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PULSE

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Meta-Analysis of the Neurophysiologic Effects of rTMS Challenges the Traditional Binary "Excitatory" and "Inhibitory" Model

Praveen P. Rajaguru MD, MPH reviewing Yassi et al., Neuroscience & Biobehavioral Reviews, 2026

In this systematic review and comparative meta-analysis, single-session rTMS produced substantially smaller and less consistent neurophysiological effects than traditionally assumed. While high-frequency rTMS and iTBS moderately increased motor evoked potential (MEP) amplitudes, low-frequency rTMS and cTBS demonstrated only weak suppressive effects that were no longer significant after sham normalization. No consistent effects were identified across paired-pulse measures or TMS-EEG metrics. Together, these results challenge the binary model of rTMS protocols as "excitatory" or "inhibitory."

IN THIS ISSUE:

Contemporary models of rTMS neurophysiology are largely derived from studies of the effects of stimulation frequency on the primary motor cortex (M1) and resulting MEP amplitudes. These studies established the binary cortical excitability model. In this model, high-frequency stimulation and iTBS have traditionally been considered excitatory, while low-frequency stimulation and cTBS are considered inhibitory based on their effects on MEP amplitudes. These assumptions were then extrapolated to non-motor cortical regions and clinical applications despite evidence of substantial variability in physiologic responses across and even within individuals. This study sought to reassess the neurophysiological effects of rTMS across stimulation protocols, cortical targets beyond solely M1, and outcome measures using contemporary studies with increasingly rigorous methodology.

This systematic review and meta-analysis utilized a PRISMA design and included studies published between 2014 and March 2025. Studies were included if they were in English and utilized a pre-post design, low or high frequency rTMS, iTBS, cTBS, to any cortical or cerebellar target, and measured motor or non-motor excitability measures. Studies were excluded if they used H-coils, bilateral rTMS, multiple interventions, or did not include neurophysiological data. Outcome measures included MEP amplitude, resting and active motor thresholds, short-interval intracortical inhibition, intracortical facilitation, long-interval intracortical inhibition, and multiple TMS-EEG measures. Standardized mean differences (SMDs) were calculated for each study and time point using outcome measures and sample sizes, with Cohen's d and Hedges' g calculated. Moderator analyses evaluated the effects of neuronavigation, sham control, test-retest design, stimulation intensity, pulse number, and publication year.

The final analysis included 202 studies, 473 datasets, and 8,079 healthy participants, with quantitative meta-analysis performed on 191 studies comprising 418 datasets and 7,265 participants. MEP amplitude accounted for more than half of all reported neurophysiological outcomes. iTBS and cTBS were the most frequently used protocols, with half of data sets utilizing neuronavigation for target selection. Across protocols for excitatory stimulation paradigms, MEP amplitudes were moderately increased (SMD = 0.45, 95% CI: 0.37 to 0.53, $p \leq 0.001$) with notable heterogeneity of individual effect sizes across studies ($Q = 648.18$, $p \leq 0.001$; $I^2 = 80\%$). Across protocols for traditionally "inhibitory" paradigms, only small suppressive effects were produced (SMD = -0.24, 95% CI: -0.35 to -0.14, $p \leq 0.001$) with high between-study heterogeneity ($Q = 717.43$, $p \leq 0.001$; $I^2 = 87\%$). Importantly, the small suppressive effects of low-frequency rTMS and cTBS were no longer statistically significant after sham normalization. No significant differences were identified between conventional high-/low-frequency protocols and their theta-burst counterparts. Across TMS-EEG measures indexing cortical excitability outside of M1, no consistent effects were observed for any protocol. Meta-regression analyses demonstrated a progressive decline in reported effect sizes over time. Studies employing neuronavigation, sham controls, and more rigorous experimental designs consistently reported smaller neurophysiological effects than their earlier counterparts. Across outcome measures, substantial overlap existed between the distributions of "excitatory" and "inhibitory" protocols.

