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REVIEW ARTICLE

The efficacy of repetitive transcranial magnetic stimulation in patients with spinocerebellar ataxia: A systematic review and meta-analysis

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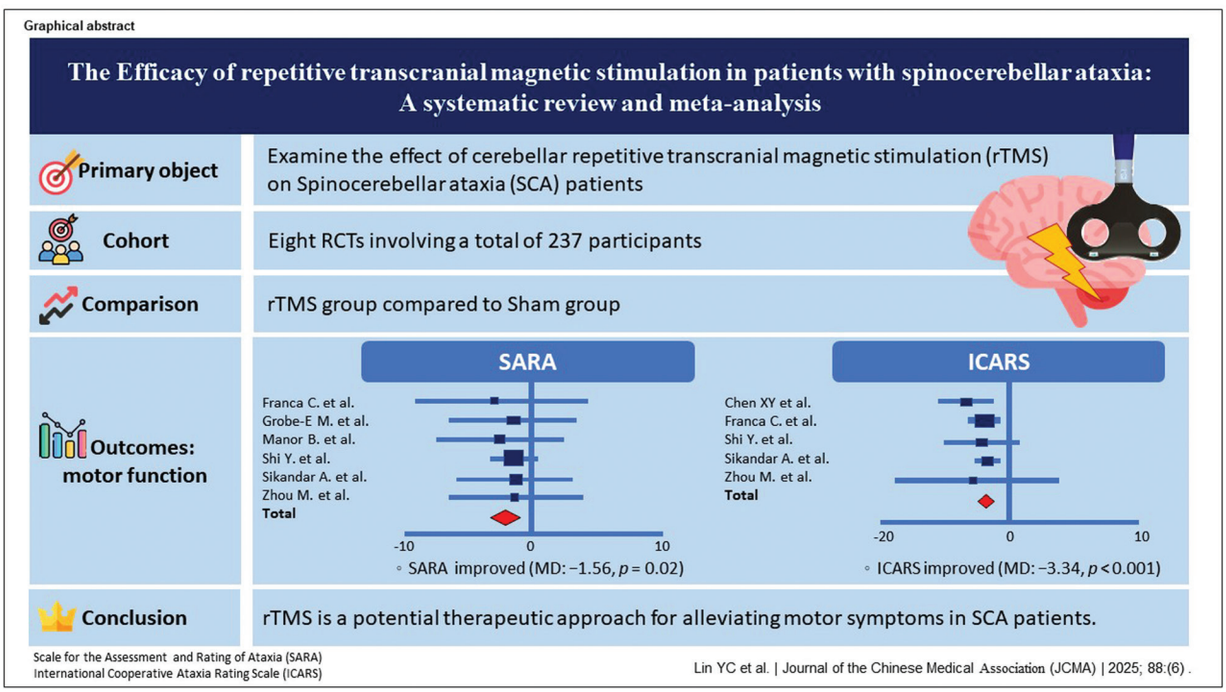
Abstract

Spinocerebellar ataxia (SCA) is a group of hereditary neurodegenerative disorders characterized by the progressive incoordination of gait, impaired motor control, and various neurological deficits. Therapeutic options for SCA remain limited. However, repetitive transcranial magnetic stimulation (rTMS) has gained attention as a potential intervention due to its noninvasive nature, ease of application, and favorable safety profile. To evaluate the therapeutic efficacy of rTMS in SCA, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs). A comprehensive search of PubMed, Medline, and the Cochrane Library databases was conducted to identify RCTs assessing rTMS for SCA management. The primary outcomes of interest included changes in motor function as measured by the Scale for the Assessment and Rating of Ataxia (SARA) or the International Cooperative Ataxia Rating Scale (ICARS). Our analysis included eight RCTs involving a total of 237 participants. Meta-analysis results demonstrated statistically significant improvements in motor function. Specifically, SARA scores showed a mean difference (MD) of −1.56 (95% CI, −2.88 to −0.24; $p = 0.02$), and ICARS scores improved with an MD of −3.16 (95% CI, −3.93 to −2.39; $p < 0.001$) compared with a sham group. To evaluate the effects of different rTMS protocols on SCA, we performed subgroup analyses of low-frequency (LF), high-frequency (HF), and intermittent theta burst stimulation (iTBS). We revealed that LF (MD, −1.60; 95% CI, −3.06 to −0.13; $p = 0.03$) and iTBS (MD, −1.68; 95% CI, −2.29 to −1.08; $p < 0.001$) were effective in significantly improving SARA. The HF group showed a reduction in SARA scores (MD, −1.52; 95% CI, −6.34 to 3.30; $p = 0.54$) but without significance because of the small sample size. These findings indicate that overall rTMS is a promising therapeutic approach for alleviating motor symptoms in hereditary SCA patients.

Keywords: Cerebellar reserve; Cerebellum; rTMS; Spinocerebellar ataxia; TBS

Graphical abstract



Lay Summary: Spinocerebellar ataxia (SCA) is a hereditary disorder that leads to problems with movement and coordination. Treatment options are limited, but repetitive transcranial magnetic stimulation (rTMS) is a promising non-invasive therapy. Researchers reviewed eight studies involving 237 participants to evaluate the effectiveness of rTMS for SCA. The results showed significant improvements in motor function compared to a placebo. Specifically, two rTMS methods—low-frequency and intermittent theta burst stimulation—were particularly effective. Overall, rTMS appears to be a hopeful treatment for enhancing movement in people with SCA.

1. INTRODUCTION

Hereditary spinocerebellar ataxias (SCAs) represent a group of rare, inherited neurodegenerative disorders characterized by significant clinical and genetic diversity.[1–4] These conditions, which fall under the broader category of hereditary ataxias, manifest with a range of neurological symptoms, mainly including motor dysfunctions such as gait instability, dysarthria, uncoordinated eye movements, and other involvement with peripheral neuropathy, pyramidal signs, and cognitive deficits.[2,3] The distribution of SCA subtypes varies geographically across different populations.[5–7] Among Caucasian populations, SCA1, SCA2, and SCA3 are the most prevalent subtypes. In contrast, SCA2, SCA3, SCA6, and dentatorubral-pallidoluysian atrophy (DRPLA) are more commonly observed in East Asian populations, including Japanese and Chinese individuals.[8–10] This regional variation underscores the importance of considering genetic and demographic factors when diagnosing and managing SCAs. However, effective therapeutic strategies for SCA remain limited in clinical practice.

