The effect of noninvasive brain stimulation on symptoms of cervical dystonia: protocol for a parallel-group randomised, clinical trial

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Abstract
Cervical dystonia (CD) is the most common form of dystonia and is characterised by excessive and involuntary muscle contractions of the muscles in the neck. Botulinum neurotoxin (BoNT) injections to the affected muscles can provide relief for CD patients, and deep brain stimulation is employed in more severe cases. However, not all patients respond to these therapies, and DBS may not be suitable for many patients not wishing to undergo surgery. Some studies have tested whether transcranial magnetic stimulation (TMS), can provide a safe, non-invasive alternative, to directly modulate abnormal brain networks in CD. However, TMS methods have been variable, and in particular, numerous different brain regions have been targeted. Therefore, findings have been inconsistent. A prior study used lesion network mapping to localise a brain network connected to 25/25 lesions causing CD, with network hubs in the cerebellum and somatosensory cortex (S1). Recently, we performed a pilot trial testing the efficacy of a 10 days (1 session per day) of continuous theta-burst stimulation (cTBS) (a form of TMS) to this S1 network hub. Real cTBS resulted in small effect sizes for reduced CD symptoms, yet these effects were not significant with respect to sham. Nevertheless, cTBS resulted in significant changes in neurophysiological outcomes, and the intervention was tolerated well by all patients. Therefore, the aim of the present study is to perform a higher-dose follow-up clinical trial of cTBS in CD patients. Bilateral cTBS will be applied 4 times per day for eight days, based on prior cTBS protocols showing efficacy in other neurological disorders.

Section 1: Administrative information
Index 1-2. (Sections/indices based on SPIRIT 2025 guidelines, Hróbjartsson, et al. [1], doi: http://dx.doi.org/10.1136/ bmj-2024-081660)

Primary registry and clinical trial number	ClinicalTrials.gov NCT07681284
Date of registration in primary registry	26/6/2026
Source(s) of monetary or material Support	European Union's Horizon 2023 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 101150147.
Primary sponsor	Fondazione Policlinico Universitario Campus Bio-Medico, Roma, Italy. Via Álvaro del Portillo, 200.
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Public title	The effect of noninvasive brain stimulation on symptoms of cervical dystonia
Scientific title	The effect of noninvasive brain stimulation on symptoms of cervical dystonia

Countries of recruitment	Italy
Health condition	Cervical dystonia
Intervention	Arm 1: real continuous theta-burst stimulation; arm 2: sham continuous theta-burst stimulation
Key inclusion and exclusion criteria	See Index number 14
Study type	Purpose: treatment Allocation: randomised controlled trial Masking: blinded (masking used) Assignment: parallel Type of endpoint: efficacy Phase: I/II
Date of first enrolment	6/7/26
Sample size	26
Recruitment status	Recruiting
Primary outcome	Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)
Key secondary outcomes	TWSTRS subscales (severity, disability, pain), Quality of Life scale, Global dystonia severity rating scale (GDS), Fahn Tolosa Marin (FTM) modified tremor scale, kinematic data of patient's movement patterns, motor evoked potentials (MEPs), and resting-state fMRI data (fMRI)
Ethics review	Status: Approved Approval date: 02/03/2026 Contact: Comitato Etico Territoriale Lazio Area 2
Data sharing statement	For patients who provide informed consent: pseudonymised brain stimulation data and code will be uploaded to the 'Big NIBS data' repository, with the associated clinical scores, and pseudonymised MRI data will be uploaded to the 'OpenNeuro' repository
Protocol version	v1.0. 7th July, 2026

Index 3a. Protocol contributions

DC and VDL conceived of the study and developed the protocol with input from AS, DN, GM, JM-H, PA, EY, EE, NP, JJ, CM, and MM. DC developed the statistical analysis plan with input from AS, PA, and VDL. DC wrote the first draft of the present protocol manuscript and subsequent revisions, with critical feedback from AS, DN, GM, JM-H, PA, EY, EE, NP, JJ, CM, MM, and VDL. All authors contributed to the preparation of this manuscript and have reviewed and approved the final version.