Impact: These results have important implications for interpreting existing studies and guiding future study designs and clinical protocols. This meta-analysis provides a landmark contemporary evaluation of rTMS neurophysiology, and its results challenge the traditional binary cortical excitability model. Although MEP-based measurements obtained in the motor cortex may support the model, these findings do not generalize to other neurophysiological measures or non-motor cortical targets. The neurophysiologic effects of single-session rTMS appear weaker, more variable, and more context-dependent than previously assumed. The findings suggest that rTMS may exert its effects through distributed neural networks rather than simple local changes in cortical excitability. Importantly, studies incorporating neuronavigation and sham controls reported substantially attenuated effects, underscoring the need for rigorous methodology and caution when interpreting prior neurophysiological findings.

Yassi IE, Das DB, Fried PJ, Pascual-Leone A, Shafi MM, Ozdemir RA. Reassessing the neurophysiological effects of repetitive transcranial magnetic stimulation: A systematic review and comparative meta-analysis across protocols, outcome measures and cortical sites. Neurosci Biobehav Rev. 2026;185:106648. doi:10.1016/j.neubiorev.2026.106648

Effectiveness of TMS on Gait and Spasticity in People with Spinal Cord Injury: A Systematic Review and Meta-Analysis

Clara D. T. Nguyen, MD, MPH reviewing Valera-Sapena et al., Spinal Cord, 2026 March.

In this meta-analysis of RCTs published through November 2024, researchers examined the effectiveness of TMS on gait velocity and spasticity in patients with spinal cord injury (SCI). Gait velocity, measured by the 10-meter walking test, did not show significant improvement with TMS. On the other hand, TMS produced statistically significant reduction in spasticity, measured by the Modified Ashworth Scale (MAS).

SCIs are multifactorial in etiology and nature, impacting the neurological and non-neurological functioning of patients on a wide spectrum. From a rehabilitative perspective, gait training can lead to critical recovery of walking ability. Gait re-education aims to capitalize on neural plasticity, but due to high variability between SCI patients, the exact method of training remains debated. rTMS poses intriguing possibilities in how it can modulate neural activity of the brain and spinal cord for patients with injury to these regions.

The systematic review and meta-analysis examined sham-controlled RCTs across PubMed, Cochrane, Web of Science, CINAHL, and PEDro. Utilizing the Participants, Intervention, Comparison, Outcomes, and Study Design (PICO(S)) method, researchers selected individuals of any age with any kind of SCI that received TMS as an intervention for gait function and spasticity. Two primary outcomes were assessed: effectiveness of TMS on gait velocity measured by 10-meter walking test, and spasticity measured by the Modified Ashworth Scale (MAS). The authors assessed bias through Cochrane Risk of Bias. The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system was used to evaluate quality of evidence, from high, moderate, low, and very low quality.

A total of 246 studies were eligible; however, after exclusion due to lack of available data, 14 articles with a total of 235 SCI patients were included in the systematic review. Of the 14 studies, 10 utilized high frequency (10-20 Hz) rTMS, 3 used iTBS, and 1 study employed a modified protocol combining single 0.2 Hz pulses with peripheral stimulation. A majority (12) of studies had a frequency of 5 TMS sessions per week, occurring over a total of 1 to 9 weeks or 1 to 45 sessions. 6 studies were designed with a crossover, including a washout period of 1 week to 2 months. 12 studies targeted the Cz vertex electrode position, aiming for the primary motor cortex to treat the lower extremities. The remaining 2 studies targeted the C3/C4 region for upper extremity symptoms. Overall effect of TMS on gait velocity was not statistically significant (SMD = −0.71; 95% CI: −1.62 to 0.20). Researchers posited that a combination of inconsistencies in data collection and very high heterogeneity between experimental and control groups ($I^2 = 81\%$, $p < 0.0001$) contributed to the very low quality of evidence on the GRADE scale. TMS intervention resulted in statistically significant improvement in spasticity in comparison to the sham group (MD = −0.56 points; 95% CI: −0.82 to −0.30) with a low level of heterogeneity ($I^2 = 0\%$, $p = 0.47$). There were no significant differences in spasticity subgroups based on number of TMS pulses ($Chi^2 = 0.06$, $p = 0.81$). However, the ≥1000 pulses subgroup showed a significant effect (MD = −0.56; 95% CI: −0.83 to −0.30) in comparison to the <1000 pulses subgroup.

Impact: This study demonstrates TMS may be helpful for spasticity in patients with SCI. However, the quality evidence of this systematic review and meta-analysis are low to very low, limiting the strength of the conclusions that can be drawn. While the findings should be interpreted cautiously, TMS may serve as a useful adjunct to established gait-training and rehabilitation protocols, pending confirmation in higher-quality studies.