Several studies have found that neuromodulation is effective.[11–13] Noninvasive neuromodulation, such as repetitive transcranial magnetic stimulation (rTMS), represents a promising alternative for managing motor symptoms in SCA and warrants further investigation. The rTMS is a safe, noninvasive technique for brain stimulation that has attracted growing interest as a treatment for ataxia due to its capacity to promote neural plasticity[14] and wide use in neurorehabilitation for various neurological and psychiatric conditions, including depression,[15] anxiety disorders,[16] Parkinson's disease,[17] Alzheimer's disease,[18] and even SCA patients.[11,12] Different rTMS protocols exhibit distinct neurophysiological mechanisms and therapeutic effects. Low-frequency (LF) rTMS, typically delivered at 1 Hz, induces long-term depression (LTD)-like effects, leading to consistent cortical inhibition and the modulation of γ-aminobutyric acid (GABA)ergic neurotransmission, whereas high-frequency (HF) rTMS (>5 Hz) increases cortical excitability through long-term potentiation (LTP)-like effects, enhancing neurogenesis and activating the brain-derived neurotrophic factor/tropomyosin receptor kinase B (BDNF/TrkB) signaling pathway.[19–21] In theta burst protocols, cTBS delivers continuous stimulation bursts that produce LTD-like effects and cortical inhibition, modulating GABA levels, whereas iTBS delivers rapid bursts (50 Hz) in a theta rhythm (5 Hz), inducing more robust and LTP plasticity.[20,22,23] Despite its potential, the literature on rTMS treatment protocols for SCA remains heterogeneous, with varying approaches and outcomes reported.

Although systematic reviews have evaluated the effects of rTMS on SCA patients,[11,12] a critical gap remains in comparative analyses of different rTMS protocols, including LF, HF, and theta burst stimulation (TBS).[11,24–26] This gap highlights the need for further studies to identify and standardize the most effective rTMS protocols for alleviating the clinical symptoms of SCA. Current literature exhibits several methodological limitations; notably, existing reviews have excluded TBS protocols despite their promising therapeutic and cost-saving effects,[27] while review analyses of LF and HF protocols frequently contain significant risks of bias. For instance, one HF subgroup analysis combined data from both multiple system atrophy-cerebellar type (MSA-c) and SCA3 patients, diluting the specificity for SCA populations.[25] Another review incorporated non-English publications without adequate quality assessment, potentially introducing methodological heterogeneity.[26] These inconsistencies underscore the need for rigorous, protocol-specific comparative studies to establish optimal neuromodulation parameters specifically tailored to SCA subtypes. This article aims to systematically review all available and qualified randomized controlled trials (RCT) investigating the use of rTMS for treating SCA. By synthesizing the efficacy of various rTMS protocols, we evaluate their impact on improving clinical symptoms in SCA patients. The findings of this meta-analysis study provide valuable insights that can inform and refine experimental designs for future clinical trials involving rTMS.

2. RESEARCH STRATEGY

A search was conducted in the PubMed, Medline, and Cochrane databases for RCTs and review articles focusing on the therapeutic applications of transcranial magnetic stimulation (TMS or rTMS) involving human adults published in English. The search included terms such as "spinocerebellar ataxia," "ataxia," "transcranial magnetic stimulation," "rTMS," "TMS," "theta burst stimulation," "TBS," and "neuromodulation." In addition, abstracts were systematically screened to identify articles eligible for a full-text assessment.

We selected relevant articles for this review based on predefined eligibility criteria encompassing the intervention, comparison, outcome, and study framework. For inclusion in the meta-analysis, studies were required to meet the following criteria: (1) The study must be original research utilizing rTMS as a therapeutic intervention for individuals with SCA. (2) All SCA patients included must have a genetically confirmed diagnosis. (3) The effectiveness of SCA treatment was required to be evaluated using at least one motor function outcome measure, accompanied by adequate statistical data to compute an independent effect size. (4) Participants must be 18 years old or older. (5) The study must be an RCT and published in a peer-reviewed journal (Fig. 1). The primary evaluation focused on assessing motor function outcome, particularly following rTMS treatment. The outcomes of interest were the differences between pre- and post-intervention in (1) Scale for the Assessment and Rating of Ataxia (SARA)[28] and (2) International Cooperative Ataxia Rating Scale (ICARS),[29] the two most common rating scales to measure cerebellar ataxia.[30,31]

Meta-analyses were conducted using Review Manager V.5.4. Study heterogeneity was evaluated through the I^2 statistic. A significance threshold of $p < 0.05$ was applied. A fixed-effects model was utilized when heterogeneity was low ($I^2 < 50\%$ or $p > 0.1$), whereas a random-effects model was applied when heterogeneity was high ($I^2 \geq 50\%$ or $p < 0.1$). For continuous variables, the mean difference (MD) with 95% CIs was calculated. When a quantitative synthesis was not feasible, results from individual studies were qualitatively summarized.

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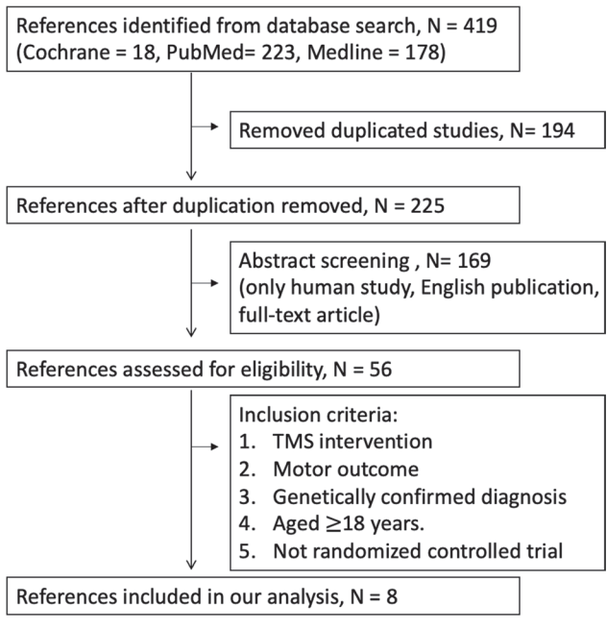

Fig. 1 Flowchart of study selection. TMS = transcranial magnetic stimulation.

