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Original Research

# Translingual Neurostimulation for the Treatment of Chronic Symptoms Due to Mild-to-Moderate Traumatic Brain Injury



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**KEYWORDS**
Balance;
Facial nerve;
Gait;
Neurostimulation;
Rehabilitation;
Trigeminal nerve

**Abstract** *Objective:* To compare the efficacy of high- and low-frequency noninvasive translingual neurostimulation (TLNS) plus targeted physical therapy (PT) for treating chronic balance and gait deficits due to mild-to-moderate traumatic brain injury (mmTBI).
*Design:* Participants were randomized 1:1 in a 26-week double-blind phase 1/2 study (NCT02158494) with 3 consecutive treatment stages: in-clinic, at-home, and no treatment. Arms were high-frequency pulse (HFP) and low-frequency pulse (LFP) TLNS.
*Setting:* TLNS plus PT training was initiated in-clinic and then continued at home.
*Participants:* Participants (N = 44; 18-65y) from across the United States were randomized into the HFP and LFP (each plus PT) arms. Forty-three participants (28 women, 15 men) completed

*List of abbreviations:* 6MWT, 6-minute walk test; AE, adverse event; ANOVA, analysis of variance; DGI, Dynamic Gait Index; HFP, high-frequency pulse; ITP, in-clinic training program; LFP, low-frequency pulse; mmTBI, mild-to-moderate traumatic brain injury; PoNS, portable neuromodulation stimulator; PSQI, Pittsburgh Sleep Quality Index; PT, physical therapy; SOT, Sensory Organization Test; TBI, traumatic brain injury; TLNS, translingual neurostimulation.

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M.T., K.K., and Y.D. are founders and owners of Advanced Neurorehabilitation, LLC (Madison, WI), which holds the intellectual property rights to the PoNS technology; these rights are exclusively licensed to Helius Medical Technologies.
M.T., K.K., and Y.D. are founders of NeuroHabilitation Corporation, and M.T. is a board member of Helius Medical Technologies (Newtown, PA), and each owns stock in Helius. K.S. is now an employee of Helius Medical Technologies (Newtown, PA) and owns stock in Helius.
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at least 1 stage of the study. Enrollment requirements included an mmTBI ≥1 year prior to screening, balance disorder due to mmTBI, a plateau in recovery with current PT, and a Sensory Organization Test (SOT) score ≥16 points below normal.
*Interventions:* Participants received TLNS (HFP or LFP) plus PT for a total of 14 weeks (2 in-clinic and 12 at home), twice daily, followed by 12 weeks without treatment.
*Main Outcome Measures:* The primary endpoint was change in SOT composite score from baseline to week 14. Secondary variables (eg, Dynamic Gait Index [DGI], 6-minute walk test [6MWT]) were also collected.
*Results:* Both arms had a significant ($P<.0001$) improvement in SOT scores from baseline at weeks 2, 5, 14 (primary endpoint), and 26. DGI scores had significant improvement ($P<.001$-.01) from baseline at the same test points; 6MWT evaluations after 2 weeks were significant. The SOT, DGI, and 6MWT scores did not significantly differ between arms at any test point. There were no treatment-related serious adverse events.
*Conclusions:* Both the HFP+PT and LFP+PT groups had significantly improved balance scores, and outcomes were sustained for 12 weeks after discontinuing TLNS treatment. Results between arms did not significantly differ from each other. Whether the 2 dosages are equally effective or whether improvements are because of provision of PT cannot be conclusively established at this time.


Traumatic brain injury (TBI) is a leading cause of injury-induced death and physical disability. Millions of people experience TBI every year,[1,2] and an estimated 5.3 million people are living with TBI-related disabilities,[3] with up to 57% of patients with TBI experiencing balance disorders.[4] Mild-to-moderate traumatic brain injury (mmTBI) encompasses most of TBI cases (83%).[5]

For many people, the signs and symptoms of mmTBI resolve with time, allowing return to normal daily activities; however, 25%-50% of patients experience chronic symptoms.[6-10] Instability or imbalance can persist after mild TBI,[11] which has a significant negative effect on functional status, capacity to return to work, and quality of life[7,12-16] and can increase the risk of falling and repeat injury.[17] Rehabilitation techniques consist of basic gait and balance training, but may also include specialized therapies, such as vestibular rehabilitation therapy, vision therapy, motor control retraining, graded exercise, and others.[18-24] Whereas some patients improve with these treatments, others do not.[18,25,26]

Neurostimulation combined with physical therapy (PT) can potentially affect rehabilitation outcomes,[27-29] and noninvasive brain stimulation can affect neural excitability and may facilitate motor skill learning.[30] Cranial nerves V and VII in the tongue and associated neural projections in the brain can be stimulated through noninvasive translingual neurostimulation (TLNS).[31] Clinical studies by our group and others indicate that TLNS with targeted PT, combined, can significantly improve outcomes in those with degenerative neurologic disease, spinal cord injury, or stroke.[32-35] In a separate study, we treated 20 persons with multiple sclerosis and an identified gait disturbance with TLNS plus targeted PT.[32] Over 14 weeks of treatment, Dynamic Gait Index (DGI) significantly improved from baseline.[32] One group reported results from 2 people with chronic incomplete spinal cord injury who completed 12 weeks of TLNS plus balance or gait PT that indicated improvements in both walking speed and skilled walking function.[34] Results from a separate randomized controlled trial demonstrated significant improvement in the Mini-Balance Evaluation Test after 2 weeks of TLNS plus targeted PT in 5 subacute stroke survivors.[33] These results, as well as similarities in neural dysfunction mechanisms of stroke and TBI,[35] support the possibility that TLNS plus targeted PT may be effective for treating chronic balance and gait deficits due to mmTBI.

