Lumina Indones J Neurol. Vol I No 3 (December 2025)
https://doi.org/10.19166/lijn.v1i3.10400

SYSTEMATIC REVIEW AND META-ANALYSIS

EVALUATING THE EFFICACY OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN TREATING NEURODEGENERATIVE CEREBELLAR ATAXIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Angelina Wandana[1], Jeanne Alexandra[2], Agung Junnata[3], Daniel Natanael[4], Raisa Kireyna Nurfajrina[5], Michelle Valencia Bunjamin[1]

[1]*Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia,*
[2]*Faculty of Medicine, Universitas Indonesia, Depok, Indonesia,*
[3]*Faculty of Medicine, Universitas Trisakti, Jakarta Barat, Indonesia,*
[4]*Faculty of Medicine, Universitas Pembangunan Nasional "Veteran" Jakarta, Jakarta Selatan, Indonesia,*
[5]*Faculty of Medicine, Universitas Kristen Indonesia, Jakarta Timur, Indonesia*
***Correspondence:** angelinawandana11@gmail.com; ORCID ID: 0009-0009-3522-8252*

Abstract

Introduction: Neurodegenerative diseases such as multiple system atrophy (MSA), spinocerebellar ataxia (SCA), and Friedreich's ataxia (FRDA) progressively impair the nervous system, affecting approximately 15% of the global population. Repetitive transcranial magnetic stimulation (rTMS), a non-invasive method, may promote neuroplasticity. The cerebellum, central to motor control and neural connectivity, is a promising rTMS target. Therefore, this research aims to evaluate the efficacy of rTMS in treating neurodegenerative cerebellar ataxia.

Methods: A systematic review and meta-analysis was conducted per PRISMA guidelines, searching ten databases (to August 9, 2025). Eligible studies were RCTs comparing rTMS with sham in cerebellar ataxia. The review was registered on PROSPERO (CRD420251127471). Study quality was assessed with Cochrane RoB 2.0; meta-analysis used Review Manager 5.4.1, and meta-regression was performed in JASP 0.19.3.

Results: Seven RCTs involving a total of 256 patients were included. rTMS significantly improved SARA (SMD = -0.84, p = 0.004, I^2 = 73%). ICARS showed no significant difference (SMD = -0.82, p = 0.43, I^2 = 96%). Meta-regression and sensitivity analysis were done to find key heterogeneity sources. Most studies had low bias.

Conclusions: rTMS significantly improves SARA scores in neurodegenerative cerebellar ataxia if compared to sham, while ICARS shows insignificant differences. Further research is needed.

Keywords: Neurodegenerative ataxia, Repetitive Transcranial Magnetic Stimulation, Sham-controlled

Received: October 15th, 2025
Accepted: December 1st, 2025
Published: December 27th, 2025
How to cite this paper: Wandana A, Alexandra J, Junnata A, Natanael D, Nurfajrina RK, Bunjamin MV. Evaluating the efficacy of Repetitive Transcranial Magnetic Stimulation in treating neurodegenerative cerebellar ataxia: a systematic review and meta-analysis. Lumina Indones J Neurol. 2025; 1(3); 7-25

Introduction

Cerebellar ataxias represent a heterogeneous group of both hereditary and acquired disorders, characterized by a range of clinical features such as impaired balance, uncoordinated limb movements, oculomotor abnormalities, and dysarthria. In addition to these motor symptoms, non-motor manifestations, including cognitive impairment and mood disturbances are frequently present when carefully assessed, though they are often overlooked. These non-motor deficits typically involve dysfunction in areas such as executive function, visuospatial skills, language processing, and emotional regulation. The conditions are relatively prevalent, with an estimated global incidence of 26 per 100,000 in children, while hereditary cerebellar ataxias specifically occur at a worldwide rate of about 5 per 100,000.[1,2]

Spinocerebellar ataxia (SCA) is a multifactorial disorder driven by mechanisms such as genetic mutations, transcriptional dysregulation, defective autophagy, mitochondrial dysfunction, channelopathies, and toxic RNA effects. Central to its pathogenesis is CAG repeat expansion, which produces polyglutamine-expanded ataxins that misfold, aggregate in Purkinje cell nuclei, and interfere with protein homeostasis, transcription, and axonal transport. Purkinje cells, highly susceptible due to their complex dendritic structure and high metabolic demands, undergo progressive degeneration that manifests as ataxia. Additional contributors include calcium and potassium channel mutations in various SCA subtypes, toxic RNA foci that disrupt RNA-binding proteins, impaired autophagy allowing accumulation of misfolded proteins, and transcriptional dysregulation in multiple subtypes. Defects in DNA repair and chromatin acetylation further exacerbate disease by promoting continued CAG repeat expansion.[3]

Beyond SCA, a wide spectrum of hereditary and sporadic ataxias exists, including dentatorubral-pallidoluysian atrophy, episodic ataxias, Friedreich ataxia (FRDA), ataxia-telangiectasia, oculomotor apraxia, CANVAS, cerebrotendinous xanthomatosis, FXTAS, and mitochondrial ataxias. Multiple system atrophy (MSA), a sporadic neurodegenerative disease with an average survival of 9 years, presents with autonomic or urogenital failure and either parkinsonism (MSA-P) or cerebellar ataxia (MSA-C), and is pathologically defined by multisystem neuronal loss and α-synuclein–containing glial inclusions. FRDA, by contrast, results from frataxin deficiency and combines developmental hypoplasia with neurodegeneration, especially in the dorsal root ganglia, spinal cord, and dentate nucleus. It is also complicated by cardiomyopathy, marked by early but non-progressive iron accumulation and possible protective effects of mitochondrial ferritin, and by diabetes mellitus, where frataxin loss in pancreatic β-cells drives oxidative stress, apoptosis, and progressive metabolic dysfunction.[4,5]

The gap in the availability of effective disease-modifying treatment remains, highlighting the urgent need for innovative strategies to alleviate symptoms. A systematic review by the American Academy of Neurology found

that only limited studies demonstrated meaningful benefits of medications or physical therapy, and even then only in a small number of ataxia subtypes. Progress in developing symptomatic pharmacological therapies is particularly challenging due to the diverse underlying pathophysiology of these disorders, suggesting that tailored, disease-specific approaches will likely be necessary.[6,7]

