Trials

STUDY PROTOCOL

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A multi-center, randomized, double-blind, sham-stimulation controlled study of transcranial magnetic stimulation with precision navigation for the treatment of multiple system atrophy

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Abstract

Background Multiple system atrophy (MSA) is recognized as an atypical Parkinsonian syndrome, distinguished by a more rapid progression than that observed in Parkinson's disease. Unfortunately, the prognosis for MSA remains poor, with a notable absence of globally recognized effective treatments. Although preliminary studies suggest that transcranial magnetic stimulation (TMS) could potentially alleviate clinical symptoms in MSA patients, there is a significant gap in the literature regarding the optimal stimulation parameters. Furthermore, the field lacks consensus due to the paucity of robust, large-scale, multicenter trials.

Methods This investigation is a multi-center, randomized, double-blind, sham-controlled trial. We aim to enroll 96 individuals diagnosed with MSA, categorized into Parkinsonian type (MSA-P) and cerebellar type (MSA-C) according to their predominant clinical features. Participants will be randomly allocated in a 1:1 ratio to either the TMS or sham stimulation group. Utilizing advanced navigation techniques, we will ensure precise targeting for the intervention, applying theta burst stimulation (TBS). To assess the efficacy of TBS on both motor and non-motor functions, a comprehensive evaluation will be conducted using internationally recognized clinical scales and gait analysis. To objectively assess changes in brain connectivity, functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) will be employed as sensitive indicators before and after the intervention.

Discussion The primary aim of this study is to ascertain whether TBS can alleviate both motor and non-motor symptoms in patients with MSA. Additionally, a critical component of our research involves elucidating the underlying mechanisms through which TBS exerts its potential therapeutic effects.

Ethics and dissemination All study protocols have been reviewed and approved by the First Affiliated Medical Ethics Committee of the Air Force Military Medical University (KY20232118-F-1).

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Trial registration Chinese Clinical Trial Registry ChiCTR2300072658. Registered on 20 June 2023.

Keywords Multiple system atrophy, Transcranial magnetic stimulation, Electroencephalography, Magnetic resonance imaging, Gait analysis

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

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Role of sponsor {5c}	The principal investigator (PI) is instrumental in every phase of the study, encompassing study design, data collection, management, analysis, and interpretation. The PI also assumes responsibility for drafting the research report and overseeing the manuscript's publication process. This trial is investigator-initiated, with the PI serving as the sponsor. It is financed by a school project, indicating that no external funding sources are involved.

Introduction

Background and rationale {6a}

Multiple system atrophy (MSA) is an atypical Parkinsonism (AP) distinguished by a constellation of symptoms including severe autonomic dysfunction, Parkinsonian manifestations, ataxia, and pyramidal tract involvement. Clinically, it is categorized into two subtypes based on the predominant symptoms: the Parkinsonian type (MSA-P) and the cerebellar type (MSA-C) [1]. With an estimated incidence of 0.6–0.7 per 100,000 individuals, MSA is a rare neurological disorder typically presenting around the age of 55. The prognosis is moderate, with an average survival span of 6–10 years post-diagnosis, although some patients may survive up to 15 years [2–5]. The financial implications of MSA are considerable. According to a 2011 survey, the 6-month treatment costs for MSA patients were notably high, with variations across countries: €28,924 in France, €25,645 in Germany, and €19,103 in the UK [6]. The disease's progression often results in the loss of independent ambulation within a few years, significantly diminishing the quality of life and compressing the survival timeline. The current standard of care is symptomatic treatment, and there is an absence of effective pharmacological or procedural interventions. Notably, therapies effective in Parkinson's disease, such as levodopa and deep brain stimulation, have demonstrated limited efficacy in MSA [7–11]. Given the paucity of effective treatments, there is an imperative to explore innovative therapeutic strategies, with a particular focus on noninvasive options. Such advancements could potentially prolong survival, ameliorate the quality of life for MSA patients, and mitigate the economic burden borne by individuals, families, and society at large.

Transcranial magnetic stimulation (TMS) is recognized as a safe and efficacious non-invasive technique for nerve stimulation, extensively utilized in both the research and clinical treatment of a spectrum of neurological and psychiatric disorders [12, 13]. While the precise mechanisms of TMS remain to be fully elucidated, it is postulated that TMS exerts its effects by modulating cerebral blood flow, the metabolic milieu, and directly influencing the excitability of the targeted cortical areas and their interconnected networks. This modulation is believed to impact synaptic plasticity and, consequently, alter brain functional connectivity [14, 15]. At the cellular and molecular levels, TMS is capable of modulating synaptic structure and functional plasticity through its effects on neuronal morphology, glutamate receptors, and neurotransmitter activity. Additionally, TMS exerts regulatory influence on the expression of brain-derived neurotrophic factor (BDNF), which in turn modulates the expression of synaptic-associated proteins, ultimately shaping synaptic plasticity [16–18]. Synaptic long-term potentiation (LTP), indicative of enhanced synaptic strength, is typically induced by high-frequency TMS stimulation (>1 Hz), whereas low-frequency TMS stimulation (≤1 Hz) is associated with long-term depression (LTD), reflecting a reduction in synaptic efficacy [15, 19–21]. These frequency-dependent effects underscore the potential of TMS to facilitate or inhibit synaptic changes, thereby offering a therapeutic avenue for modulating neural circuits implicated in various pathophysiological conditions. Theta burst stimulation (TBS), a variant of repetitive transcranial magnetic stimulation (rTMS), offers distinct advantages in terms of efficiency and efficacy. intermittent theta burst stimulation (iTBS) is recognized for its ability to enhance neuronal excitability, potentially facilitating therapeutic effects in various conditions. Conversely, continuous theta burst stimulation (cTBS) effectively reduces neuronal excitability. It is of note that the plasticity mechanisms of the cerebellum appear to differ from those of the motor cortex. rTMS at 1 Hz targeting the parallel fibers-Purkinje cell synapses in the cerebellum can induce LTP [22, 23]. Therefore, we hypothesize that the neural regulation within the cerebellum may exhibit opposite effects when subjected to the same modulatory approach as the motor cortex. Of course, this hypothesis necessitates further validation through animal experiments and at the cellular and molecular levels of investigation. Published research underscores the benefits of TBS, including a shorter stimulation duration compared to rTMS, a more enduring impact on neurophysiological states, and a closer resemblance to the natural fluctuations of brain activity. These attributes render TBS particularly advantageous in the context of neurological and psychiatric disorders. Moreover, application of TBS has been associated with a minimal incidence of adverse effects, broadening its therapeutic potential [24–28].

