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The Role of Baseline Functional MRI as a Predictor of Post-Stroke Rehabilitation Efficacy in Patients with Moderate to Severe Upper Extremity Dysfunction

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Abstract

Introduction: Upper extremity impairment is one of the common complications following a stroke. There are numerous rehabilitation strategies to address this problem. However, patients with moderate to severe upper limb disabilities respond differently to the same rehabilitation protocol. Apart from each patient's unique characteristics, there are specific brain reorganizing patterns that affect the post-rehabilitation response rate. Functional magnetic resonance imaging (fMRI) determines brain activation area and connectivity patterns and has been utilized in the neurorehabilitation field. **Material and Methods:** Six stroke patients who suffered from moderate to severe upper extremity dysfunction were enrolled in this pilot study. Upper extremity function tests including the Fugl-Meyer assessment test for upper extremity (FMA-UE), and Wolf Motor Function Test (WMFT) were utilized before and after completing an intensive rehabilitation. The intensive rehabilitation program was conducted one hour a day for five days per week for four weeks. Moreover, fMRI was applied before initiating rehabilitation. The regions of interest were those associated with movement, including Brodmann areas (BA) BA1-BA6. **Results:** Six stroke patients in the sub-acute to chronic phase and ages ranging between 33 - 75 years were enrolled. All patients showed an improvement in upper limb function after four weeks of rehabilitation. Patient number one (Pt1) had the most improvement in FMA-UE, while patient number four (Pt4) recovered the most measured by WMFT. Pt1 demonstrated increased activity in all contralesional regions, whereas Pt4 had only increased activity in ipsilesional areas. Furthermore, patients with greater activation in the ipsilesional BA6 (Pt1, Pt4, Pt5, and Pt6) had better responses to the rehabilitation therapy. **Conclusion:** Patients with greater activation in the baseline fMRI, particularly ipsilesional BA6, had a better response to the intensive rehabilitation therapy. However, the patients with the most severe hand dysfunction showed lesser improvement despite the same brain activity as others in the initial fMRI.

Keywords

Stroke, Functional MRI, Rehabilitation, Upper Extremity

1. Introduction

Stroke is one of the most important causes of disability worldwide. The incidence and mortality of stroke are increasing due to the growing elderly population [1] [2]. Contralateral upper limb hemiparesis is the most prevalent impairment following a stroke, affecting more than 80% of acute stroke patients and more than 40% of chronic ones. Upper-extremity motor paresis may be accompanied by additional neurological symptoms that impede motor function recovery, necessitating targeted rehabilitation therapy [3].

The primary goal of post-stroke management is to re-establish daily activities through different rehabilitation methods despite the residual impairments [4]. Neurological recovery follows a nonlinear, logarithmic pattern, meaning that most recovery is expected in the first three months after a stroke. Furthermore, recovery from a stroke can be characterized as an improvement in several outcomes, starting with biological and neurologic changes that appear to improve performance and activity-based behavioral measures. Adaptation, regeneration, and neuroplasticity are the three fundamental mechanisms in brain recovery following a stroke. Adaptation happens by using alternate physical movements or equipment to compensate for functional loss. Regeneration is known as the growth of damaged neural cells into new tissue to restore function. The main recovery mechanism is neuroplasticity, characterized by alterations or rewiring within the neural network [3] [4] [5].

Functional disabilities after a stroke affect the patient's quality of life and leave a significant financial burden on society [6]. In addition, only a few patients with severe hand dysfunction will show promising results after the rehabilitation program [7]. However, it is relatively difficult to predict the recovery outcome and success rate only based on the clinical data in severely disabled patients. Thus, a prognostic tool to determine long-term motor recovery in terms of rehabilitation efficacy costs many expenses. Previous clinical studies have suggested the effectiveness of intensive motor training paired with repetitive transcranial magnetic stimulation (rTMS), muscular electrical stimulation, brain-computer interfaces, and robotic devices in upper limb rehabilitation in stroke patients [8] [9].