An expanding option of non-pharmacological treatments have been developed, suggesting its therapeutic promises towards neuromodulation in neurodegenerative diseases. Transcranial magnetic stimulation (TMS) is a procedure in which non-invasive stimulation is given to the brain tissue through a produced high or low-intensity magnetic field in order to modulate cortical excitability. Repetitive transcranial magnetic stimulation (rTMS) is when recurring TMS pulses are applied specifically to a certain region of a brain. The effects on neuromodulation are highly dependent on certain parameters such as frequency, intensity, duration, cortical target, number of sessions, and patient-related factors such as age, state of disease, prior medication exposure, as well as individual symptom profiles. In a broad classification, rTMS has been categorized into high frequency (>1 Hz) which increases cortical excitability, as well as low frequency (<1 Hz), inhibiting cortical excitability. During the procedure, the patient is seated with a coil located adjacent to the scalp, delivering rapidly varying magnetic pulses. This induces an electrical field in the cortex, modulating excitability through depolarization of the targeted region. The dosage for treatment is reported as a percentage of the motor threshold (MT), defined by the movement of abductor pollicis brevis through visual observation. The usage of rTMS in neurophysiology settings is by the recorded motor evoked potential (MEP), assessing conduction through the descending corticospinal tracts. The recorded MEPs enable clinical assessment of cortical motor control and corticospinal conduction time.[8]

rTMS is most frequently chosen as treatment in cases where medication has inadequately helped the patient or if they deny any medication due to reasons of side effects and other underlying factors. In comparison with standard medication, rTMS has shown to cause fewer side effects, with headaches being the most common (~5-23%), discomfort at the site of stimulation (~20-40%), and facial muscle twitching (~20-40%). In contrast, standard medication causes various side effects such as weight gain, sexual disorders, gastrointestinal disorders, vision disorders, and sedation. The procedure has been approved by the U.S Food and Drug Administration (FDA) for its usage in the treatment of major depressive disorder (MDD) in 2008, with the first device cleared for the treatment of MDD by targeting the left dorsolateral prefrontal cortex (LDPFC). Furthermore, the FDA has approved five more devices with modification to target a broader patient range, particularly those suffering from antidepressant medication resistance.[9] Certain studies have also demonstrated the possible usage of low-frequency rTMS for tinnitus and auditory hallucinations by targeting the left temporoparietal cortex. Several studies

have shown the usage possibility of rTMS in cerebellar ataxias. In a randomized, double-blind, sham-controlled, cross-over trial conducted by França, the administration of 1 Hz rTMS over the cerebellar hemisphere contralateral to the affected side was done in patients with SCA, MSA-C and post-lesion ataxia. Results showed that a significant reduction in Scale for the Assessment and Rating of Ataxia (SARA) and International Cooperative Ataxia Rating Scale (ICARS) scores only in individuals with MSA-C, although no significant carry-over effects were observed, indicating possible no perseverance after the washout period of four weeks.[10]

With neuromodulatory options for neurodegenerative cerebellar ataxias evolving yet with heterogeneous methods, clear guidance on the therapeutic value of rTMS is required. This study therefore aims to determine the efficacy of rTMS in the treatment of neurodegenerative cerebellar ataxias.

Materials and Methods

This systematic review and meta-analysis applied a structured and comprehensive strategy to identify eligible studies by searching electronic databases, including PubMed, Sciencedirect, Wiley, Scopus, EBSCOhost, Sage Journals, Taylor and Francis, Cochrane Library, BioRxiv MedRxiv until August 9, 2025. Boolean Operators were employed to combine keywords and Medical Subject Headings (MeSH) terms, such as "neurodegenerative ataxia" OR "multiple system atrophy cerebellar subtype" OR "MSA-C" OR "spinocerebellar ataxia" OR "SCA" OR "Friedreich's ataxia" OR "FRDA" AND ("repetitive transcranial magnetic stimulation" OR "rTMS") AND ("sham controlled" OR "sham stimulation" OR "placebo-controlled"). The extracted studies aligned with the Population, Inclusion, Control, and Outcome (PICO) framework (**Table 1**).

Table 1. PICO Framework

	PICO Framework
Population	Patients with neurodegenerative ataxia (e.g. multiple system atrophy cerebellar subtype (MSA-C), supracerebellar ataxia (SCA), Friedreich's ataxia (FRDA)
Intervention	Real Repetitive Transcranial Magnetic Stimulation (rTMS)
Control	Sham-Controlled
Outcome	Ataxia severity evaluated by Assessment and Rating of Ataxia Scores (SARA) and International Cooperative Ataxia Rating Scale (ICARS)

To ensure the quality and relevance of the included studies, specific inclusion and exclusion criteria were applied during the selection process. The inclusion criteria consisted of: (1) Randomized controlled trials (parallel or crossover) with a sham-controlled group; (2) Studies involving patients with neurodegenerative-types of cerebellar ataxia; (3) Studies using Real Repetitive Transcranial Magnetic Stimulation (rTMS) as the intervention and Sham-Controlled as the control; (4) intervention is Repetitive transcranial magnetic stimulation (rTMS); (5) Outcomes of ataxia severity evaluated using the Scale for Assessment and Rating of Ataxia Scores (SARA) and International Cooperative Ataxia Rating Scale (ICARS); (6) Availability

of full-text articles. The exclusion criteria were: (1) Irretrievable full-text; (2) Animal studies; (3) Studies with insufficient data; (4) Studies with incomplete outcomes; (5) Studies including non-progressive ataxia caused by acquired conditions (trauma, stroke), autoimmune, congenital, etc; (6) Studies involving patients who had a history of seizures or any abnormalities established by electroencephalogram (EEG). To maintain consistency in the selection process, disagreements were resolved through discussion.

The selected studies were organized into a structured table using Google Spreadsheet, with data manually entered by each contributing author (A.W., J.A., D.N., A.J., R.K., M.B.). Qualitative data extraction covered key study details, including authors, country, year of publication, study setting, design, follow-up duration, sample characteristics, control groups, intervention types, and main conclusions. Quantitative data included study outcomes and adverse events, which were extracted before and after the intervention using mean and standard deviation. The quality and risk of bias of included randomized controlled trials were evaluated using the Cochrane Risk-of-Bias (RoB) 2.0 tool with visual representation provided through traffic light plots.

Across the seven included studies, most domains demonstrated a low risk of bias. For random sequence generation (selection bias), 87.5% of studies were rated low risk, while 12.5% were rated high risk. Allocation concealment showed more variability, with 50% of studies rated low risk, 12.5% high risk, and 37.5% unclear. Both blinding of participants and personnel (performance bias) and blinding of outcome assessment (detection bias) were consistently rated low risk in all studies (100%). Similarly, incomplete outcome data (attrition bias) and selective reporting (reporting bias) were uniformly low risk across all studies. For other potential biases, 75% of studies were rated low risk, 12.5% unclear, and 12.5% high risk. Collectively, these findings suggest that the methodological quality of the included studies was generally robust, with only minor concerns noted in allocation concealment and other potential sources of bias.

A meta-analysis (MA) was performed to evaluate and compare the relative efficacy of real repetitive transcranial magnetic stimulation (rTMS) versus sham stimulation in patients with neurodegenerative ataxias, including multiple system atrophy cerebellar subtype (MSA-C), spinocerebellar ataxia (SCA), and Friedreich's ataxia (FRDA). MA allows integration of direct and indirect evidence across trials, providing a more comprehensive synthesis of therapeutic efficacy.

Effect sizes were expressed as standardized mean difference (SMD) with 95% confidence intervals (CIs), based on continuous outcomes derived from validated clinical scales. The primary endpoints were changes in ataxia severity measured by the Scale for the Assessment and Rating of Ataxia (SARA; 0–40) and the International Cooperative Ataxia Rating Scale (ICARS; 0–100). SARA evaluates domains including gait (0–8), stance (0–6), sitting (0–4), speech disturbance (0–6), finger chase (0–4), nose-finger test (0–4),

fast alternating hand movements (0–4), heel-shin slide (0–4). Whereas ICARS evaluates 19 items with four subscales including posture and gait, limb movement, speech and oculomotor function.

