Journal of Chemical Health Risks

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JCHR (2026) 16(2), 1953-1961 | ISSN:2251-6727

Neuroplasticity Modulation through the Synergy of Theta Burst Stimulation and Mirror Therapy: Motor Functional Recovery of Subacute Ischemic Stroke

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(Received: 16 January 2026 Revised: 25 February 2026 Accepted: 17 March 2026)

KEYWORDS
Ischemic Stroke;
Neuroplasticity;
DTABR;
Theta Burst Stimulation;
FMA-UE;
FMA-LE;
qEEG

ABSTRACT:

Introduction: Ischemic stroke often causes motor disability. Neurorehabilitation with Theta Burst Stimulation and mirror therapy is promising for motor function recovery. This study aims to evaluate the efficacy of the combination of TBS and mirror therapy on motor function and brain activity (qEEG) in ischemic stroke patients, compared to TBS therapy alone.

Materials and Methods: This research study was an experimental study with a True Experimental design. Thirty-two ischemic stroke patients with motor impairment were divided into a combination group (TBS + mirror therapy) and a single group. FMA-UE, FMA-LE, and qEEG measurements were performed before and after the intervention, then analyzed using the Wilcoxon and Mann Whitney tests.

Results: The combination group showed significant increases in FMA-UE (p=0.001), FMA-LE (p=0.001), and decreases in qEEG DTABR (p=0.002). The single TBS group also showed significant increases in FMA-UE and FMA-LE, decreases in DTABR also. The combination was significantly more effective in improving Δ FMA-UE (p=0.028), Δ FMA-LE (p=0.007), and changes in Δ DTABR (p=0.043) than either therapy alone.

Conclusions: The combination of Theta Burst Stimulation and mirror therapy is more effective in improving motor function and modulating brain activity in ischemic stroke patients than TBS alone, indicating synergistic potential in supporting neuroplasticity.

1. Introduction

Stroke is a clinical syndrome characterized by focal or global cerebral dysfunction that can lead to disability or death, often caused by spontaneous bleeding or inadequate blood supply to brain tissue. Ischemic stroke, which is the more common type of stroke, is characterized by the sudden loss of blood circulation to a specific area of the brain, resulting in loss of neurological function in that area [1]. Globally, stroke is the second leading cause of death and the third leading cause of disability and death worldwide [2]. In Indonesia, the prevalence of stroke has also shown a significant increase [3].

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JCHR (2026) 16(2), 1953-1961 | ISSN:2251-6727

After a brain injury caused by stroke, the body responds by forming new neurons (neurogenesis), new blood vessels (angiogenesis), and new connections between neurons (synaptogenesis). However, post-stroke motor impairments, such as muscle weakness, impaired coordination, and spasticity, can significantly impact a patient's ability to perform daily activities. Multidisciplinary rehabilitation in the acute and subacute phases can help most patients achieve functional recovery [4].

Theta Burst Stimulation (TBS), a non-invasive form of brain stimulation, is known to stimulate the brain's recovery process by increasing neuronal plasticity, while mirror therapy helps patients overcome motor impairments by using mirrors to improve the perception of body movement. The combination of these two therapies is expected to accelerate motor function recovery in ischemic stroke patients by optimizing rehabilitation and reducing motor disability [5].

In an effort to improve functional recovery, advances in neurorestoration and technology have brought innovations in rehabilitation approaches. Repetitive Transcranial Magnetic Stimulation (rTMS) has proven help recovery post -stroke. Theta Burst Stimulation is type rTMS new offering duration more short , intensity more low, and effect relative neuromodulation more strong [5]. TBS can induce changes in cortical plasticity and robust neural activity [1,5,6]. Meanwhile, Mirror Therapy uses mirror visual feedback to enhance motor relearning [1,7,8].