In 2019, the International Parkinson and Movement Disorder Society published research progress on the use of transcranial magnetic stimulation (TMS) for the treatment of movement disorders, demonstrating that TMS can ameliorate the motor symptoms and depressive conditions associated with Parkinson's disease. However, the therapeutic efficacy of TMS on other movement disorders requires further exploration [29]. Based on the currently published studies, MSA, as a subtype of the Parkinsonian syndrome, may also benefit from TMS treatment.

It has been found that TMS can not only improve motor symptoms such as parkinsonism-like and ataxia, but also improve non-motor symptoms such as anxiety and depression. But there is a lack of high-quality multicenter clinical studies to confirm it. At present, there is no consensus on the therapeutic targets for TMS treatment in MSA. In the following discussion, we categorize the research into three main areas: targeting the primary motor cortex, cerebellar targeting, and studies focusing on non-motor symptoms, which will be addressed separately.

During the stage of employing TMS as a research tool, it has been observed that in MSA patients, even with the administration of levodopa, the levels of MEPs exhibit a sustained decrease following the second stimulus when compared to PD patients. This finding suggests a persistent cortical inhibition in MSA patients relative to those with PD [30]. Kawashima et al. utilized paired associative stimulation (PAS) to investigate MEP amplitudes in 10 patients with PD and 10 with MSA-P. The study revealed that dopaminergic therapy in MSA-P patients did not restore the PAS-induced increase in MEP amplitudes. These findings suggest that corticostriatal circuit activation may play a significant role in the cortical plasticity of the human M1 [31]. These findings provide a basis for the therapeutic targeting of M1 with TMS in MSA. Liu Z et al. [32] found that 5 Hz TMS stimulation of M1 and the cerebellum increases the complexity of the brain's resting state in MSA patients and reduces the severity of motor impairments. Han Wang et al. [33] applied 5 Hz rTMS targeting the M1 in MSA-P patients, with a sham stimulation as control. The study found that high-frequency rTMS ameliorated motor symptoms in MSA and, using task-based fMRI, revealed increased cerebellar activation. Ying-hui Chou et al. [34] demonstrated that 5 Hz rTMS over the M1 region may ameliorate

motor symptoms by modulating functional connectivity within the default mode, cerebellar, and limbic networks. Therefore, it can be inferred that high-frequency TMS targeted at the M1 region may alleviate the symptoms of MSA.

According to published research results, there is controversy surrounding cerebellar-targeted TMS treatment. The 2014 non-invasive cerebellar neuromodulation consensus indicates that cerebellar TMS is an effective method for evaluating the function of the cerebellar-thalamocortical circuit and studying the pathophysiology of ataxia [35]. Low-frequency TMS targeting the cerebellum can reduce the Scale for Assessment and Rating of Ataxia, (SARA) and the International Cooperative Ataxia Rating Scale(ICARS) scores of patients with MSA-C [36]. A double-blind, prospective, randomized, sham-controlled trial involving 18 patients with spinocerebellar ataxia type 3 observed improvements in ICARS scores post-treatment. Additionally, analysis of magnetic resonance spectroscopy (MRS) before and after treatment indicated enhancements in cerebellar local metabolism and microenvironment [37]. Although MSA-C differs etiologically from spinocerebellar ataxia, a shared pathophysiological basis may underlie the ataxia they induce [38]. Interestingly, iTBS with activating effects can also improve motor imbalance in MSA by modulating cerebello-cortical plasticity [39]. Despite the use of opposing stimulation paradigms in these studies, both appear to exert therapeutic effects on MSA. We speculate that the pathways through which these two distinct modes act may differ and warrant further investigation.

In addition to improving motor symptoms in MSA, TMS seems to have some efficacy in non-motor symptoms. Chou et al. [40] used HF-rTMS to stimulate M1 in patients with MSA-P. And found that the functional connectivity of edge networks was increased. This may be noticed as an improvement of some non-motor symptoms (e.g., orthostatic hypotension or urinary and bowel dysfunction). Although the improvement effect of TMS on autonomic symptoms needs to be further confirmed, the study provides new ideas for this. Additionally, high-frequency stimulation of the left dorsolateral prefrontal cortex may ameliorate fatigue in MSA patients [41] Unilateral cerebellar low-frequency stimulation may aid in improving cognition in MSA patients [36]. These findings provide a foundation for the treatment of non-motor symptoms in MSA.

The existed researches are mostly small-sample, single-center studies; the determination of stimulation intensity and mode is ambiguous; the target localization is not accurate enough; the treatment plan lacks a unified standard; and no in-depth mechanistic exploration is performed. Therefore, it is necessary to further carry out high-quality multi-center clinical studies to clarify its effect and explore its mechanism in order to provide a scientific clinical basis for TMS in the treatment of MSA.

Objectives {7}

This investigation employs a multicenter, randomized, double-blind, sham-stimulation controlled trial to elucidate the impact of TBS on both motor and non-motor functions. Furthermore, the study delves into the underlying mechanisms by assessing the neural connectivity using a synergistic approach that integrates motor evoked potentials (MEPs), electroencephalography (EEG), and functional magnetic resonance imaging (fMRI) data.

