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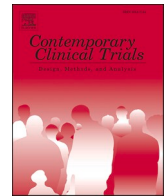
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Translingual neurostimulation combined with physical therapy to improve walking and balance in multiple sclerosis (NeuroMSTraLS): Study protocol for a randomized controlled trial

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ABSTRACT

Introduction: Physical rehabilitation restores lost function and promotes brain plasticity in people with Multiple Sclerosis (MS). Research groups worldwide are testing the therapeutic effects of combining non-invasive neuromodulation with physical therapy (PT) to further improve functional outcomes in neurological disorders but with mixed results. Whether such devices enhance function is not clear. We present the rationale and study design for a randomized controlled trial evaluating if there is additional benefit to the synergistic pairing of translingual neurostimulation (TLNS) with PT to improve walking and balance in MS.

Methods and analysis: A parallel group [PT + TLNS or PT + Sham], quadruple-blinded, randomized controlled trial. Participants ($N = 52$) with gait and balance deficits due to relapsing-remitting or progressive MS, who are between 18 and 70 years of age, will be recruited through patient registries in Newfoundland & Labrador and Saskatchewan, Canada. All participants will receive 14 weeks of PT while wearing either a TLNS or sham device. Dynamic Gait Index is the primary outcome. Secondary outcomes include fast walking speed, subjective ratings of fatigue, MS impact, and quality of life. Outcomes are assessed at baseline (Pre), after 14 weeks of therapy (Post), and 26 weeks (Follow Up). We employ multiple methods to ensure treatment fidelity including activity and device use monitoring. Primary and secondary outcomes will be analyzed using linear mixed-effect models. We will control for baseline score and site to test the effects of Time (Post vs. Follow-Up), Group and the Group x Time interaction as fixed effects. A random intercept of participant will account for the repeated measures in the Time variable. Participants must complete the Post testing to be included in the analysis.

Ethics and dissemination: The Human Research Ethics Boards in Newfoundland & Labrador (HREB#2021.085) & Saskatchewan (HREB Bio 2578) approved the protocol. Dissemination avenues include peer-reviewed journals, conferences and patient-oriented communications.

1. Introduction

Over 70% of people with Multiple sclerosis (MS) report problems with walking and balance [1] which often occur together and are referred to as the mobility impairment dyad [2–5]. Evidence in neurological disorders such as stroke, traumatic brain injury and MS, supports that physical therapy (PT) focusing on the mobility dyad enhances neuroplasticity and improves performance [3,6–8]. However, recovery

is usually incomplete.

Neuromodulation is a therapeutic approach used to alter the function of neuronal networks. Neuromodulation can be either invasive, such as deep brain stimulation, or non-invasive, such as using repetitive transcranial magnetic stimulation. Research groups worldwide are testing the therapeutic benefits of non-invasive neuromodulation combined with rehabilitation to improve outcomes in stroke [9], traumatic brain injury [10], Parkinson's disease [11] and MS [12], with mixed results. One

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method of modulating neuronal networks employs stimulation of cranial nerves, typically the vagus nerve [13] or the trigeminal and facial nerves via the tongue [14,15]. Translingual neurostimulation (TLNS) delivers electrical stimulation to the tongue and is purported to engage neuronal networks of the brainstem and cerebellum [14,16]. A recent consensus paper suggests that stimulation of the cerebellum could benefit various neurological and neuropsychiatric conditions [17]. Although there is growing interest in TLNS and preliminary studies showed feasibility and safety, it is not yet known whether there are added and sustained benefits when pairing TLNS with PT vs. PT alone [18]. In a pilot study among 20 people with MS [16], 14 weeks of PT + TLNS (delivered via the Portable Neuromodulation Stimulator device (PoNS™, Helius Medical Technologies, Newtown, PA, USA)) resulted in greater improvements in the Dynamic Gait Index compared to PT and a sham device (Sham). Although informative, the sample was small and authors did not complete a sample size calculation. There was no follow-up to determine whether benefits were sustained after treatment had ended. Furthermore, much of the intervention took place independently at home without objective monitoring, so the fidelity of the PT intervention could not be assured.