Considering that Theta Burst Stimulation and mirror therapy are two promising rehabilitation interventions for restoring motor function in stroke patients, this study was conducted to evaluate the efficacy of the combination of these two therapies. The parameters to be assessed include the Fugl-Meyer Assessment Upper Extremity, Fugl-Meyer Assessment Lower Extremity, and Quantitative Electroence-phalography (qEEG), which will be measured before and after the intervention. FMA itself is the first quantitative evaluative instrument to measure sensorimotor recovery after stroke [9]. In addition, qEEG can provide meaningful prognostic information regarding motor and functional recovery in stroke patients, with indices such as the Delta Theta to Alpha Beta Ratio potentially predicting post-stroke disability [10]. This study aims to determine the efficacy of the combination of TBS and mirror therapy on motor impairment in ischemic stroke patients using these parameters.

2. Methods

Study Design

This study is an experimental study with a True Experimental design at Wahidin Sudirohusodo General Hospital. This study uses a comparative design with a pre-post intervention approach, involving two study groups: a combination intervention group and a single intervention group.

Sample Criteria

The population in this study were all subacute ischemic stroke patients based on the results of neurological physical examination and neuroimaging examination (head CT Scan without contrast) in the neurology polyclinic of Dr. Wahidin Sudirohusodo General Hospital. The variables in this study included improvements in upper extremity motor function (Fugl-Meyer Assessment Upper Extremity/FMA-UE), lower extremity motor function (Fugl-Meyer Assessment Lower Extremity/FMA-LE), as well as neurophysiological indicators such as the Delta Theta to Alpha Beta Ratio from Quantitative Electroencephalography (qEEG), to assess the response to the intervention. Patients were recruited based on strict inclusion criteria to obtain a relatively homogeneous study population.

Research Procedures

Patients diagnosed with subacute ischemic stroke who met the inclusion and exclusion criteria were recruited after a physical examination, history taking, and non-contrast head CT scan. After informed consent was obtained, qEEG and Fugl-Meyer Assessment (FMA) were performed as baseline assessments. The sample was randomly divided into two groups: a single TBS group and a combination of TBS and mirror therapy. All participants received standard pharmacological and rehabilitation therapy. The TBS intervention was conducted for 10 sessions (5 consecutive sessions, 2 days off, and repeated). Mirror therapy was conducted twice daily, each session consisting of 15 minutes of upper and lower extremity exercises, followed by task-based

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therapy. After completion of therapy, reassessment was performed using qEEG and FMA.

Motor Function Assessment

Motor function and brain activity were assessed using several methods. FMA-UE score was used to measure sensorimotor impairment in the upper extremities. Each item was scored as 0 (unable), 1 (partial), or 2 (perfect), with a maximum score of 66 points, and assessments were conducted on the first day before the intervention and on the 13th day after the intervention. Similarly, the FMA-LE score was used to assess sensorimotor impairment in the lower extremities, with the same score, and assessments were conducted at the same time. In addition, qEEG was used to analyze brain activity through digital EEG signal recording. Parameters measured included the Delta Theta-Alpha Beta Ratio (DTABR) in the ipsilesional motor cortex. A decrease in the DTABR ratios indicates an improvement in cortical function, which may indicate a positive effect of the therapy.

Data and Statistics Analysis

The collected data were analyzed using non-parametric statistical tests. The Wilcoxon test was used to analyze differences in pre-test and post-test scores within groups. The Mann-Whitney test was used to compare the effectiveness of the intervention between groups. Statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) software version 2.7 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as a p -value <0.05, indicating a difference between the intervention groups.

Ethics approval and consent to participate:

This study was approved by the institutional review board and conducted in accordance with the principles of the Declaration of Helsinki. Ethical clearance was obtained from the Health Research Ethics Committee, Faculty of Medicine, Hasanuddin University, under protocol number 783/UN4.6.4.5.31/ PP36/2025) on October 13, 2025.

3. Results

The study was conducted at Wahidin Sudirohusodo Hospital Makassar and its network hospitals from October to December 2025. A total of 32 patients diagnosed with ischemic stroke with motor disorders were then given an intervention that combined TBS intervention and mirror therapy. Before and after the intervention, measurements of the FMA-UE, FMA-LE, and qEEG were performed.