This 26-week, randomized trial (Clinicaltrials.gov, NCT02158494) was developed to investigate high-frequency pulse (HFP) TLNS plus PT, as treatment for individuals with persistent balance deficit due to mmTBI, compared with low-frequency pulse (LFP) TLNS plus PT as a control. Since trial registration, notable difficulties in establishing controls in neurostimulation studies have become more prominent in the field, particularly focusing on how a low, minimally perceived stimulus serving as a sham can trigger neural activity and produce a response.[36-40] This determination of optimal stimulation parameters has proven challenging across the neurostimulation field, including studies with transcutaneous electrical nerve stimulation,[36,37,41-43] noninvasive trigeminal nerve stimulation,[38,39,44] and TLNS.[32] Because of these difficulties, the focus of this study shifted from using the LFP as a control to one of a comparison between the treatment arms (PT plus either HFP or LFP); balance assessment after 14 weeks of treatment was the primary outcome measure.

## Methods

### Study design

This 26-week, randomized, double-blind phase 1/2 study (NCT02158494) was performed at a single site in the United

States from April 29, 2014, to October 31, 2017, and included 3 stages: twice-daily in-clinic training program (ITP) for 2 weeks (with at-home training during the intervening weekend); (2) a 12-week home training program; and (3) 12 weeks with no treatment and a return to normal activities. The University of Wisconsin Institutional Review Board approved the protocol. After initial approval, on discovery that minimally perceived stimulus in neurostimulation studies can trigger neural activity and produce a response,[36,37,39,40] the focus of this study was shifted from using the LFP plus PT arm as a control to one of a dosage comparison between PT plus either HFP or LFP stimulation (details are described in supplemental appendix S1, available online only at http://www.archives-pmr.org/). This study was performed in accordance with the Declaration of Helsinki and in agreement with the International Conference on Harmonisation Guidelines on Good Clinical Practice. All participants provided written informed consent prior to study participation.

## Participants

Participants were recruited through print and radio advertising and were required to have mmTBI that occurred ≥1 year before enrollment, reached a functional plateau in their recovery (as defined by a discharge note from their physical therapist), and a NeuroCom[a] Sensory Organization Test (SOT) composite score ≥16 points below normal after adjustment for age. Mild and moderate TBI diagnoses were made based on guidelines established by Veterans Affairs/Department of Defense.[45] All participants had a nonremarkable neuroradiographic report after their most recent TBI, meaning that the findings were not significant per the clinical judgement of the neuroradiologist. Reports were reviewed to rule out refractory subdural hematomas, evidence of tumors, anatomical anomalies, or evidence of loss of gray matter. Neuroradiographic reports and therapy discharge notes were obtained through a medical records request; magnetic resonance imaging prior to enrollment was required if a participant lacked a neuroradiographic report.

Potential participants were excluded if they had oral or other health problems that would preclude TLNS or, in the opinion of the investigators, were unable to successfully complete the stimulation intensity level setting procedure for the device. Additional inclusion and exclusion criteria are available in supplemental appendix S1. Rolling recruitment was used, and enrolled participants had a unique 3-digit identifier that was used for double blinding and 1:1 randomization by a clinical monitor.

## Treatment

TLNS was delivered through the portable neuromodulation stimulator (PoNS).[b] As previously described,[46] PoNS uses 143 electrodes on the tongue array to deliver 19-volt amplitude-controlled, pulse-width modulated, unbalanced biphasic pulses to the anterior, superior surface of the tongue; a zero net direct current minimizes the potential for tissue irritation. The 2 stimulation conditions evaluated in this study were an HFP (study-defined active arm) and an LFP (study-defined control arm); the HFP/LFP stimulation ratio is 1875:1 (supplemental table S1, available online only at http://www.archives-pmr.org). The experimental stimulus intensity used during study treatments was determined during ITP in both groups (see supplemental appendix S1).

Participants completed training sessions of TLNS treatment (TLNS plus PT) 3 times daily for 14 weeks (table 1), with program intensity tailored to each participant's functional ability throughout the study. In stage 1 (ITP), participants completed 2 training sessions daily under physical therapist supervision and 1 session daily at home, independently. In stage 2, the training sessions were carried out at home 6 days weekly, and participants returned to the clinic once weekly for a training program update. The PoNS device logged stimulation level, time, and date to monitor protocol compliance. During stage 3, participants did not undergo TLNS treatment and returned to normal daily activity. The type, frequency, and duration of exercise were documented and tabulated.