Trial design {8}

The present study is designed as a multicenter, randomized, double-blind, sham-stimulation controlled randomized clinical trial (RCT), adhering to the principles outlined in the Declaration of Helsinki. And this is a superiority trial. The RCT will be executed across five distinguished medical centers, namely: The Xijing Hospital and The Tangdu Hospital of the Air Force Military Medical University, Xi'an Central Hospital, Shaanxi Provincial People's Hospital, and the First Affiliated Hospital of Xi'an Jiaotong University. Data collection for this trial spanned from January 2023 to December 2025. Informed consent will be obtained from all participants prior to their enrollment in the study. The study protocols have been reviewed and granted approval by the Ethics Committee of the First Affiliated Hospital of the Air Force Military Medical University, with the reference number KY20232118-F-1. The trial has been registered with the China Clinical Trial Registry under the identifier ChiCTR2300072658. The study protocol conforms to the guidelines set forth in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement.

Methods: participants, interventions and outcomes

Study setting {9}

Recruitment details for this randomized controlled trial shall be disseminated via the Xijing Hospital's official communication platform and through informational posters displayed at the outpatient clinics. Eligible patients, conforming to the established inclusion criteria, will be invited to participate in the study at the following institutions: The Xijing Hospital and The Tangdu Hospital of the Air Force Military Medical University, Xi'an Central Hospital, Shaanxi Provincial People's Hospital, and the First Affiliated Hospital of Xi'an Jiaotong University.

Eligibility criteria {10}

Inclusion criteria

1. Participants must fulfill the diagnostic criteria for clinically confirmed and probable MSA as outlined by the Movement Disorder Society (MDS) in 2022, and have been evaluated by physicians with over 5 years of expertise in Parkinson's disease and dyskinesia;
2. Participants should provide a detailed and reliable recollection of their medical history;
3. Participants must sign the informed consent form, indicating voluntary participation and understanding of the study's nature, procedures, benefits, and risks.

Exclusion criteria

1. Presence of other chronic, progressive neurodegenerative disorders;
2. Individuals with concurrent medical conditions and severe comorbidities;
3. Etiological factors of limb movement disorders unrelated to the study's focus or those that may confound the assessment of the primary condition;
4. Contraindications for TMS treatment, including (i) absolute contraindications, such as the presence of metallic or electronic devices in proximity to the stimulation coil, including but not limited to cochlear implants, cardiac pacemakers, and medical infusion pumps; (ii) relative contraindications encompassing conditions that pose a risk of seizure induction or other unforeseen risks, for instance (A) a history of epilepsy; (B) conditions such as traumatic brain injury, intracranial tumors, encephalitis, cerebrovascular accidents, and cerebral metabolic disorders; (C) Use of medications known to reduce the seizure threshold without concurrent anticonvulsant therapy; and (D) states of sleep deprivation, circadian rhythm disruption, intoxication, or extreme fatigue. (iii) Factors that elevate risk and introduce uncertainty, such as (A) the presence of intracranial electrodes; (B) pregnancy; and (C) severe or recent cardiovascular diseases;
5. Patient contraindications for MRI scanning, including the presence of metallic implants or other conditions precluding cooperation with the imaging procedure.

Dropout criteria

1. Incapacitating or severe adverse reactions encountered during the treatment phase;
2. Concurrent engagement in other physical therapeutic interventions;
3. Demonstrated non-adherence to the treatment protocol;
4. Subject's voluntary giving up to continue with the treatment protocol.

Who will take informed consent? {26a}

Prior to commencing the trial, all prospective participants must receive a comprehensive disclosure from the subject screening personnel, who are qualified clinicians, detailing the study's objectives, anticipated benefits, and potential risks associated with their involvement. Following this informed discussion, participants are required to provide their consent by signing a written informed consent form, affirming their voluntary agreement to participate in the study.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Informed consent will be secured from each participant regarding the acquisition and utilization of their data within the study. It is important to note that the study protocol does not involve the collection of any biological specimens.

Interventions

Explanation for the choice of comparators {6b}

The control intervention in the experimental design is a sham stimulation procedure, administered at the identical stimulation site, to mitigate the potential influence of placebo effects within the experimental cohort.

Intervention description {11a}

The study is bifurcated into two distinct phases; the initial phase aims to elucidate the clinical efficacy of TBS on patients afflicted with MSA. Participants will be randomly assigned to either the intervention group, receiving active TBS, or the control group, receiving sham stimulation. MRI, integrated with precision navigation systems, will be utilized to facilitate personalized and accurate identification of stimulation targets. Patients diagnosed with MSA-P will be stratified into two cohorts: one receiving iTBS and the other sham stimulation, both utilizing a figure-eight coil configuration. For the iTBS cohort, the target will be the bilateral primary motor cortex (M1) regions. Conversely, the sham group will have the coil inverted by 180° during the intervention, maintaining the same target location. Patients diagnosed with MSA-C will be allocated into two groups: one undergoing cTBS and the other receiving sham stimulation. Owing to the cerebellum's deep anatomical position, a double-cone coil, designed for deeper brain stimulation, will be employed. The cTBS group will

	Study Period				
	Recruitment	Allocation	After Allocation		
Time Point	Day0	Day0	Day1	Day1-10	Day10
Recruitment	x				
Screening	x				
Informed Consent	x				
Other procedures	x				
Allocation		x			
Intervention Measures				▲	
Assessments					
Baseline Assessment [Scale Assessment] [Gait Analysis] [EEG] [fMRI] [MEP]			x		
Outcome Assessment [Scale Assessment] [Gait Analysis] [EEG] [fMRI] [MEP]					x
Adverse Events				x	

