A Prospective, Multicenter Study to Assess the Safety and Efficacy of Translingual Neurostimulation Plus Physical Therapy for the Treatment of a Chronic Balance Deficit Due to Mild-to-Moderate Traumatic Brain Injury

Alain Ptito, PhD*; Linda Papa, MD, MSc[†]; Kenton Gregory, MD[‡];
Robert L. Folmer, PhD[§¶]; William C. Walker, MD[**];
Vivek Prabhakaran, MD, PhD[††]; Rima Wardini, MSc[‡‡1];
Kim Skinner, PT, DPT[§§]; Michael Yochelson, MD, MBA[¶¶***]

Objectives: Translingual neurostimulation (TLNS) studies indicate improved outcomes in neurodegenerative disease or spinal cord injury patients. This study was designed to assess the safety and efficacy of TLNS plus targeted physical therapy (PT) in people with a chronic balance deficit after mild-to-moderate traumatic brain injury (mmTBI).

Materials and Methods: This international, multicenter, randomized study enrolled 122 participants with a chronic balance deficit who had undergone PT following an mmTBI and had plateaued in recovery. Randomized participants received PT plus either high-frequency pulse (HFP; $n = 59$) or low-frequency pulse (LFP; $n = 63$) TLNS. The primary efficacy and safety endpoints were the proportion of sensory organization test (SOT) responders (SOT composite score improvement of ≥15 points) and fall frequency after five weeks of treatment, respectively.

Results: The proportion of SOT responders was significant in the HFP + PT (71.2%) and LFP + PT (63.5%) groups compared with baseline ($p < 0.0005$). For the pooled population, the SOT responder rate was 67.2% ($p < 0.00005$), and there were clinically and statistically significant improvements in SOT composite scores after two and five weeks ($p < 0.0005$). Both groups had reductions in falls and headache disability index scores. Mean dynamic gait index scores in both groups also significantly increased from baseline at weeks 2 and 5.

Conclusions: Significant improvements in balance and gait, in addition to headaches, sleep quality, and fall frequency, were observed with TLNS plus targeted PT; in participants who had a chronic balance deficit following an mmTBI and had plateaued on prior conventional physiotherapy.

Address correspondence to: Alain Ptito, PhD, Psychology Department, McGill University Health Centre; Montreal Neurological Institute and Hospital, 3801 Université, Montréal, Québec, Canada, H3A 2B4. Email: alain.ptito@mcgill.ca

* Psychology Department, McGill University Health Centre; Montreal Neurological Institute and Hospital, Montreal, QC, Canada;
[†] Department of Emergency Medicine, Orlando Health, Orlando, FL, USA;
[‡] Center for Regenerative Medicine, Oregon Health and Science University, Portland, OR, USA;
[§] Department of Otolaryngology, Oregon Health and Science University, Portland, OR, USA;
[¶] National Center for Rehabilitative Auditory Research, VA Portland Health Care System, Portland, OR, USA;
[**] Department of Physical Medicine and Rehabilitation, Virginia Commonwealth University, Richmond, VA, USA;
[††] Department of Radiology, University of Wisconsin Hospitals and Clinics, University of Wisconsin, Madison, WI, USA;
[‡‡] Helius Medical Inc Canada, Vancouver, BC, Canada;
[§§] Helius Medical Inc, Newtown, PA, USA;
[¶¶] Shepherd Center, Atlanta, GA, USA; and
[***] MedStar National Rehabilitation Network, Washington, DC, USA

[1]Denotes author's affiliation at the time the study was conducted.