The objective of this study is to examine the benefits of adding TLNS to 14 weeks of PT aimed at improving walking and balance in people with MS and assess the sustained effects three months later. It is hypothesized that both groups will improve from baseline to 14 weeks (post PT), but if the TLNS does enhance neuromodulation, then a difference between groups should be seen at follow up.

2. Methods

2.1. Design

This study will be conducted at two sites (St. John's, Newfoundland & Labrador and Saskatoon, Saskatchewan, Canada) as a parallel-group, quadruple-blinded (participants, physical therapists, assessors and investigators) randomized controlled trial. The research protocol was registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT05275049).

2.2. Sample size

Sample size was calculated using G*Power [19] (Heinrich Heine Universität Düsseldorf) and based on the Dynamic Gait Index (DGI) values at the post-test and effect size reported by Tyler et al. [16] For our a priori power analysis, we conservatively estimated the “true” group difference as 80% of the point-estimate observed in Tyler et al. because early phase studies often overestimate true effects. The correlation between pre- and post-test in Tyler et al. was relatively strong (0.67 in the treatment group and 0.92 in the placebo). Thus, we tested a range of effect sizes for the effect of Group controlling for pre-test, partial r^2 's of 0.14 to 0.19, assuming different correlations between pre- and post-test. Assuming a two-tailed alpha of 0.05, $N = 51$ to 36 participants will be required for 80% statistical power to detect group differences at post-test controlling for baseline. We will recruit 52 participants which would allow for a 15% dropout rate and still keep the sample size (i.e., $N > 44$) at the high-end of our estimated range for 80% power. Thus, the study is designed to detect between group differences in DGI at post-test, all other analyses should be treated as exploratory.

2.3. Inclusion and exclusion criteria

Inclusion criteria were selected to identify participants with MS-related walking impairments but with the ability to still participate in the intensity of PT provided in the intervention. The inclusion criteria are, 1) neurologist-confirmed MS diagnosis, 2) mild to moderate gait deficit due to relapsing-remitting or progressive MS as measured by Expanded Disability Status Scale [20] score of ≤ 6.5 and Patient Determined Disease Steps (PDDS) score from 3 to 6 [21], 3) between 18 and

70 years of age (thereafter walking speed declines due to age) [22], 4) able to walk at least 10 m with or without the use of walking aids, 5) relapse-free in the previous 90 days, and 6) agree to the study time and travel commitment. Individuals who are currently attending physical rehabilitation, are already functional community ambulators (gait speed > 120 cm/s) [23], are pregnant or have contraindications to the use of TLNS according to manufacturer's instructions (active or suspected malignant tumor, recent bleeding or open wounds in mouth, or sensitivity to nickel, gold or copper) will be excluded. We will also exclude those who score > 30 on the Beck Depression Inventory, which is suggestive of severe depression [24].

2.4. Withdrawal and drop-out criteria

Participants will be terminated from the study if they, 1. wish to discontinue for any reason or 2. experience a serious adverse event. Participants must complete the Post (Week 15) testing to be included in the analysis.

2.5. Recruitment and screening

Recruitment will take place through the MS clinics at each site, through flyers posted in PT clinics and via the MS Society of Canada Research Portal. Interested participants will contact the site research coordinator who will perform the screening. Potential participants will be screened verbally using a yes/no check list according to inclusion and exclusion criteria. If eligible and interested, they attend a baseline visit to complete informed written consent and collect demographic and baseline data. At this point eligible participants can choose whether are not to enrol in the study.

2.6. Randomization and allocation concealment

After completing a baseline assessment, enrolled participants will be randomly assigned in blocks of four using the research electronic data capture (REDCap) stratified randomization function. The same REDCap randomization is used across sites. To ensure similar distribution of walking impairment severity between groups, during randomization, we will stratify participants into two groups based on the PDDS score (PDDS 3 + 4 (mild walking problems) vs. 5 + 6 (moderate walking problems)).

The study coordinator at each site is the only team member aware of participant allocation and is the only person authorized to monitor the operation of TLNS/Sham devices. Participants are informed that they will receive either an Alpha or Delta PoNS™ unit, with no indication that there is a sham device.

2.7. Participant demographic information

We will record date of birth, sex, gender, race and comorbidities. Disease-related variables including MS history, type, disease duration, use of walking aids, use of disease-modifying drugs, and history of medication use will also be recorded. Any relapses, changes to medications or gait aids, and adverse events will be monitored and documented throughout the study.