Index 3b-c. Trial sponsor
The study is sponsored by Fondazione Policlinico Universitario Campus Bio-Medico, Roma, Italy. Via Álvaro del Portillo, 200. The sponsor does not have any influence on study design, collection, management, analysis and interpretation of data, writing of the report and the decision to submit for publication.

Index 3d. Steering committee
The steering committee is comprised of DC, VDL, MM, and AS, and all members report no relevant conflicts of interest. The steering committee is responsible for the design, integrity, and progress of the trial and all executive decisions relating to trial conduct and protocol modifications.

Section 2. Open science
Index 4. Trial registration number
ClinicalTrials.gov Identifier (NCT number): NCT07681284.

Index 5. Protocol and statistical analysis plan
The present protocol can be accessed at: https://clinicaltrials.gov/study/NCT07681284. The statistical analysis plan can be accessed alongside the trial registration at this same URL.

Index 6. Data sharing
For patients who provide informed consent, pseudonymised brain stimulation data and code will be uploaded to the 'Big NIBS data' repository, with the associated clinical score outcomes. Pseudonymised MRI data will be uploaded to the 'OpenNeuro' repository. Links to the associated brain stimulation/MRI data will be provided across both repositories.

Index 7. Funding and conflicts of interest
The project is funded by European Union's Horizon 2023 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 101150147. Neither the sponsor or funder have influence on study design, collection, management, analysis and interpretation of data, writing of the report and the decision to submit for publication. The authors report no relevant conflicts of interest.

Index 8. Dissemination policy
Findings will be published in peer-reviewed journals. Pre-prints will be published on medRxiv after analyses are complete. Participants will be sent a copy of the pre-print when it is published. This and the final peer-reviewed publication will be linked to publicly on social media.

Section 3. Introduction
Index 9-10. Background, rationale and objectives
Cervical dystonia (CD) is the most common form of dystonia and is characterised by excessive and involuntary contractions of the muscles in the neck [2]. Whilst botulinum neurotoxin (BoNT) injections to the affected muscles can provide therapeutic relief to CD patients, up to one-third of patients report an inadequate response to treatment [3].

In more severe cases, deep brain stimulation (DBS) of the globus pallidus interna (GPi) or subthalamic nucleus is an effective treatment for CD symptoms, directly and indirectly modulating networks thought to be abnormal in CD [4]. TMS trials have previously been conducted to investigate its potential to ameliorate CD symptoms [5]. These studies have shown limited success, with small sample sizes, and variable results. A major factor limiting the more effective use of TMS in CD is that it is not yet known where to target with TMS, given the many structures implicated in the neurobiology of the disorder. A prior study using lesion network mapping in CD attempted to address this issue by localising a brain network connected to lesions causing CD. Corp, et al. [6] demonstrated that although causal lesions were located throughout the brain, all lesions were functionally connected to a brain network involving positive connectivity to the cerebellum and negative connectivity to the somatosensory cortex (S1). Preliminary work from our group examined the effect of targeting this lesion network mapping-derived S1 cluster using TMS. First, a single session of continuous theta-burst stimulation (cTBS) to the S1 indicated target engagement, as demonstrated by abnormal metabolic response in CD patients [7], and next, a pilot trial of 10 days of daily cTBS demonstrated a 12% reduction in CD symptoms. The primary aim of this study is to assess whether a higher-dose of (4x daily) cTBS to this S1 target can increase therapeutic effect.

Section 4. Methods: Patient and public involvement, trial design

Index 11. Patient and public involvement

While participants or patient groups were not directly involved in the design of the trial, throughout the study we will engage a range of community and advocacy groups in the implementation and dissemination of the research. These include 'Dystonia Europe', 'Dystonia Network of Australia', 'Dystonia Medical Research Foundation', and 'Dystonia Coalition'.

Index 12. Trial design

This study will be a parallel-group, randomised, sham-controlled, double-blind study, with a 1:1 treatment allocation ratio. Patients and assessors for clinical scales will be blinded from allocation group, while investigators delivering the intervention will not be blinded, as this is not feasible. The trial will test for superiority of real cTBS compared to sham cTBS on the primary outcome of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score.