## Assessments and endpoints

Endpoints and assessment time points are summarized in table 2. The primary endpoint was the change in composite SOT score (see supplemental appendix S1) from baseline to week 14. The SOT score was also determined at the end of each stage and every 3 weeks during stages 2 and 3. Key secondary endpoints were the 6-minute walk test (6MWT) and DGI. For the primary and key secondary endpoints, outcomes in each treatment arm and at each time point were compared to help determine any differences in efficacy between the 2 dosages.

Other exploratory endpoints included the Neurobehavioral Symptom Inventory, Brief Symptom Inventory 18, Pittsburgh Sleep Quality Index (PSQI), and Headache Disability Index. Videonystagmography was performed at baseline and at weeks 14 and 26 to observe potential changes in oculomotor function. Adverse events (AEs) were recorded throughout the study.

## Sample size

R (version 3.4.1)[c] was used for power analysis and sample size calculation. This study was powered for the primary outcome measure (SOT) only. Based on pilot study results of a mean improvement of 26.3 points in the SOT composite score after 2 weeks of treatment, it was assumed that the LFP group would achieve half of this improvement (13.2 points).[47] Based on this assumption, a sample size of 17 participants in each group would have 80% power to detect a significant difference between the HFP and LFP groups using an independent *t* test with a 2-sided significance level of $<.05$. A previous controlled pilot study[32] experienced a dropout rate of ≤25%, so the sample size for this study was increased from 34 to 44 participants, with 22 participants in each arm.[47]

## Statistical analysis

The intent-to-treat population, the primary population for efficacy analyses, was analyzed using VassarStats[d] and

**Table 1** Daily training* schedule

| Time of Day | Treatment Type | Duration |
|---|---|---|
| Morning session | Warm-up exercises without PoNS | 10 min |
| | Balance training† with PoNS | 20 min |
| | Gait training‡ with PoNS | 20 min |
| | BAT§ with PoNS | 20 min |
| Break | | 3-4 h |
| Afternoon session | Balance training with PoNS | 20 min |
| | Movement control‖ exercises w/o PoNS | 20 min |
| | Gait training with PoNS | 20 min |
| Break | | |
| Evening session | BAT§ with PoNS | 20 min |

Abbreviations: BAT, breathing awareness training; w/o, without.

* Exercises were progressed in difficulty as participants demonstrated mastery.

† Balance training focused on developing stable balance while standing in progressively challenging conditions during PoNS treatment. The goal of balance training was to create body awareness, correct postural alignment, and improve stability by recalibrating proprioceptive, tactile, and vestibular inputs. Each balance training session required that the clinician work with participants to determine an appropriately challenging position based on their ability, progressing them during the study as they improved.

‡ Gait training, in which participants walked on a treadmill and over ground at progressive speeds and were challenged to re-establish appropriate dynamic balance and gait patterns during PoNS treatment.

§ Breathing and awareness training aimed at developing relaxed and mindful respiration and body awareness during PoNS treatment.

‖ Movement control training aimed at helping the participant develop the proper movement patterns and synergies. Emphasis was placed on the quality of movements performed with accurate control. Exercises included lower extremity isolation, core strengthening, and/or upper extremity movement to improve arm swing.

included all participants who were randomized to either the HFP or LFP treatment group. The per-protocol population included all randomized participants who had no significant protocol violation. All participants receiving at least 1 TLNS treatment (HFP or LFP) were included in the safety analysis.

Statistical comparisons between groups used *t* tests and chi-squared procedures for interval and categorical data, respectively. There was no imputation for missing data; a data analysis was performed on the existing data set as is. Changes from baseline at weeks 2, 14, and 26 (using paired *t* tests) and post hoc for week 5 were determined. The *P* value accepted for significance was .0125 (Bonferroni correction) for all secondary measures.

Multivariate repeated measures analysis of variance (ANOVA) testing was performed for the results of the SOT, DGI, and 6MWT assessments using Statistical Analysis System 2019.[e] For all 3 assessments, the independent variables consisted of 2 levels of treatment (HFP and LFP, combined) and 5 time points (baseline and weeks 2, 5, 14, 26). Descriptive statistics were provided for demographic variables and exploratory endpoints.