3. RESULTS

3.1. Characteristics of included studies

An initial screening of 419 studies was conducted through the predefined keywords search, and we removed 194 duplicate studies. After screening the title and abstract, 169 studies were excluded due to not meeting the criteria of being a human study resulting in a publication in English with a full text. Ultimately, based on the inclusion criteria, eight studies were ultimately selected for review (Table 1).[32–39] This review total involved 237 SCA patients with a genetically confirmed diagnosis; the majority of included patients were diagnosed with SCA3, while others had less frequent subtypes, such as SCA1, SCA2, and SCA6. These studies, published between 2000 and 2024, primarily employed double-controlled, parallel-group designs, with one study using a single-controlled design.[36] In total, 237 participants were included, with a higher proportion of men (68.35%) compared with women (31.65%). Sample sizes ranged from 5 to 37 participants, and the duration of rTMS treatment spanned from 5 to 28 days. The stimulation locations focus primarily on the bilateral cerebellum, with two studies targeting midline vermis and the bilateral cerebellum.[32,35] The outcome assessments using SARA and ICARS, and the change in these scores after rTMS, were compared with the sham group. The risk of bias graph and summary are presented in Fig. 2.

Table 1

Basic characteristics of randomized controlled trials

Study	N	Sex (F)	Design	SCA	Duration	Sham	Protocols	Stimulation locations	Outcome measurement	Main results
Zhou et al[32]	16	7	Randomly, double blind	SCA3	14 d	+	HF, 10 Hz, 100% MT, 800 pulses, 20 min	Vermis, bil cerebellum	ICARS, SARA	SARA and ICARS scores decreased in SCA3
Chen et al[33]	18	10	Randomly, double blind	SCA3	15 d	+	LF, 1 Hz, 100% MT, 900 pulses, 30 min	Bil cerebellum	ICARS, SARA	The ICARS scores in both groups decreased
Sikandar et al[34]	44	20	Randomly, double blind	SCA3	15 d	+	LF, 1 Hz, 900 pulses, 30 min	Bil cerebellum	ICARS, SARA, BBS	SARA and ICARS scores decreased in SCA3
Manor et al[35]	20	14	Randomly, double blind	1 SCA1, 1 SCA2, 13 SCA3, 3 SCA6, 1 SCA8, 1 SCA14	28 d	+	LF, 0.2 Hz, 100% RMT, 600 pulses, 36 min	Vermis, bil cerebellum	SARA, 9-hole peg test, TUG	rTMS improved the total scores of SARA but did not influence the 9-hole peg test, TUG, or gait kinematics
Shi et al[36]	109	63	Randomly, single blind	SCA3	14 d	+	LF, 1 Hz, 100% RMT, 600 pulses, 20 min; iTBS, 1200 pulses, 20 min	Bil cerebellum	ICARS, SARA	Both 1 Hz rTMS and iTBS were effective in improving the SARA and ICARS scores in SCA3
Franca et al[37]	9	7	Randomly, double blind	9 SCA3	5 d	+	LF, 1 Hz, 100% RMT, 600 pulses, 20 min	Bil cerebellum	ICARS, SARA	LF-rTMS improved the SARA and ICARS scores
Grobe-Einsler et al[38]	33	25	Randomly, double blind	14 SCA1, 6 SCA2, 5 SCA3, 1 SCA5, 5 SCA6, 1 SCA7, 1 SCA28	5 d	+	iTBS, 15 sessions (3 sessions per day, applied hourly)	Bil cerebellum	SARA, Walk-Test, PRT, CCAS	SARA scores decreased by 1.6 points in the rTMS group
Liu et al[39]	22	16	Randomly, double blind	SCA3	15 d	+	LF, 1 Hz, 1800 pulses per day, 30 min	Bil cerebellum	ICARS, regional brain activity (MRI)	ICARS scores decreased in the rTMS group with increased ALFF in the posterior cerebellar lobe and cerebellar tonsil

The target location of bilateral cerebellum: 4-cm right cerebellum from the inion and the left cerebellum from the inion.

ALFF = amplitude of low-frequency fluctuation; BBS = Berg Balance score; bil = bilateral; CCAS = the Cerebellar Cognitive Affective syndrome; iBTS = intermittent theta burst stimulation; ICARS = International Cooperative Ataxia Rating Scale; LF = low-frequency; MRI = magnetic resonance imaging; PRT = PATA Rate Test; RMT = resting motor threshold; rTMS = repetitive transcranial magnetic stimulation; SARA = Scale for Assessment and Rating of Ataxia; SCA = spinocerebellar ataxia; TUG = Timed Up-and-Go test.

Fig. 2 Risk of bias graph and summary. The bias assessment for each study is presented, with green, yellow, and red indicating low, unclear, and high risk of bias, respectively. One study employed a single-blind design, and some studies raised some concerns due to the lack of clarity regarding allocation concealment. In addition, some studies noted incomplete outcome assessments. Finally, one study had a significant difference between the control and rTMS groups. rTMS = repetitive transcranial magnetic stimulation.

3.2. Meta-analysis

We studied SARA and ICARS as the primary motor function outcome after rTMS treatment. For the SARA scores, six studies including 190 patients were considered to report changes in total SARA scores. The results indicated a significant reduction, with an MD of –1.56 (95% CI, –2.88 to –0.24; $p = 0.02$) in the rTMS stimulation condition compared to sham condition. The I^2 statistic showed uniformity across the studies, with no evidence of heterogeneity ($I^2 = 0\%$; Fig. 3A). Outcomes assessed using the ICARS were reported in five studies involving 201 participants. The meta-analysis demonstrated a significant therapeutic benefit of rTMS in SCA patients, with an MD of –3.16 (95% CI, –3.93 to –2.39; $p < 0.001$) over sham stimulation and low heterogeneity ($I^2 = 28\%$; Fig. 3B). In conclusion, our meta-analysis results showed that both SARA and ICARS scores improved after the rTMS stimulation compared to the sham group. No obvious adverse events were noted in these RCTs.