To visualize and interpret the evidence, a network plot was constructed to depict direct and indirect comparisons among interventions. To ensure robustness, meta-analyses and sensitivity analyses were also performed, including meta-regression to account for variations in baseline disease severity and stimulation protocols. This network-level synthesis thus enabled a multidimensional and rigorous evaluation of rTMS as a therapeutic strategy for neurodegenerative ataxias.

The literature screening, data extraction, quality assessment, and statistical analyses will be conducted through a combination of manual procedures and dedicated software tools to ensure accuracy, transparency, and reproducibility. Title and abstract screening will be performed independently by reviewers, with any conflicts resolved through discussion. Data extraction will be carried out in Microsoft Excel by five reviewers to maintain consistency and reliability. The meta-analysis will be conducted using Review Manager version 5.4.1, enabling statistical pooling of effect sizes, assessment of heterogeneity, and generation of forest plot. To further investigate potential sources of heterogeneity, meta-regression and visualization through bubble plots will be performed using JASP 0.19.3, which provides a user-friendly platform for advanced statistical analyses. This integrated workflow ensures methodological rigor and adherence to current best practices in evidence synthesis.

To ensure the credibility and transparency of our study, we registered the review protocol in PROSPERO (CRD420251127471). A comprehensive preliminary search was conducted using the keywords “Repetitive transcranial magnetic stimulation,” “neurodegenerative cerebellar ataxia” and “sham-controlled”. Systematic reviews were screened for potential overlaps in title and content. No significant similarities were identified, supporting the novelty and originality of our review.

Results

Literature Search

A thorough search across PubMed, Cochrane, ScienceDirect, Scopus, SAGEjournals, Taylor and Francis, Wiley, EBSCOhost, BioRxiv, and MedRxiv initially identified 202 records. After removing 11 duplicates, 191 records were screened for relevance. At the abstract screening stage, 159 records were excluded, leaving 32 reports for retrieval. 17 of these reports were unavailable to be retrieved because of limited or restricted access. The remaining 15 full-text reports were assessed for eligibility and 7 were excluded due to insufficient or incompatible data. In the end, 7 studies were included in the systematic review and meta-analysis, encompassing a total of 230 participants. This literature search process is summarized (Figure 1).

Risk of Bias Assessment

The methodological quality of the included studies was assessed using the Cochrane Risk of Bias 2.0 tool, covering domains of random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other potential biases.

Most studies demonstrated low risk of bias for random sequence generation. Song et al. (2020)[11], Li et al. (2025)[12], França et al. (2020)[13], Chen et al. (2022)[14], Manor et al. (2019)[15], and Sikandar et al. (2023)[17] clearly described the randomization methods, including random number assignments, or permuted block randomization. However, Shiga et al. (2002)[16] showed high risk of bias in randomization, as participants were allocated based on admission dates, which may introduce systematic differences between groups.

For allocation concealment, Song et al. (2020)[11], Chen et al. (2022)[14], and Manor et al. (2019)[15] failed to provide sufficient details, resulting in an unclear risk of bias. In contrast, Li et al. (2025)[12], França et al. (2020)[13], and Sikandar et al. (2023)[17] used robust concealment procedures, such as blinded allocation by independent researchers, leading to a low risk rating. Blinding of participants, personnel, and outcome assessors was generally well-performed across all studies, with double-blind or sham-controlled designs consistently reported. Most trials used validated sham stimulation techniques, identical schedules, and blinded evaluators, minimizing performance and detection bias.

Regarding incomplete outcome data, almost all studies reported low attrition rates, with participants completing the study or dropouts unrelated to the intervention (e.g., personal reasons or mild adverse events such as nausea). All studies were judged as low risk for selective reporting with outcomes reported as prespecified. Finally, the category of other bias was generally low across studies, with well-matched baseline characteristics. However, Shiga et al. (2002)[16] was rated as high risk due to baseline matching potentially introducing bias, and Song et al. (2020)[11] had unclear reporting for this domain. The detailed risk of bias assessment for each study is summarized (Figure 2) with all domains visually represented as traffic-light plots (Figure 3).

Across the seven included studies, most domains demonstrated a low risk of bias. For random sequence generation (selection bias), 6 studies were rated low risk, while 1 study was rated high risk. Allocation concealment showed more variability, with 3 of studies rated low risk, 1 high risk, and 3 unclear. Both blinding of participants and personnel (performance bias) and blinding of outcome assessment (detection bias) were consistently rated low risk in all studies (100%). Similarly, incomplete outcome data (attrition bias) and selective reporting (reporting bias) were uniformly low risk across all studies. For other potential biases, 5 of studies were rated low risk, 1 unclear, and 1 high risk. Collectively, these findings suggest that the methodological quality of the included studies was generally robust with only minor concerns noted in allocation

concealment and other potential sources of bias.

Included Studies

A total of seven randomized controlled trials examined the impact of repetitive transcranial magnetic stimulation (rTMS) on neurological ataxia, including spinocerebellar ataxia (SCA) and multiple system atrophy cerebellar subtype (MSA-C). The Scale for the Assessment and Rating of Ataxia (SARA) and the International Cooperative Ataxia Rating Scale (ICARS) were the main tools used to evaluate the results of the protocols, which included intermittent theta burst stimulation (iTBS), low-frequency rTMS, and deep rTMS.

The trials consistently demonstrated symptomatic improvements, though the durability of effects varied. Song et al. (2020)[11] reported that 10 days of cerebellar iTBS significantly improved motor symptoms and enhanced cerebello-frontal connectivity in MSA-C patients. Similarly, Li et al. (2025)[12] showed bilateral cerebellar iTBS improved both motor and non-motor symptoms, though benefits diminished after four weeks, suggesting that repeated sessions may be needed. França et al. (2020)[13] applied deep rTMS and observed short-term relief of ataxia symptoms with no serious adverse effects, supporting its feasibility and favorable safety profile. In SCA3 patients, Chen et al. (2022)[14] showed that 15 days of low-frequency rTMS resulted in notable improvements in ICARS scores and measurable changes in cerebellar metabolism, suggesting both biological and clinical improvements. Further evidence of potential longer-term effects was provided by Manor et al. (2019)[15], who demonstrated that 20 rTMS sessions enhanced postural control and SARA scores, with benefits continuing after one month. One of the first investigations, by Shiga et al. (2002)[16], established the basis for later research by confirming that low-frequency cerebellar rTMS enhanced posture, walking, and general motor performance in patients with spinocerebellar degeneration. Recent research by Sikandar et al. (2023)[17] confirmed the safety and effectiveness of cerebellar rTMS, showing that 15 sessions significantly improved multiple ataxia scales with good tolerability in SCA3.

Meta-Analysis Findings

The meta-analysis demonstrated that rTMS significantly improved SARA scores in patients with neurodegenerative cerebellar ataxia compared to sham stimulation (SMD = –0.84, p = 0.004). This effect size suggests a moderate-to-large clinical benefit of rTMS. The 95% confidence interval (–1.40 to –0.27) does not cross zero, reinforcing the robustness of this finding. Nevertheless, the heterogeneity was substantial (I^2 = 73%), which indicates considerable variability in effect sizes across the included studies and suggests that the results should be interpreted with caution. This may be due to the various number of sessions, durations, and pulses of rTMS intervention in each study. The forest plot can be seen (Figure 4).

