, are superimposed on a coregistered T1-weighted anatomical image of the subject.

tively related to organization of the transcallosal motor fibers (Wahl et al., 2007) and increased transcallosal fiber microstructure was reported to predict interhemispheric inhibitory capacity in normal subjects (Fling et al., 2013). Notably, in the case of stroke patients, pathological inhibition from contralesional M1 to lesional M1 was shown to correlate with hand motor dysfunction (Grefkes et al., 2008). In the current study, we have shown that higher transcallosal fiber FA was linearly related to positive outcome following rTMS; on the other hand, we were devoid of neurophysiological information regarding the interhemispheric inhibition from the contralesional to the ipsilesional hemisphere as our patients had no MEPs in their affected hand. Referring to previous data relating higher callosal FA with increased transcallosal inhibiton, one could speculate that patients with better transcallosal integrity may have a higher potential to inhibit the lesional hemisphere than the ones with lower transcallosal FA values. In these individuals, low-frequency rTMS applied over the contralesional M1 may reduce this unopposed excessive transcallosal inhibition from contralesional to the lesional M1 and increase the excitability of the stroke hemisphere, allowing the individuals to recover their full potential (Takeuchi et al., 2005; Fregni et al., 2006). Further, integrity of the main anatomical substrate that the rTMS-effects are conveyed through may enable more successful transmission of the elicited neuronal modulation. Our finding expands upon the recent evidence implicating the importance of transcallosal fibers in motor recovery and interhemispheric reorganization in chronic stroke (Wang et al., 2012).

The strengths of this study include the systematical assessment of safety for the first time in a standardized group of chronic severe stroke patients who had no TMS-elicited MEPs in their affected hand, and close monitorization of the patients in the CRC unit to ensure the their safety. The use of a neuronavigation system enabled precise targetting of the hand motor cortex-hence allowed exact match of stimulation location and underlying white matter for DTI analysis. The main limitation is the open-label design and absence of a control intervention, which was not included because of our primary objective to establish the safety of this approach in severe stroke and to observe higher number of patients receiving real-rTMS. The absence of MEPs in the affected limb of our subjects prevented further testing of the measures of transcallosal inhibition from contralesional hemisphere to lesional hemisphere; however, correlating the changes in TCI with our clinical and neuroimaging findings would be more explanatory. While no seizures were observed during the study, the use of online neurophysiological monitoring via EEG and EMG might have provided additional safety measures.

In conclusion, the results from this study suggest safety of rTMS modulation of the contralesional hemisphere in a group of chronic severe stroke patients and indicate that DTI-derived measures of transcallosal structural integrity may be valuable to guide processes of interhemispheric neuroplasticity induced by rTMS. Changes in the intracortical plasticity underline that contralesional hemisphere may asist induction of adaptive plasticity even in the chronic term. Further research is warranted to establish the clinical value of these findings in the neurorehabilitation settings for subjects with chronic severe stroke.

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Declaration of interest

APL serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, and Neosync; and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation (TMS) with electroencephalography (EEG) and magnetic resonance imaging (MRI).

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