## Results

### Participants

Fifty-seven candidates were screened and 44 were randomized (16 men, 28 women) to receive TLNS treatment (TLNS+PT) at an HFP or an LFP (fig 1). Forty-three participants completed at least 1 stage of the study (intent-to-treat population: 22 HFP, 21 LFP), and 39 and 37 participants completed 2 and 3 stages, respectively. Participants in the treatment arms were well balanced for all demographic and clinical variables (table 3), except for the 6MWT, which was significantly higher in the LFP group than in the HFP group ($P=.031$). The mean time from the qualifying injury to enrollment was 6.5 years (range, 1-33y), and the mean age was 55.0 years (standard deviation,

**Table 2** Endpoints and assessment timing

| Endpoint | Timing of Assessment |
|---|---|
| Primary endpoint | |
| SOT | Baseline, end of each stage, and every 3 wk during stages 2 and 3 |
| Secondary endpoint | |
| 6MWT | Baseline, end of stage 1, every 3 wk during stages 2 and 3 |
| DGI | Baseline, end of stage 1, every 3 wk during stages 2 and 3 |
| Exploratory endpoint | |
| NSI | Baseline, end of each stage |
| BSI 18 | Baseline, end of each stage |
| PSQI | Baseline, end of each stage |
| HDI | Baseline, end of each stage |

Abbreviations: BSI, Brief Symptom Inventory; HDI, Headache Disability Index; NSI, Neurobehavioral Symptom Inventory.

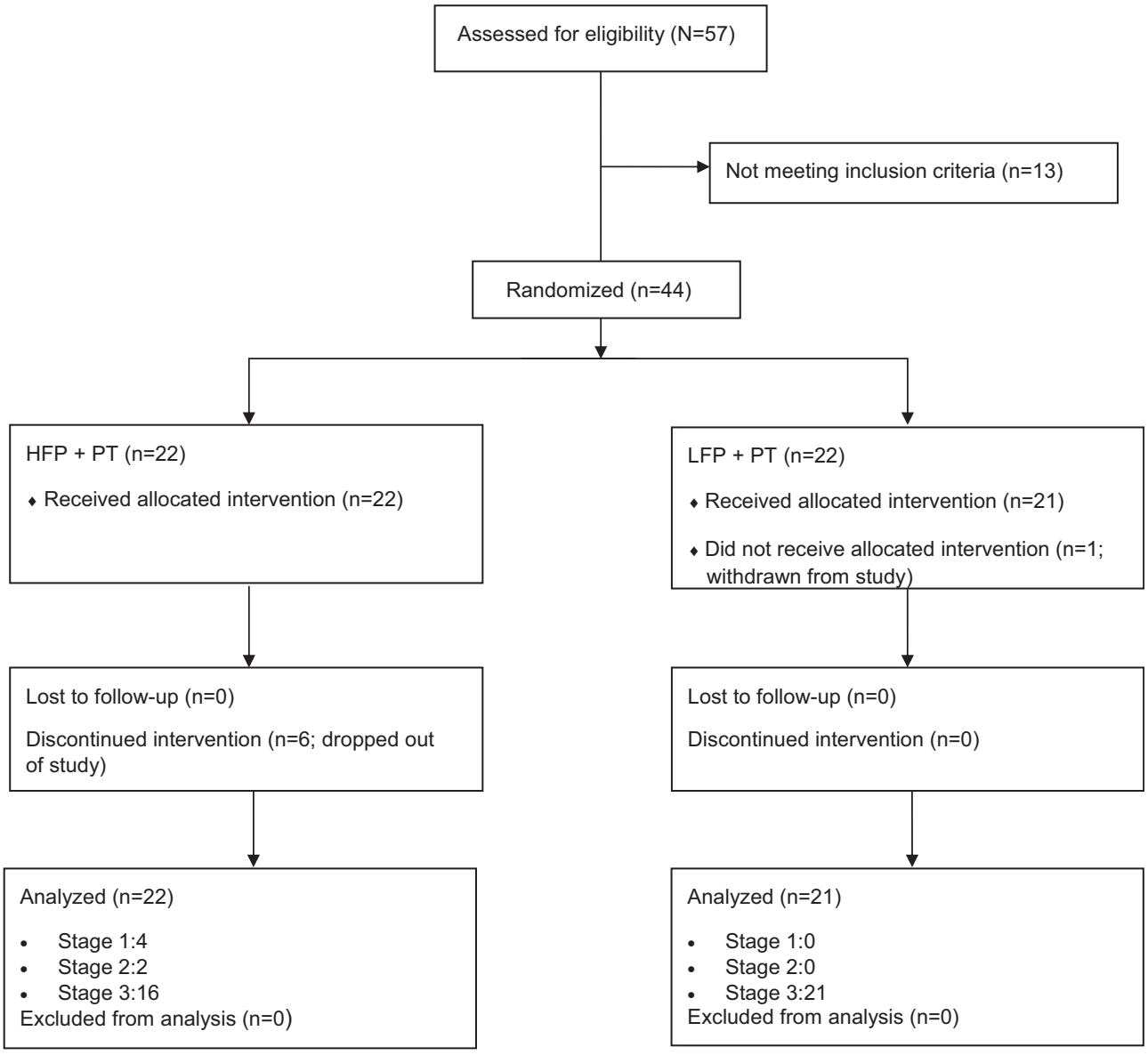


**Fig 1** CONSORT diagram.

8.4y). After initial injury, participants underwent a mean ± SD of 5.4±7.6 months of outpatient PT for balance and other injury-related issues. Most therapies were provided in individual treatment sessions scheduled from 1 to 5 times weekly.