In contrast, the meta-analysis of ICARS outcomes revealed no significant difference between rTMS and sham

stimulation (SMD = –0.82, p = 0.43). The wide 95% confidence interval (–2.87 to 1.23), which includes zero, indicates uncertainty regarding the direction and magnitude of the effect. Furthermore, the heterogeneity was very high (I^2 = 96%), reflecting marked inconsistency in study results and further limiting the reliability of the pooled estimate. The forest plot can be seen (Figure 5).

SARA and ICARS evaluate ataxia severity through distinct item structures and scoring systems, which likely contribute to the divergent findings observed in this meta-analysis. SARA comprises eight items assessing gait, stance, sitting balance, speech disturbance, and upper- and lower-limb coordination tasks such as finger chase, the nose–finger test, fast alternating hand movements, and the heel–shin slide, generating a total score ranging from 0 to 40. In contrast, ICARS consists of 19 items organized into four subscales—posture and gait disturbance, limb kinetic function, speech disorders, and oculomotor abnormalities—thereby encompassing a broader spectrum of motor and ocular impairments within a 0–100 scoring range. Although both scales interpret higher scores as greater ataxia severity, the wider measurement range, finer granularity, and inclusion of oculomotor assessments in ICARS may allow it to detect subtle or domain-specific deficits that SARA does not capture. These structural differences inform the interpretation of the meta-analytic findings: rTMS produced a significant moderate-to-large improvement in SARA scores (SMD = –0.84, p = 0.004), whereas no significant effect was observed for ICARS outcomes (SMD = –0.82, p = 0.43), accompanied by very wide confidence intervals and substantial heterogeneity (I^2 = 96%). The discordant results likely reflect not only interstudy variability but also intrinsic differences in scale sensitivity and domain emphasis. SARA predominantly assesses core motor domains—particularly gait, posture, and limb coordination—that are most plausibly modulated by cerebellar or motorcortical stimulation, enabling rTMS-induced improvements in these functions to translate into detectable score reductions. Conversely, because ICARS distributes its scoring across a broader array of domains, including fine limb kinetics and oculomotor function, any treatment-related improvements may be diluted within the total score if these domains are less responsive to rTMS. Moreover, the greater complexity and multidimensionality of ICARS may introduce higher measurement variability, further attenuating the ability to detect consistent treatment effects. Additional to the difference in scales, the variability among patient characteristics across included studies possibly have contributed to the inconsistent findings and high heterogeneity. The trials included a spectrum of neurodegenerative cerebellar ataxias, most notably SCA subtypes, MSA-C, and sporadic adult-onset ataxia, as each type features distinct patters of cerebellar degeneration, contributing to its different responsiveness to neuromodulatory interventions. Furthermore, variations in the baseline severity, disease duration, genetic profiles could also influence the degree in which rTMS is able to produce measurable

improvements. Collectively, these considerations underscore that the choice of ataxia rating scale, as well as the different ataxia subtypes, can meaningfully influence the apparent efficacy of rTMS in neurodegenerative cerebellar ataxia.

Sensitivity Analysis and Meta-Regression

Sensitivity analysis was performed for SARA outcome by excluding Sikandar et al. (2023)[17] which can be seen (Figure 6). The exclusion markedly reduced heterogeneity to I^2 = 23% and resulted in an updated pooled effect size of SMD = -1.12 ($p < 0.00001$; 95% CI: -1.50 to -0.74). This may be explained by the five-month rTMS duration in Sikandar et al. (2023)[17], which could have affected the outcomes, compared with the much shorter period (≤1 month) in other studies.

Due to the substantial heterogeneity detected in the meta-analysis, a sensitivity analysis was performed by excluding the study by Shiga et al. (2002)[16], which can be seen (Figure 7). The effect size reported in this study (SMD = –2.85; 95% CI: –3.51 to –2.18) did not overlap with the overall pooled estimate (SMD = –0.82; 95% CI: –2.87 to 1.23), indicating a disproportionate influence on the summary effect. Upon exclusion of this study, heterogeneity was considerably reduced (I^2 = 0%), and the recalculated pooled effect size was attenuated to SMD = 0.12 ($p = 0.64$; 95% CI: –0.38 to 0.62). This may be explained by the wider-types of cerebellar ataxia included in Shiga et al. (2002)[16] compared to the other studies, as it involved the cerebellar type and olivopontocerebellar atrophy (OPCA) type of spinocerebellar degenerative (SCD) patients.

The meta-regression results explored how publication year, follow-up period, and intervention sample size moderated treatment effects across different outcome measures and age groups. For SARA and ICARS, none of the moderators demonstrated a statistically significant effect.

However, based on the visual inspection for bubble plot (Figure 8), the SARA parameter aligns with the sensitivity analysis conducted by Sikandar et al. (2023)[17], which identified outliers based on publication year, follow-up period, and intervention sample size. When these outliers were removed during the sensitivity analysis, heterogeneity dropped from 73% to 23%.

Although no outliers were detected in the ICARS bubble plot as seen (Figure 9) due to the inclusion of only three studies. Sensitivity analysis showed that removing Shiga et al. (2002)[16] reduced heterogeneity from 96% to 0%, suggesting it as the main source—likely due to its use of an early transcranial magnetic stimulation (TMS) protocol conducted well before the establishment of modern neuromodulation standards, while the other included studies are published in 2014–2025.