2.8. Intervention

Both treatment groups will receive the 14 week PT intervention (two weeks in person and 12 weeks at home) while wearing a device. The TLNS device delivers stimulation in 20-min blocks. Participants wear the device for five stimulation blocks per day. Device use is always paired with individualized PT. Participants receive two stimulation blocks while completing walking treatment, two stimulation blocks while completing balance treatment, and one stimulation block at the end of the day for breathing and mental practice. After completing the 14 week PT intervention, participants will be instructed to continue to exercise

independently (without wearing a device) according to the evidence-based Physical Activity Guidelines in MS [25] for a subsequent 12 weeks and will be reassessed at the end of that time (Follow-Up at Week 26) (Fig. 1).

2.8.1. Physical therapy intervention

Physical therapists with expertise in neurological rehabilitation provide the intervention and receive standardized training (via six hours of presentations and video modules) to ensure consistency of approach. The first two weeks of PT intervention takes place in a clinic to ensure that participants learn treatment elements and how to use the device. The research coordinator (unblinded) will be onsite to help with any device-related needs. PT intervention during these first two weeks involves individualized one-on-one PT sessions; 1–2 times per day, five days per week (for a total of 18, 60 min sessions). Guided by a 10 point level of exertion scale, walking and balance treatments target moderate intensity level of difficulty. Balance tasks become progressively more challenging by reducing base of support and de-stabilizing the standing surface. Participants are provided a foam mat for this purpose (Airex Balance Pad, 3A Composites Core Materials, Switzerland). Walking will be progressed by reducing assistance, increasing speed and distance, and progressing to real-world tasks (e.g., dual-tasking, variable terrain). Therapists record heart rate, step count, and rating of perceived exertion to monitor for potential adverse events and ensure that training targets are met. This information informs the choice of tasks and task intensities of the subsequent 12-week home program. The therapists check-in (virtually or in person) weekly to monitor and modify the exercises that are completed by participants two times per day five days/week.

2.8.2. TLNS or sham stimulation

The PoNS™ device will be worn (Fig. 2) during PT for in-person and at-home sessions (14 weeks in total). PoNS™ delivers amplitude-controlled, biphasic pulses to the anterior superior surface of the

tongue through gold-plated electrodes on a polyimide substrate for minimal tissue irritation [26]. The sham device looks identical to the PoNS™. The sham PoNS™ contains functioning operator controls but will not deliver stimulation. Increased salivation is common during the initial weeks of use, so participants will be taught swallowing strategies to manage saliva volume when the device is in place. A previous study reported that some participants experienced headaches and temporomandibular joint pain [16], so initial training will include techniques to relax the jaw, refrain from biting the device and breathing uniformly.

2.8.3. Treatment adherence

To ensure compliance and safety, we will implement four methods of participant coaching and monitoring during the 12 weeks of in-home sessions. First, we will require participants to complete a daily log checklist in which they indicate the activities performed with duration, repetitions, and intensity (e.g., heart rate and perceived level of exertion) recorded. Secondly, participants are provided a Fitbit activity tracking watch (Inspire 2™, Fitbit, San Francisco CA) to track their heart rate and activity patterns. Third, participants will receive a weekly virtual or in-home session with the PT to review activity and heart rate data. During that session, the participant will demonstrate the exercises, which will be progressed as necessary by the therapist to the appropriate level of challenge while ensuring safety. Finally, device usage data is automatically recorded by the TLNS/Sham device. The research coordinator will upload and review device usage data at regular intervals (Week 1, 2, 8, 15) and provide participant feedback on device usage to support prescribed wear and use. In addition to participant monitoring, we will support intervention fidelity by auditing study interventionists (e.g., a researcher will view an intervention session for each PT within the first 2 weeks).

2.9. Outcome assessment

Primary and secondary outcomes will be assessed at Baseline (Pre), Week 15 (Post, after completion of the 14-week intervention), and at Week 26 (three-month Follow-Up). For the purposes of the primary endpoints, Dynamic Gait Index at 15 and 26 weeks will be considered the primary trial outcome. Assessors are PTs who do not provide the PT intervention and are masked to group allocation. They receive standardized training on the assessments.