Section 5. Methods: Participants, interventions, and outcomes

Index 13. Trial setting

The trial will be conducted in a hospital setting at Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy. The interventions will be delivered by neuroscientists, neurologists, or PhD or medical degree students, or by research assistants with appropriate training in the safety and administration of TMS [8, 9].

Index 14. Eligibility criteria

<u>Inclusion Criteria</u>

- Aged between 18 and 85 years
- Diagnosis of idiopathic cervical dystonia made by an expert physician

- Last botulinum toxin injection administered at least two months before the start of participation in the study [2]

Exclusion Criteria

- Head or neck trauma occurring less than 12 months before the onset of dystonia
- Acquired dystonia (e.g., drug-induced, brain lesions or trauma)
- History of major psychiatric disorders (e.g., bipolar disorder, schizophrenia, obsessive-compulsive disorder)
- History of neurological diseases other than CD (e.g., epilepsy, Parkinson's disease)
- Other contraindications for TMS or brain MRI (e.g., metal in the head)
- Pregnant or breastfeeding women
- History of substance abuse or dependence

Index 15a. Intervention and comparator

cTBS will be delivered using a Magstim Rapid machine connected to a 70mm cooled coil at 80% of a participants resting motor threshold (RMT) defined using the TMS Motor Threshold Assessment Tool (MTAT 2.1), with the option for refinement of a raw threshold value selected [10]. An MEP will be defined as a recognisable peak-to-peak deflection 50 microvolts in amplitude, at the appropriate latency of a hand muscle MEP (approximately 19-25 milliseconds after the TMS pulse) [11]. cTBS will consist of three-pulse bursts at 50Hz repeated every 200ms (5Hz) for 40 seconds (600 pulses total) [12]. All cTBS procedures will be conducted bilaterally, with application first over the left hemisphere, before moving to the right (approximately one minute will separate each hemisphere). The target will be the same S1 lesion network hub as in our pilot study, yet the target coordinates will be slightly modified based on updated lesion network mapping analyses in CD in a larger sample [13]. Bilateral cTBS will be delivered four times daily, over eight days (excluding weekends), for a total of 32 bilateral cTBS sessions. This 4x day protocol will follow prior studies in neglect patients, delivered at time intervals of 0, 15, 60, and 75 minutes [14-16]. Sham cTBS procedures will be identical but applied using a 70mm sham TMS coil.

Index 15b. Criteria for discontinuation

Patients can request to discontinue the intervention at any time throughout the study. Where a participant elects to withdraw from the study, we will retain and use any data collected prior to withdrawal. The principal investigator may decide to discontinue participation in the trial if: the subject's health condition changes and participation in the trial is potentially harmful; new information becomes available and the trial is no longer in the patient's best interest; the patient does not follow the approved regulations for trial participation; pregnancy; or if the trial is terminated by the relevant authority or the sponsor.

Index 15c. Strategies to improve adherence

Adherence will be promoted through flexible scheduling of study visits, appointment reminders, and clear verbal and written instructions regarding study procedures. Participant burden will be minimised where possible. Adherence will be monitored by recording session attendance for each participant. Missed or discontinued sessions

and reasons for non-adherence will be documented. Adherence monitoring and procedures will be identical for active and sham groups.

Index 15d. Concomitant care that is permitted or prohibited during the trial
Patients will not be permitted to receive BoNT injections throughout the enrolment period. Patients will be instructed to continue stable medications during the trial to not interfere with their medical care and avoid withdrawal effects. Routine care, such as massage (either self or by a therapist) will be permitted to continue throughout the trial, as long as this does not constitute a change in usual routine. Initiation of new treatments, such as physiotherapy, or other neuromodulation protocols will be prohibited during the enrolment period. All concomitant care will be documented throughout the study.