## SOT composite score

Significant improvements in the SOT composite scores from baseline to each postbaseline assessment ($P<.0001$) were demonstrated for both treatment groups (fig 2). No significant difference in SOT score was observed between the 2 treatment groups at baseline or at weeks 2, 5, 14, or 26.

## DGI and 6MWT

Both treatment groups showed significant improvement in DGI from baseline to weeks 2, 5, 14, and 26, and there was no significant difference between the 2 treatment groups at these times (fig 3). A significant improvement in 6MWT distance from baseline was observed for each treatment group at weeks 5, 14, and 26 and for the LFP group at week 2 (fig 4). There was no significant difference in 6MWT distance between the treatment groups at any of the assessment time points.

## Multivariate ANOVA

ANOVA testing of scores from the SOT assessments calculated a significant improvement in SOT score from baseline to week 2 ($P<.0001$) and from week 2 to week 14 ($P=.0178$). In this analysis, the difference in SOT score was not significant between weeks 2 and 5 ($P=.2368$) or weeks 5 and 14 ($P=.2234$).

For the DGI assessment, statistically significant improvements were observed from baseline to week 2

**Table 3** Baseline demographic and clinical characteristics

| Variable | HFP+PT | LFP+PT | *P* Value |
|---|---|---|---|
| N | 22 | 21 | |
| Age | 54.05±5.91 | 53.24±10.55 | .757 |
| Sex (%) | | | >.99 |
| Female | 14±63.6 | 14±66.7 | |
| Male | 8±36.4 | 7±33.3 | |
| Race (%) | | | .261 |
| African American | 2±9.1 | 0±0.0 | |
| American Indian | 0±0.0 | 1±4.8 | |
| Interracial | 1±4.5 | 0±0.0 | |
| White | 19±86.4 | 20±95.2 | |
| Ethnicity (%) | | | >.99 |
| Non-Hispanic | 20±90.0 | 20±95.2 | |
| Unknown | 2±9.1 | 1±4.8 | |
| Education (y) | 14.86±3.26 | 15.90±2.51 | .248 |
| Age at most recent traumatic brain injury (y) | 47.73±10.20 | 46.76±11.09 | .768 |
| SOT* | 42.77±17.54 | 36.24±16.09 | .211 |
| 6MWT (m) | 358.10±78.55 | 407.80±66.83 | .031 |
| DGI | 17.95±5.29 | 19.29±3.72 | .173 |
| NSI | 38.59±18.23 | 36.62±15.98 | .709 |
| BSI-18 | 60.77±10.90 | 59.90±12.33 | .808 |
| PSQI | 9.32±4.87 | 9.18±4.93 | .926 |
| HDI | 40.91±27.39 | 40.76±29.32 | .987 |

NOTE. Values are mean ± SD unless otherwise indicated.
Abbreviations: BSI, Brief Symptom Inventory; HDI, Headache Disability Index; NSI, Neurobehavioral Symptom Inventory.
* Imbalance is considered with a SOT score ≤69.

(*P*<.0001) and between weeks 2 and 14 (*P*=.0126) and weeks 5 and 14 (*P*=.0479). For the 6MWT, statistically significant improvements were observed from baseline to week 2 (*P*<.0001), week 2 to week 14 (*P*=.0009), week 5 to week 14 (*P*=.0472).

## Efficacy—exploratory endpoints

Results for the exploratory endpoints showing improvements from baseline for both the HFP and LFP groups are shown in table 4. Although these results were not assessed with inferential statistics, there appeared to be improvements from baseline for both groups.

## Safety

There were no deaths during the study. A total of 91 AEs were reported, 87 mild or moderate in severity. Most of AEs were considered related to musculoskeletal injuries, headaches, or illnesses that normally occur in this population; the most common AEs are summarized in table 5. The 4 severe AEs reported during this study were general disorder/other (nausea, high fever, impaired balance that required hospital admission), a gallbladder obstruction, a urinary tract obstruction, and a neoplasm. None of these severe AEs were considered related to TLNS treatment. There were 2 mild and 6 moderate AEs related to treatment: 3 were considered possibly related, 2 probably, and 3 definitely (vertigo, pain, or headache). There were 4 device-related AEs and all were considered mild.

## Discussion

Results from this double-blind, randomized, clinical trial demonstrated significant improvement in balance. Improvements in the SOT composite score from baseline to all time points evaluated for both TLNS treatment arms ([HFP or LFP]+PT) were statistically significant; however, there was not a significant difference between the HFP and LFP arms. The mean composite SOT scores for both groups reached the normal range (>69)[48] by week 14 and improved by week 26 in the HFP group; the LFP group showed a small decline in score during the withdrawal phase.