3.3.Subgroup analysis: Different rTMS protocol comparison

In the SARA subgroup analysis, we evaluated the effects of different rTMS protocol parameters, including LF, HF, and TBS. The overall pooled analysis revealed a statistically significant improvement of SARA scores (MD, –1.67; 95% CI, –2.22 to –1.11; $p < 0.001$) with low heterogeneity ($\chi^2 = 0.31$, df = 6, $p = 1.00$, $I^2 = 0.00\%$) between the overall rTMS stimulation group and the sham group. Regarding the subgroup analysis, the LF protocol showed a significant change compared with the sham group, with an MD of –1.60 (95% CI, –3.06 to –0.13; $p = 0.03$) and no heterogeneity ($\chi^2 = 0.26$, df = 3, $p = 0.97$, $I^2 = 0\%$). The HF protocol, assessed in a single study, yielded a reduced but nonsignificant change (MD, –1.52; 95% CI, –6.34 to 3.30; $p = 0.54$) when compared with the sham group. For iTBS, although only two studies were included after inclusion criteria, a significant change was observed, with an MD of –1.68 (95% CI, –2.29 to –1.08; $p < 0.001$) and no heterogeneity ($\chi^2 = 0.04$, df = 1, $p = 0.85$, $I^2 = 0\%$) when compared with the sham group (Fig. 4). Notably, as no studies utilized continuous theta burst stimulation (cTBS) for SCA patients, we only enrolled iTBS in our meta-analysis.

In the ICARS subgroup analysis, we evaluated the effects of different rTMS protocol parameters, including LF and HF. Notably, no studies utilizing TBS were identified, and only one study was identified in the HF subgroup. The total pooled

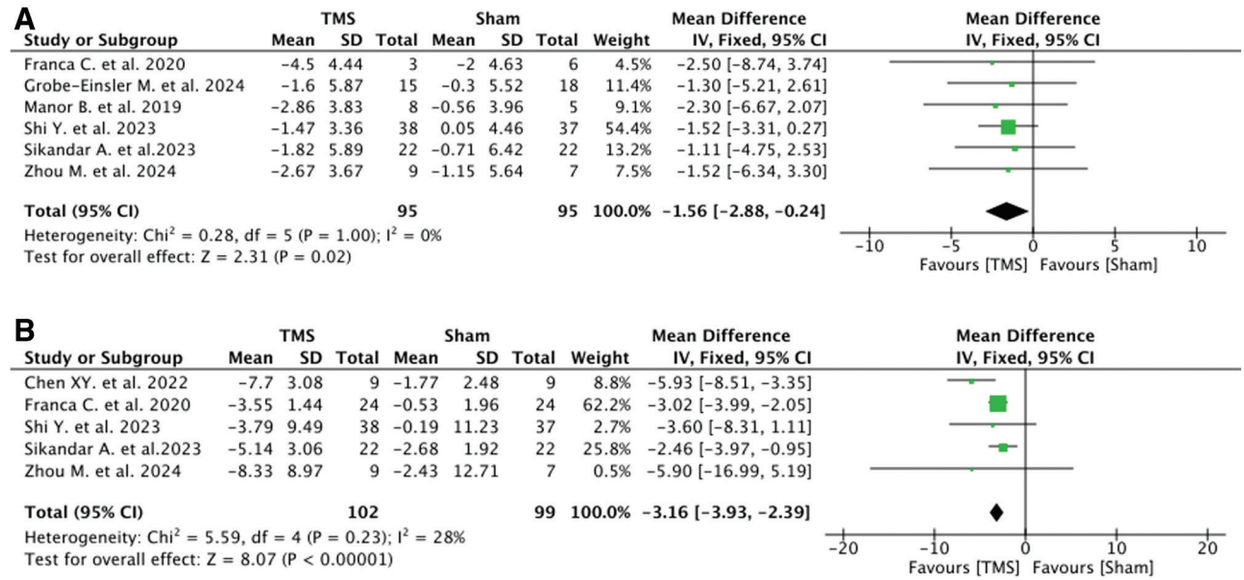

Fig. 3 Forest plot for meta-analytic estimates of post-rTMS changes in scale for the SARA and ICARS. A, The results of post-rTMS changes in scale for the SARA, (B) the results of post-rTMS changes in scale for the ICARS. ICARS = International Cooperative Ataxia Rating Scale; rTMS = repetitive transcranial magnetic stimulation; SARA = Scale for Assessment and Rating of Ataxia.

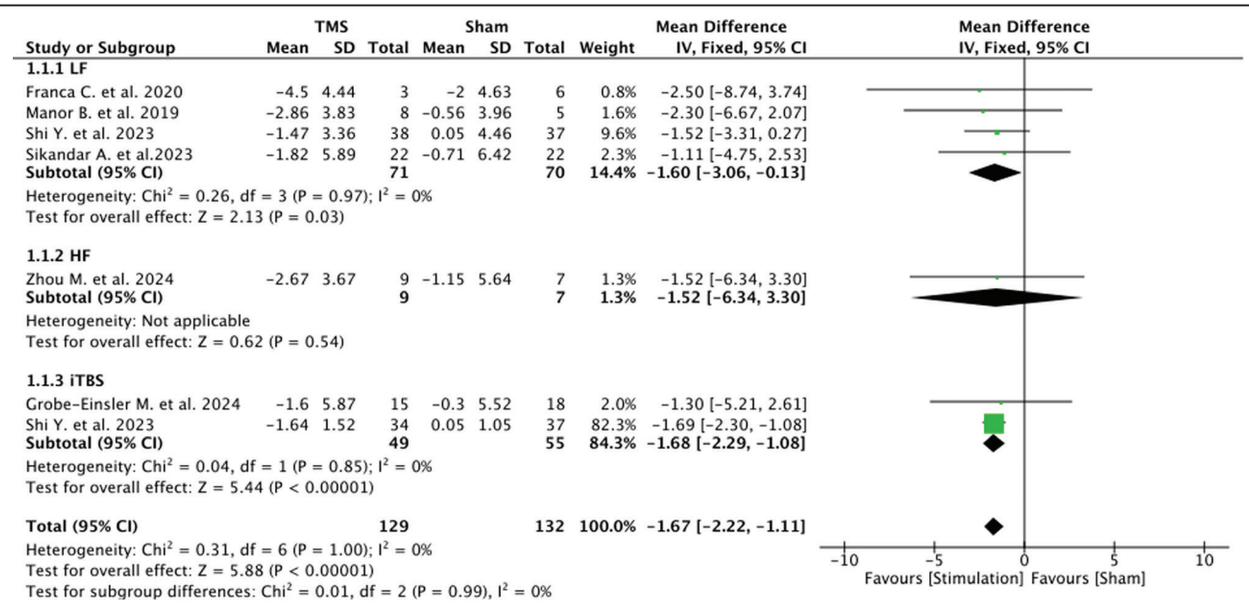

Fig. 4 Forest plot for meta-analytic estimates of post-rTMS changes in SARA subgroup: LF, HF, and iTBS. The results of post-rTMS changes in scale for the SARA subgroup according to LF (1.1.1), HF (1.1.2), and iTBS (1.1.3) as well as the overall effect of rTMS. HF = high-frequency; iTBS = intermittent theta burst stimulation; LF = low-frequency; rTMS = repetitive transcranial magnetic stimulation; SARA = Scale for Assessment and Rating of Ataxia.