Index 16. Primary and secondary outcomes
The primary outcome will be the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score. Secondary outcomes will be the TWSTRS subscales (severity, disability, pain), Quality of Life scale, Global dystonia severity rating scale (GDS), Fahn Tolosa Marin (FTM) modified (to include only questions relevant to head/neck tremor) tremor scale, kinematic data measuring patient's movement patterns captured from wearable motion sensor, motor evoked potentials (MEPs), and resting-state fMRI data (fMRI). Symptom and MEP data will not be transformed or presented as change statistics from baseline; scores as they are recorded for each subject and timepoint will be included in the corresponding linear mixed-effects model (see index 27). MRI data will be pre-processed and analysed according to standard pipelines, as documented in the statistical analysis plan.

Index 17. Harms
Harms will be defined as any adverse events occurring during the study period, whether or not considered related to the intervention. Harms will be assessed systematically at each study visit and session through participant self-report and investigator inquiry, and recorded using standardised adverse event reporting procedures. Adverse events will be documented and reported in accordance with Good Clinical Practice guidelines.

Index 18. Participant timeline

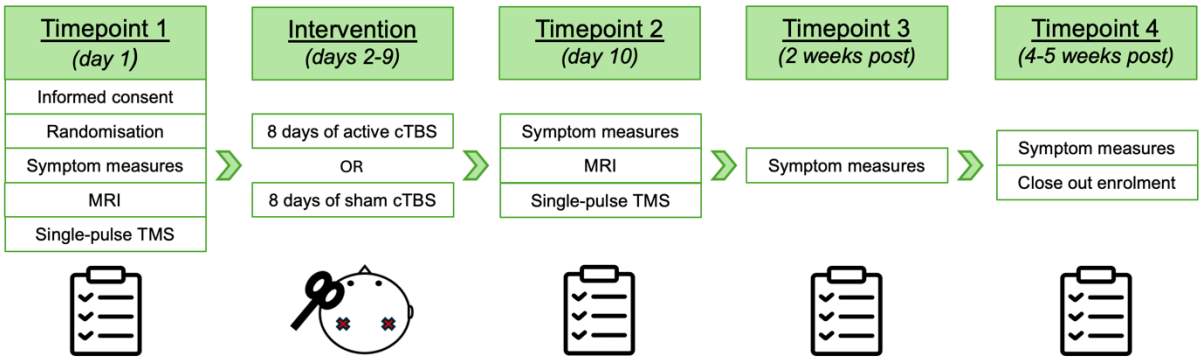

Figure 1. Trial timeline. Patients will be screened for eligibility prior to Timepoint 1 (T1), then if eligible, attend the hospital for informed consent at T1. Patients will then be randomised to receive either real or sham cTBS, delivered for 8 consecutive days not including weekends. All other procedures will be identical for these parallel groups. As described in section 9 and the statistical analysis plan, those who are allocated to receive sham cTBS will be offered the opportunity to return after their final session to receive the real cTBS.

Index 19. Sample size
An a priori power analysis indicated that a total sample size of 20 participants (10 per group) would be sufficient to detect the primary endpoint interaction effect between time and condition, with 80% power. Allowing for 20% attrition, the target recruitment was increased to 26 participants (13 per group). See the Statistical analysis plan for details.

Index 20. Recruitment
Patients will be recruited from Campus Bio-Medico hospital. Collaborations with neurologists who see CD patients will ensure adequate patient enrolment.

Section 6. Methods: assignment of interventions
Index 21-24. Randomisation
There will be an equal number of participants allocated to the active and sham conditions. A computerised adaptive randomisation procedure will be performed, adjusting for baseline characteristics (total TWSTRS score, age, and sex). Randomisation will be completed by a team member not delivering symptom assessments, who will provide group information to the investigators delivering the intervention. Patients and investigators measuring patient symptoms will be blinded from allocation group, investigators delivering the cTBS intervention will not be blinded, as this is not feasible.

