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RESEARCH

Motor network pre-habilitation by low-frequency repetitive transcranial magnetic stimulation. A proof-of-concept

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Abstract

Background Tumors involving motor-eloquent brain regions pose a significant surgical challenge, as maximizing resection while preserving motor function requires a delicate balance. Neuromodulation-induced cortical prehabilitation (NICP) has emerged as a potential strategy to promote functional reorganization before surgery, potentially expanding the margins of safe resection.

Objective This pilot study aimed to investigate whether accelerated, low-frequency repetitive transcranial magnetic stimulation (rTMS) targeting the right primary motor cortex (M1) could induce functional and microstructural changes in the motor network.

Methods Two healthy subjects underwent a seven-day intervention consisting of twice-daily sessions of inhibitory rTMS over the right M1 (14 sessions in total). Pre- and post-intervention imaging included resting-state functional MRI (rs-fMRI) and diffusion tensor imaging (DTI). Functional changes were assessed descriptively using seed-based and ROI-to-ROI connectivity analyses. Microstructural changes were evaluated through tract-specific comparisons of fractional anisotropy (FA).

Results Both subjects exhibited increased interhemispheric functional connectivity and strengthening of compensatory motor pathways, including the supplementary motor areas and bilateral precentral and postcentral gyri. DTI revealed tract-specific changes in FA, with evidence of microstructural modulation in regions such as the SMA, corpus callosum, and corticospinal tract. The magnitude and spatial distribution of changes varied between individuals.

Conclusion These preliminary findings provide exploratory support for the hypothesis that inhibitory rTMS can induce functional and structural reorganization of the motor network. The combined use of rs-fMRI and DTI highlights the potential of NICP as a prehabilitation strategy in neurosurgical contexts. Further studies in clinical populations are warranted.

Keywords Glioma · Plasticity · Transcranial magnetic stimulation · Accelerated rTMS · Functional connectivity · Sensorimotor Network · Prehabilitation · Neuromodulation · Neurorehabilitation · Neurosurgery

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Introduction

Brain tumors remain among the leading causes of cancer-related death in individuals under 50, with a five-year survival rate of just 33 [40, 45, 52]. Beyond histological grade, the extent of resection (EOR) is the most important prognostic factor. However, when tumors are located in or near eloquent brain regions, achieving maximal resection is often limited by the need to preserve neurological function. In such cases, the balance between maximizing tumor removal and minimizing postoperative deficits poses a cost–benefit dilemma: supratotal resection may increase survival but risks significant functional impairment, whereas subtotal resection may preserve function at the expense of long-term disease control [18, 33].

In the last few years, it has been proposed to apply a conditioning intervention before surgery (prehabilitation) to modulate neuroplasticity, called neuromodulation-induced cortical prehabilitation (NICP) [19, 27]. The objective was to reduce the functional relevance of brain areas close to the tumor (critical areas) in favor of a more distributed brain network, functionally associated with the targeted area but anatomically distant from the tumor. This way, neurosurgeons may apply a more radical approach without the associated risk of functional impairments; from this perspective, it is argued that NICP could represent the optimal therapeutic intervention before intraoperative cortical-subcortical mapping to tailor the resection up to the functional boundaries (hopefully widened by previous neuroplastic changes induced with NICP) [19].

NICP can be performed with invasive or non-invasive modalities. Invasive neuromodulation typically involves surgical implantation of epidural, subdural, or parenchymal electrodes connected to a pulse generator device [3, 41, 47], whereas non-invasive neuromodulation, typically involves the delivery of an electric or magnetic stimulus over the scalp corresponding to a specific cortical region.

The most extensively investigated form of brain stimulation is transcranial magnetic stimulation (TMS) – a non-invasive neuromodulation technique that has demonstrated considerable therapeutic potential and reasonable safety for several neurological and psychiatric disorders [2, 7, 9, 21, 23, 30, 31, 43, 46]. By delivering repetitive TMS (rTMS) it is possible to induce changes in brain excitability that outlast the stimulation period [15, 25, 49–51]. Several protocols of rTMS have been introduced: (1) "simple" (or conventional) rTMS protocols; (2) "patterned" protocols such as theta-burst stimulation (TBS) and paired-pulse rTMS at I-wave periodicity; (3) protocols of paired associative stimulation [36, 43]. These protocols may have excitatory or inhibitory effects on cortical output depending on the stimulus frequency, the stimulus intensity, the total number of stimuli, and the interval between the TMS pulses of the train of stimuli. Inhibitory protocols, such as conventional low-frequency repetitive TMS (LF-rTMS) and continuous theta burst stimulation (cTBS), have shown particular promise in facilitating adaptive plasticity.

For instance, Barcia et al. reported the case of a 59-year-old woman with a recurrent left-sided oligodendroglioma infiltrating Broca's area [4]. The patient received 13 sessions of continuous theta-burst stimulation (cTBS) over the posterior part of the left inferior frontal gyrus, targeting Broca's area, immediately followed by brief speech therapy sessions. The intervention spanned three weeks. Language performance—specifically repetition and naming—temporarily worsened after rTMS but consistently improved after speech therapy, with baseline performance gradually increasing across sessions. Magnetoencephalography (MEG) performed during the third week showed greater bilateralization of speech production, while task-based fMRI remained unchanged, with persistent left-dominant peritumoral activation. Despite these functional adaptations, awake surgery revealed no topographical displacement of Broca's area, and postoperative language scores declined compared to preoperative levels.

In a subsequent study, Dadario et al. described a case study of prehabilitation and rehabilitation using theta burst stimulation (TBS) in a patient with recurrent high-grade glioma involving the right motor cortex [12]. TMS targets were selected based on structural and resting-state functional connectivity data. The prehabilitation phase consisted of 10 sessions over two weeks, combining continuous TBS (cTBS) over area 4 of the precentral gyrus—aimed at reducing hyperconnectivity at the planned surgical entry point—with intermittent TBS (iTBS) over area 3a in the central sulcus, intended to enhance connectivity in surrounding hypoconnected nodes. Following a resection limited to the cingulate motor area, the patient awoke from surgery with severe left-sided hemiparesis (muscle strength 1/5), despite anatomical preservation of the corticospinal tract and supplementary motor area (SMA) connectivity. Postoperative rehabilitation included 8 sessions of iTBS over two weeks, targeting the left primary motor cortex (area 1 of the sensorimotor network) and bilateral parietal regions within the default mode network (areas F and part m), with stimulation delivered at 80% RMT. One-month post-surgery, motor strength in the left arm improved to 4 +/5 and all other extremities returned to 5/5. Cognitive function also recovered to baseline. The patient survived for an additional two years, with presumed death due to disease progression.

More recently, Boccuni et al. described a case series of ten patients who underwent a prehabilitation protocol consisting of daily neuromodulation coupled with intensive functional training over two to four weeks [6]. Neuromodulation was delivered either as LF-rTMS at 90% of

the RMT or as multichannel transcranial direct current stimulation (tDCS), depending on whether the target was a focal cortical site or a broader region. Among patients treated with rTMS, three had tumors involving the precentral gyrus and three had lesions affecting language-related areas. Relevant plasticity changes—defined as an increased distance between the tumor and peak fMRI activation—were observed in only two patients, both of whom received stimulation precisely targeted to the main fMRI cluster closest to the tumor.