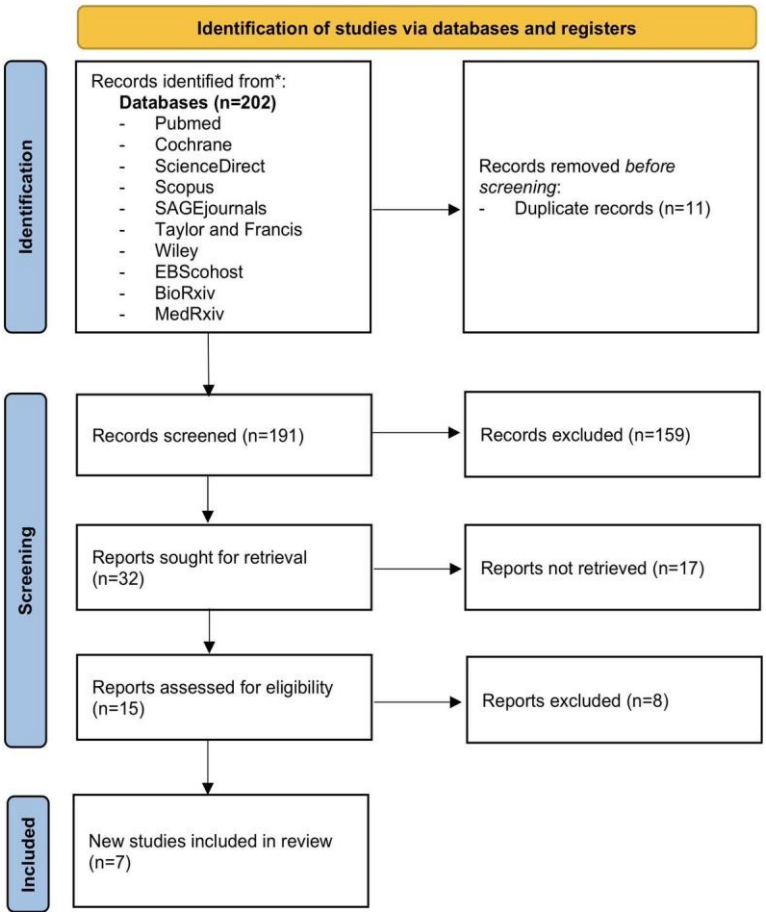

Figure 1. PRISMA 2020 Flowchart

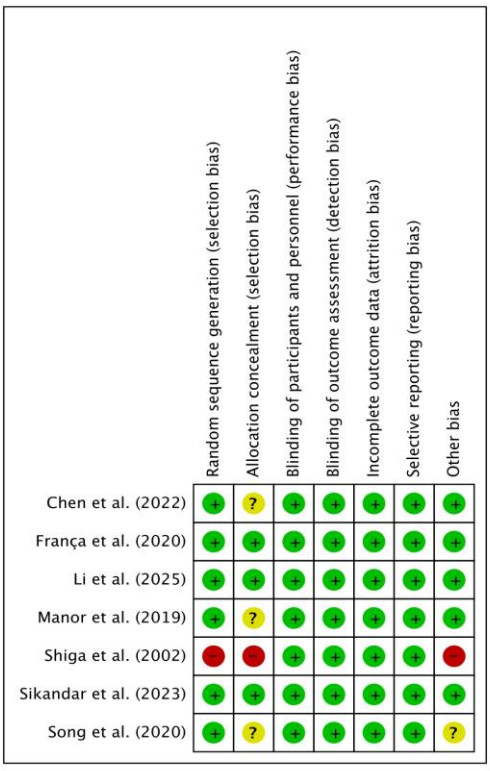

Figure 2. Risk of Bias Traffic Light

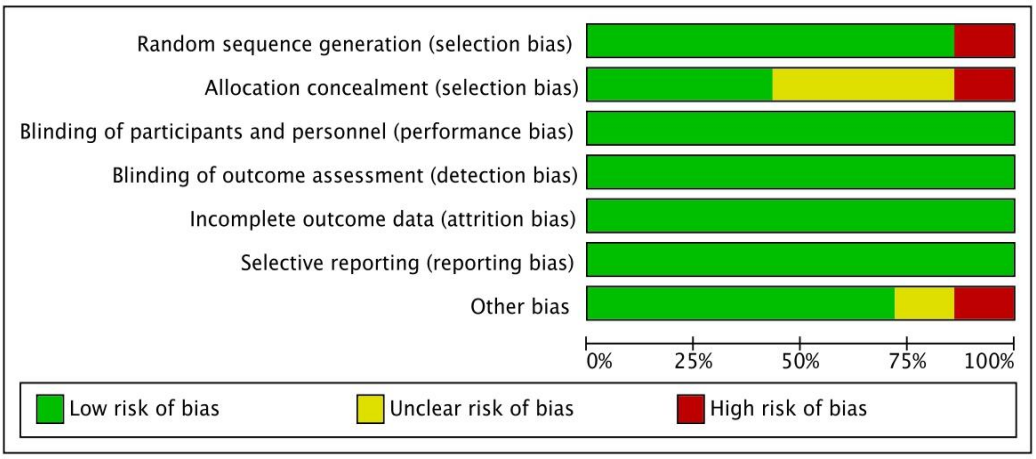

Figure 3. Risk of Bias Summary

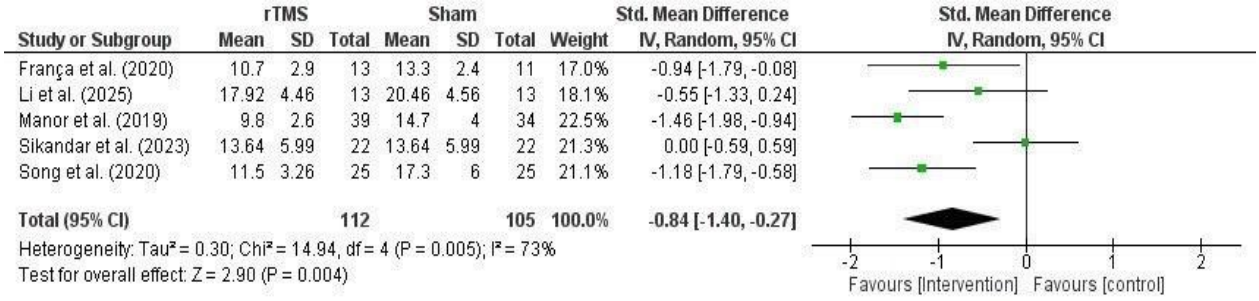

Figure 4. Forest Plot for rTMS vs Sham on SARA

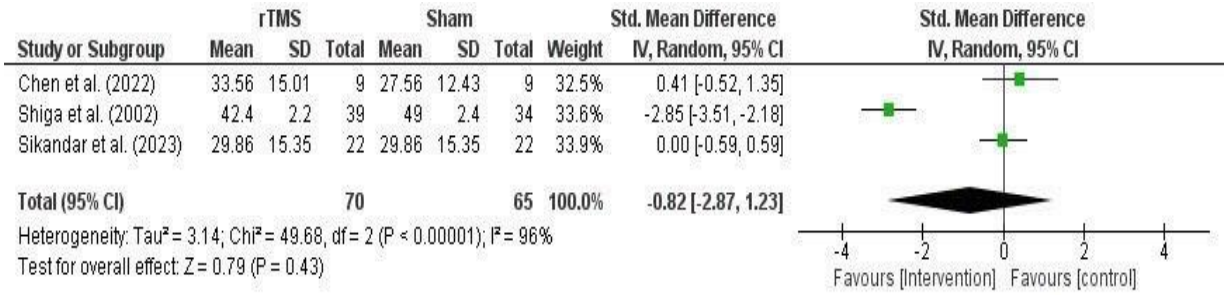

Figure 5. Forest Plot for rTMS vs Sham on ICARS

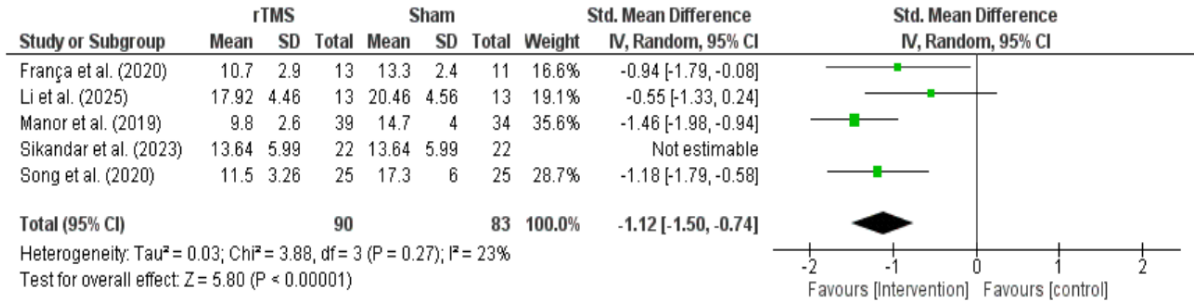

Figure 6. Sensitivity Analysis Forest Plot of The Plot for rTMS vs Sham on SARA

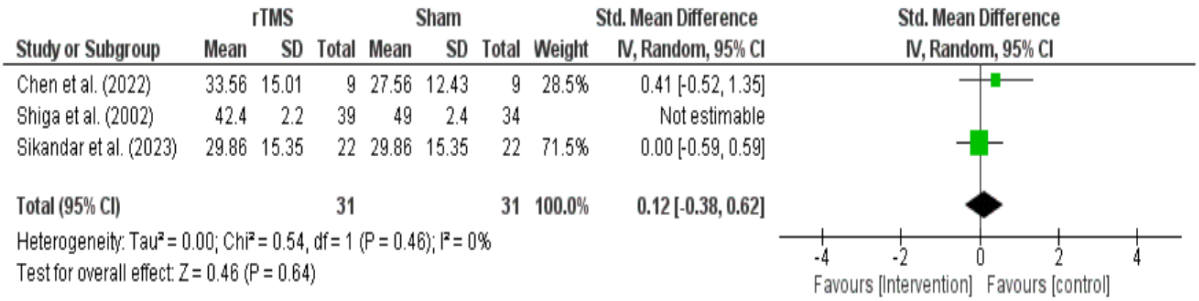

Figure 7. Sensitivity Analysis Forest Plot of The Plot for rTMS vs Sham on ICARS

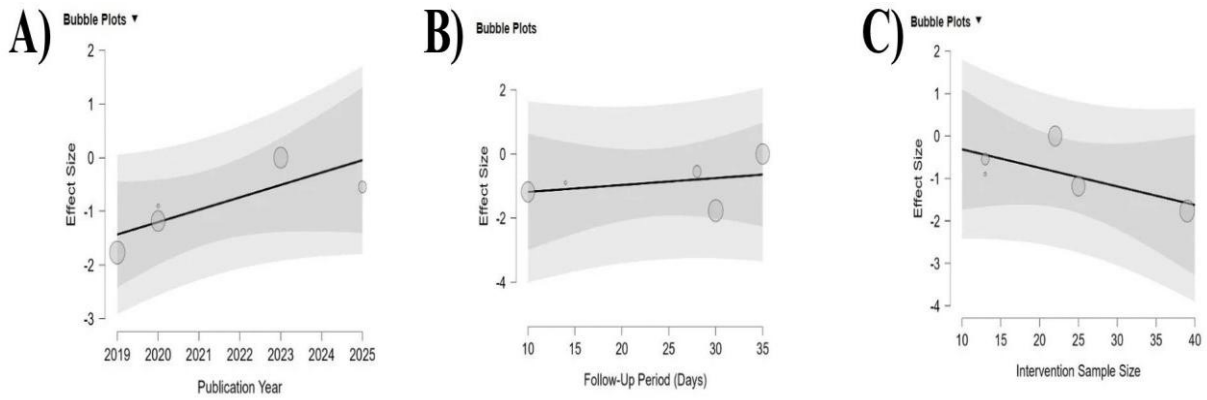

Figure 8. A) Bubble plot publication year for SARA; B) Bubble plot follow-up period (days) for SARA; C) Bubble plot intervention sample size for SARA

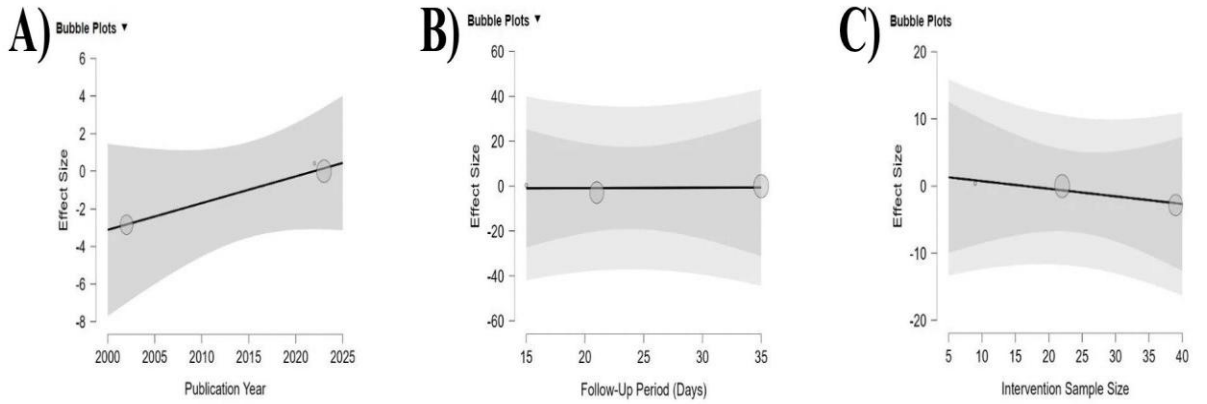

Figure 9. A) Bubble plot publication year for ICARS; B) Bubble plot follow-up period (days) for ICARS; C) Bubble plot intervention sample size for ICARS

Discussion

Differences of Non-genetic Physical Neuromodulation Techniques

Neuromodulation technologies represent a diverse set of approaches that aim to modulate neuronal activity through invasive and non-invasive methods. Deep Brain Stimulation (DBS) involves the implantation of bipolar electrodes into deep brain nuclei, inducing extracellular electric fields that modulate excitation and inhibition via voltage-gated ion channels. Clinically, DBS is FDA-approved for Parkinson's disease, obsessive-compulsive disorder (OCD), dystonia, and epilepsy, and it is also being investigated for depression, treatment-resistant disorders, and bipolar disorder. Its major advantages include high efficacy in treatment-resistant conditions, precise targeting, and adjustable parameters, with emerging closed-loop systems. However, DBS remains invasive, with risks of surgical complications, chronic immune responses, and the need for frequent reprogramming and device maintenance.[18]