Notably, stroke patients are more likely to have permanent functional deficits because the non-activated brain has a limited neuroplasticity capacity. Neuroplasticity is also affected by the type of intervention, the patient's age, the location of the lesion, and handedness. Therefore, tools like functional magnetic resonance imaging (fMRI) are utilized to investigate brain activity and the influence of neurorehabilitation methods on neuroplasticity in addition to clinical disability assessment tools. FMRI has an excellent spatial resolution, allowing researchers to gain insight into the brain reorganization process and its associated functional recovery after stroke neurorehabilitation [10]. In general, fMRI captures the blood oxygen level-dependent (BOLD) signal is captured using T2*-weighted imaging. Higher neuron activity is associated with higher blood flow in the related areas, increasing the oxyhemoglobin-to ratio and the signal [11]. Task performance during fMRI causes hemodynamic response function (HRF) in the motor cortex area, which changes the BOLD signal recorded by the MRI machine.

We conducted this study using the fMRI as a prognostic tool for upper limb functional recovery after intensive rehabilitation from a stroke. Although these findings should not exclude the most severe patients from rehabilitation therapy, but also help to define the realistic rehab consequences for both therapist and patients.

2. Methods and Materials

Patients with clinically diagnosed stroke and upper limb dysfunction were referred to the Physical Medicine and rehabilitation center of the Shariati Hospital from the neurology clinic. An occupational therapist first examined patients, and their motor impairment level and upper limb function were assessed with a validated Persian version of the Fugl-Meyer assessment scale for upper extremity (FMA-UE) and Wolf Motor Function Test (WMFT) [12] [13]. FMA-UE with a score range of 0 - 66 and WMFT with a range of 0 - 75 were used.

Inclusion criteria were the age > 18 years and severe unilateral upper limb impairment following stroke. Exclusion criteria were the active phase of the disease, pregnancy, severe aphasia, any underlying disease affecting the upper extremity, severe psychiatric conditions, cognitive disorders, dementia, and patients with a history of stroke or any other brain injury.

Intervention Protocols:

An intensive rehabilitation program designed by a rehabilitation specialist, including anodal transcranial direct current stimulation (tDCS) over C3 and C4 areas with an intensity of 1.5 mA for 20 minutes, neuromuscular electrical stimulation (NMES) over affected muscles, and occupational therapy consisting of strengthening techniques, stretching, mirror therapy, proprioceptive neuromuscular facilitation (PNF), constraint-induced movement therapy (CIMT), and Brunnstrom. The program was conducted five days per week for four weeks at the same time of the day. Upper limb function was also measured using FMA-UE and WMFT questionnaires before and after completing the sessions.

FMRI data acquisition and processing:

Patients underwent a pre-treatment fMRI. FMRI data were collected using a 3Tesla MRI scanner. During the imaging, patients saw a display along with the magnet with the help of a mirror placed on the coil. The patient was instructed to tap their fingers repetitively on his thumb when they saw the "go" command until the "stop" command was displayed. The operator also monitored this process. A task-based block design fMRI was performed on patients, which included 20 seconds of activity followed by 20 seconds of rest. The technician examined the images for the presence of artifacts. Finally, a biomedical engineering expert analyzed the imaging data. Images were analyzed using FSL (http://www.fmrib.ox.ac.uk/fsl) software. Before the final processing, several pre-processing steps were performed, including registration, motion correction, slice-timing correction, non-brain removal using BET (Brain Extraction Tool), spatial smoothing, high pass temporal filtering, intensity normalization, and statistical analysis using FILM pre-whitening [14] [15] [16] [17]. Z statistic images were threshold non-parametrically using clusters determined by $Z > 3.1$ and a cluster significance threshold of $P = 0.05$.

Brodmann areas (BA) of the cerebral cortex were first defined by the German anatomist Korbinian Brodmann in the early 1900s, based on their cytoarchitecture [18]. Our regions of interest included those associated with movement, including BA1-BA6. We examined BA1, BA2, BA3, BA4, and BA6. BA1, BA2, and BA3 correspond to the primary somatosensory cortex, located in the post-central gyrus. BA4 corresponds to the primary motor cortex in the precentral gyrus. Finally, BA6 is associated with the premotor and supplementary motor cortex located in the frontal cortex [18] [19] [20].

3. Results

Patients' characteristics are described in **Table 1**. Six stroke patients were enrolled aged from 33 - 75, of which one was female. The time from stroke onset ranged from 1 - 6 months. **Table 2** demonstrates FMA-UE and WMFT scores at baseline and after four weeks of post-stroke upper limb rehabilitation. According to the pretreatment assessment, patients demonstrated moderate to severe impairment in upper limb functional ability. Patient number four (Pt4) had the highest FMA-UE score = 39, while Pt5 had a better WMFT score = 40 at baseline. All patients showed an improvement in upper limb function (both FMA-UE and WMFT) after four weeks of rehabilitation. Pt1 had the most improvement in the FMA-UE test = 22, followed by Pt4 = 19 and Pt6 = 14. In contrast, Pt4 recovered the most measured by WMFT scores = 15.