To summarize, seminal findings from previous studies suggest that NICP can induce clinically meaningful neuroplastic changes, although the optimal stimulation parameters and duration remain unclear. Notably, all protocols reported to date have spanned at least two weeks, typically involving single daily sessions and conventional stimulation intensities. In contrast, the present study introduces a novel, accelerated approach: a one-week protocol featuring twice-daily sessions of inhibitory stimulation delivered at 110% of the resting motor threshold over the right primary motor cortex (M1). We have recently demonstrated preliminary evidence supporting the safety and feasibility of this intensified prehabilitation strategy [16].

In this exploratory, multimodal pilot study, we investigated whether such a condensed intervention could induce functional and structural reorganization of the motor network in two healthy volunteers. Resting-state fMRI was used to evaluate changes in functional connectivity, while diffusion tensor imaging (DTI) assessed microstructural adaptations. Our goal was to determine whether a brief, yet intensive protocol could promote measurable neuroplasticity, thus supporting its potential utility in preoperative neurosurgical settings.

Materials and methods

Subjects

Two healthy volunteers participated in this study (30 years old female, and 28 years old male). Both participants were naive to rTMS and provided written informed consent and completed screening forms for contraindications to MRI and TMS. TMS exclusion criteria were history of epilepsy (also within the family), migraine, tinnitus, history of neurological or psychiatric illness, pregnancy, and intake of prescription drugs within the past 14 days. MRI exclusion criteria included claustrophobia, implanted ferromagnetic devices, and pregnancy).

The study was designed as single-blind, approved by our ethics committee [prot. 88,612 July 22nd, 2024] and conducted in accordance with the Declaration of Helsinki.

MRI acquisition

MR images were acquired before and immediately after the final rTMS session.

The MR study was performed using a 1.5 T scanner (Philips, Ingenia, Netherlands) with the following specifications: T1-weighted, Gradient-Echo multiplanar reconstruction (MPR), echo time (TE) = 3.4 ms, repetition time (TR) = 7.4 ms; T2 weighted echo planar imaging (EPI) sensitized to blood oxygenation level-dependent imaging (BOLD) contrast, TE = 50 ms, TR = 2000 ms, Flip angle = 90°, 22 axial slices, Acquisition matrix (M × P) = 84 × 80, (resting-state fMRI). For resting-state fMRI acquisition (eight minutes), the subjects were trained to hold their eyes closed, trying not to think about anything and to remain awake. Diffusion MRI data were acquired with a single-shell DTI protocol: 32 diffusion directions, b-value of 1000 s/mm^2, in-plane resolution of 1.953 mm, and slice thickness of 2.0 mm. Acquisition parameters included TR = 4836 ms, TE = 90.7 ms, and parallel imaging using SENSE.

Navigated repetitive TMS procedure

A T1-weighted structural MRI (TR = 2,500 ms; TE = 2.22 ms; TI = 1,000 ms; flip angle = 8°; voxel size = 0.8 × 0.8 × 0.8 mm; 208 slices) was used as the subject-specific navigation dataset for TMS. A Nexstim NBS 5 stimulator (Nexstim, Helsinki, Finland) with a figure-of-eight coil (70 mm outer diameter) was used for neuro-navigated TMS.

The above-mentioned figure-of-eight coil was placed flat on the scalp, at the level of the right primary motor cortex (precentral gyrus, M1). Motor-evoked potentials were recorded from the first dorsal interosseous muscle (FDI) using disposable Ag/AgCl surface electrodes (Neuoline 700; Ambu, Ballerup, Denmark). The reference electrode was placed at the left wrist. Muscle activity of the target muscle was monitored to remain below a maximally tolerated baseline activity of 10 µV. For each subject, we determined the optimal stimulation site ('hot spot'), as well as the direction of the electric field and the angle that consistently elicits the largest amplitude motor evoked potentials from the contralateral FDI muscle. The resting motor threshold (RMT) was determined before the first rTMS session using the automatic threshold-finding algorithm integrated into the system [28].

The accelerated rTMS intervention (a-rTMS) comprised 14 sessions of low-frequency rTMS, spread over seven consecutive days (two sessions a day). In each session, 1800 pulses of 1 Hz rTMS set at 110% of the RMT, were delivered for 30 min to the previously defined motor hotspot of each subject. Directly after the stimulation, a motor training

of 10 min targeted to the stimulated hand muscles was performed to support the reorganization of motor function via the recruitment of other brain areas. To this purpose, subjects completed exercises such as writing or performing the nine-hole peg test. Between sessions, a 90-min break was applied. Sessions of rTMS were well tolerated and there were no adverse effects observed. During the session, a minor tingling sensation was reported, consistent with the rTMS safety literature [20].

Functional MRI analysis

Resting-state fMRI data were preprocessed and analyzed using the CONN toolbox (v22.v2407) and SPM12 [14, 34, 44, 48, 53]. Preprocessing included realignment with susceptibility distortion correction, outlier detection, segmentation, MNI normalization, and smoothing. Data were denoised by regressing out white matter and CSF signals, motion parameters and their derivatives, outlier scans, session effects, and linear trends, followed by band-pass filtering (0.008–0.09 Hz) [26].

Functional connectivity was assessed using:

- Seed-Based Connectivity (SBC): The right primary motor cortex (M1; precentral gyrus) was used as a seed to compute whole-brain voxel-wise correlations.
- ROI-to-ROI Connectivity (RRC): Fisher-transformed correlations were calculated between predefined sensorimotor network ROIs in both hemispheres.
- Interhemispheric Correlation (IHC): Connectivity was evaluated between homologous voxel pairs across hemispheres, using mirrored MNI coordinates.

Second-level analysis used CONN's GLM framework to descriptively compare pre- and post-intervention connectivity patterns within each subject. These voxelwise changes are exploratory and hypothesis-generating rather than statistically powered group-level results.

Diffusion MRI analysis

In the current study, we used the DSI Studio (http://dsi-studio.labsolver.org) software package to perform a DTI-based connectometry analysis comparing pre- and post-rTMS scans in two healthy subjects, focusing on the potential for structural adaptation within the motor system.

Generalized q-sampling imaging (GQI) was applied with a diffusion sampling length ratio of 1.25 [22]. Tensor metrics were derived from volumes with b-values < 1750s/mm^2. Tractography was performed using a deterministic algorithm with augmented tracking strategies [55]. A seeding region was placed in the right primary motor cortex, as delineated by the Julich Brain Atlas (Area 4a-R; MNI coordinates 88, 130, 140) [1]. One million seeds were generated. Tracking parameters included an anisotropy threshold between 0.5–0.7 (Otsu method), angular threshold of 45–90°, step size equal to voxel spacing, and track length between 30–200 mm.