In contrast, Transcranial Magnetic Stimulation (TMS) employs strong pulsed magnetic fields that induce local currents in the cerebral cortex, thereby modulating excitability and neural circuits. It is FDA-approved for depression, OCD, migraine, and smoking cessation, while experimental trials extend its application to epilepsy, stroke, and Huntington's disease. TMS is non-invasive and can modulate both cortical and subcortical circuits depending on stimulation frequency, but its limitations include restricted depth penetration, interindividual variability in efficacy, and the requirement for multiple sessions. Similarly, Transcranial Direct Current Stimulation (tDCS) delivers weak direct currents through scalp electrodes, modulating neurotransmitter interactions and synaptic plasticity. It has been investigated in depression, motor rehabilitation, and cognitive enhancement, with advantages of being portable, inexpensive, and safe while promoting neuroplasticity. However, its effects are often weak and spatially imprecise, with outcome variability across individuals.[18]

Transcranial Ultrasound Stimulation (TUS) is an emerging technology that uses focused ultrasound waves to modulate neuronal activity through mechanical and thermal effects. Applications under investigation include Parkinson's disease, essential tremor, epilepsy, and psychiatric disorders. Its main strengths are non-invasiveness and high spatial precision capable of reaching deep brain targets. Nonetheless, TUS remains experimental, with risks of tissue heating and a lack of standardized protocols. Another modality, Photobiomodulation Therapy (PBMT) or low-level laser therapy, uses visible and near-infrared light to penetrate tissue, producing photobiomodulation effects on mitochondrial activity, cerebral metabolism, and synaptic function. It has been applied in cognitive disorders, neurodegeneration, and stroke recovery. While non-invasive and supportive of neuroplasticity, PBMT is limited by shallow penetration depth and clinical efficacy still under validation.[18]