Fig. 1 Timeline. Scale Assessment: UMSARS, UPDRS III, ICARS, COMPASS-31, MOCA, MMSE, HAMA, HAMD. *MSA-P* Multiple System Atrophy Parkinsonian type, *MSA-C* Multiple System Atrophy cerebellar type, *MEP* Motor Evoked Potential, *iTBS* Intermittent TBS, *cTBS* Continuous TBS, *EEG* Electroencephalogram, *fMRI* Functional Magnetic Resonance Imaging, *M1* primary motor cortex

target the bilateral cerebellar cortices, whereas the sham group will have the coil positioned 3 cm away from the actual stimulation site during the intervention. The stimulation parameters will be set at 80% of the resting motor threshold (RMT), delivering 1200 pulses per day unilaterally, equating to a total of 2400 pulses per day over a 10-day period. Comparative analysis of motor function scores, non-motor function scores, and gait parameters pre- and post-treatment will ascertain the therapeutic impact of TBS on alleviating MSA symptoms. The second phase of the study is dedicated to investigating the underlying mechanisms by which TBS ameliorates MSA symptoms. Potential mechanisms will be explored through comparative assessments of EEG, MEPs, and fMRI data, both pre- and post-intervention. A schematic of the participant timeline is presented in Fig. 1, while the flowchart illustrating the trial's participant progression is depicted in Fig. 2.

1. Scale assessment

   Motor function will be evaluated using a battery of standardized scales, including the Unified Multiple System Atrophy Rating Scale (UMSARS), the Hoehn & Yahr staging, the Motor Section of the Unified Parkinson's Disease Rating Scale part III (UPDRS III) for MSA-P patients, the International Cooperative Ataxia Rating Scale (ICARS) for MSA-C patients, and the Berg Balance Scale. Non-motor functions will be assessed using a comprehensive set of scales, such as the Composite Autonomic Symptom Score-31 (COMPASS-31) for autonomic symptoms, the Hamilton Depression Scale (HAMD) for depressive symptoms, the Hamilton Anxiety Scale (HAMA) for anxiety symptoms, the Mini-Mental State Examination (MMSE) for cognitive status, and the Montreal Cognitive Assessment (MOCA) for a more detailed cognitive function evaluation. Administration and

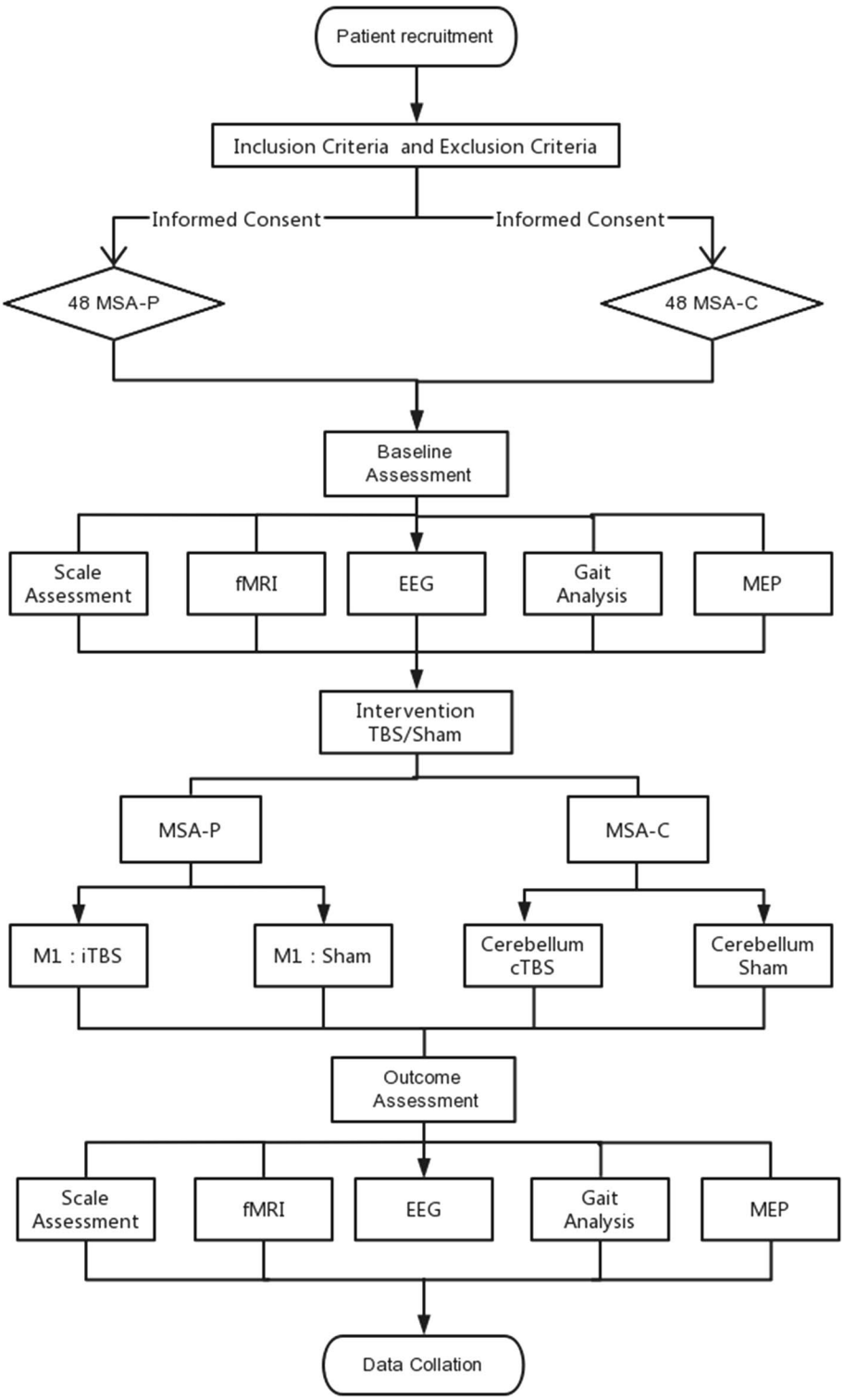

Fig. 2 Flow chart. Scale Assessment: UMSARS, UPDRS III, ICARS, COMPASS-31, MOCA, MMSE, HAMA, HAMD. *MSA-P* Multiple System Atrophy Parkinsonian type, *MSA-C* Multiple System Atrophy cerebellar type, *MEP* Motor Evoked Potential, *iTBS* Intermittent TBS, *cTBS* Continuous TBS, *EEG* Electroencephalogram, *fMRI* Functional Magnetic Resonance Imaging, *M1* primary motor cortex

interpretation of all scales will be conducted by specialized clinicians with expertise in Parkinson's disease and movement disorders, ensuring standardized and reliable assessment procedures.