The primary outcome measure was fractional anisotropy (FA)—the most extensively studied diffusivity parameter compared to the other diffusivity measures (i.e. mean diffusivity, parallel and axial diffusivity). FA reflects the degree of directional coherence of water diffusivity and has been reported to successfully and reliably measure directionally restricted water diffusion in both healthy and damaged brains [11, 13, 37]. In particular, short-term changes in FA values have been reported as feasible in the literature and are thought to reflect alterations in neuronal activity or connectivity [8, 16, 32].

FA values were extracted from regions of interest (ROIs) including bilateral M1 (Area 4a), pre-SMA and SMA proper (Area 6ma and 6mp), corpus callosum, right corticospinal tract, right superior longitudinal fasciculus, and right thalamocortical sensory pathways.

Results

We analyzed changes in motor network connectivity and white matter microstructure before and after the neuromodulation protocol using Seed-Based and ROI-to-ROI analyses of rs-fMRI, along with fractional anisotropy (FA) derived from diffusion tensor imaging (DTI). The findings are reported by subject and modality, followed by a synthesis comparing the two cases. Given the exploratory nature of this study and its two-subject design, all reported findings are descriptive and not intended to support statistical inference.

Functional connectivity (rs-fMRI)

Post-intervention scans revealed patterns of altered connectivity consistent with short-term reorganization of the motor network.

In **Subject 1**, Seed-Based connectivity (SBC) analysis of the right M1 revealed increased connectivity with the contralateral precentral gyrus, bilateral postcentral gyri, the right temporal pole, and anterior inferior temporal regions. A corresponding decrease in connectivity was observed in the right superior and middle frontal gyri, frontal pole, precuneus, and left cerebellum (Fig. 1 and 2). ROI-to-ROI

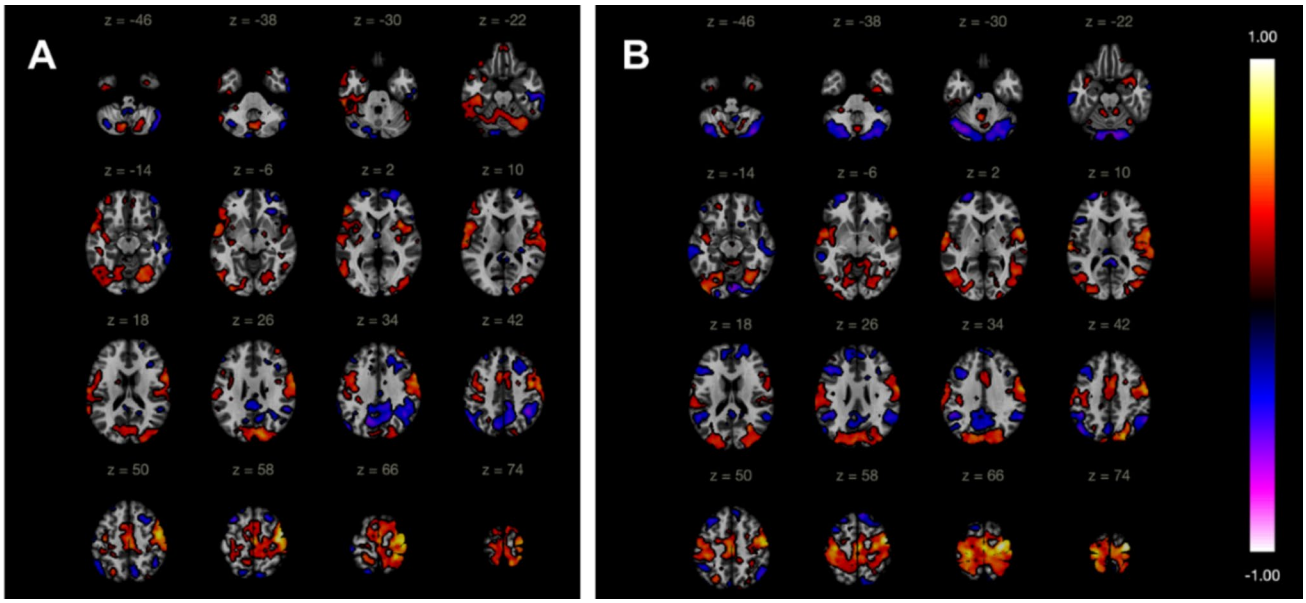

Fig. 1 Seed-based connectivity (SBC) maps with the right precentral gyrus as seed. Before (**A**) and after (**B**) rTMS stimulation. The color scale reflects Fisher-transformed correlation coefficients

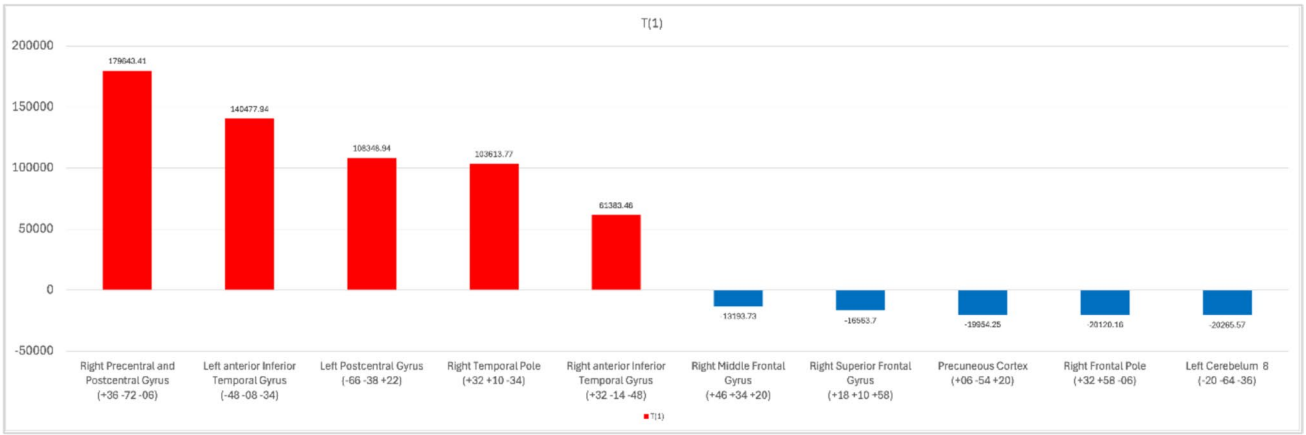

Fig. 2 Anatomical location, MNI coordinates, and T-values of peak clusters identified in the Seed-Based analysis of the right primary motor cortex. Red clusters represent increased connectivity post-stimulation; blue clusters represent reduced connectivity. Note: These T-values reflect descriptive thresholds applied within a single-subject analysis; no group-level inference was performed