analysis revealed a statistically significant improvement of ICARS scores (MD, −3.34; 95% CI, −4.47 to −2.22; $p = 0.007$) with low heterogeneity ($\tau^2 = 0.45$, $\chi^2 = 5.59$, df = 4, $p = 0.23$, $I^2 = 28\%$) between the overall rTMS stimulation group and the sham group. Regarding the subgroup analysis, the LF protocol showed a significant change with an MD of −3.37 (95% CI, −4.63 to −2.11; $p = 0.01$) and low heterogeneity ($\tau^2 = 0.68$, $\chi^2 = 5.35$, df = 3, $p = 0.15$, $I^2 = 44\%$). The HF protocol, assessed in a single study, yielded a reduced but nonsignificant change (MD = −5.90, 95% CI, −16.99 to 5.19, $p = 0.30$; Fig. 5).

In conclusion, the LF inhibitory stimulation showed a significant effect for both SARA and ICARS motor outcomes for SCA patients whereas the HF excitatory stimulation showed an improving trend without significance due to finding only one RCT. Regarding the TBS, although only two qualified randomized studies of iTBS excitatory stimulation were pooled into our meta-analysis, the results showed the potential effects for the motor functions mainly in SCA3 patients. In addition, no adverse events were reported across these trials, consistent with the well-established safety profile of rTMS when administered according to standard protocols.

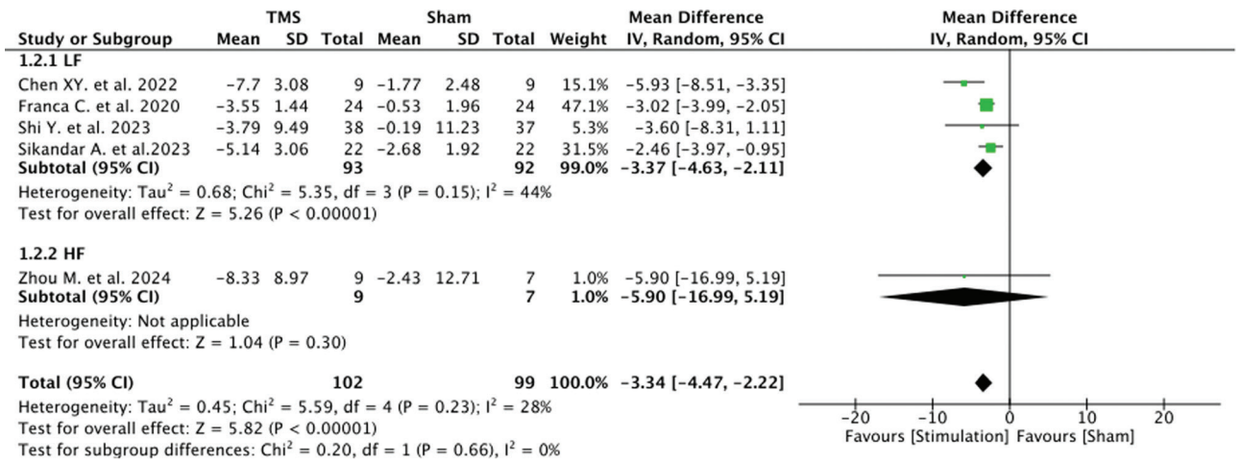

Fig. 5 Forest plot for meta-analytic estimates of post-rTMS changes in ICARS subgroup: LF and HF. The results of post-rTMS changes in scale for the ICARS subgroup according to LF (1.2.1), HF (1.2.2), and iTBS (1.2.3) as well as the overall effect of rTMS. HF = high-frequency; ICARS = International Cooperative Ataxia Rating Scale; iTBS = intermittent theta burst stimulation; LF = low-frequency; rTMS = repetitive transcranial magnetic stimulation.

4. DISCUSSION

This study presents a systematic review and meta-analysis evaluating the effects of rTMS as a treatment for SCA patients. Our findings demonstrate that rTMS has a significant impact on improving motor outcomes in SCA patients. The results highlight rTMS as a promising therapeutic approach for mitigating motor symptoms in hereditary SCA. Our study is the first systematic review of different TBS protocols in SCA patients and included the latest studies within 1 year.[32,38,39] However, the annual progression rate of SARA scores varies across SCA subtypes due to genetic heterogeneity,[8,10,40–42] necessitating careful consideration of subtype-specific responses to rTMS. Among the studies included in our analysis, most patients were diagnosed with SCA3, which has an annual SARA progression rate of 0.65 to 1.61.[8,40,42,43] Notably, our meta-analysis revealed a mean reduction of 1.56 points in SARA scores following rTMS, exceeding the natural progression rate. This suggests that rTMS alleviates motor symptoms of disease progression.

The cerebellum, traditionally regarded as controlling the motor coordination function, is now recognized as playing a significant role in cognitive processes. Functional imaging studies[44–46] and clinical observations[47–50] have found that patients with cerebellar damage experience impairments in executive function, spatial awareness, emotions, and language, leading to the definition of the cerebellar cognitive affective syndrome (CCAS).[47,51] Despite this expanded understanding, most clinical studies on SCA continue to rely on motor-centric outcome measures, such as the SARA and the ICARS scores. To fully capture the spectrum of SCA symptoms, non-motor outcome assessments like the CCAS scale[47,51] or the Cerebellar Impulsivity–Compulsivity Assessment scale (CIA)[52] can be incorporated into future clinical trials. Indeed, future clinical studies on SCA should prioritize the development and integration of more sensitive tools for assessing both motor and non-motor symptoms to provide a comprehensive evaluation of therapeutic efficacy.