2.9.1. Primary outcome

Gait and balance will be assessed using the Dynamic Gait Index and fast walking speed. The Dynamic Gait Index involves eight walking conditions (e.g., changing speeds, head turns, navigating obstacles etc.). Performance is rated on a 4-point ordinal scale ranging from 0 (severe impairment) to 3 (normal); maximum score of 24 [27]. The Index demonstrates high sensitivity in identifying fallers and moderate to strong convergent and discriminant validity in ambulatory persons with MS [28].

2.9.2. Secondary outcomes

To determine fast walking speed over a short distance, the Timed 25 Foot Walk Test (T25FWT) will be used. Participants will be timed as they are asked to walk 25 ft as quickly as possible while maintaining safety. Both time to complete the T25FWT and walking speed will be calculated. A lower time and faster walking speed indicates better walking performance. The T25FWT is commonly used to assess treatment outcomes in MS. It has excellent test/retest (ICC = 0.88) and interrater (ICC = 0.94) reliability, and excellent construct validity with disease severity ($r = 0.67$; $p < 0.001$) [29–31].

A number of valid and reliable patient-reported outcome measures will be used to capture MS symptom severity and health related quality of life. We will ask participants to rate the impact of MS symptoms in the previous two weeks using the Multiple Sclerosis Impact Scale-29 (MSIS-29) [32]. This questionnaire is divided into two sections; physical (20

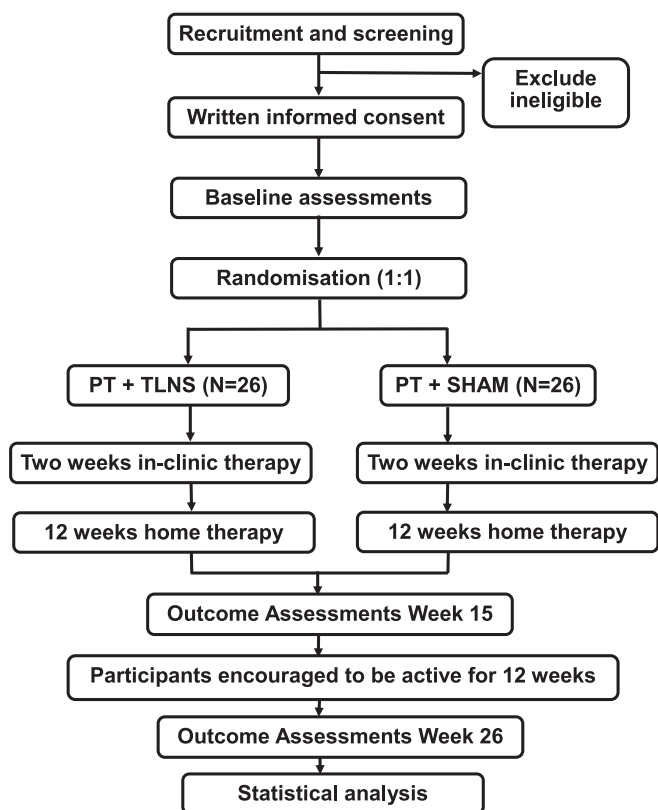


Fig. 1. Study Flow Chart. PT, Physical Therapy; TLNS, Translingual neurostimulation; SHAM, Sham device.

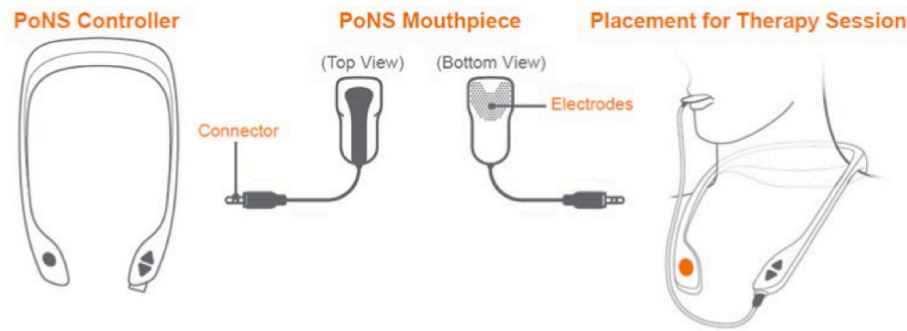


Fig. 2. Components of Translingual Neurostimulation (PoNSTM) device (Image provided by permission from Helius Medical Technologies, Newtown, PA, USA).