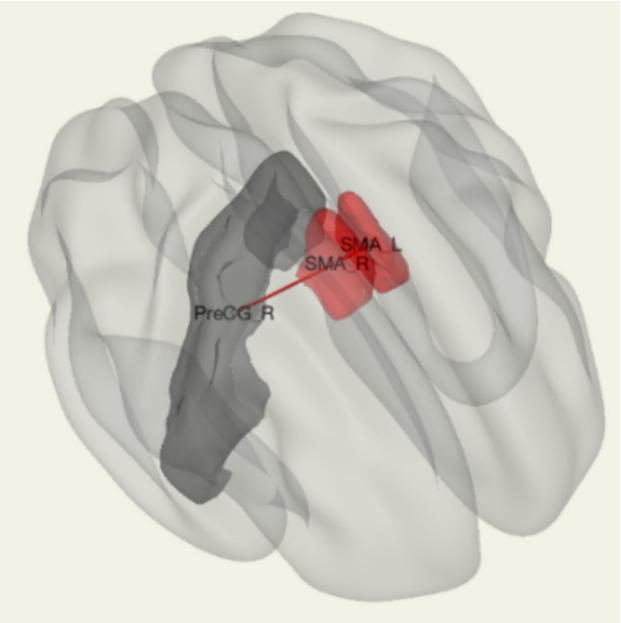

Fig. 3 ROI-to-ROI analysis with seed on the right precentral gyrus. 3D brain reconstruction showing the above threshold connections (p-uncorrected <0.05). Following the intervention, resting state fMRI unveiled a significant correlation between the right precentral gyrus (stimulated area) and both right and left supplementary motor areas (p-uncorrected =0.0022 and 0.010 respectively). Note: Quantitative analysis is reported in Table 1

Table 1 ROI-to-ROI analysis with seed on the right precentral gyrus

Targets	beta (Z)	T-score	p- uncorrected	*p*-FDR
Right SMA	0.61	302.48	0.002105	0.014733
Left SMA	0.42	58.44	0.010893	0.038127
Right postcentral gyrus	0.86	5.9	0.106816	0.249238
Right Frontal Pole	−0.22	−3.17	0.194788	0.340879
Left precentral gyrus	0.66	2.41	0.250461	0.350646
Left postcentral gyrus	0.43	1.73	0.33344	0.389014
Left Frontal Pole	−0.08	−0.46	0.723792	0.723792

Values reported represent descriptive connectivity strength between ROIs, based on within-subject analysis. T-scores and *p*-values are thresholded for visualization purposes and do not indicate statistical significance in the inferential sense

analysis confirmed these findings, showing enhanced coupling between the right precentral gyrus and bilateral SMAs. When the right SMA was used as a seed, increased connectivity was also observed with bilateral precentral gyri, the right postcentral gyrus, and the contralateral SMA (Fig. 3; Table 1). Interhemispheric correlation (IHC) maps demonstrated increased connectivity between homologous regions, notably in the cingulate cortex, precuneus, bilateral intracalcarine cortices, and precentral gyri (Fig. 4).

Subject 2 exhibited a more focal pattern of change. SBC maps revealed increased connectivity between the right M1 and the left postcentral gyrus, the left superior temporal gyrus, and the right postcentral gyrus. Reductions in connectivity were found in left frontal regions, including the frontal pole and middle frontal gyrus (Fig. 5). ROI-to-ROI analysis identified the strongest increase in connectivity between the right precentral gyrus and left postcentral gyrus, with moderate increases in connectivity to the left precentral gyrus. A marginal increase in connectivity was also observed between the right M1 and the SMAs (Fig. 6; Table 2). IHC analysis showed enhanced interhemispheric coherence in the precentral gyri, postcentral gyri, paracingulate gyri, cingulate cortex, medial frontal cortex, and frontal poles (Fig. 7).

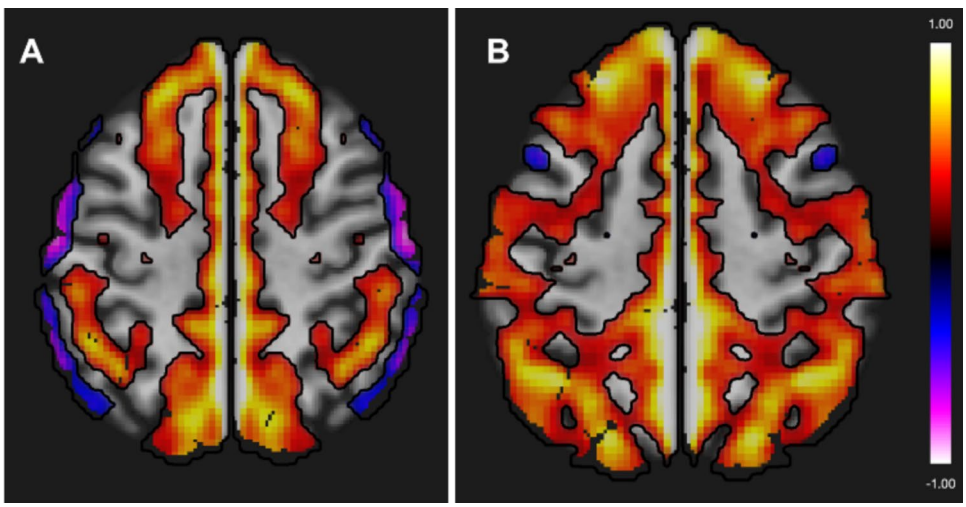

Fig. 4 Interhemispheric connectivity. Before (**A**) and after (**B**) stimulation. The color bar represents the Z-score of Fisher-transformed correlation coefficients