Section 7. Methods: Data collection, management, and analysis
Index 25. Data collection methods
Data quality will be ensured through standard operating procedures (SOPs) for each key step of the trial as per Good Clinical Practice (GCP) guidelines. This involves SOPs for informed consent, clinical scales, MRI, single-pulse TMS, and neuronavigated cTBS, and (both created in line with current safety and best practice guidelines for TMS as recommended by the International Federation of Clinical Neurophysiology [8, 9, 17]). Clinical scales will be administered by a neurologist or by another study member with appropriate training. The same investigator will deliver the scales across timepoints within the same patient. MRI parameters will closely match those in our pilot study Morrison-Ham et al., (ACTRN12621000417886; in preparation), which were decided after expert consultation. All team members will be provided with training relative to their duties, which will be recorded through training logs, and delegation logs, respectively.

Index 26. Data management
Upon enrolment, patients will be assigned a unique identification code, which will be used on all study documents to protect personal health information. The registry

containing the identification logs is kept exclusively by the trial site within a password protected electronic document on a password protected computer, accessible only to approved individuals with appropriate credentials, when strictly essential. Patient data will be collected in electronic and paper format and collated into a coded electronic Case Report Form (CRF) for each participant in the study. Physical copies of collected data will be stored in locked filing cabinets with access restricted to authorised individuals. Electronic data will be stored on encrypted, password protected devices. A secure back-up of all data will be maintained.

Index 27. Statistical methods
Total TWSTRS score (primary outcome) will be analysed using a linear mixed-effects model fitted using restricted maximum likelihood estimation, with fixed effects represented by time and experimental condition. The random intercept will be represented by participants. Age and sex will be included as covariates in the model to improve precision, irrespective of baseline group differences.

The primary endpoint/inferential test condition determining whether the active cTBS is superior to the sham cTBS in ameliorating CD symptoms will be the time (T1, T2, T3) by condition (active and sham) interaction. A separate analysis will assess whether the effects of the cTBS are still present at the follow-up timepoint 4-5 weeks after the intervention (T4). This will be an additional endpoint to assess the durability of the effect. See the statistical analysis plan for full details, including secondary outcomes.

Section 8. Methods: Monitoring
Index 28 and 29. Data monitoring committee
Given the trial's short duration, a data monitoring committee will not be established [1], but instead data and trial monitoring will be monitored by trial investigators, the sponsor, and the overseeing ethics committee.

Section 9. Ethics
Index 30. Ethics approval
The protocol, informed consent forms, and all other study material were approved by the Comitato Etico Territoriale Lazio Area 2 on 02/03/2026. Trial code: 270.25 CET2 cbm.

Index 31. Protocol amendments
Any protocol modifications will be submitted to the ethics committee for approval. No modifications to the study procedures will take place prior to approval. All modifications will be reflected in new versions to the associated documentation as necessary (e.g., protocol, statistical analysis plan, etc.). All amendments will be discussed with trial members and the final decision will be made by DC and VDL.

Index 32. Consent or assent
Informed consent will take place in a face-to-face meeting at the university hospital, by a trained member of the trial team. All study procedures will be explained to patients, who will have ample time to ask questions and ensure understanding. Patients will sign a paper document if they would like to consent to participation. An additional section in

the informed consent document will explain the opportunity for patients to return to receive real cTBS if they are allocated to receive sham cTBS in the main study. Here, patients can consent (by signing) to return, extending their enrolment by a minimum of two weeks and a maximum of eight weeks (patients must return within six weeks). Patients can revoke informed consent at any time.

Index 33. Confidentiality
Upon enrolment, patients will be assigned a unique identification code, which will be used on all study documents to protect personal health information. Regarding data sharing, an additional section in the informed consent form will explain this process; here, patients can consent (signed paper document) to having their pseudonymised data available for data sharing at the conclusion of the study. If they do not consent to this, it will not affect their participation in the study. Refer to the data management plan, available at: https://clinicaltrials.gov/study/NCT07681284, for detailed information.

Index 34. Ancillary and post-trial care
As per the Declaration of Helsinki, subjects who are harmed as a result of participating in the research will receive appropriate compensation and treatment. Treatment will be provided at no financial cost to the patients and extends beyond their enrolment in the study. Patients who are allocated to receive sham cTBS will be offered the opportunity to return after their final session is completed to receive the real cTBS. See the statistical analysis plan for how these data will be handled and analysed.

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