Valera-Sapena, F., Bravo-Aparicio, J., Serrano-Muñoz, D., Pérez-Nombela, S., Avendaño-Coy, J., & Gómez-Soriano, J. (2026). Effectiveness of transcranial magnetic stimulation on gait and spasticity in people with spinal cord injury: a systematic review and meta-analysis. Spinal cord, 64(4), 303–316. https://doi.org/10.1038/s41393-026-01193-2

Cerebellar Vermis iTBS Enhances Balance Recovery via Cerebello-Visual Network Reorganization in Subacute Stroke Patients

Meghan Y. Reddy, MD reviewing Huang et al., Brain Stimulation, Feb 2026

This RCT found that a three-week course of iTBS over the cerebellar vermis significantly improved balance, trunk control, and lower-limb function in patients with subacute stroke. This was also associated with changes in functional connectivity between the cerebellar vermis and visual processing regions, suggesting a mechanism of optimized visual feedback integration.

Balance dysfunction is a leading cause of disability after stroke, and falls and persistent postural instability remain common even after intensive rehabilitation. While rTMS has been used to target the primary motor cortex for motor recovery, the cerebellar vermis has remained largely underexplored as a neuromodulation target. This study aimed to evaluate whether iTBS at the vermis could facilitate balance recovery.

Researchers enrolled 52 patients with subacute subcortical stroke and balance impairment, randomizing them to receive either 15 sessions of active iTBS (n=23) or sham stimulation (n=25) over three weeks. Each session consisted of 600 pulses delivered at 80% of Active Motor Threshold to the cerebellar vermis and was followed by 1 hour of a conventional rehabilitation program. Sham stimulation was delivered using a customized sham coil with magnetic shielding, reducing the effective magnetic field to a negligible level (<5% of active stimulation). The primary outcome was the change in the Berg Balance Scale (BBS) score at week three. Secondary outcome measures included the Fugl–Meyer Assessment-Lower Extremity (FMA-LE) to assess lower-limb motor recovery, the Trunk Impairment Scale (TIS) to assess trunk stability and coordination, and the Postural Assessment Scale for Stroke Patients (PASS) to assess postural deficits post-stroke. The Modified Barthel Index (MBI) was used to measure functional independence in ADLs. Surface electromyography (sEMG) was used to quantify neuromuscular activation, and resting-state fMRI (rs-fMRI) was used to conduct functional connectivity (FC) analyses of eight vermal regions. Analyses included ANOVA and Pearson correlation.

The iTBS group demonstrated significantly greater improvements than the sham group across the primary and key secondary motor scales, with effects persisting at 6-week follow up. For the primary outcome, the iTBS group showed a between-group difference in BBS improvement of 4.14 points ($p<0.001$), and a significantly higher proportion achieved the minimal clinically important difference (65.2% vs. 32.0%). MBI and PASS did not show significant interactions. sEMG results showed selective increases in the activation of the rectus abdominis and rectus femoris, suggesting the treatment preferentially facilitated proximal and axial postural control. rs-fMRI analyses revealed that iTBS enhanced functional connectivity (FC) between Vermis X and bilateral occipitotemporal visual processing regions, including the fusiform and inferior temporal gyri ($F = 26.12$, $\eta^2_p = 0.36$) and the inferior and middle occipital gyri ($F = 23.44$, $\eta^2_p = 0.33$). This increase in Vermis X visual connectivity was positively correlated with individual balance improvements ($r = 0.649$, $p<0.001$). Exploratory subgroup analyses suggested that individuals who displayed an overall increase versus decrease in whole-brain FC may experience different response trajectories. The FC-decrease subgroup had improved balance gains at the end of treatment, which were not maintained at follow-up, whereas the FC-increase subgroup demonstrated improvements that occurred early in treatment and was more durable at follow-up.

Impact: These RCT findings provide evidence that cerebellar vermis iTBS is a safe and effective intervention for post-stroke balance rehabilitation. The study highlights a novel neural mechanism, wherein stimulation facilitates balance by optimizing the integration of visual feedback through cerebello-visual pathways. Furthermore, the discovery of divergent reorganization patterns suggests that the therapeutic effects of cerebellar stimulation are not uniform but instead support individualized network optimization. This patient-specific plasticity underscores the potential for future neuromodulation protocols to be tailored based on a patient's baseline connectivity profile to maximize clinical outcomes. However, it must be noted that the subgroup analyses were conducted with a moderate sample size and require validation in larger cohorts.