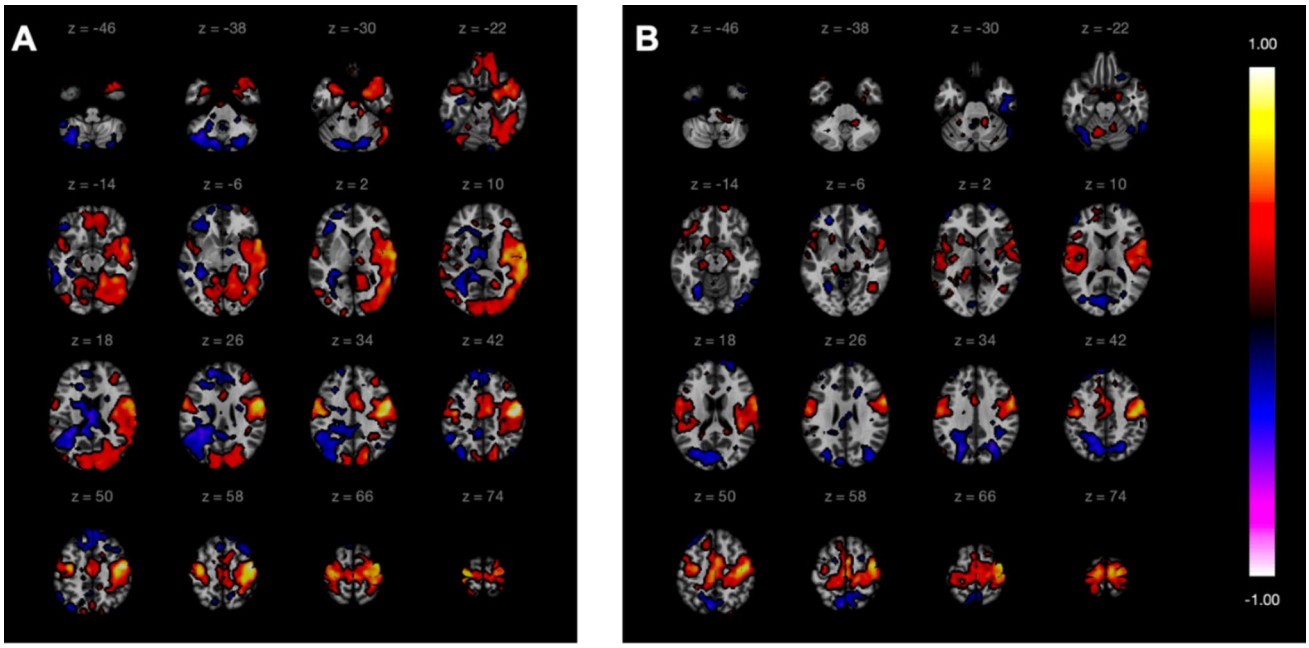

Fig. 5 Seed-Based connectivity (SBC) maps with the right precentral gyrus as seed. Before (**A**) and after (**B**) rTMS stimulation. The color scale reflects Fisher-transformed correlation coefficients

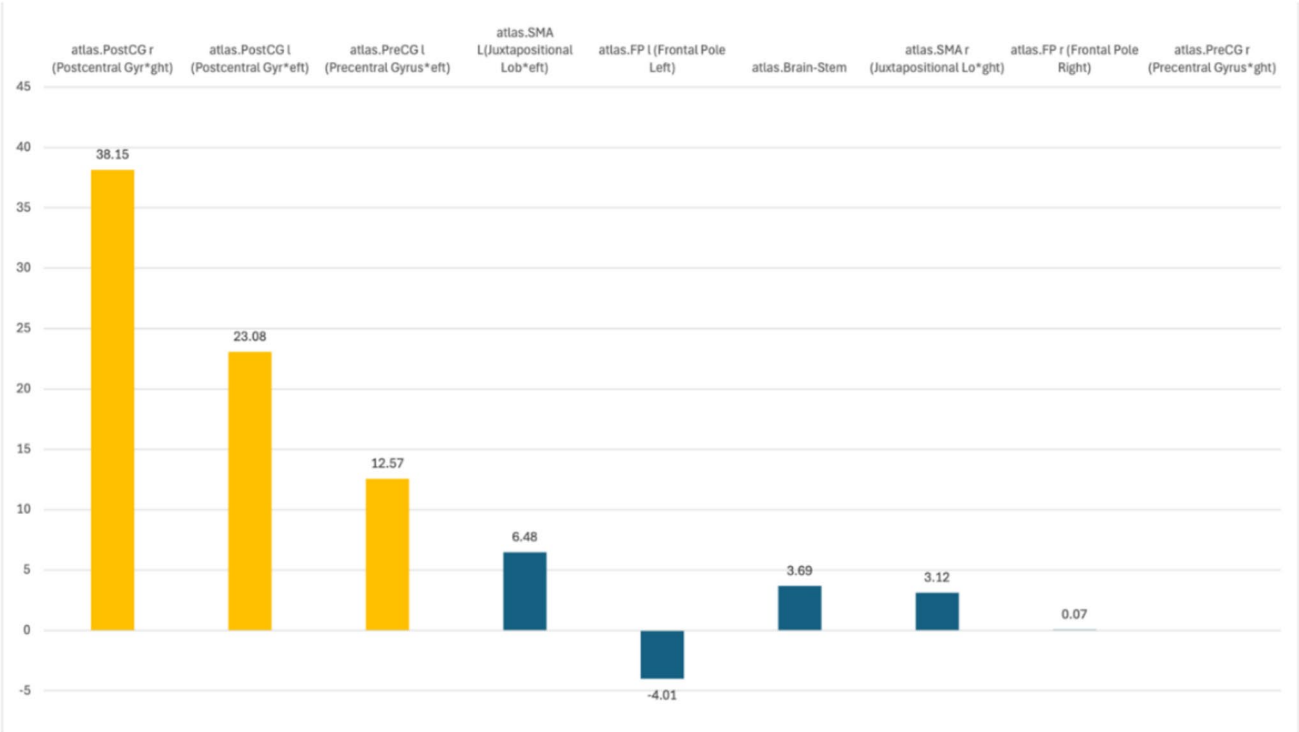

Fig. 6 ROI-to-ROI connectivity after rTMS with seed in the right precentral gyrus. Yellow bars indicate observed increases above the descriptive threshold (p-uncorrected < 0.05). Note: All connectivity changes are descriptive and based on single-subject analysis

Table 2 ROI-to-ROI analysis with seed on the right precentral gyrus. Significant connections (p-uncorrected < 0.05) are seen with the right postcentral gyrus, left postcentral gyrus, and left precentral gyrus

Targets	beta (Z)	T-score	p-unc	p-FDR
Right Postcentral gyrus	0.730168	38.145928	0.016685	0.116797
Left postcentral gyrus	0.342003	23.078077	0.027568	0.128652
Left precentral gyrus	0.770908	12.56644	0.050554	0.176938
Left SMA	0.401695	6.47518	0.097546	0.227608
Right SMA	0.526945	3.117117	0.19763	0.338273

Reported values reflect connectivity changes from ROI-to-ROI analysis using the right precentral gyrus as seed. T-scores and p-values are shown for descriptive purposes only; no group-level or inferential statistical analysis was performed

Microstructural changes (DTI)

DTI analyses revealed tract-specific changes in fractional anisotropy (FA) following the intervention.

In **Subject 1**, FA increased bilaterally in the SMA (pre-SMA and SMA proper), most prominently in the left hemisphere. Increases were also noted in the left M1 (Area 4a) and the corpus callosum (Fig. 8; Table 3). These changes may reflect compensatory recruitment of higher-order motor regions and increased interhemispheric communication. In contrast, FA decreased in right-hemispheric sensorimotor tracts, including the right corticospinal tract, superior longitudinal fasciculus/cingulum, medial lemniscus, and thalamic radiation, potentially indicating reduced reliance on the stimulated hemisphere's output pathways Table 4.