Table 3 shows the mean activation of each patient's BA in right and left sides. Baseline fMRI illustrated increased activity in all contralesional regions in

Table 1. Demographic characteristics.

Subject	Age (years)	Gender (M/F)	Time from stroke (months)	Affected limb
Pt1	38	M	2	Right
Pt2	75	F	2	Right
Pt3	68	M	6	Right
Pt4	60	M	1	Right
Pt5	33	M	2.5	Right
Pt6	50	M	4	Left

Table 2. Motor function assessment test results.

Subject	FMA-UE			WMFT		
	Pretreatment	Post-treatment	Difference	Pretreatment	Post-treatment	Difference
Pt1	18	40	22	12	15	3
Pt2	5	6	1	3	6	3
Pt3	8	14	6	2	6	4
Pt4	39	58	19	40	55	15
Pt5	9	25	14	11	13	2
Pt6	38	46	8	52	55	3

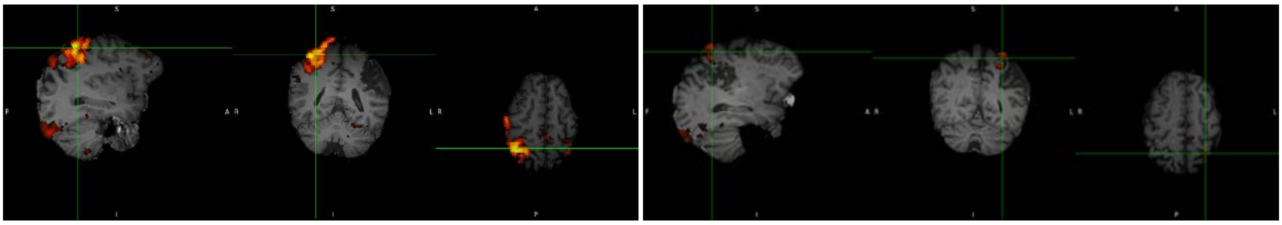
Abbreviations: Fugl-Meyer assessment scale for upper extremity (FMA-UE), Wolf Motor Function Test (WMFT).

Table 3. Baseline fMRI characteristics.

BA	Region	Pt1 MA	Pt2 MA	Pt3 MA	Pt4 MA	Pt5 MA	Pt6 MA
BA1R	Right Postcentral Gyrus (Primary Somatosensory Cortex)	5.854	4.367	0.818	1.419	4.069	3.223
BA2R		5.274	4.352	0.901	1.379	3.931	3.242
BA3aR		5.457	4.708	0.354	0.457	3.497	3.260
BA3bR		5.928	4.486	0.635	1.062	3.935	3.209
BA4aR	Right Precentral Gyrus (Primary Motor Cortex)	6.663	4.515	0.464	1.002	4.05	3.291
BA4pR		6.074	4.553	1.063	0.867	3.975	3.244
BA6R	Right Frontal Cortex (Premotor & Supplementary Motor Cortex)	6.061	4.669	0.440	0.957	3.982	3.878
BA1L	Left Postcentral Gyrus (Primary Somatosensory Cortex)	0.752	4.796	1.182	3.997	4.241	3.718
BA2L		0.459	4.711	1.03	4.103	4.189	3.567
BA3aL		0.126	4.06	0.942	3.994	3.784	3.7
BA3bL		0.617	4.347	1.338	4.106	4.272	3.661
BA4aL	Left Precentral Gyrus (Primary Motor Cortex)	1.044	3.866	1.294	4.156	4.017	3.687
BA4pL		0.533	3.967	0.908	4.144	4.157	3.67
BA6L	Left Frontal Cortex (Premotor & Supplementary Motor Cortex)	1.683	3.763	1.402	4.248	4.347	3.734