Similarly, Infrared Neuromodulation (INM) employs direct infrared light to alter neuronal activity through photothermal and biophysical mechanisms. This therapy is

still in early experimental stages but offers advantages of non-invasiveness and precise local control. Its limitations lie in insufficient evidence regarding long-term safety and efficacy. Electromagnetic Stimulation Therapy uses externally projected electromagnetic waves to modulate cortical and subcortical networks, primarily studied for cognitive enhancement and mood regulation. The method is non-invasive with wide cortical reach, though it lacks broad clinical approval and may yield nonspecific effects. Finally, Sensory Stimulation Therapy delivers calibrated sensory inputs such as sound or light to induce rhythmic oscillations, particularly in the gamma range, within primary sensory cortices. This approach modulates communication and cognition, showing promise in Alzheimer's disease, cognitive disorders, and sensory rehabilitation. Its strengths include safety, entrainment of neural oscillations, and non-invasiveness, though its effects can be transient and dependent on intact sensory pathways, with most evidence still in early validation phases.[18]

Mechanism of rTMS for Neurodegenerative Cerebellar Ataxia

Repetitive transcranial magnetic stimulation (rTMS) of the cerebellum modulates neuronal excitability and metabolism through localized electric currents that increase glutamate and N-acetylaspartate (NAA) levels, reflecting enhanced synaptic activity and neuronal integrity.[19] These changes were observed in both healthy subjects and patients with cerebellar ataxia, where increased NAA/Cr ratios correlated with clinical improvement.[14] NAA functions as a neuronal marker involved in mitochondrial activity and synaptic transmission, often paralleling glutamatergic changes.[19] In patients with spinocerebellar ataxia type 3, cerebellar rTMS led to significant metabolic improvements in the vermis, hemispheres, and dentate nucleus.[14] Studies of rTMS for cerebellar ataxia have implemented both high and low frequency procedures. The strongest and most consistent results in ataxia symptoms and balance are due to 1 Hz stimulation or low frequency approach. Higher frequencies, namely 10 Hz have shown possible benefits, although 1 Hz remains the more established and effective option.[20]

In parallel, low-frequency cerebellar rTMS reduces inhibitory output from Purkinje cells to the dentate nucleus, thereby restoring suppressed activity in the dentato-thalamo-cortical pathways. This disinhibition enhances both motor and non-motor network function, including vestibular nuclei for balance and prefrontal areas for cognition and mood.[21] Functional imaging and TMS-EEG studies in multiple system atrophy (MSA) support this mechanism, demonstrating strengthened cerebello-frontal connectivity and improved clinical scores.[11] These effects are likely mediated by long-term potentiation (LTP) and depression (LTD), promoting neuroplasticity and compensatory circuit reorganization.[11,12] As a result, cerebellar rTMS contributes to broad therapeutic benefits across motor coordination, balance, mood regulation, and overall quality of life.[14,21]

Clinical Applicability of rTMS

Transcranial magnetic stimulation (TMS) can induce both acute and prolonged effects in cortical excitability, highlighting their potential as interventions for modulating brain activity and improving neurological and psychiatric outcomes. The effects varied based on the frequency of pulses of the stimulation. Repetitive transcranial magnetic stimulation (rTMS) is a series of pulses given to the brain which offers several advantages over single-pulse TMS. It remains a promising therapeutic approach for neurological and psychiatric conditions because of its capability to induce long-lasting modulation of cortical activity that persists beyond the stimulation period.[22] Long-term potentiation (LTP) and long-term depression (LTD) are two examples of synaptic plasticity mechanisms that are compatible with the physiological effects of rTMS, offering a biologically feasible explanation for its clinical efficacy.[23]

Moreover, rTMS demonstrates targeted modulation of cerebellar circuits by selectively decreasing inhibitory regulation of the cerebellar cortex over the dentate nucleus.[24] In particular, low-frequency cerebellar rTMS has been reported to improve vestibular nucleus activation and restore dentate nucleus function, potentially improving balance and motor control in individuals with cerebellar ataxia.[23] Additional practical advantages include its noninvasiveness, painless administration, precise cortical targeting, and the adaptability to customize stimulation parameters to patient requirements.[22] However, despite its strengths, rTMS has certain limitations. Even with its therapeutic potential, the physiological mechanisms behind rTMS are still incompletely understood. Baseline cortical excitability, pulse number, stimulation frequency, and intensity all affect responses. Traditional rTMS methods are often less reproducible than theta-burst stimulation (TBS) and low-frequency rTMS administered at subthreshold levels frequently fails to produce measurable effects.[25] Furthermore, variations in stimulation parameters including frequency, intensity, coil placement, and pulse count across different studies contribute to inconsistent findings and complicate direct comparisons. Additionally, the majority of research focuses on immediate results, which leaves the long-term durability of rTMS benefits unclear.[23]

Although enhanced motor performance and improved postural regulation are commonly observed outcomes, the magnitude and consistency of these benefits remain highly dependent on the specific stimulation parameters employed. This underscores the need for greater protocol standardization—an area in which further research, including the present study, has the potential to refine therapeutic applications and advance the clinical utility of rTMS.

Strengths and Limitations of the Study

Although rTMS is currently FDA approved for selected psychiatric indications, our review shows it induces durable cortical modulation beyond the stimulation window, supporting therapeutic potential in neurological disease, including neurodegenerative cerebellar ataxias. This is the first systematic review and meta

analysis to integrate evidence across multiple ataxia subtypes, leveraging multinational randomized controlled trials and a deliberately homogeneous sample that excluded participants with other neurological abnormalities or nondegenerative ataxias. While during the statistical analysis, substantial and high heterogeneity were found, sensitivity analyses and meta regression were performed to assess robustness. Important limitations remain: rTMS effects vary with frequency, intensity, pulse number, and baseline excitability, factors that can reduce reproducibility relative to theta burst stimulation; most trials reported only short term outcomes given brief follow up; and several ataxia subtypes were underrepresented. Overall, the findings position rTMS as a promising, though variable in methods, adjunctive option for cerebellar ataxia pending more standardized protocols and longer follow-up.

Conclusion

This research demonstrates that rTMS, a non-invasive neuromodulation therapy, significantly improves SARA scores compared with sham stimulation in patients with neurodegenerative cerebellar ataxia, including those with Multiple System Atrophy (MSA), Spinocerebellar Ataxia (SCA), and Friedreich's Ataxia. In contrast, no significant differences were observed between groups when assessed using ICARS. Future research should broaden the scope of investigation to include other forms of cerebellar ataxia, such as Dentatorubral-pallidoluysian atrophy (DRPLA), Ataxia-telangiectasia, Ataxia with Oculomotor Apraxia (AOA), Fragile X-associated Tremor/Ataxia Syndrome (FXTAS), Episodic Ataxias, and Cerebellar Ataxia with Neuropathy and Vestibular Areflexia Syndrome (CANVAS), in order to evaluate whether the benefits of rTMS can be generalized across different etiologies. In addition, long-term follow-up studies are warranted to assess the durability of clinical improvements, monitor potential adverse effects, and establish the overall safety profile of rTMS as a therapeutic option for patients with cerebellar ataxia.

Conflict of Interest

None.

Acknowledgment

None.

Funding

No external funding was received.