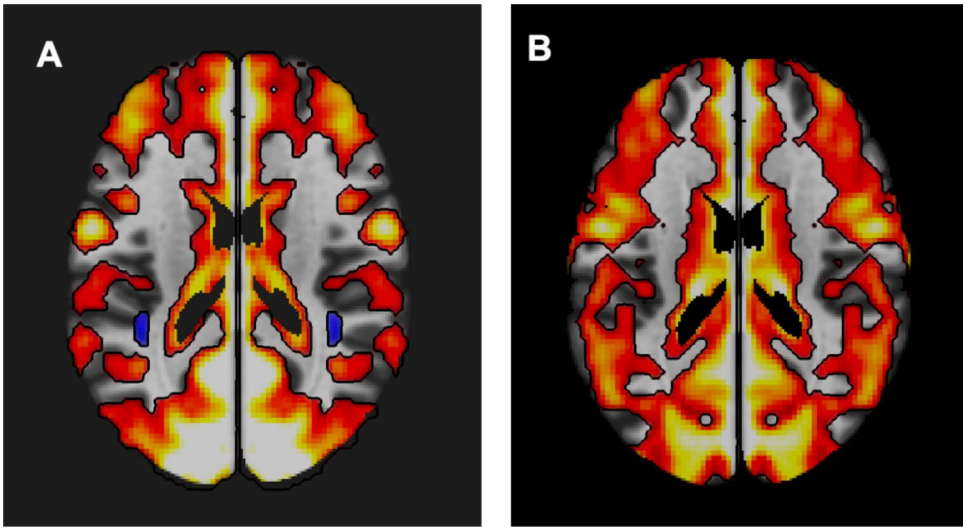

Fig. 7 Interhemispheric connectivity maps. Before (**A**) and after (**B**) rTMS, showing Z-score differences in correlation strength. Note: Results are visualized using descriptive voxel-wise thresholds; no inferential statistical conclusions are drawn

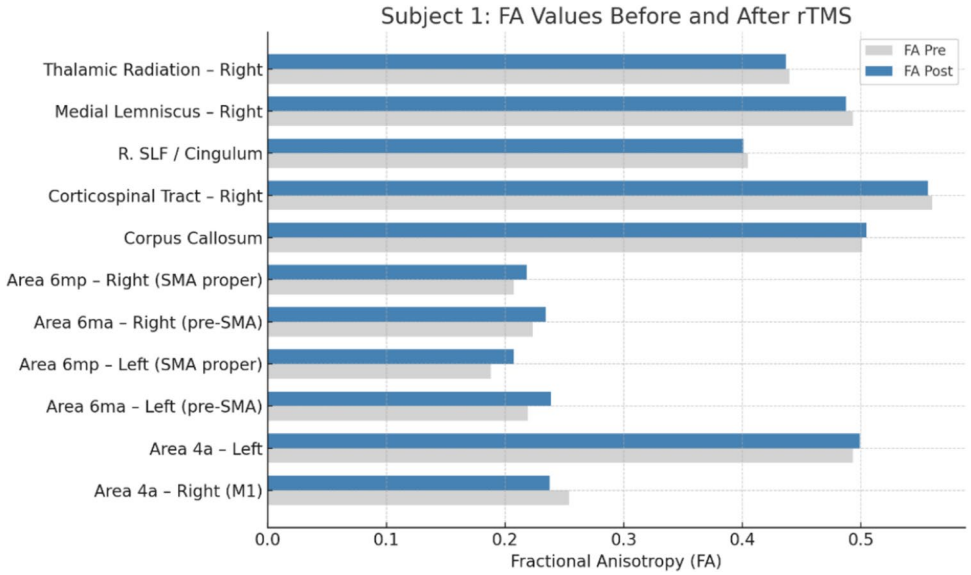

Fig. 8 Fractional anisotropy (FA) values pre- and post-rTMS in Subject 1 across selected motor-related white matter regions. Each bar represents the FA value before (gray) and after (blue) the rTMS intervention. Note: Quantitative analysis is reported in Table 3

Table 3 A summary of mean FA values across selected motor-related regions and tracts

Region/Tract	FA Pre	FA Post	Δ FA (Post – Pre)
Area 4a – Right (M1)	0.253634	0.237745	–0.0159
Area 4a – Left	0.493147	0.499099	0.0059
Area 6ma – Left (pre-SMA)	0.219084	0.238697	0.0196
Area 6mp – Left (SMA proper)	0.188042	0.207331	0.0193
Area 6ma – Right (pre-SMA)	0.223259	0.23434	0.0111
Area 6mp – Right (SMA proper)	0.20712	0.218388	0.0113
Corpus Callosum	0.500761	0.504344	0.0036
Corticospinal Tract – Right	0.559721	0.556508	–0.0032
R. SLF/Cingulum	0.404407	0.40085	–0.0036
Medial Lemniscus – Right	0.493402	0.487191	–0.0062
Thalamic Radiation – Right	0.439626	0.436611	–0.0030

Table 4 A summary of mean FA values across selected motor-related regions and tracts

Region/Tract	FA Pre	FA Post	Δ FA (Post – Pre)
Area 4a – Right (M1)	0.50676	0.505561	−0.001199
Area 4a – Left	0.489557	0.486547	−0.00301
Area 6ma – Left (pre-SMA)	0.520421	0.505975	−0.014446
Area 6mp – Left (SMA proper)	0.539573	0.207331	−0.014446
Area 6ma – Right (pre-SMA)	0.491937	0.480468	−0.011469
Area 6mp – Right (SMA proper)	0.463579	0.471293	0.007714
Corpus Callosum	0.523754	0.523197	−0.000557
Corticospinal Tract – Right	0.518193	0.517382	−0.000811
R. SLF/Cingulum	0.403649	0.40361	–0.000039
Medial Lemniscus – Right	0.486809	0.481385	−0.005424
Thalamic Radiation – Right	0.460806	0.465018	0.004212

In **Subject 2**, the post-intervention scans exhibited a marked reduction of FA in the left SMA proper (Area 6mp-L). Subtle reductions in FA were observed in the right M1, right pre-SMA, and left pre-SMA. FA increased modestly in the right SMA proper thalamic radiation, while values remained stable in the corpus callosum, right CST, and right SLF/cingulum. A slight decrease was noted in the right medial lemniscus (Fig. 9; Table 4).

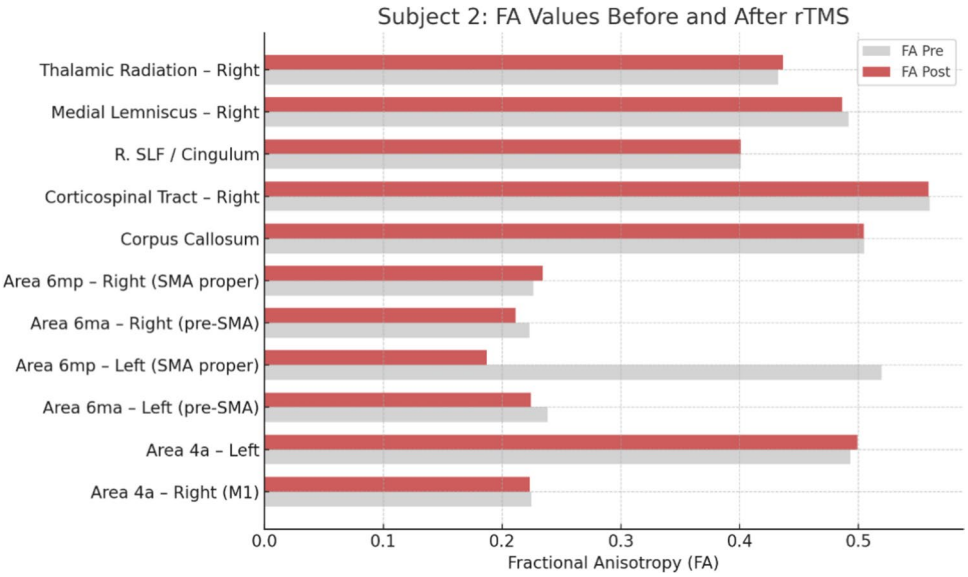

Fig. 9 Fractional anisotropy (FA) values pre- and post-rTMS in Subject 2 across selected motor-related white matter regions. Each bar represents the FA value before (gray) and after (red) the rTMS intervention