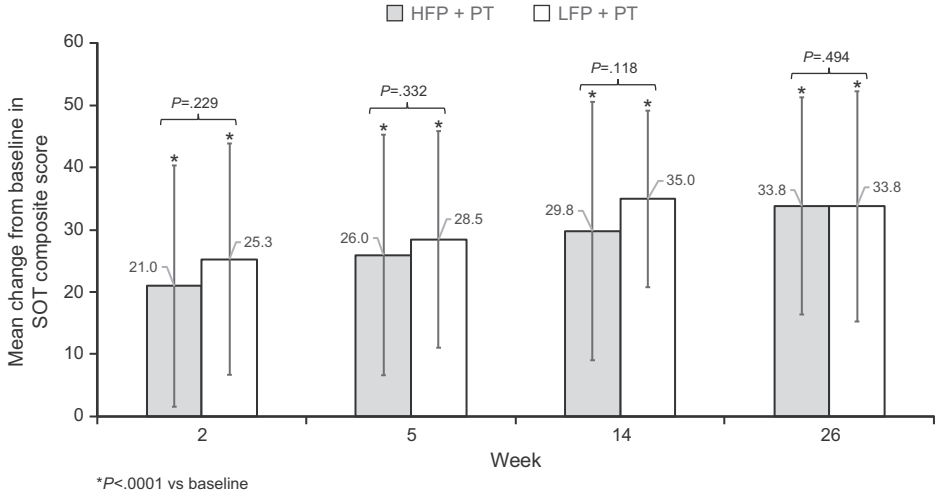


**Fig 2** Mean changes ± SD from baseline to weeks 2, 5, 14, and 26 in SOT composite score for the HFP and LFP groups. Mean SOT composite score change from baseline to each assessment point was calculated for both the HFP (dark gray) and LFP (light gray) treatment arms. *P* values for comparison between the 2 arms are shown on the graph; an * denotes *P*<.0001 for changes from baseline at each assessment time.

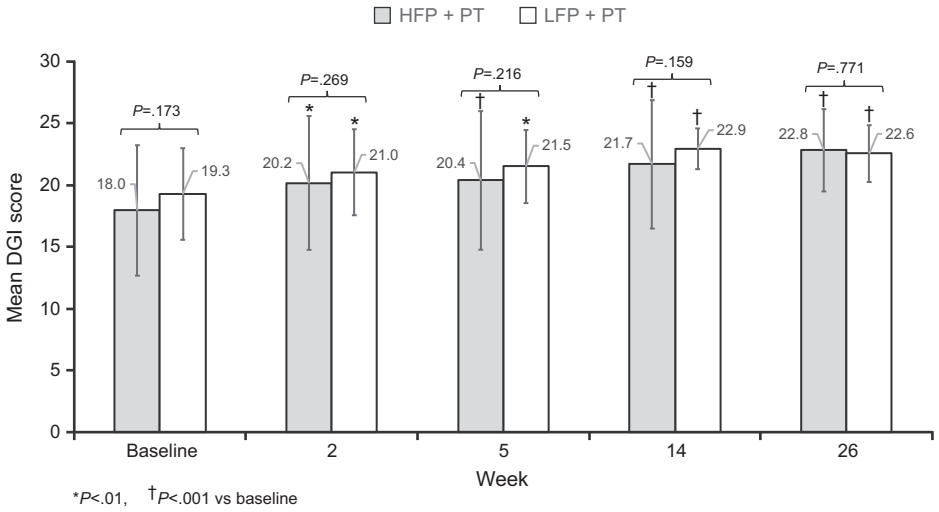


**Fig 3** Mean DGI score ± SD by HFP and LFP treatment arm. The mean DGI score at baseline and at each assessment time is shown for both the HFP (dark gray) and LFP (light gray) treatment arms. *P* values for comparison between the 2 arms are shown on the graph. *Denotes a *P* value <.01 and †*P*<.001.

Improvements in the SOT score after combining the treatment groups ranged from >20 points at week 2 to >30 points at week 26. These increases greatly exceeded an 8.48-point increase in the SOT composite score considered clinically significant for individuals with concussion[47] or who received vestibular rehabilitation therapy (8-13 points).[26,49,50]

Results for the key secondary endpoints related to gait and balance also suggest a clinically meaningful benefit of TLNS treatment. DGI scores <19 are indicative of an elevated risk of falls,[46] and a change of 3 points is generally considered clinically significant.[51-53] DGI scores improved to near-normal levels at weeks 14 and 26, changing 3 points from baseline. Similarly, by the end of the study, participants in both groups exhibited clinically meaningful increases in 6MWT distance, approaching normal values.[54-56] Significant improvements in SOT, DGI, and 6MWT scores were all noted after multivariate repeated measures ANOVA testing. These findings support that the study was sufficiently powered to avoid a Type I error and confirms the key results of the primary analysis.