2. Gait analysis
   The three-dimensional gait analysis system comprises a trolley, host computer, display, high-precision visual sensors, Time-of-Flight (TOF) depth sensors, and proprietary test software. During the execution of standardized evaluative movements, the system employs a high-precision visual sensor in conjunction with an artificial intelligence (AI) algorithm to identify ten anatomical landmarks on the patient's body in real time. Concurrently, the TOF depth sensor establishes a three-dimensional spatial coordinate system that calculates the instantaneous positional data of each skeletal landmark within the 3D space as the subject moves, facilitating precise digital reconstruction. Key gait parameters, including stride length, cadence, amplitude, step width, step height, and stride length variability, are recorded and the data are concurrently relayed to the analytical software for processing and analysis. Gait analysis assessments will be conducted on all participants prior to, and subsequent to, both TMS treatment and sham stimulation, with parameters such as stride amplitude, cadence, gait velocity, gait cycle time, walking phases, and stride length variability being meticulously documented.
3. EEG signal acquisition and analysis
   We will use a German Brain Products Synamps 2 EEG amplifier with a sampling frequency of 16,000 Hz and a 32-electrode conductive cap placed according to the international 10–20 system. The amplifier has a bandwidth of 800 Hz, a 16-bit digital-to-analog converter, and a signal noise level of ≤ 1 μVpp. It features a low-pass filter at 1000 Hz and a high-pass filter at 0.016 Hz. The reference electrode is placed overhead, and electrode impedance was maintained below 20 KΩ throughout the experiment. EEG data are analyzed by two independent EEG experts blinded to the patients' clinical data.
   EEG data preprocessing will be performed using EEGLAB (v14.1.2) [42]. We will apply a bandpass filter from 0.5 to 70 Hz and a notch filter at 50 Hz to remove noise and industrial frequency interference [43, 44]. Contaminated EEG channels will be corrected using spherical interpolation. Independent component analysis will be used to remove artifacts caused by eye movements and heartbeats from the EEG signal. Finally, all EEG channels will be averaged and re-referenced.
   Network connectivity analysis will be conducted on the artifact-free EEG channels post-preprocessing. To mitigate pseudo-connections arising from volume conduction through the head, we will compute network connectivity in delta (4–7 Hz), theta (8–12 Hz), alpha (13–30 Hz), beta, and gamma (30–70 Hz) sub-bands using a phase-based phase lag index method. Furthermore, we will investigate the alterations induced by TBS on various sub-band brain networks and their correlation with assessment scales. In addition, we will employ short-time Fourier transform (STFT) to transition EEG signals from the time domain to the time–frequency domain, enabling the construction of directed time-varying EEG networks and the determination of their causal interactions.
4. Functional MRI scans and data analysis
   All functional brain MRI images will be acquired using a 3.0 T GE imaging system with an 8-channel phased-array head coil (Erlangen, Germany). Each enrolled patient will undergo 3D high-resolution T1-weighted imaging (T1WI) and BOLD-fMRI scans. For 3D high-resolution T1WI, high-resolution 3D T1-weighted structural images will be acquired with whole-brain sagittal imaging. The scanning parameters are as follows: TR/TE = 7.8 ms/3 ms, FOV: 256 mm × 256 mm^3, matrix: 256 × 256, NEX: 1, slice thickness: 1 mm, no gap, bandwidth: 31.25 Hz, flip angle (FA) = 12°, inversion time: 450 ms, scan time: 208 s, with 196 images acquired. After acquiring T2 FLAIR and T1WI images, an experienced diagnostic radiologist will review them to assess for intracranial organic lesions. Subjects with significant lesions will be excluded from the study. Resting-state BOLD-fMRI images will be acquired using echo-planar imaging (EPI) with the following parameters: TR: 2000 ms, TE: 40 ms, 33 slices, 4 mm slice thickness, no gap, FA: 90°, FOV: 240 × 240, matrix: 64 × 64, with a total of 21 time points. The scanning time will be 7 min, resulting in 9650 images acquired.
   Magnetic resonance data preprocessing will primarily utilize SPM12 and Matlab (The MathWorks, Natick, MA, USA). Following slice timing correction, all images will undergo rigid transformation to align with the initial image. Head motion detection will be conducted, and image slices with head translation or rotation exceeding 2 mm will be excluded. Subsequently, spatial normalization will be performed by aligning the resting-state image with the structural image, followed by alignment of the aligned structural image with the standard space to obtain the corresponding transform. This transform will then be applied to the resting-state MR image to align it with the standard space. Functional MR images will

Table 1 Stimulation parameters

Mode	Intensity	IntraPlexus frequency	IntraPlexus number	Interplexus frequency	Interplexus number	Stimulus time	Plexus interval	Repetition	Total pulses	Total time
iTBS	80% RMT	50 HZ	3	5 HZ	10	2 s	8 s	40	1200	4 min
cTBS	80% RMT	50 HZ	3	5 HZ	200	40 s	0	2	1200	1 min

be smoothed using a 6 mm half-height wide Gaussian kernel to improve the image signal-to-noise ratio. In the functional connectivity analysis, additional steps to mitigate the effects of interfering signals will be employed. These include de-linearization drift, low-pass filtering (frequency band 0.01–0.08 Hz), and removal of other covariates (six head movement parameters, white matter, cerebrospinal fluid, and whole-brain covariates) that could influence the results.