Our findings demonstrated that both inhibitory LF stimulation and excitatory iTBS may improve motor function in SCA patients, particularly SCA3. LF stimulation is typically associated with LTD in the cerebellum,[53] whereas HF stimulation and iTBS promote LTP in presynaptic neurons.[54,55] Interestingly, motor-evoked potential (MEP) responses, modulated by the dentato-thalamo-cortical (DTC) pathway, differ based on the stimulation protocol: MEPs exhibit distinct responses to different stimulation protocols, decreasing after continuous cTBS but increasing with LF or iTBS.[56–59] These outcomes are closely tied to the function of Purkinje cells, which govern the DTC pathway. By coordinating the firing patterns of cerebellar nuclei cells, Purkinje cells establish precise timing that is critical for effective motor control and modulation.[60,61] These results support the concept of cerebellar plasticity,[62] highlighting the cerebellum's capacity for adaptation and reorganization in response to external stimulation. Despite these insights, the specific mechanisms through which rTMS protocols modulate activity in the cerebellum and its connected networks remain unclear. To address this gap, future research should combine rTMS with advanced neuroimaging techniques, such as magnetic resonance spectroscopy (MRS), and electrophysiological tools to deepen our understanding of cerebellar function in SCA and elucidate the mechanisms underlying rTMS effects.[63,64]

Our studies have some limitations. The first limitation is the small sample size of the enrolled randomized controlled studies: only one RCT for the HF group and two RCTs for the iTBS group. However, the number of enrolled studies in previous meta-analyses on the same topic is less than our study.[11,12,65,66] Second, most of the patients are SCA3; we should cautiously apply this result to all the SCA subtypes. Third, the treatment duration is variable from 5 to 28 days, and most of the studies only measured the short-term effect. Long-term effects of rTMS should be considered in future study designs. Fourth, this study did not incorporate wearable sensors, which is a possible clinical assessment for SCA patients.[67,68] Finally, the lack of non-motor outcome measures in the included studies limited our ability to capture the full clinical spectrum of SCA symptoms. Future research should incorporate assessments such as the CCAS,[47,51] CIA scores,[52] and the PROM-ataxia[69] to better evaluate non-motor symptoms.

Despite these limitations, our study provides valuable insights into the efficacy of rTMS protocols for treating SCA. These findings contribute to the growing body of evidence supporting the use of rTMS as a therapeutic option and underscore the need for further studies to refine and expand its application in SCA management.

Our study informs stratified treatment approaches based on genetic subtypes, with SCA3 patients potentially prioritized for rTMS interventions. Future clinical protocols should consider personalized stimulation parameters, with the potential for optimization based on individual cerebellar network connectivity patterns assessed through functional neuroimaging. Critically, magnetic resonance imaging (MRI)–guided neuronavigation

should be incorporated into treatment protocols, as it has been demonstrated to be the most precise method for localizing and positioning rTMS coils to targets,[70] with evidence suggesting it contributes to improved clinical response rates.[71,72] The implementation of rTMS in standard care pathways would require the development of standardized protocols addressing stimulation parameters (frequency, intensity, duration), treatment schedules (daily vs intermittent), and maintenance regimens to sustain therapeutic benefits. Furthermore, our findings highlight the need for specialized neuromodulation facilities with expertise in cerebellar stimulation techniques for SCA patients.

In conclusion, to assess the therapeutic potential of rTMS in SCA patients, we conducted a systematic review and meta-analysis. Our analysis revealed statistically significant improvements in motor function following rTMS compared to sham interventions. These results support the potential of rTMS as a therapeutic strategy for mitigating motor symptoms in patients with hereditary SCA. These findings align with the concept of cerebellar plasticity,[62] supporting the idea that the cerebellum can adapt and reorganize in response to external stimulation. Further research is required to elucidate the underlying neural mechanisms[63] and their relationship with cerebellar neuromodulation, which may pave the way for novel therapeutic applications.