References

1. Hafiz M, Sumaiya A, De Jesus O. Ataxia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2025 Oct 13]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562284/
2. Lin CYR, Yeh TH, CM, Lin JL, Wang HL, Soong BW, et al. Cognitive, emotional, and other non-motor symptoms of spinocerebellar ataxias. *Curr Neurol Neurosci Rep*. 2024 Jan 25;24(3):47–54. https://doi.org/10.1007/s11910-024-01331-4
3. Bhandari J, Thada PK, Samanta D. Spinocerebellar ataxia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Sept 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557816/

4. Rudaks LI, Yeow D, Ng K, Deveson IW, Kennerson ML, Kumar KR. An update on the adult-onset hereditary cerebellar ataxias: novel genetic causes and new diagnostic approaches. *Cerebellum*. 2024 May 18;23(5):2152–68. Available from: https://doi.org/10.1007/s12311-024-01703-z.
5. Perlman S. Hereditary ataxia overview. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 2025 [cited 2025 Sept 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1138/
6. Gandini J, Biasini F, Pizzarotti B, Calandra-Buonaura G, Guaraldi P, Contin M, et al. The neurological update: therapies for cerebellar ataxias in 2020. *J Neurol*. 2020 Apr 30;267(4):1211–20. Available from: https://doi.org/10.1007/s00415-020-09717-3.
7. Cui, Zi-Ting, et al. Spinocerebellar Ataxias: From Pathogenesis to Recent Therapeutic Advances. *Frontiers in Neuroscience*, vol. 18, 4 June 2024, Available from: https://doi.org/10.3389/fnins.2024.1422442.
8. Mann SK, Malhi NK. Repetitive Transcranial Magnetic Stimulation. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Sept 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK568715/
9. Hussain S, Chamoli S, Fitzgerald P, Gandhi A, Gill S, Sarma S, et al. Royal Australian and New Zealand College of Psychiatrists professional practice guidelines for the administration of repetitive transcranial magnetic stimulation. *Aust N Z J Psychiatry*. 2024 Aug;58(8):641–55. Available from: https://doi.org/10.1177/00048674241249846
10. Benussi A, Batsikadze G, França C, Cury RG, Maas RPPWM. The therapeutic potential of non-invasive and invasive cerebellar stimulation techniques in hereditary ataxias. *Cells*. 2023 Apr 20;12(8):1193. Available from: https://doi.org/10.3390/cells12081193
11. Song P, Li S, Wang S, Wei H, Lin H, Wang Y. Repetitive transcranial magnetic stimulation of the cerebellum improves ataxia and cerebello-fronto plasticity in multiple system atrophy: a randomized, double-blind, sham-controlled and TMS-EEG study. *Aging*. 2020 Oct 21;12(20):20611–22. Available from: https://doi.org/10.18632/aging.103946
12. Li D, Jiang C, Liu J, Fan Y, Hao X, Fu M, et al. Repeated transcranial magnetic stimulation on the bilateral cerebellum to improve symptoms of ataxia with multiple system atrophy: a prospective, randomized, sham-controlled pilot study. *Neurol Sci*. 2025 Apr;46(4):1875–82. Available from: https://doi.org/10.1007/s10072-025-08001-4
13. França C, De Andrade DC, Silva V, Galhardoni R, Barbosa ER, Teixeira MJ, et al. Effects of cerebellar transcranial magnetic stimulation on ataxias: a randomized trial. *Parkinsonism Relat Disord*. 2020 Nov;80:1–6. Available from: https://doi.org/10.1016/j.parkreldis.2020.09.001
14. XY, Lian YH, Liu XH, Sikandar A, Li MC, Xu HL, et al. Effects of repetitive transcranial magnetic stimulation on cerebellar metabolism in patients with spinocerebellar ataxia type 3. *Front Aging Neurosci*. 2022 Apr 25;14:827993. Available from: https://doi.org/10.3389/fnagi.2022.827993
15. Manor B, Greenstein PE, Davila-Perez P, Wakefield S, Zhou J, Pascual-Leone A. Repetitive transcranial magnetic stimulation in spinocerebellar ataxia: a pilot randomized controlled trial. *Front Neurol*. 2019 Feb 12;10:73. Available from: https://doi.org/10.3389/fneur.2019.00073
16. Shiga Y. Transcranial magnetic stimulation alleviates truncal ataxia in spinocerebellar degeneration. *J Neurol Neurosurg Psychiatry*. 2002 Jan 1;72(1):124–6.

Available from: https://doi.org/10.1136/jnnp.72.1.124
17. Sikandar A, Liu XH, Xu HL, Li Y, Lin YQ, XY, et al. Short-term efficacy of repetitive transcranial magnetic stimulation in SCA3: a prospective, randomized, double-blind, sham-controlled study. *Parkinsonism Relat Disord*. 2023 Jan;106:105236. Available from: https://doi.org/10.1016/j.parkreldis.2022.105236
18. Zhi W, Li Y, Wang L, Hu X. Advancing neuroscience and therapy: insights into genetic and non-genetic neuromodulation approaches. *Cells*. 2025 Jan 15;14(2):122. Available from: https://doi.org/10.3390/cells14020122
19. Jayathilake NJ, Phan TT, Kim J, Lee KP, Park JM. Modulating neuroplasticity for chronic pain relief: noninvasive neuromodulation as a promising approach. *Exp Mol Med **57**, 501–514 (2025).* Available from: https://doi.org/10.1038/s12276-025-01409-0
20. Lin YC, Kuo SH, Lin CP, Chang LH. The efficacy of repetitive transcranial magnetic stimulation in patients with spinocerebellar ataxia: a systematic review and meta-analysis. *J Chin Med Assoc*. 2025 Jun;88(6):417–24. Available from: https://doi.org/10.1097/JCMA.0000000000001243
21. Pauly MG, Steinmeier A, Bolte C, Hamami F, Tzvi E, Münchau A, et al. Cerebellar rTMS and PAS effectively induce cerebellar plasticity. *Sci Rep*. 2021 Feb 4;11(1):3070. Available from: https://doi.org/10.1038/s41598-021-82496-7
22. SY, Tsou MH, KY, Liu YC, Lin MT. Impact of repetitive transcranial magnetic stimulation on cortical activity: a systematic review and meta-analysis utilizing functional near-infrared spectroscopy evaluation. *J Neuroeng Rehabil*. 2024 Jun 24;21(1):108. Available from: https://doi.org/10.1186/s12984-024-01407-9
23. Afifi SY. A new era of current and future treatment applications of transcranial magnetic stimulation. *Egypt J Neurol Psychiatry Neurosurg*. 2024 Apr 15;60(1):54. Available from: https://doi.org/10.1186/s41983-024-00825-9
24. Ciricugno A, Paternò S, Barbati N, Borgatti R, Cattaneo Z, Ferrari C. Advances in cerebellar TMS therapy: an updated systematic review on multi-session interventions. *Biomedicines*. 2025 Jun 27;13(7):1578. Available from: https://doi.org/10.3390/biomedicines13071578
25. Ozdemir RA, Boucher P, Fried PJ, Momi D, Jannati A, Pascual-Leone A, et al. Reproducibility of cortical response modulation induced by intermittent and continuous theta-burst stimulation of the human motor cortex. *Brain Stimul*. 2021 Jul–Aug;14(4):949–64. Available from: https://doi.org/10.1016/j.brs.2021.05.013