Functional connectivity analysis and whole-brain functional network construction will involve selecting 90 brain regions from the AAL template (Anatomical Automatic Labeling) as network nodes (45 on each side). The mean time series of each brain region (network node) will be extracted, and Pearson correlation analysis will be conducted between pairs of brain regions to calculate the correlation coefficient for each subject. We will utilize the general linear model (GLM) to compare differences in functional MR brain networks between groups.

5. Neuroimaging navigation
   Participants enrolled will utilize a 3.0-Tesla PHILIPS Ingenia CX 3.0 T scanner to acquire high-resolution imaging data. The resultant MRI T1-weighted images will then be integrated into a state-of-the-art neuroimaging navigation system for the purpose of generating a detailed three-dimensional (3-D) brain reconstruction. Specific targets for stimulation will be delineated within the primary motor cortex (M1) area and the cerebellar hemisphere on the 3-D brain model. The neuroimaging navigation system will facilitate real-time tracking of the transcranial magnetic stimulation (TMS) coil, ensuring precise targeting during the procedure.
6. Transcranial magnetic stimulation
   The investigation will employ a NeuroMS/D stimulator from Neurosoft LLC, Ivanovo, Russia, utilizing either a figure-of-eight coil or a double-cone coil. The RMT will be ascertained for patients undergoing treatment for the first time. With the target muscle, the abductor pollicis brevis, in a relaxed state, the muscle is stimulated on ten occasions to determine the minimum stimulator output intensity required to elicit a MEP amplitude surpassing 50 μV in at least five instances, defining the RMT. Stimulation targets are designated as the primary motor cortex (M1) for MSA-P subtype and the cerebellar hemispheres for MSA-C subtype. The stimulus intensity is set at 80% of the individual's RMT. The protocol mandates a total of ten treatment sessions, delivering 2400 pulses Per treatment (1200 pulses per hemisphere). Sham stimulation will be executed by flipping the stimulus head 180°for MSA-P, or 3 cm away from the intended stimulation site for MSA-C, while maintaining all other stimulation parameters congruent with the active treatment group. Specific parameter settings are delineated in Table 1.
7. Electromyography (EMG) measurement
   RMTs and MEPs will be recorded utilizing surface electrodes positioned over the right thenar eminence. Surface electrodes for recording will be symmetrically positioned adjacent to the thenar muscle, with reference electrodes located 1 cm away to ensure optimal signal acquisition. A ground electrode in the form of a disc will be positioned at the proximal aspect of the radial styloid process to minimize electromagnetic interference with the electromyography (EMG) signals.

Criteria for discontinuing or modifying allocated interventions {11b}

Participants will have the option to discontinue participation or withdraw from the study at any juncture if they encounter disease exacerbation, severe adverse events, or develop intolerance to the treatment, as determined by the principal investigator. Furthermore, participants retain the right to withdraw their consent and exit the study at any time, without detriment to their clinical care, should they elect not to proceed.

Strategies to improve adherence to interventions {11c}

Each clinical site shall furnish a complimentary, tailored treatment plan to address participant concerns, with provisions for continuous monitoring of therapeutic responses and disease progression. A dedicated study coordinator shall be appointed to manage participant follow-up communications. To enhance the follow-up response rate, participants will be requested to supply three distinct contact methods.

Relevant concomitant care permitted or prohibited during the trial {11d}

Basic pharmacological interventions and standard nursing practices will be permitted throughout the trial, with the stipulation that these remain consistent. In the absence of a standardized treatment protocol for Multiple System Atrophy (MSA), this study will draw from clinical experiences as reported by Mayo Clinic in 2021 [45]. The range of therapeutic medications will encompass anti-Parkinsonian agents such as levodopa, medications to ameliorate ataxic symptoms such as buspirone, agents to manage orthostatic hypotension including droxidopa and midodrine, as well as medications for comorbid conditions like hypoglycemics and antihypertensives. A meticulous record of these treatments will be maintained, and it is imperative that the medication regimen remains unchanged for the duration of the trial.

Provisions for post-trial care {30}

Participants will be provided with TMS therapy at no cost. In the event that participants experience any adverse effects associated with the trial, the study protocol will be immediately suspended, and appropriate medical intervention will be promptly offered.

Outcomes {12}

Primary outcome measure

The primary outcome measure will be the UMSRS score.

Secondary outcome measures

Secondary outcomes will encompass a spectrum of assessments, including the UPDRS III for MSA-P, ICARS for MSA-C, EEG, fMRI, MEPs, quantitative gait analysis, the Berg Balance Scale, and COMPASS-31, HAMA, HAMD, MMSE, and MOCA.

Safety and adverse events

Safety monitoring will encompass the surveillance of adverse effects, such as treatment-related dizziness, headache, neck pain, tinnitus, auditory impairment, and seizures. Any adverse reactions must be reported collaboratively by participants and investigators. In the event of serious adverse effects, including seizures, the study will be immediately halted, and appropriate medical interventions will be administered.

Participant timeline {13}

The participant timeline is shown in Fig. 1.