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REFERENCES

1. Soong BW, Morrison PJ. Spinocerebellar ataxias. *Handb Clin Neurol* 2018;155:143–74.
2. Kuo SH. Ataxia. *Continuum (Minneap Minn)* 2019;25:1036–54.
3. Sullivan R, Yau WY, O'Connor E, Houlden H. Spinocerebellar ataxia: an update. *J Neurol* 2019;266:533–44.
4. Klockgether T, Mariotti C, Paulson HL. Spinocerebellar ataxia. *Nat Rev Dis Primers* 2019;5:24.
5. Schöls L, Bauer P, Schmidt T, Schulte T, Riess O. Autosomal dominant cerebellar ataxias: clinical features, genetics, and pathogenesis. *Lancet Neurol* 2004;3:291–304.
6. Ruano L, Melo C, Silva MC, Coutinho P. The global epidemiology of hereditary ataxia and spastic paraplegia: a systematic review of prevalence studies. *Neuroepidemiology* 2014;42:174–83.
7. Soong BW, Paulson HL. Spinocerebellar ataxias: an update. *Curr Opin Neurol* 2007;20:438–46.
8. Lin YC, Lee YC, Hsu TY, Liao YC, Soong BW. Comparable progression of spinocerebellar ataxias between Caucasians and Chinese. *Parkinsonism Relat Disord* 2019;62:156–62.
9. Maruyama H, Izumi Y, Morino H, Oda M, Toji H, Nakamura S, et al. Difference in disease-free survival curve and regional distribution according to subtype of spinocerebellar ataxia: a study of 1,286 Japanese patients. *Am J Med Genet* 2002;114:578–83.
10. Jacobi H, Bauer P, Giunti P, Labrum R, Sweeney MG, Charles P, et al. The natural history of spinocerebellar ataxia type 1, 2, 3, and 6: a 2-year follow-up study. *Neurology* 2011;77:1035–41.
11. Qiu M, Wang R, Shen Y, Hu Z, Zhang Y. Efficacy and safety of repetitive transcranial magnetic stimulation in spinocerebellar ataxia type 3: a systematic review and meta-analysis of randomized controlled trials. *Cerebellum* 2024;23:1604–13.
12. Liu Y, Ma Y, Zhang J, Yan X, Ouyang Y. Effects of non-invasive brain stimulation on hereditary ataxia: a systematic review and meta-analysis. *Cerebellum* 2024;23:1614–25.
13. Ciricugno A, Oldrati V, Cattaneo Z, Leggio M, Urgesi C, Olivito G. Cerebellar neurostimulation for boosting social and affective functions: implications for the rehabilitation of hereditary ataxia patients. *Cerebellum* 2024;23:1651–77.
14. Jannati A, Oberman LM, Rotenberg A, Pascual-Leone A. Assessing the mechanisms of brain plasticity by transcranial magnetic stimulation. *Neuropsychopharmacology* 2023;48:191–208.
15. Rizvi S, Khan AM. Use of transcranial magnetic stimulation for depression. *Cureus* 2019;11:e4736.
16. Cox J, Thakur B, Alvarado L, Shokar N, Thompson PM, Dwivedi AK. Repetitive transcranial magnetic stimulation for generalized anxiety and panic disorders: a systematic review and meta-analysis. *Ann Clin Psychiatry* 2022;34:e2–e24.
17. Chou YH, Hickey PT, Sundman M, Song AW, Chen NK. Effects of repetitive transcranial magnetic stimulation on motor symptoms in Parkinson disease: a systematic review and meta-analysis. *JAMA Neurol* 2015;72:432–40.
18. Chou YH, Ton That V, Sundman M. A systematic review and meta-analysis of rTMS effects on cognitive enhancement in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* 2020;86:1–10.
19. Di Lazzaro V, Dileone M, Pilato F, Capone F, Musumeci G, Ranieri F, et al. Modulation of motor cortex neuronal networks by rTMS: comparison of local and remote effects of six different protocols of stimulation. *J Neurophysiol* 2011;105:2150–6.
20. Funke K, Benali A. Cortical cellular actions of transcranial magnetic stimulation. *Restor Neurol Neurosci* 2010;28:399–417.
21. Luo J, Zheng H, Zhang L, Zhang Q, Li L, Pei Z, et al. High-frequency repetitive transcranial magnetic stimulation (rTMS) improves functional recovery by enhancing neurogenesis and activating BDNF/TrkB signaling in ischemic rats. *Int J Mol Sci* 2017;18:455.
22. Lee CW, Chu MC, Wu HF, Chung YJ, Hsieh TH, Chang CY, et al. Different synaptic mechanisms of intermittent and continuous theta-burst stimulations in a severe foot-shock induced and treatment-resistant depression in a rat model. *Exp Neurol* 2023;362:114338.
23. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron* 2005;45:201–6.
24. Brunoni AR, Sampaio-Junior B, Moffa AH, Aparicio LV, Gordon P, Klein I, et al. Noninvasive brain stimulation in psychiatric disorders: a primer. *Braz J Psych* 2019;41:70–81.
25. Yin L, Wang X, Chen L, Liu D, Li H, Liu Z, et al. Repetitive transcranial magnetic stimulation for cerebellar ataxia: a systematic review and meta-analysis. *Front Neurol* 2023;14:1177746.
26. Qiu YT, Chen Y, Tan HX, Su W, Guo QF, Gao Q. Efficacy and safety of repetitive transcranial magnetic stimulation in cerebellar ataxia: a systematic review and meta-analysis. *Cerebellum* 2024;23:243–54.
27. Mendlowitz AB, Shanbour A, Downar J, Vila-Rodriguez F, Daskalakis ZJ, Isaranuwatchai W, et al. Implementation of intermittent theta burst stimulation compared to conventional repetitive transcranial magnetic stimulation in patients with treatment resistant depression: a cost analysis. *PLoS One* 2019;14:e0222546.
28. Schmitz-Hubsch T, du Montcel ST, Baliko L, Berciano J, Boesch S, Depondt C, et al. Scale for the assessment and rating of ataxia: development of a new clinical scale. *Neurology* 2006;66:1717–20.
29. Salci Y, Fil A, Keklicek H, Cetin B, Armutlu K, Dolgun A, et al. Validity and reliability of the International Cooperative Ataxia Rating Scale (ICARS) and the Scale for the Assessment and Rating of Ataxia (SARA) in multiple sclerosis patients with ataxia. *Mult Scler Relat Disord* 2017;18:135–40.
30. Chen ML, Lin CC, Rosenthal LS, Opal P, Kuo SH. Rating scales and biomarkers for CAG-repeat spinocerebellar ataxias: implications for therapy development. *J Neurol Sci* 2021;424:117417.
31. Brooker SM, Edamakanti CR, Akasha SM, Kuo SH, Opal P. Spinocerebellar ataxia clinical trials: opportunities and challenges. *Ann Clin Transl Neurol* 2021;8:1543–56.
32. Zhou M, Qiu M, Jin Y, Li D, Tao C, Lou D, et al. Effectiveness of high-frequency repetitive transcranial magnetic stimulation in patients with spinocerebellar ataxia type 3. *J ECT* 2024;40:15–9.
33. Chen 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;14:827993.
34. Sikandar A, Liu XH, Xu HL, Li Y, Lin YQ, Chen 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;106:105236.
35. Manor B, Greenstein PE, Davila-Perez P, Wakefield S, Zhou J, Pascual-Leone, et al. Repetitive transcranial magnetic stimulation in spinocerebellar ataxia: a pilot randomized controlled trial. *Front Neurol* 2019;10:73.