The benefit of TLNS treatment was also observed in additional assessments. In both treatment arms, Headache Disability Index scores were reduced by approximately 40%, driven primarily by lower headache severity and frequency. The Pittsburgh Sleep Quality Index also improved, primarily in the sleep-wake cycle. Both groups had baseline NSI values exceeding 24 at baseline (considered clinically elevated).[57,58] After treatment, there was a 31% and a 23% decrease in mean NSI score for the HFP and LFP groups, respectively, suggesting a reduced effect of TBI symptoms on participants. Finally, BSI scores dropped from the upper

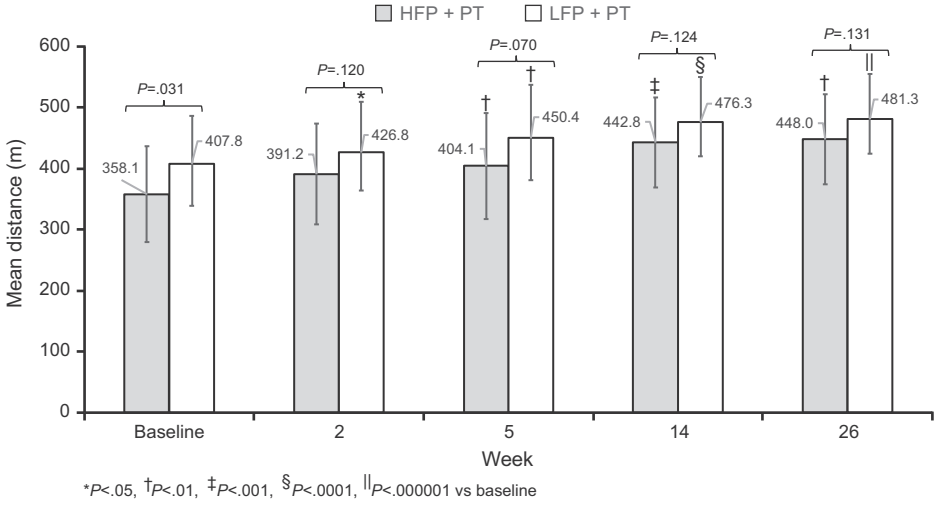


**Fig 4** Mean 6MWT score ± SD for 6MWT by HFP and LFP treatment arm. The mean DGI score at baseline and at each assessment time is shown for both the HFP (dark gray) and LFP (light gray) treatment arms. *P* values for comparison between the 2 arms are shown on the graph. *Denotes a *P* value <.05, †<.01, ‡<.001, §<.0001, and ‖<.000001.

**Table 4** Mean measure for exploratory assessments at baseline and wk 2, 14, and 26

| Measure | HFP+PT | | | | LFP+PT | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline | Wk 2 | Wk 14 | Wk 26 | Baseline | Wk 2 | Wk 14 | Wk 26 |
| NSI* | 38.59 | 26.38 | 30.47 | 31.33 | 36.62 | 29.10 | 28.25 | 26.95 |
| BSI* | 60.77 | 56.91 | 58.74 | 55.67 | 59.90 | 57.86 | 56.55 | 57.00 |
| PSQI* | 9.32 | 8.68 | 8.61 | 8.29 | 9.18 | 7.81 | 8.71 | 8.24 |
| HDI* | 40.91 | 24.91 | 33.26 | 30.67 | 40.76 | 36.68 | 28.40 | 25.80 |

NOTE. All values are means.
Abbreviations: BSI, Brief Symptom Inventory; HDI, Headache Disability Index; NSI, Neurobehavioral Symptom Inventory.
* Lower score represents improvement.

limit of the normal range[59] to within the normal range (<59) for both treatment groups. These trends demonstrate that TLNS treatment, targeted to improve balance and gait, has the potential to affect a multitude of mmTBI-related symptoms. Further analysis of secondary and exploratory endpoints is underway.

Importantly, the improvements achieved with TLNS treatment persisted for at least 12 weeks after the treatment was terminated. One possible explanation is that participants were less encumbered, leading to more activity, possibly influencing plasticity. Also, the intervention may have activated a currently unknown neurological mechanism that continued to function during the neurorehabilitation process. Other studies of electrical or magnetic nerve stimulation have demonstrated clinical benefits for 1 month[60] to 12 months[61] after the termination of neuromodulation.

In studies comparing high- and low-frequency stimulation, it is not uncommon to observe little or no difference in treatment effect. The results with HFP and LFP TLNS treatment are similar to those from transcutaneous electrical nerve stimulation studies, which have indicated significant benefits of both low- and high-frequency stimulation.[36-39,41,42,44] A study of vagus nerve stimulation for treatment-resistant depression also indicated that there was no significant difference between low-, medium-, and high-frequency stimulation.[43] These reports prompted study design deviations (see supplemental appendix S1) to investigate outcomes from devices with 2 different stimulus levels as opposed to considering the LFP device a control. Regarding the potential for a placebo effect, high- and low-frequency stimulation does not differ in experimental animal studies,[62-64] a setting in which *participant* expectations regarding potential treatment benefit are unlikely to influence study results.[65]

**Table 5** Any-cause AEs with ≥1 occurrence in either treatment group

| AE | HFP+PT (n=22) | LFP+PT (n=21) |
|---|---|---|
| Any event | 54 | 37 |
| Ear pain | 2 | 0 |
| Falls | 9 | 3 |
| Cold | 3 | 4 |
| Headache | 5 | 5 |
| Muscle weakness | 3 | 3 |
| Musculoskeletal injury | 5 | 0 |
| Neck pain | 2 | 3 |
| Pain in extremity | 3 | 5 |
| Surgical and medical procedures | 2 | 0 |
| Urinary tract infection | 2 | 0 |