Sample size {14}

Building on prior research, the sample size was determined utilizing PASS software, based on the UMSARS II scores, employing the comparison of means between two independent samples. $\alpha = 0.05$, $1-\beta = 0.8$. The study design incorporates an equal distribution between the experimental and control groups at a 1:1 ratio, with an allowance for a 10% dropout rate. Based on the MSA-P subtype data, the calculated sample size indicates a minimum of 24 participants per group, reflecting the mean and standard deviation of changes in the test group (-3.39 ± 2.41) and sham group (-1.45 ± 2.07) as reported in the 2015 Brain Connect study. In the absence of precise data on ICAR score changes post-intervention for MSA-C, the sample size estimation is extrapolated from the MSA-P subtype, necessitating 48 participants for MSA-P and 48 for MSA-C, totaling 96 MSA patients enrolled in the study.

Recruitment {15}

Recruitment details for this randomized controlled trial shall be disseminated through the Xijing Hospital's official public communication channels and via informational posters placed in the outpatient clinic areas. Prospective participants will be directed to contact the recruiting staff via telephone or electronic mail, following which they must sign an informed consent form before their enrollment. The recruitment team will provide comprehensive information about the trial to patients and facilitate the enrollment process for those who agree to participate. Eligible patients, conforming to the predefined inclusion criteria, will be invited to participate in the study at one of the participating sites, which include Xijing Hospital, Tangdu Hospital, Xi'an Central Hospital, Shaanxi Provincial People's Hospital, and the First Affiliated Hospital of Xi'an Jiaotong University.

Assignment of interventions: allocation

Sequence generation {16a}

The study aims to recruit a total of 96 patients with MSA, comprising 48 individuals with the MSA-P subtype and 48 with the MSA-C subtype. Patients with MSA-P and MSA-C will be randomized in a 1:1 ratio to either the

intervention or sham stimulation group. A computer-generated randomization sequence will be created, with the numbers sorted in descending order. For the MSA-P subtype/MAS-C subtype, patients ranked 1 to 24 will be allocated to the intervention group, and those ranked 25 to 48 to the control group.

Concealment mechanism {16b}

To ensure blinding and prevent the disclosure of participant information, individuals involved in the patient screening process are precluded from engaging in the randomization procedure. The randomization schedule is produced in triplicate, securely sealed within radiopaque envelopes, and distributed such that one copy is retained by the principal investigator, another by the trial coordinator, and the third by the designated statistician.

Implementation {16c}

Clinicians are responsible for the initial screening and enrollment of potential subjects. Upon ascertaining a subject's eligibility, the clinician shall notify the statistical researcher. Subsequently, the statistical researcher will generate an allocation sequence to assign the subject to their respective group.

Assignment of interventions: blinding

Who will be blinded {17a}

The processes of randomization, baseline assessment, trial execution, and follow-up evaluation will be conducted under blinded conditions. Both participants and outcome assessors will remain unaware of treatment allocation, ensuring blinding is maintained throughout the study. Data analysis will be performed independently by two statisticians who are not otherwise involved in the trial procedures, further ensuring the objectivity of the results.

Procedure for unblinding if needed {17b}

We will employ the split-unblinding technique to disclose group assignments post-trial termination and following the initial data entry lock, anticipated for December 2024. Subsequently, the specific interventions will be revealed subsequent to the finalization of data analysis, projected for January 2025.

Data collection and management

Plans for assessment and collection of outcomes {18a}

The 2022 MDS diagnostic criteria for Multiple System Atrophy (MSA) will guide our patient selection, ensuring only those who meet the study's strict inclusion and exclusion criteria are enrolled. A tertiary physician will apply these criteria to confirm diagnoses. During the trial, a trained team of evaluators will consistently apply these standards for assessment and follow-up, maintaining the reliability of our findings.

Plans to promote participant retention and complete follow-up {18b}

To enhance participant compliance, a designated individual will oversee follow-up procedures. Each participant will provide three contact details to facilitate communication and ensure ongoing engagement in the study.

Data management {19}

Participant demographic details will be documented in medical records, while baseline and post-treatment data will be captured in Case Report Forms (CRFs). A designated team will verify CRF completeness and establish a database for ongoing follow-up. Data entry will be executed by trained personnel using Epi Data, ensuring all information is accurately entered and checked for inconsistencies or errors. Corrections will be made based on the original records to maintain data integrity. To safeguard the data, it will be encrypted and stored on a secure hard drive, with regular backups scheduled every quarter.

Confidentiality {27}

Participant identification will be strictly numerical for privacy, with all ID information and consent forms stored securely in separate locations. All investigators involved in the trial are required to sign confidentiality agreements to guarantee the protection of participant information throughout the study. Patient data will remain confidential and will not be disclosed in any published research outputs.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable; no samples were collected.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Scale data will be meticulously organized, coded, quantified, and assigned before being dutifully entered into the EpiData database through a double-entry process. Following entry, data verification will be conducted. Subsequent statistical analysis will be executed utilizing SPSS 26.0 software, employing Chi-square tests, t-tests, analysis of variance, and logistic multiple regression to determine odds ratios (OR) along with their respective 95% confidence

intervals (CI). The threshold for statistical significance will be established at the conventional 0.05 level for all analyses.

Interim analyses {21b}

Interim analyses will be conducted 1 year prior to the trial's scheduled conclusion. Enrollment will cease upon reaching a total of 96 fully enrolled and completed participants. The trial director, in conjunction with the data monitoring committee, will have exclusive access to these interim findings and will be responsible for making the definitive decision regarding the trial's discontinuation.

Methods for additional analyses (e.g., subgroup analyses) {20b}

There are no subgroup analyses planned.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

In instances of protocol deviation, prompt reporting to the principal investigator, ethics committee, and data monitoring committee is mandatory, along with a thorough analysis of the underlying causes. Should an error occur in subject enrollment, the affected data will be excluded during data processing. The remaining data will be analyzed using intention-to-treat principles, thereby preserving the benefits of randomization and maintaining the integrity of the sample size.