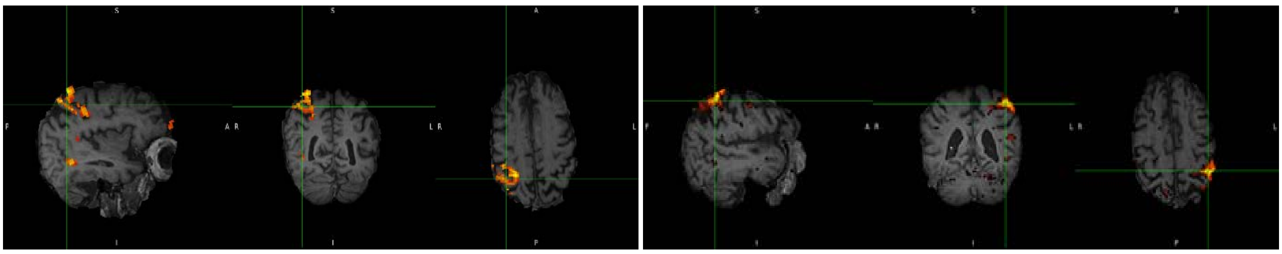
Abbreviations: Brodmann area (BA), Mean activation (MA), Patient (Pt), R: Right, L: Left, a: anterior, p: posterior.

patient 1 (**Figure 1**). All regions (bilateral post-central gyrus, precentral gyrus, and frontal gyrus) demonstrated increased activities in Pt2 (**Figure 2**). Interestingly, there was no significant increase in Pt3's fMRI results (**Figure 3**). Pt4 only had increased activity in ipsilesional areas (**Figure 4**). Pt5 and Pt6 (**Figure 5** and **Figure 6**) had increased activities in all movement-related areas.



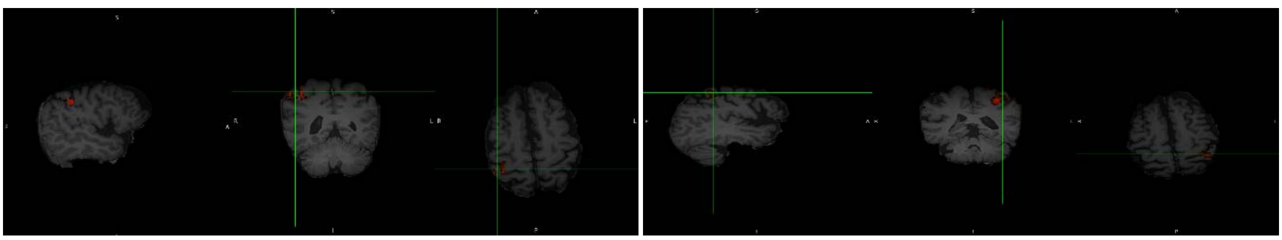
(a) (b)

Figure 1. fMRI activation map for patient 1 undergoing the motor task for left hand (unaffected hand) before rehabilitation (a), and right hand (affected hand) before rehabilitation (b).



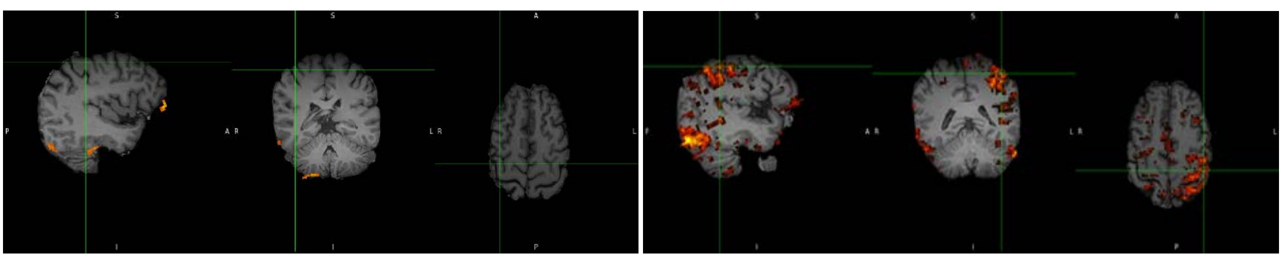
(a) (b)

Figure 2. fMRI activation map for patient 2 undergoing the motor task for left hand (unaffected hand) before rehabilitation (a), and right hand (affected hand) before rehabilitation (b).