The underlying neurological mechanisms of the neurorehabilitation process are only now beginning to be understood. Recent animal studies help demonstrate the promising strategy of trigeminal nerve stimulation in TBI symptom management. In a rat model of stroke, infarction volume was decreased after trigeminal nerve stimulation via the forehead; changes comparable to a *diving response*, which can have a neuroprotective component and potential therapeutic benefit,[66] were also elicited. In related animal research, direct stimulation of the trigeminal nerve induced a pressor response and improved cerebral blood flow by causing cerebrovasodilation through activation of the trigemino-cerebrovascular system and trigemino-parasympathetic reflex[67]; beneficial effects included increased cerebral perfusion and reduction in edema, blood–brain barrier disruption, and lesion volume.

That participants in both treatment arms responded robustly to TLNS plus PT, after plateauing on previous PT, suggests that TLNS treatment may activate a neural or glial network associated with the targeted activities, which then reaches a sensory threshold and activates a neural network. The significant increases from baseline in the SOT composite score suggest improvements in somatosensory, visual, and vestibular systems that contribute to postural control. There were also significant improvements in both the DGI and 6MWT and a positive trend in the ancillary measures of sleep, headache, neurobehavioral symptoms, and cognitive performance. The threshold of neural activation may be more important than how many pulses are generated, as LFP stimulation yielded only slightly lower assessment scores than HFP stimulation, with no significant difference between the HFP and LFP arms for any of the endpoints evaluated. These findings suggest that both dosages were above a currently unknown activation threshold for effecting functional neurorehabilitation.

## Study limitations

One limitation of this study is the inherent variable presentation of TBI[68]; however, the indication of mmTBI helped to create a more homogeneous cohort. Differences in the nature of mmTBI, participant age, symptom number

and severity, time since injury, age at time of injury, and degree of success with prior therapy could each have contributed to the variability observed with each assessment. Furthermore, even with matched representation between treatment arms, sex differences in physiologic and neurologic responses to both the initial brain injury and to physical activity could have affected the results.[69] Although men experience approximately 1.4 times as many TBIs as women,[70] the number of female participants in this study was 1.75 times more than males. This difference may be attributed to the recruitment method, the fact that women are more likely than men to seek medical care for symptoms, or simply participant availability. Also, the presence or absence of oculomotor deficits in the participant cohort was not controlled for in this study. Although most participants had normal or corrected vision and normal videonystagmography scores, 5 of the 44 participants exhibited significant oculomotor control abnormalities, which could contribute to postural and gait instability, difficulties with visual attention and reading, and headache severity.[9,19]

Although all participants had previously completed some form of balance or gait rehabilitation therapy, each had his/her own physical, cognitive, and emotional capacity for the training program. Study participation required a large commitment of time, energy, and resources (eg, material, financial, emotional support). Many of the participants were not local, creating challenges with respect to travel to the study site. Dedicating 2-3 hours to treatment 6 days weekly over 14 weeks was challenging and was the primary factor in participant attrition. Even so, 37 of the 43 participants (86%) completed the entire 26-week study. Absence of data for the participants who did not complete the study may have contributed to the variance in the results, because imputation for absent data was not employed. External factors likely had variable influence on participant level of exertion for the daily treatments and then monthly monitoring visits during the withdrawal period.

Factors that may affect the response to an intervention include the placebo effect, Hawthorne effect, and nonspecific attention and care.[71,72] There may be an elevated placebo effect when using a medical device, but the evidence is inconclusive.[73] For example, studies using transcutaneous electrical nerve stimulation demonstrated that it is no more effective than treatment with a placebo.[74-76] The personal view of one's own disease condition may also result in the placebo effect; by believing that TBI-related symptoms are transient or improving, study participants may increase their effort in the therapeutic intervention or may develop higher expectations based on experiences with previous treatments.[71] Many, if not all, of the participants in this study agreed to join because their symptoms had stopped improving and had not fully resolved in response to previous PT. This point leaves open the possibility that participants could have had the expectation that this was a better type of PT, which could contribute to a placebo effect.

## Conclusions

The results of this clinical trial demonstrate that there were statistically significant improvements from baseline for balance and gait assessments in both treatment arms. There was no significant difference in outcomes of TLNS treatment between the HFP and LFP groups. Importantly, the observed benefits produced sustained improvements for another 12 weeks after treatment discontinuation. Whether these improvements can be associated with an equal effectiveness of the 2 dosages or whether they result from the provision of PT to both groups cannot be conclusively established at this time. Future research is needed to assess the dosing parameters of TLNS, as well as additional and longer-term benefits of this treatment.

## Suppliers

a. NeuroCom Sensory Organization Test; Natus Medical.
b. PoNS; Simplex Scientific.
c. R (version 3.4.1); R Foundation for Statistical Computing.
d. VassarStats; VassarStats.
e. Statistical Analysis System; SAS Institute.

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