Plans to give access to the full protocol, participant-level data and statistical code {31c}

This study utilizes the China Clinical Trial Registry's comprehensive trial site (https://www.chictr.org.cn] (https://www.chictr.org.cn). Data from the study will be made available upon reasonable request to the corresponding author, in compliance with the Air Force Military Medical University's research and data sharing policies.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The Department of Statistics, functioning as an independent data monitoring committee, will be responsible for verifying the accuracy and plausibility of the data, ensuring the integrity of the study's findings.

Composition of the data monitoring committee, its role and reporting structure {21a}

The Department of Statistics will independently chair a Data Monitoring Committee (DMC), separate from the trial sponsor, to ensure data accuracy and integrity.

Adverse event reporting and harms {22}

The decision to terminate the clinical trial rests with both the trial director and the participant, who are also jointly responsible for reporting adverse events including headaches, dizziness, hearing loss, and epilepsy. A neurologist will then ascertain the relationship between these events and the intervention.

Frequency and plans for auditing trial conduct {23}

Routine audits will be executed every 3 months by independent assessors, unaffiliated with the trial's investigators and sponsors, to verify the documentation's completeness and ensure trial integrity.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

Should the need for protocol amendments arise after trial commencement, a request for such revisions must be submitted to the Ethics Committee for review. Any amendments that could significantly affect the well-being of participants must be communicated through the acquisition of renewed informed consent and by updating the revised protocol at the trial registration center.

Dissemination plans {31a}

The outcomes of the trial, whether positive or negative, will be documented and published in internationally recognized, peer-reviewed journals.

Discussion

The therapeutic mechanism of TMS remains not fully elucidated, with the stimulation target, frequency, and intensity being pivotal parameters influencing treatment efficacy. While existing research has indicated that TMS may alleviate Parkinsonian or ataxic symptoms in patients with MSA, the findings have been inconsistent. Potential reasons for this variability are as follows: (1) diverse study protocols: variations across studies include different stimulation sites, parameters, and intervention durations. The majority of published studies have focused on high-frequency stimulation of the primary motor cortex (M1) and both high- and low-frequency cerebellar stimulation. These approaches have not been tailored to the subtypes and specific clinical presentations of MSA patients, potentially leading to inconsistent outcomes; (2) limited sample size: all studies were conducted within single centers, restricting the generalizability of the findings. The largest study on TMS for ataxia improvement included 74 patients with spinocerebellar ataxia, highlighting the need for larger, multicenter trials to strengthen the evidence base [46]. Furthermore, the majority of MSA-P studies have involved just 10 to

20 patients, emphasizing the need for larger cohorts to ensure the findings' wider applicability and statistical robustness; (3) the scarcity of RCTs in MSA research is attributed to the rarity of the disease, which hampers the recruitment of adequate sample sizes. Consequently, many studies have relied on self-controlled pre-post comparisons rather than the gold standard RCT design. To date, no randomized, double-blind studies have been executed in this field, indicating a need for more rigorous research methodologies to bolster the evidence for treatment efficacy in MSA; (4) the current TMS studies for MSA predominantly rely on scale-based outcome measures, which are inherently subjective. In the absence of blinding, these assessments are susceptible to researcher bias, potentially skewing the results. To ensure objectivity, it is imperative to implement blinded assessment protocols in future studies; (5) the heterogeneity in outcome measures across studies is notable. Predominantly, classical scales like UPDRS and UMSARS have been utilized, which are subject to assessor bias. To enhance the reliability and standardization of future research, it is essential to adopt more objective and consistent outcome assessment tools; (6) Publication bias also made the reliability of the reported results uncertain.

This study aims to employ a multi-center, randomized, double-blind, sham-controlled trial to assess the impact of TBS on motor and non-motor functions in patients with MSA subtypes MSA-P and MSA-C. By evaluating changes in function pre- and post-treatment, we intend to observe the therapeutic effects of TBS on MSA-related symptoms. Additionally, we will utilize MEP measurements, EEG, and fMRI to analyze brain functional connectivity before and after treatment. This comprehensive approach will elucidate the clinical efficacy of TBS with different stimulation parameters across various sites and explore its underlying mechanisms, thereby offering a scientific foundation for MSA treatment strategies.

Trial status

Patient recruitment officially commenced on June 28, 2023, with the current protocol version 2.0 dated March 23, 2023. As of November 21, 2024, a total of 36 patients have been enrolled. We anticipate completing the recruitment phase by December 2024.

Abbreviations

MSA	Multiple system atrophy
TMS	Transcranial magnetic stimulation
TBS	Theta burst stimulation
MEP	Motor evoked potential
iTBS	Intermittent TBS
cTBS	Continuous TBS
EEG	Electroencephalogram
fMRI	Functional magnetic resonance imaging

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08458-2.

Supplementary Material 1.

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Authors' contributions {31b}
Xuedong Liu, Jing Bai and Ya Bai, provide research and experimental design. Xiaobing Li, Yaqian Mu, Xiaolong Sun and Bo Wang are involved in improving the protocol. Shang Lei, Rui Li[1] is responsible for design of data analysis method. Zheng Di, Wei Zhang, Jin Qiao, Rui Li[8], Xin Guo, Xinyao Liu and Yan Shi manage and the experimental process. Jing Bai is responsible writing the initial draft. Xuedong Liu , Ya Bai and Xiaobing Li are responsible for reviewing and revising the initial draft. All authors read and approved the final manuscript.

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Availability of data and materials {29}
The investigators involved in this trial will have access to the final dataset, which is designated for scientific research purposes only. It is imperative that they adhere to confidentiality protocols and refrain from disclosing participant information or any related materials without authorization.

Declarations

Ethics approval and consent to participate {24}
The study protocols were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of the Air Force Military Medical University, with the reference number KY20232118-F-1. All participants provided written informed consent prior to their involvement in the trial.

Consent for publication {32}
The informed consent form will be provided as Appendix 1.

Competing interests {28}
The authors affirm that neither the principal investigators nor any study site has financial or competing interests related to the trial.

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