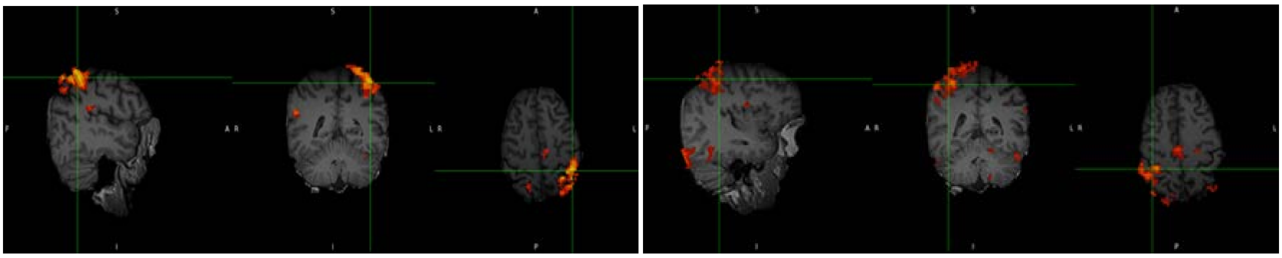
(a) (b)

Figure 3. fMRI activation map for patient 3 undergoing the motor task for left hand (unaffected hand) before rehabilitation (a), and right hand (affected hand) before rehabilitation (b).



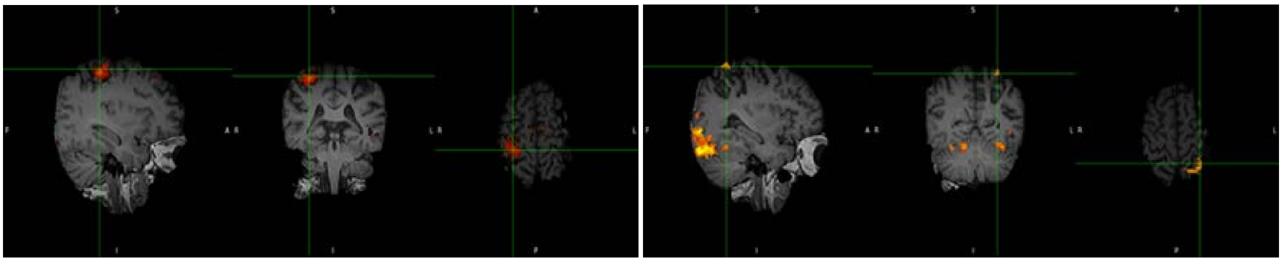
(a) (b)

Figure 4. fMRI activation map for patient 4 undergoing the motor task for left hand (unaffected hand) before rehabilitation (a), and right hand (affected hand) before rehabilitation (b).



(a) (b)

Figure 5. fMRI activation map for patient 5 undergoing the motor task for left hand (unaffected hand) before rehabilitation (a), and right hand (affected hand) before rehabilitation (b).



(a) (b)

Figure 6. fMRI activation map for patient 6 undergoing the motor task for left hand (affected hand) before rehabilitation (a), and right hand (unaffected hand) before rehabilitation (b).

4. Discussion

Prediction of the rehabilitation consequences in the stroke population with more severe upper extremity dysfunction remained challenging for therapists. Therefore, using an objective tool to represent the correlation between pre-treatment status and the post-rehabilitation outcome helps determine the realistic goal for the patient. We conducted this study to examine the impact of an intensive neurorehabilitation program on post-stroke upper limb functional recovery and explore the effect of baseline fMRI activity patterns on stroke recovery.

The post-stroke neurological recovery follows a nonlinear, logarithmic pattern. Most neural reorganization happened in the first three months after a stroke. However, evidence suggests that recovery is not restricted to this time frame, and upper extremity recovery can be continued for several years after stroke onset. Stroke recovery happens as a result of a complex combination of spontaneous and learning-dependent processes [5].

Stroke patients are known to demonstrate higher diffuse activation in multiple brain regions, including motor-related areas while performing motor tasks during the early stages [21]. The lateralization and focus on the contralateral primary sensorimotor cortex are minimized during unilateral motor functions in stroke patients. Good recovery is mainly associated with near-normal network parameters. Decreased interaction of the premotor and supplementary motor areas with the ipsilesional motor cortex is a sign of functional impairment [22].