Huang G, Zhao Z, Wang D, et al. Cerebellar functional reorganization after intermittent theta burst stimulation over vermis on balance recovery in subacute stroke patients. Brain Stimul. 2026;19(2):103055. doi:10.1016/j.brs.2026.103055

Transcranial Ultrasound Neuromodulation: A Registry-Based Analysis of Global Clinical Trials

Zack Blumenfeld, MD, PhD, reviewing Loh et al., Brain Stimulation, 2026 Mar

In this review, investigators analyzed the largest international clinical trial registries to evaluate the use of transcranial ultrasound (TUS) neuromodulation. Trial registration has increased markedly since 2019, particularly in the United States and China. Psychiatric patients comprise the largest share of study participants, and most trials target subcortical regions. However, substantial heterogeneity in trial design and stimulation parameters remains a major barrier to treatment standardization and further advancement of the therapeutic paradigm.

Various neuromodulation techniques – including DBS, TMS, and tDCS – have expanded the repertoire of treatments for neuropsychiatric disorders. TUS is an emerging treatment modality, whereby low-intensity and focused ultrasonic waves can modulate the activity of both cortical and subcortical regions. Nonetheless, barriers remain with regard to optimization of stimulation parameters. Building on initial animal studies, which suggested TUS could modulate – rather than ablate – neuronal activity, the first studies in human participants were performed in 2014, demonstrating its safety and efficacy. The variety of applications for TUS has only grown since, which has simultaneously created a greater need for discerning which targets and frequencies can reliably produce intended clinical effects. This study sought to provide both a summary of the current clinical literature on TUS trials and commentary on possible future improvements to the way in which TUS trials are conducted.

Nine of the largest international clinical trial registries were queried through September of 2025 for trials conducted using TUS for neuromodulation in humans. Studies investigating ultrasound for ablative or diagnostic purposes were excluded, as were trials focused on non-neuropsychiatric interventions. Trials utilizing transcranial pulse stimulation (TPS), in which shorter waveforms are used than in TUS, were included given that both have the intent to alter neurophysiology. Candidate trials were characterized across multiple domains, including study type, country of origin, target diagnosis, brain region, study enrollment and design, outcome measures, devices used, stimulation parameters, funding sources, and publication of original research articles. Descriptive statistics were then used to calculate the number or percentage of trials for each domain's set of categorical variables.

Out of an initial group of 1101 trials across the aforementioned registries, 177 trials met inclusion criteria, with seven of those being TPS trials (4%). 85% of those trials (150 trials) were registered from 2020–2025. The two largest countries of origin of clinical trials were the United States (96 trials, 52%) and China (33 trials, 18%), with the rest mostly concentrated in East Asia and the Anglophone world. Psychiatric disorders accounted for the largest proportion of TUS trials (58 trials, 32%). A substantial number of studies also enrolled healthy participants (28 trials, 16%), primarily to examine TUS-induced changes in cognitive or motor performance. Neurologic indications included pain (19 trials, 11%), cognitive disorders (19 trials, 11%), movement disorders (16 trials, 9%), epilepsy (13 trials, 7%), stroke (9 trials, 5%), and disorders of consciousness (7 trials, 4%). While over a third of the trials did not report a brain region of interest (66 trials), of the trials with identifiable targets (111 trials), subcortical regions comprised the majority (56 trials, 51%), followed by cortex (44 trials, 40%), both subcortex and cortex (8 trials, 7%), and cerebellum (3 trials, 3%). The top three targeted subcortical structures were the thalamus (26 trials, 24%), nucleus accumbens/ventral capsule-ventral striatum (11 trials, 10%), and basal ganglia (7 trials, 6%), while the top three targeted cortical structures were the mesial temporal lobe (21 trials, 20%), dorsolateral prefrontal cortex (16 trials, 15%), and primary motor cortex (15 trials, 14%). Among all 177 trials, mean enrollment was 43 participants and median enrollment was 30 participants, and all trials were conducted on adults. About 40% (70 trials) met the highest trial standards of being multi-arm, randomized, and at least double-blinded. Trials used both metrics-based clinical outcomes (127 trials, 72%) as well as subjective patient report (99 trials, 56%; many trials used imaging (76 trials, 43%), neurophysiological measures such as EEG and LFP (44 trials, 25%), and blood or CSF markers (5 trials, 3%) as outcomes. Of the minority of trials with information on the TUS devices (56 trials, 32%), three devices – BrainSonix Pulsar 1002, NaviFUS, and NeuroFUS – accounted for over half (33 trials, 59%). A majority of studies (103 trials, 58%) did not