Characteristics of Study Participants

The characteristics of the study participants are presented to provide an overview of their distribution based on demographic variables, clinical features, and risk factors. Detailed data are summarized in Table 1.

As shown in Table 1, the study included a total of 32 participants, equally divided into two groups: the Combination group (n = 16; 50%) and the Single group (n = 16; 50%). In both groups, male participants predominated, accounting for 68.8% (n = 11) in the Combination group and 75% (n = 12) in the Single group. The median age was identical in both groups, at 52 years, with an age range of 22–60 years.

Regarding disease onset, most participants in both groups were in the second month post-onset, with 43.8% (n = 7) in the Combination group and 31.2% (n = 5) in the Single group. Clinically, right-sided hemiparesis was the most frequently observed presentation in both groups, affecting 56.2% (n = 9) of participants in each group. In terms of risk factors, hypertension was the most prevalent, occurring in 56.3% (n = 9) of the Combination group and 50% (n = 8) of the Single group. Statistical analysis showed that all baseline characteristics had p-values greater than 0.05, indicating no significant differences between the two groups.

Baseline Comparison of Functional Scores Between Groups

The comparative analysis of baseline functional outcomes between the Combination and Single groups is presented in Table 2. Significant differences were observed in FMA UE and FMA LE scores prior to intervention.

For the FMA UE assessment, the Combination group demonstrated a median score of 40 (range 20–49), whereas the Single group showed a higher median score of 47 (range 20–61). The Mann–Whitney test revealed a statistically significant difference between the two groups ($p = 0.004$).

Similarly, baseline FMA LE scores differed significantly between groups. The Combination group had a median score of 24.5 (range 15–30), while the Single group had

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a median score of 28.5 (range 20–30), with a p-value of 0.003.

In contrast, DTABR scores at baseline did not differ significantly between the two groups. The Combination group had a median score of 0.94 (range −2.21 to 4.76), while the Single group had a median score of 1.08 within the same range, yielding a p-value of 0.956.

Pre- and Post-Intervention Changes in the Combination Group

The analysis of pre- and post-intervention outcomes in the Combination group (TBS and Mirror Therapy) is summarized in Table 3. Significant improvements were observed across all measured variables. The FMA UE score increased from a median of 40.00 (range 20–49) at baseline to 42.50 (range 20–52) after intervention, with a p-value of 0.001. Similarly, FMA LE scores improved from a median of 24.5 (range 15–30) to 28.50 (range 15–33), also showing a statistically significant change (p = 0.001). For DTABR, the median score decreased from 0.94 (range −2.21 to 4.76) at pre-test to −0.6943 (range −26.33 to 1.19) at post-test. This reduction was statistically significant, with a p-value of 0.002.

Pre- and Post-Intervention Changes in the Single Group

The pre- and post-test comparisons for the Single group (TBS only) are presented in Table 4. All outcome measures showed statistically significant changes following the intervention. The median FMA UE score increased from 47.00 (range 20–61) at baseline to 49.00 (range 20–61) post-intervention, with a p-value of 0.001. FMA LE scores also showed a modest but significant increase, from a median of 28.50 (range 20–30) to 30.00 (range 20–31), with a p-value of 0.015. DTABR scores demonstrated a significant decrease, with median values declining from 1.08 (range −2.74 to 21.10) at pre-test to −0.22 (range −3.02 to 19.73) at post-test. This change was statistically significant (p = 0.001).

Comparative Effectiveness of Combination and Single Interventions

The comparative effectiveness of the Combination and Single interventions based on changes in outcome measures is summarized in Table 5, while the distributions of change scores (Δ) are illustrated in Figures 1–3 using box plots. Overall, the Combination intervention demonstrated greater and more consistent improvements across all evaluated outcomes compared with the Single intervention.