36. Shi Y, Zou G, Chen Z, Wan L, Peng L, Peng H, et al. Efficacy of cerebellar transcranial magnetic stimulation in spinocerebellar ataxia type 3: a randomized, single-blinded, controlled trial. *J Neurol* 2023;270:5372–9.
37. Franca 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;80:1–6.
38. Grobe-Einsler M, Bork F, Faikus A, Hurlemann R, Kaut O. Effects of cerebellar repetitive transcranial magnetic stimulation plus physiotherapy in spinocerebellar ataxias—a randomized clinical trial. *CNS Neurosci Ther* 2024;30:e14797.
39. Liu X, Zhang L, Xu HL, Liu XH, Sikandar A, Li MC, et al; Members of the Organization in South-East China for Cerebellar Ataxia Research (OSCCAR). Effect of regional brain activity following repeat transcranial magnetic stimulation in SCA3: a secondary analysis of a randomized clinical trial. *Cerebellum* 2024;23:1923–31.
40. Jacobi H, du Montcel ST, Bauer P, Giunti P, Cook A, Labrum R, et al. Long-term disease progression in spinocerebellar ataxia types 1, 2, 3, and 6: a longitudinal cohort study. *Lancet Neurol* 2015;14:1101–8.
41. Yasui K, Yabe I, Yoshida K, Kanai K, Arai K, Ito M, et al. A 3-year cohort study of the natural history of spinocerebellar ataxia type 6 in Japan. *Orphanet J Rare Dis* 2014;9:118.
42. Ashizawa T, Figueroa KP, Perlman SL, Gomez CM, Wilmot GR, Schmahmann JD, et al. Clinical characteristics of patients with spinocerebellar ataxias 1, 2, 3 and 6 in the US: a prospective observational study. *Orphanet J Rare Dis* 2013;8:177.
43. Peng Y, Peng L, Chen Z, Peng H, Wang P, Zhang Y, et al. The natural history of spinocerebellar ataxia type 3 in Mainland China: a 2-year cohort study. *Front Aging Neurosci* 2022;14:917126.
44. Stoodley CJ, Schmahmann JD. Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. *Neuroimage* 2009;44:489–501.
45. Bernard JA, Seidler RD, Hassevoort KM, Benson BL, Welsh RC, Wiggins JL, et al. Resting state cortico-cerebellar functional connectivity networks: a comparison of anatomical and self-organizing map approaches. *Front Neuroanat* 2012;6:31.
46. Buckner RL, Krienen FM, Castellanos A, Diaz JC, Yeo BT. The organization of the human cerebellum estimated by intrinsic functional connectivity. *J Neurophysiol* 2011;106:2322–45.
47. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. *Brain* 1998;121 (Pt 4):561–79.
48. Jacobi H, Faber J, Timmann D, Klockgether T. Update cerebellum and cognition. *J Neurol* 2021;268:3921–5.
49. Amokrane N, Viswanathan A, Freedman S, Yang CY, Desai NA, Pan MK, et al. Impulsivity in cerebellar ataxias: testing the cerebellar reward hypothesis in humans. *Mov Disord* 2020;35:1491–3.
50. Lin YC, Hsu CH, Wang PN, Lin CP, Chang LH. The relationship between zebrin expression and cerebellar functions: insights from neuroimaging studies. *Front Neurol* 2020;11:315.
51. Schmahmann JD. Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. *J Neuropsychiatry Clin Neurosci* 2004;16:367–78.
52. Lin CR, Amokrane N, Chen S, Chen TX, Lai RY, Trinh P, et al. Cerebellar impulsivity-compulsivity assessment scale. *Ann Clin Transl Neurol* 2023;10:48–57.
53. Hirano T. Long-term depression and other synaptic plasticity in the cerebellum. *Proc Jpn Acad Ser B Phys Biol Sci* 2013;89:183–95.
54. Wang DJ, Su LD, Wang YN, Yang D, Sun CL, Zhou L, et al. Long-term potentiation at cerebellar parallel fiber-Purkinje cell synapses requires presynaptic and postsynaptic signaling cascades. *J Neurosci* 2014;34:2355–64.
55. Guerra A, Suppa A, Bologna M, D'Onofrio V, Bianchini E, Brown P, et al. Boosting the LTP-like plasticity effect of intermittent theta-burst stimulation using gamma transcranial alternating current stimulation. *Brain Stimul* 2018;11:734–42.
56. Celnik P. Understanding and modulating motor learning with cerebellar stimulation. *Cerebellum* 2015;14:171–4.
57. Miterko LN, Baker KB, Beckinghausen J, Bradnam LV, Cheng MY, Cooperrider J, et al. Consensus paper: experimental neurostimulation of the cerebellum. *Cerebellum* 2019;18:1064–97.
58. Popa T, Russo M, Meunier S. Long-lasting inhibition of cerebellar output. *Brain Stimul* 2010;3:161–9.
59. Chen Y, Wei QC, Zhang MZ, Xie YJ, Liao LY, Tan HX, et al. Cerebellar intermittent theta-burst stimulation reduces upper limb spasticity after subacute stroke: a randomized controlled trial. *Front Neural Circuits* 2021;15:655502.
60. Gassmann L, Gordon PC, Ziemann U. Assessing effective connectivity of the cerebellum with cerebral cortex using TMS-EEG. *Brain Stimul* 2022;15:1354–69.
61. Tremblay S, Austin D, Hannah R, Rothwell JC. Non-invasive brain stimulation as a tool to study cerebellar-M1 interactions in humans. *Cerebellum Ataxias* 2016;3:19.
62. Mitoma H, Buffo A, Gelfo F, Guell X, Fuca E, Kakei S, et al. Consensus paper. Cerebellar reserve: from cerebellar physiology to cerebellar disorders. *Cerebellum* 2020;19:131–53.
63. Hawkes R. Purkinje cell stripes and long-term depression at the parallel fiber-Purkinje cell synapse. *Front Syst Neurosci* 2014;8:41.
64. Azevedo FA, Carvalho LR, Grinberg LT, Farfel JM, Ferretti RE, Leite RE, et al. Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. *J Comp Neurol* 2009;513:532–41.
65. Billeri L, Naro A. A narrative review on non-invasive stimulation of the cerebellum in neurological diseases. *Neurol Sci* 2021;42:2191–209.
66. Wang Y, Zhang D, Wang J, Ma J, Lu L, Jin S. Effects of transcranial magnetic stimulation on cerebellar ataxia: a systematic review and meta-analysis. *Front Neurol* 2023;14:1049813.
67. Shah VV, Rodriguez-Labrada R, Horak FB, McNames J, Casey H, Hansson Floyd K, et al. Gait variability in spinocerebellar ataxia assessed using wearable inertial sensors. *Mov Disord* 2021;36:2922–31.
68. Zhou H, Nguyen H, Enriquez A, Morsy L, Curtis M, Piser T, et al. Assessment of gait and balance impairment in people with spinocerebellar ataxia using wearable sensors. *Neurol Sci* 2022;43:2589–99.
69. Schmahmann JD, Pierce S, MacMore J, L'Italien GJ. Development and validation of a patient-reported outcome measure of ataxia. *Mov Disord* 2021;36:2367–77.
70. Sack AT, Cohen Kadosh R, Schuhmann T, Moerel M, Walsh V, Goebel R. Optimizing functional accuracy of TMS in cognitive studies: a comparison of methods. *J Cogn Neurosci* 2009;21:207–21.
71. Downar J, Daskalakis ZJ. New targets for rTMS in depression: a review of convergent evidence. *Brain Stimul* 2013;6:231–40.
72. Burns MR, Hermiller MS. Quantifying and reporting the precision of transcranial magnetic stimulation targeting. *Brain Res* 2025;1849:149350.