include any information on sonication parameters, while only a small fraction (16 trials, 9%) gave a full set of sonication parameters (frequency, intensity, and pulse duration/duty cycle).

Impact: In this review surveying the current state of clinical trials using TUS, the surging popularity of focused ultrasound for treatment of an ever-expanding list of medically refractory diagnoses has led to both increased promise as well as increased scrutiny. The lack of standardization of study designs as well as many trials containing varying degrees of information regarding stimulation parameters and targets of interest warrants additional reflection on both how to incorporate the data being made available from ongoing trials as well as how to best approach the planning of future studies. Further development of the paradigm for use in neurological disease as well as introduction into the pediatric population will require investigators to agree upon and meet the rigorous standards already developed for other neuromodulation techniques.

Loh A, Attalla G, Darmani G, et al. Transcranial ultrasound neuromodulation: A registry-based analysis of global clinical trials. Brain Stimulation. 2026 May-Jun;19(3):103076. doi: 10.1016/j.brs.2026.103076

cTBS (continuous theta burst stimulation)
DBS (deep brain stimulation)
dTMS (deep transcranial magnetic stimulation)
ECT (electroconvulsive therapy)
HFL (high frequency left, 10 Hz stimulation to left DLPFC)
HF-rTMS (high frequency repetitive transcranial magnetic stimulation; 10 Hz unless otherwise stated)
iTBS (intermittent theta burst stimulation)
MST (magnetic seizure therapy)
TBS (theta-burst stimulation; TMS delivered as triplet burst pulses at 50 Hz, repeated at 5 Hz)
TENS (transcutaneous electrical nerve stimulation)
TMS (transcranial magnetic stimulation)
rTMS (repetitive transcranial magnetic stimulation)
tDCS (transcranial direct current stimulation)
tACS (transcranial alternating current stimulation)
TPS (transcranial pulse stimulation)

BOLD (blood oxygen level dependent)
DTI (diffusion tensor imaging)
EEG (electroencephalography)
EMG (electromyography)
fMRI (functional magnetic resonance imaging)
MRI (magnetic resonance imaging)
MT (motor threshold)
RMT (resting MT)

ADHD (attention-deficit/hyperactivity disorder)
AUD (alcohol use disorder)
GAD (generalized anxiety disorder)
MDD (major depressive disorder)
OCD (obsessive compulsive disorder)
PTSD (post-traumatic stress disorder)
SUD (substance use disorder)
TRD (treatment resistant depression)

BAI (Beck Anxiety Inventory)
BDI (Beck Depression Inventory)
CGI (clinical global impression scale)
HAM-A (Hamilton Anxiety Rating Scale)
HAM-D / HDRS (Hamilton Depression Rating Scale)
MADRS (Montgomery-Asberg Depression Rating Scale)
MoCA (Montreal Cognitive Assessment)
PANSS (Positive and Negative Symptom Scale)
QIDS (Quick Inventory of Depressive Symptomatology)
YBOCS (Yale-Brown Obsessive Compulsive Scale)

ANOVA (analysis of variance)
AUC (area under the curve)
CI (confidence interval)
FDA (United States Food and Drug Administration)
ICA (independent component analysis)
ITT (intention to treat)
OR (odds ratio)
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)
RCT (randomized controlled trial)
ROC (receiver operating characteristic)
SMD (standard mean difference)

BA (Brodmann area)
DLPFC (dorsolateral prefrontal cortex)
DMPFC (dorsomedial prefrontal cortex)
M1 (primary motor cortex)
mPFC (medial prefrontal cortex)
OFC (orbitofrontal cortex)
SMA (supplementary motor area)