questions) and psychological (9 questions). Each of the 29 questions are answered using a rating scale from 1 (not at all) to 5 (extremely). The MSIS-29 has strong reliability, construct validity and responsiveness to disease changes [32]. Participants will also rate their walking and balance problems in the last two weeks using the MS Walking Scale-12 (MSWS-12). The scale ranges from (not at all) to 5 (extremely) [33]. The MSWS-12 has excellent reliability [34], internal consistency [33], and criterion validity with disease severity [35] and walking ability [36]. The Short Form 36 Health Survey Questionnaire (SF-36), will capture participant reported health-related quality of life [37], found to be responsive in our previous research [38]. The Fatigue Scale for Motor and Cognitive Function (FSMC) will be used to determine fatigue severity [39]. The FSMC is highly sensitive in detecting fatigue in people with MS and the subscales adequately differentiate between motor and cognitive fatigue [39]. The subdomains of cognitive and motor fatigue each include 10 questions with ratings from 1 (does not apply at all) to 5 (applies completely).

2.10. Safety evaluation

Adverse events and protocol deviations will be recorded by the research coordinator. Mild adverse events such as excess salivation will be recorded in the data management system, via REDCap, and the participant will be provided management techniques. At each assessment, we will ask participants to rate their present feelings of pain and fatigue using a Visual Analogue Scale (VAS). At the 15 and 26-week assessments, we will ask participant to rate their satisfaction with the device and the PT intervention. Serious adverse events will be reported immediately to the Health Research Ethics Board and discussed with the participant's neurologist who will provide medical follow-up as necessary. Participant may withdraw if they choose to do so, or on the advice of the neurologist.

2.11. Data management, auditing and monitoring

Data collected via patient-reported outcome measures is sent and received electronically using REDCap. Primary outcome data will be recorded by the assessor on printed case report forms and then entered into REDCap by the research coordinator. REDCap and case report forms will be accessible to the contracted (by the funder) Study Monitor, for monitoring and auditing, through secure document manager. Auditing will take place on or about when the 15th participant at each site completes Post assessment and again when all participants complete the 26th week follow-up assessment. All participant data is coded and protected and securely stored for at least 10 years.

Protocol amendments (e.g., changes to eligibility criteria, outcomes, analyses) are first approved by the Health Research Ethics Boards and then amended in the Clinical Trials registry.

2.12. Statistical analysis plan

Primary and secondary outcomes will be analyzed using linear mixed-effect models [40]. These models will include fixed effects of baseline score, site, Time (Post and Follow-Up), Group, and the Group x Time interaction. A random-effect of Participant will account for the within-subject nature of the Time factor. (In theory, site could be treated as a random-effect as well, with Participants nested within Sites, but with only two-levels of site it is better to treat this factor as a fixed effect.) The Time variable will be treatment coded, with post-test as the reference level. In this way, the coefficient for Group provides a statistical test of the difference between groups on the post-test. The Group x Time interaction then tests for differences in how groups change from the post-test to follow-up assessment. For our primary outcome of DGI, the significance threshold is set at 0.05, consistent with our a priori power analysis.

For tests of secondary outcomes (e.g., gait speed, patient reported outcomes), we will apply the Holm-Bonferroni method to correct for multiple hypotheses within families of related tests (i.e., effects of Time, Group, and Group x Time interactions will be considered "families" and corrected for m dependent variables within each family). This method was chosen to control the family-wise Type I error rate at $\alpha = 0.05$ in our secondary analyses, but with less of a cost to the Type II error rate compared to other methods (e.g., Bonferroni correction).

Raw effect sizes will be reported as the coefficients from the regression model and their 95% confidence intervals. Standardized effect sizes will also be reported as a pseudo- r^2 as appropriate [41]. Participants must complete the Post testing to be included in the analysis. Baseline differences will be evaluated by inspect mean differences and their 95% confidence intervals; variables with large baseline differences and/or strong theoretical rationales will be included as covariates in a sensitivity analysis.