For Δ FMA UE (Figure 1), the Combination group showed a higher median improvement of 3.0 (range 0–10) compared with 1.0 (range 0–3) in the Single group. This difference was statistically significant (p = 0.028), as reflected by the upward shift and wider distribution of improvement values in the Combination group.

A similar pattern was observed for Δ FMA LE (Figure 2). The Combination group achieved a median increase of 2.0 (range 0–10), whereas the Single group demonstrated no median improvement (0.0; range 0–2). The between-group difference was statistically significant (p = 0.007), with the box plot illustrating a clearer and more pronounced improvement in the Combination group.

Regarding Δ DTABR (Figure 3), the Combination group exhibited a greater median reduction (−1.54; range −30.79 to −2.85) compared with the Single group (−0.62; range −2.61 to −0.66). This difference reached statistical significance (p = 0.043). As shown in the box plot, the Combination group demonstrated a larger magnitude and more consistent decrease in Δ DTABR values than the Single group.

4. Discussion

This study evaluated 32 patients with ischemic stroke and motor impairment who were equally assigned to a Combination group (TBS plus mirror therapy) or a Single group (TBS alone). Baseline demographic and clinical characteristics were comparable between groups, including age, sex distribution, stroke onset, clinical presentation, and vascular risk factors, ensuring valid comparisons of treatment effects. The study population reflects typical stroke rehabilitation cohorts, with a median age of 52 years consistent with prior reports [11,12]. Although stroke prevalence is often higher in women due to longer life expectancy, male predominance has been frequently reported in rehabilitation studies [11–14]. Most participants were in the subacute phase, a critical period for recovery during which early rehabilitation has been shown to significantly improve functional outcomes [4]. The predominance of ischemic stroke and hypertension aligns with global epidemiological data [15,16].

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The primary finding of this study is the superior efficacy of combined TBS and mirror therapy compared with TBS alone. The Combination group demonstrated significantly greater improvements in ΔFMA-UE and ΔFMA-LE, along with a larger reduction in ΔDTABR. These results indicate a synergistic effect when both interventions are applied concurrently. This enhanced efficacy is likely driven by complementary neuroplastic mechanisms. TBS modulates cortical excitability and facilitates synaptic plasticity essential for post-stroke reorganization, while mirror therapy activates the mirror neuron system through visual feedback, promoting motor relearning [17]. TBS may prime the motor cortex, creating a window of heightened plasticity that enhances the effects of mirror therapy.

These findings are consistent with previous studies supporting multimodal neurorehabilitation strategies. Combining non-invasive brain stimulation with physical or task-based therapies has been shown to yield superior motor outcomes compared with single-modality interventions [18]. Improvements in FMA-UE following iTBS have been widely reported, and combined stimulation approaches have demonstrated additional functional gains [19–22].

In addition to motor recovery, the combined intervention produced significant neurophysiological changes. Improvements in FMA scores were accompanied by a significant reduction in DTABR, suggesting normalization of cortical activity. Elevated low-frequency EEG activity is associated with greater stroke severity and poorer prognosis, whereas reductions in DTABR reflect cortical reorganization and recovery [10,23]. The Fugl-Meyer Assessment remains the gold standard for evaluating post-stroke motor impairment, underscoring the clinical relevance of these findings [24].

Recent evidence supports the role of qEEG as a biomarker for monitoring recovery and therapeutic response. Changes in EEG rhythms, particularly reductions in delta activity and increases in alpha and beta power, correlate with improved motor outcomes and functional recovery [25–27].

In summary, this study demonstrates that combining Theta Burst Stimulation with mirror therapy is more effective than TBS alone in improving motor function and modulating brain activity in patients with ischemic stroke. These results support the use of a multimodal neurorehabilitation approach to maximize neuroplasticity and functional recovery.