We used a combination of NEMS, tDCS, and occupational therapy methods as our rehabilitation program. These results are similar to a recent systematic review reporting the effectiveness of cyclic NMES in hemiplegic patients with acute and sub-acute stroke on improving motor function of the upper limb and increased FMA-UE scores compared to healthy controls. They also confirmed the effectiveness of NMES in upper limb motor recovery in chronic stroke. However, these results mainly consisted of small case series with no control group [23]. Moreover, a meta-analysis by Elsner investigated the impact of tDCS on improving activities of daily living (ADL) and arm function after stroke. This study found no evidence of the effectiveness of either tDCS method on post-stroke upper limb function assessed by FMA-UE [24]. In contrast, another meta-analysis confirmed the positive effects of tDCS on post-stroke rehabilitation of the upper limb. Also, they found an increased effect of tDCS in chronic stroke compared to acute and sub-acute stroke and suggested that the modulation of neural activity between interhemispheric could be the underlying mechanism [25].

The evidence also suggests the effectiveness of CIMT on arm motor function, arm motor activity, and quality of movement even in patients with chronic stroke [26]. Furthermore, CIMT increased perfusion of the affected hemisphere in motor-related areas such as the precentral gyrus, premotor and frontal cortex [27].

A clinical trial on 95 patients with sub-acute stroke revealed that the baseline severity of motor dysfunction, particularly the baseline FMA score is the most potent determinant of upper limb rehabilitation following four weeks of cyclic NMES [28]. It showed that cyclic NMES appeared to be more effective in patients who still had remaining movement at baseline. These results confirmed our findings.

All patients showed an improvement in upper limb function tests (FMA-UE and WMFT) after four weeks of rehabilitation. However, patients with moderate impairment had a better outcome. Moreover, those who had greater brain activity patterns notably in the affected hemisphere responded better to the therapy. FMRI study by Fu *et al.* on twenty-four stroke patients also discovered the increased activity of the bilateral premotor area and the bilateral supplementary motor area in stroke patients during active movement of the fingers [29].

These results match those mentioned in an earlier cohort fMRI study by Backhaus *et al.* on 19 women with severe stroke during its acute phase. They reported a significantly increased coupling in the ipsilesional parietofrontal between the anterior intraparietal sulcus and the primary motor cortex. This pattern is accompanied by more severe upper limb dysfunction and global disability at the late sub-acute stage than baseline assessment and suggested considering the parietofrontal networks of the ipsilesional hemispheres as a predictive factor in future neurorehabilitation programs [30].

Previous studies have shown a positive correlation between BA4a activity and motor recovery post-stroke, regardless of the treatment [31] [32]. However, in the current study, intensive rehabilitation was carried out for patients and there was an association between ipsilateral BA6 activation and better motor outcomes. A study by Nelles *et al.* exhibited greater activity in the bilateral BA6 after task-oriented arm training [33]. They stated that apart from the primary motor cortex area, premotor and supplementary motor areas also play an important role in the recovery process. Furthermore, they reported that the temporary inactivation of BA6 in the ipsilesional region leads to the worsening of motor function, while BA4 deactivation did not have the same effect. This emphasizes the prominent contribution of BA6 in the central motor network [34].

Intensive rehabilitation therapy is a time and money-consuming process, and most patients and therapists are eager to know whether worth it or not, especially in the lower income countries. Although we cannot deprive patients of rehabilitation care, scrutinizing the cost and benefit of this specific rehabilitation is required. In the current study, patients with modest hand dysfunction responded better regardless of pre-treatment fMRI activation, and those subjects with prominent brain activity responded with much better results. On the other hand, the patients with an extreme disability had lower recovery despite the same brain activity as patients with moderate hand dysfunction.

Study Limitations

Our study is limited by the small sample size due to the COVID-19 pandemic, and lesser subjects tend to participate in the intensive rehabilitation program for one month. This study may be considered a preliminary study, and further studies with larger sample sizes and different designs evaluating pre-treatment fMRI patterns are recommended.

5. Conclusion

As a result, patients with minor motor dysfunction at baseline had higher response to neurorehabilitation. In addition, the baseline fMRI results revealed that increased activity in the ipsilesional hemisphere, particularly in the premotor and supplementary motor cortex, was associated with higher upper limb function and movement quality after the treatment.

Ethical Considerations

Compliance with Ethical Guidelines

This study was approved by the Ethical Committee of Tehran University of Medical Sciences (code: IR.TUMS.MEDICINE.REC.1397.748). The study participants signed a written informed consent form.

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Authors' Contributions

All authors equally contributed to preparing this article.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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