2.13. Ethics

The Health Research Ethics Board, Newfoundland and Labrador (HREB#2021.085) & Saskatchewan (HREB Bio 2578) granted ethical approval. All participants will complete informed written consent before proceeding in the trial. All staff will complete Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TDPS) Course (<https://tcps2core.ca/>). Data is anonymized and stored in password-protected REDCap.

2.14. Dissemination

Dissemination avenues include peer-reviewed journals, scientific conferences and patient-oriented communications.

3. Discussion

Prolonged performance improvement following rehabilitative

training suggests that neuroplasticity has taken place. [2,4,42] A previous pilot study, that paired TLNS with PT [16] demonstrated promising results, however, sustained benefits could not be ascertained. Similarly, Hou et al. investigated neuropsychological changes associated with synergistic pairing of neuromodulation and rehabilitation in traumatic brain injury patients [43], but without examining outcomes at follow-up. Consensus from neuromodulation studies supports the need for longer term follow-up [44]. This clinical trial, to our knowledge, is the first adequately powered randomized controlled trial to examine the sustained (at follow-up) benefits of pairing non-invasive neuromodulation with evidence-based walking and balance rehabilitation in MS. Such information is critical to advancing our knowledge of what additional benefits might be seen when pairing non-invasive neuromodulation with PT vs. PT alone. Depending on the results, the researchers for this study envision 3 potential scenarios: 1) neuromodulation shows enhanced benefit in addition to PT – this builds a case for TLNS neuromodulation to be incorporated into clinical practice, supports potential advocacy for insurance coverage for device use, and for mechanisms of device effectiveness to be further explored; 2) neuromodulation shows no added benefit – new devices should be considered and/or different training paradigms should be investigated, or 3) device is useful for a subset of individuals - this will help guide matching the optimal protocol to the most appropriate patient.

It is important in a clinical trial that participants receive the treatment as intended [45]. Trials of complex interventions such as this one are subject to adherence issues. The study employs a multi-pronged strategy to measure treatment fidelity and encourage participant adherence. Participants wear a physical activity tracking watch, complete an exercise checklist and receive weekly PT visits when exercising at home. Importantly, the use of the TLNS/Sham device is monitored by an integrated recording system. Furthermore, therapists receive standardized training on the walking and balance treatment to ensure consistency of therapeutic approach between therapists, participants and sites.

4. Limitations

Although the results of this study could have important implications in the fields of rehabilitation and neuromodulation, there are some limitations. For instance, MS symptoms fluctuate day to day. We do not record fatigue, for example, during every treatment but we do record heart rate, level of exertion and activity (using a Fitbit watch). Further, not all participants will be at the same fitness level to start with, so their ability to engage will vary. This may have limitations in understanding the most beneficial intensities of PT training needed to support long-term functional improvements. There is always the possibility that participants will be able to ascertain which device they have (e.g., stimulation vs sham). However, we are attempting to minimize this by blinding participants to the fact that there is a sham device (e.g., participants are told there is a high and a low stimulation device).

5. Trial status

This trial was registered on March 11, 2022. Recruitment start date was October 15, 2021. The estimated data collection completion date is December 2022.

Article summary

Strengths and limitations of the study

- The first multi-center, quadruple-blinded, powered study testing the effects of translingual neurostimulation, combined with physical therapy, for balance and gait problems in multiple sclerosis.
- Integrates intervention compliance data recorded from the device and from activity watches.

- Includes both objective and subjective outcomes and a follow-up timepoint.

Author contributions

MP, SJD and KRL designed the study, obtained funding, will oversee data collection, and assisted with writing the manuscript and editing the final version.

GRW and SB assisted with methodological aspects including ethics, outcomes and data collection and management. They assisted with drafting the manuscript and approved the final version.

MS, FC and ML provide site expertise in recruitment and management of adverse events. They approved the manuscript.

KRL provides statistical expertise and approved the manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

This study was supported by an Independent Investigator –led Grant from Helius Medical, the company that makes the PoNS units. They and their employees had no involvement in the design and conduct of this study.

Helius Medical technologies provided the PoNS™ (both TLNS and sham) devices. They have no involvement in data collection, analysis or reporting.

Data availability

Data will be available from corresponding author upon reasonable request.

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