5. Limitations

The present study acknowledges several limitations. Firstly, its specific focus on ischemic stroke patients with an onset of 1 to 3 months restricts the generalizability of the findings to patients in other stroke phases (e.g., chronic) or to other types of stroke (e.g., hemorrhagic stroke). Additionally, the study has not comprehensively explored the optimization of specific parameters within the intervention protocol, such as the frequency, duration, and intensity of TBS, as well as the detailed aspects of the mirror therapy protocol. Finally, outcome assessments were conducted only after two weeks of intervention, leaving the long-term effectiveness of this combined therapy on motor function, quality of life, and participation in daily activities unevaluated.

6. Conclusion

This study concluded that the combined intervention of Theta Burst Stimulation and mirror therapy was significantly more effective in improving upper and lower extremity motor function in ischemic stroke patients compared to TBS alone. Significant improvements in FMA-UE and FMA-LE scores were observed in the group receiving the combination therapy. Meanwhile, the single TBS group also showed a significant increase in FMA-UE and FMA-LE. In addition, qEEG recordings showed significant positive changes in the Delta Theta to Alpha Beta Ratio in both groups, with the combination group showing a greater decrease, indicating better cortical reorganization and recovery of neural function. Overall, the combination of TBS and mirror therapy demonstrated better efficacy in promoting functional and neurophysiological recovery in ischemic stroke patients with motor impairment.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR'S CONTRIBUTIONS

RWD and JT were responsible for the study conceptualization and methodology. Software development, formal analysis, investigation, and project

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administration were conducted by RWD. Validation and visualization of the data involved collaborative contributions from RWD, JT, ADW, and RBL. Data curation and resource provision were carried out by RWD in collaboration with JT. The original draft of the manuscript was prepared by RWD and JT, while critical review and editing were performed jointly by RWD, JT, ADW, and RBL. Supervision of the study was provided by JT and ADW. Funding acquisition was supported collectively by RWD, JT, ADW, and RBL. All authors have reviewed and approved the final version of the manuscript.

ACKNOWLEDGEMENTS

The authors would like to express their sincere gratitude to all patients who participated in this study. We also acknowledge the support and cooperation of the medical and nursing staff of the Department of Neurology, Faculty of Medicine, Hasanuddin University, and Dr. Wahidin Sudirohusodo General Hospital, Makassar, for their assistance during patient recruitment, intervention implementation, and data collection. Special appreciation is extended to the Hasanuddin University Medical Research Center for providing research facilities and technical support. The authors are also thankful to all colleagues who contributed valuable input during the preparation of this manuscript.

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TABLES

Table 1. Characteristics Subject Study

Variables	Category	n (%)		Total	P value
		Combination	Single		
Gender	Man	11 (68.8%)	12 (75.0%)	23 (71.9%)	0.500
	Woman	5 (31.2%)	4 (25.0%)	9 (28.1%)	
Age (years)	Median (Min -Max)	52 (22-60)	52 (23-60)	52 (22-60)	0.820
Onset	1 month	4 (25.0%)	3 (18.8%)	7 (21.9%)	
	2 months	7 (43.8)	5 (31.2%)	12 (37.5%)	0.657
	3 months	5 (31.2%)	8 (50.0%)	13 (40.6%)	
Clinical (Hemiparesis)	Dextra	9 (56.2%)	9 (56.2%)	18 (56.3%)	0.639
	Sinistra	7 (43.8%)	7 (43.8%)	14 (43.7%)	
Risk Factors	Diabetes mellitus	1 (6.3%)	3 (18.75%)	4 (12.5%)	1,000
	DM + HT	4 (25.0%)	4 (25.0%)	8 (25.5%)	
	Atrial Fibrillation	1 (6.3%)	0 (0.0%)	1 (3.1%)	
	Hypertension	8 (56.3%)	8 (50.0%)	16 (53.1%)	
	Smoke	1 (6.3%)	1 (6.3%)	2 (6.2%)	
	Total	16 (50.0%)	16 (50.0)	32 (100%)	

Fisher's Exact test.