Inter-subject variability in motor network plasticity

The individual results described above are summarized in a qualitative comparison to highlight the differences and similarities in connectivity profiles. In both subjects, post-intervention imaging revealed increased interhemispheric functional connectivity, particularly between homologous motor regions—including the primary motor cortices (M1), supplementary motor areas (SMA), and cingulate cortices. Notably, Subject 1 exhibited a broader pattern of bilateral engagement, while Subject 2 showed a more localized and lateralized response, characterized by enhanced coupling between the right M1 and contralateral somatosensory regions, with comparatively limited SMA involvement. Intrahemispheric changes were also observed, primarily reflecting strengthened connectivity between the right M1 and the ipsilateral SMA (Fig. 10).

These functional changes were mirrored, to varying degrees, in DTI-based measures of microstructural integrity. Subject 1 demonstrated FA increases in bilateral SMA regions, left M1, and the corpus callosum, while FA decreased in right-sided tracts, including the corticospinal tract and medial lemniscus—suggesting a shift toward contralateral recruitment. In contrast, Subject 2 showed a more focal response, including prominent FA reduction in the left SMA and more stable values in other tracts. These findings are summarized in Fig. 11, providing a descriptive comparison of ΔFA across motor-related white matter regions.

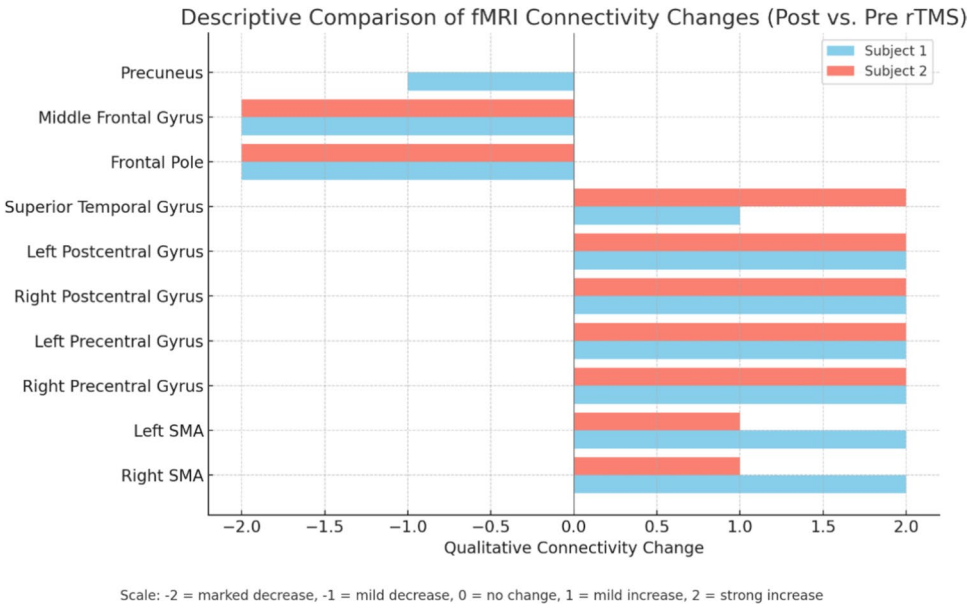

Fig. 10 Descriptive comparison of fMRI connectivity changes (post vs. pre rTMS) in Subject 1 and Subject 2. The bar graph represents qualitative changes in functional connectivity between the right M1 and various motor and associative regions following inhibitory rTMS. Ratings were derived from Seed-Based and ROI-to-ROI analyses, interpreted on a qualitative scale: −2 = marked decrease, −1 = mild decrease, 0 = no change, 1 = mild increase, 2 = strong increase. Both subjects exhibited increased connectivity in core sensorimotor areas (e.g., precentral and postcentral gyri, SMA), while reductions were observed in frontal associative regions, with notable inter-subject differences in the extent and direction of changes

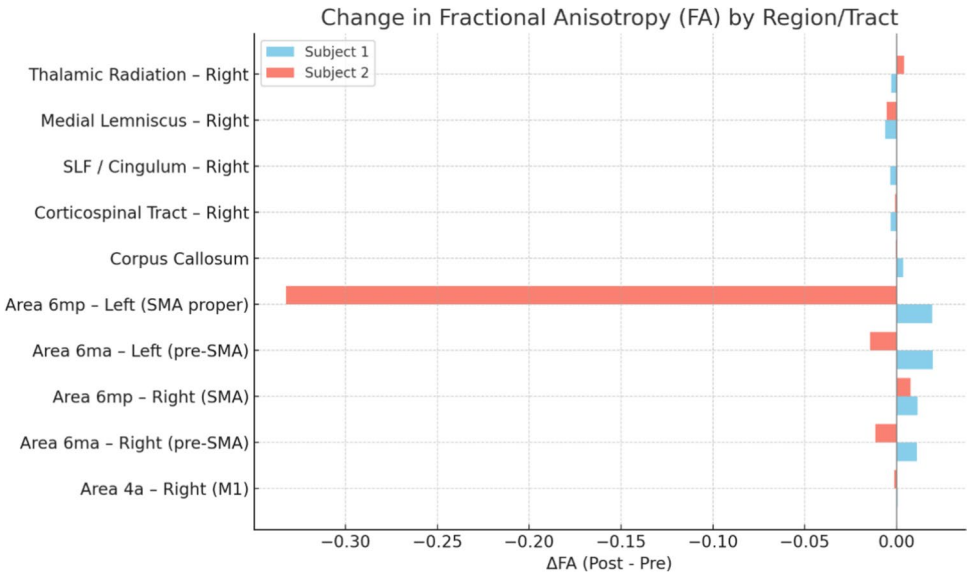

Fig. 11 Change in fractional anisotropy (ΔFA) across motor-related white matter regions and tracts following rTMS intervention. Bar graph showing the difference in FA values (post – pre) for Subject 1 (blue) and Subject 2 (red) across ten selected regions of interest (ROIs), including primary motor and premotor areas, the corpus callosum, and key projection and association tracts. Positive values indicate increased FA post-intervention; negative values reflect reductions. Notable variability was observed between subjects, with some tracts (e.g., right SMA, right CST) showing similar trends, and others (e.g., left SMA proper) displaying opposite patterns. These results are presented descriptively and should be interpreted as exploratory, given the single-subject design

Discussion

This exploratory study provides preliminary evidence that a short, intensive course of low frequency rTMS can induce functional and structural reorganization of the motor network in healthy individuals. Using resting-state fMRI and diffusion tensor imaging (DTI), we identified increased interhemispheric and intrahemispheric connectivity involving M1, SMA, and the cingulate cortex, along with microstructural alterations in key motor tracts. While descriptive, these findings support the hypothesis that inhibitory neuromodulation, even when delivered over a short timescale, can engage compensatory and associative motor pathways—suggesting potential applicability as a prehabilitation strategy in neurosurgical settings.