Table 2. Comparative Analysis of FMA UE, FMA LE and DTABR Scores Before Intervention

Assessment Results	Median (Min – Max)		P value
	Combination	Single	
EU FMA	40 (20–49)	47 (20–61)	0.004
FMA LE	24.5 (15–30)	28.50 (20–30)	0.003
DTABR	0.94 (-2.21–4.76)	1.08 (-2.74–21.10)	0.956

*Mann Whitney Test Analysis

Table 3. Analysis of Differences in FMA UE, FMA LE and DTABR Scores in the Combination Group

Assessment Results	Median (Min – Max)		P value
	Pre-Test	Post Test	
EU FMA	40.00 (20–49)	42.50 (20–52)	0.001
FMA LE	24.5 (15–30)	28.50 (15–33)	0.001
DTABR	0.94 (-2.21-4.76)	-0.6943 (-26.33-1.19)	0.002

*Wilcoxon test analysis

Table 4. Analysis of Differences in FMA UE, FMA LE and DTABR Scores in Single Group (TBS)

Assessment Results	Median (Min – Max)		P value
	Pre-Test	Post Test	
EU FMA	47 (20–61)	49 (20–61)	0.001
FMA LE	28.50 (20–30)	30.00 (20–31)	0.015
DTABR	1.08 (-2.74–21.10)	-0.22 (-3.02–19.73)	0.001

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*Wilcoxon test analysis

Table 5. Comparative Analysis of the Effectiveness of Combination Interventions (TBS and Mirror) and Single (TBS)

Variables	Median (Min – Max)		P value
	Combination (TBS and Mirror)	Single (TBS)	
Δ EU FMA	3.0 (0 –10)	1.0 (0 –3)	0.028
Δ FMA LE	2.0 (0 –10)	0.0 (0 –2)	0.007
Δ DTABR	−1.54 (−30.79 – 2.85)	-0.62 (-2.61– 0.66)	0.043

*Mann Whitney test analysis

FIGURE

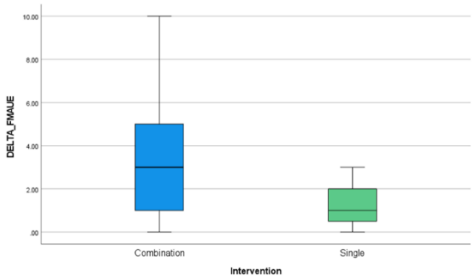

Figure 1. Box Plot Comparison of Δ FMA UE Values for Combination and Single Groups

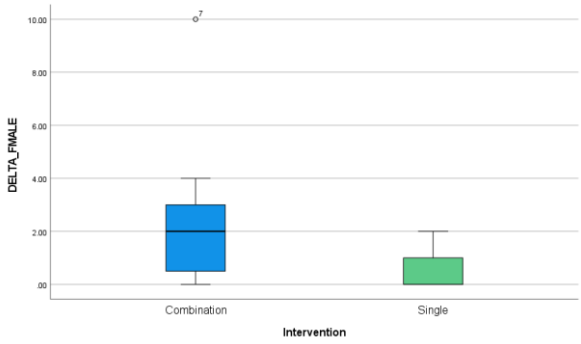

Figure 2. Box Plot Comparison of Δ FMA LE Values for Combination and Single Groups

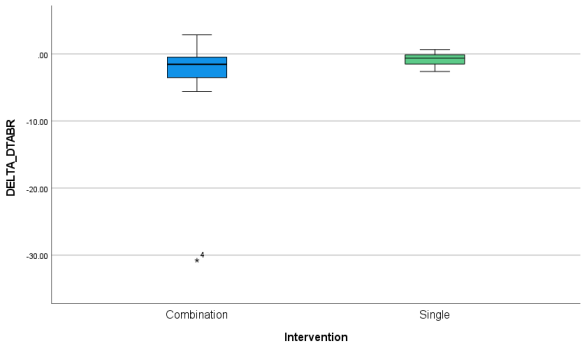

Figure 3. Box Plot Comparison of Δ DTABR Values for Combination and Single Groups