Insights from stroke rehabilitation studies

Our results are also informed by the stroke rehabilitation literature, where several studies have demonstrated that short rTMS protocols can modulate cortical excitability and promote motor recovery [5, 13, 25, 31, 38, 54, 56]. For instance, Du et al. investigated the effects of 1 Hz rTMS over the unaffected hemisphere in stroke patients for five consecutive days, reporting improvements in hand motor function and favorable changes in cortical excitability (increased MEP amplitude and decreased rMT in the affected hemisphere). However, this study did not include imaging measures of plasticity [17].

Similarly, Fregni et al. found that five sessions of inhibitory rTMS to the contralesional M1 improved motor abilities in stroke-affected hands [24]. A follow-up by Demirtas-Tatlidede et al. extended the protocol to ten days, observing prolonged motor improvements and an increase in transcallosal FA on DTI [13]. While these studies confirm the capacity of short rTMS protocols to elicit motor plasticity, they primarily relied on clinical and physiological markers, without investigating whole-network connectivity or the involvement of secondary motor areas. In contrast, our study combines fMRI and DTI to capture both functional and structural correlates of network reorganization, thus allowing a richer and more precise understanding of rTMS-induced neuroplasticity.

Novelty and comparison to existing NICP literature

To our knowledge, this is the first study to demonstrate both functional and structural plasticity of the motor system induced by an accelerated rTMS protocol—specifically, seven days of twice-daily inhibitory stimulation at 110% RMT—in healthy subjects. Existing studies on neuromodulation-induced cortical prehabilitation (NICP) have typically employed protocols lasting two weeks or more, using different neuromodulation protocols.

For example, Dadario et al. described a case of motor prehabilitation and postoperative rehabilitation using TBS in a patient with recurrent high-grade glioma involving the right motor cortex. After a prehabilitation protocol consisting of 10 sessions over two weeks, the patient awoke from surgery with significant left hemiparesis following a pure cingulate-motor resection. Postoperative iTBS over the contralateral motor and parietal regions led to partial motor recovery within one month. However, it remains unclear whether this clinical improvement was attributable solely to the prehabilitation intervention, as no imaging or physiological markers of motor network reorganization were reported. Furthermore, as the authors themselves noted, it is possible that the prior surgical insult facilitated cortical reorganization during perioperative neuromodulation, consistent with earlier findings by Robles et al. (2008) [42].

In a recent case series, Boccuni et al. applied LF-rTMS at 90% RMT over two to four weeks in patients with motor- or language-eloquent tumors. Relevant fMRI displacement was observed in only two patients. One had a right parasagittal superior frontal meningioma and received rTMS targeting a motor area identified by task-based fMRI. The other had a left fronto-temporo-insular astrocytoma and underwent a combined protocol for language prehabilitation, consisting of morning rTMS and multichannel tDCS.

A more comparable short-term intervention was reported by Lang et al., who conducted a proof-of-concept pilot study using preoperative tDCS in eight patients with left-sided gliomas [29]. Over four consecutive days, patients received tDCS paired with motor training, with the anode placed over the left M1 and the cathode over the contralateral supraorbital area. The intervention led to increased global and local M1 connectivity; however, no significant clusters emerged in the seed-to-whole-brain analysis, interhemispheric connectivity remained unchanged, and connectivity in the supplementary motor area (SMA) decreased.

Clinical relevance and implications

Although our findings are preliminary and based on only two healthy subjects, they provide encouraging support for the use of short-term rTMS protocols to enhance motor system plasticity before surgery. The increased connectivity observed between M1, SMA, and the cingulate motor areas —demonstrated through both rs-fMRI and DTI analyses—may have important implications for neurosurgical planning and risk mitigation.

There is growing recognition that motor network integrity—particularly the presence of redundant and

interconnected pathways—plays a critical role in determining a patient's capacity to withstand surgical intervention without incurring lasting deficits [10, 35, 38, 39, 56]. For example, Otten et al. found that robust intra- and interhemispheric connectivity between M1 and SMA correlated with lower incidence of postoperative motor deficits and better functional outcomes in patients undergoing resection of motor-eloquent gliomas [35].

Our results also highlight enhanced engagement of the cingulate motor cortex, a region whose contribution to motor preservation may be underrecognized. Notably, Dadario et al. reported a case in which pure cingulate-motor resection resulted in hemiparesis, despite an intact corticospinal tract and preserved SMA connectivity. This suggests that disruption of the cingulate motor area alone can result in significant motor deficits, likely due to its role in higher-order motor initiation and its functional integration with the SMA and primary motor cortex. In this light, the increased cingulate motor connectivity observed in our study is particularly noteworthy, as it may reflect a strengthening of broader motor pathways that support functional resilience and could help reduce the risk of postoperative deficits.

Taken together, these observations reinforce the potential utility of network-based prehabilitation strategies, such as the accelerated rTMS protocol used in this study. By enhancing connectivity within a broader motor system—including secondary and associative regions—such approaches may improve the brain's resilience to surgical insult, especially in cases where tumors encroach upon or displace key motor nodes.

Limitations and future directions

Naturally, these findings must be interpreted in light of the study's limitations, including the small sample size, the absence of behavioral endpoints, and the exploratory nature of the analyses. Nonetheless, the convergence of fMRI and DTI findings across both subjects strengthens the plausibility of the observed effects. Future studies should extend this work to larger cohorts, include clinical populations with motor-eloquent tumors, and incorporate behavioral assessments to clarify the functional significance of observed connectivity changes.

Conclusions

This small-scale pilot study provides proof of concept that accelerated, low-frequency rTMS over the primary motor cortex can induce functional and structural reorganization of the motor network. Overall, this research supports the potential of rTMS-based prehabilitation to inform novel strategies for the treatment of eloquent brain tumors, particularly in enhancing functional resilience before surgery. Although the results remain descriptive and limited to healthy individuals, they align with compelling findings from other studies and underscore the clinical relevance of early network reorganization.

To validate and extend these observations, further studies are needed to assess the safety, feasibility, and efficacy of this protocol in larger samples, including both healthy volunteers and patient populations. In our view, these efforts are fully warranted by the results presented here and by the growing body of evidence supporting neuromodulation as a promising adjunct to neurosurgical planning.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Informed consent Written informed consent has been obtained from the patient to publish this paper.

Institutional review board statement The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of CE-AVEC Azienda USL Bologna and Azienda USL Imola (protocol code N° 362–2024-OSS-AUSLBO approved on July 18th, 2024).

Competing interests The authors declare no competing interests.

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