INTRODUCTION

The severity of a traumatic brain injury (TBI) is clinically categorized as mild, moderate, or severe (1–4), which is traditionally based upon clinical measures for acutely altered consciousness combined with imaging findings (5,6). The Department of Defense/Veterans Administration definition of TBI severity (which does not include penetrating injury) was used for this study (2). The incidence of mild-to-moderate TBI (mmTBI) accounts for the great majority (>80%) of global TBIs (7), and typically both mild and moderate injuries have better outcomes than severe TBI (2,8); however, nearly one quarter of individuals suffering from a mild TBI have persistent postconcussive symptoms (9). Symptoms including cognitive, somatic, and emotional problems may persist ≥1 year post injury, interfering with daily activities and resulting in disability, lost workplace productivity, and a significant burden on the individual and to society (9).

Current treatment options for balance impairment after mmTBI are limited. Approximately 14.6 million people, globally, suffer from a chronic balance deficit after mmTBI (10–12), stressing the unmet need in this patient population. Traditional treatment involves physical therapy (PT), often vestibular based. Evaluations of this approach have indicated that it can result in full recovery (i.e., return to normal balance and gait function) in many, but not all, patients; therefore, controlled studies are needed to draw definitive conclusions with regard to optimal treatment (13).

For many patients, the signs and symptoms of mmTBI resolve with time, and patients can return to normal daily activities; however, 10%–50% of patients experience one or more chronic symptoms, such as difficulty with memory, attention, and executive function; dysregulation of sleep, speech, mood, eye movement control; and increases in headache frequency/magnitude (14–19). Postural instability or imbalance can also persist after TBI (10,20), which has a major negative impact on functional status, capacity to return to work, and quality of life (17,21–25).

Recently, neuromodulation targeting cranial nerves via noninvasive neurostimulation has emerged as a potential treatment approach for patients with chronic pain and neurological disorders (26). Neurostimulation devices targeting the trigeminal nerve or vagus nerve by application to the forehead or neck, respectively, have been approved by the US Food and Drug Administration to treat migraine and/or cluster headache (26–29). Both noninvasive neurostimulation and motor training/physical exercise have been shown to independently promote neuroplastic changes (30). When considering combining these approaches to enhance outcomes, it has been proposed that neurostimulation may prime neuronal networks, recruit task-specific synaptic connections, and/or consolidate new signal pathways when used before, during, or after a physical rehabilitation task (30).

Translingual neurostimulation (TLNS) is a noninvasive method used to elicit neural changes by stimulating cranial nerves via the anterior third of the tongue (31,32). The tongue is a desirable organ for stimulation because it is highly innervated, provides an environment with a constant pH level and temperature, and has a low excitability threshold (31). TLNS delivers sequenced patterns of electrical stimulation to sensory fibers approximately 300–400 µm from the tongue surface to create action potentials through multiple existing synaptic connections (31). This stimulation engages a flow of signals through naturally occurring neural networks via activation of the lingual branch of the trigeminal nerve (cranial nerve Vc) and the chorda tympani branch of the facial nerve (cranial nerve VII) (33,34). Although the primary function of the chorda tympani is to relay information regarding taste (31), there is considerable intermingling of cranial and other nerves, which can provide an opportunity for chorda tympani activation to occur alongside stimulation of facial or other nerve branches (e.g., trigeminal nerve) (35). Using high-density electroencephalography, Frehlick et al. reported that TLNS significantly changed resting-state brain activity (36). Additionally, high-resolution image processing has allowed observation of changes in functional activity in the brainstem, pons, and cerebellum, which are major sensory integration and movement control centers of the brain (34,37–39). Together, these data help explain the potential link between the physiological mechanism of neurostimulation, the underlying neural changes, and any clinical effects that may be observed.

The results from clinical reports and preliminary studies have indicated that TLNS plus targeted PT can significantly improve patient outcomes (31,34,37,40–48). Improvements in balance and gait function have specifically been noted in patients with cerebellar degeneration (42), chronic multiple sclerosis (MS) (43,44), spinal cord injury (45), and stroke (46). In addition, the results from two open-label TLNS studies indicated that noninvasive cranial nerve neurostimulation can improve dynamic gait index (DGI), activities-specific balance confidence scale, and dizziness handicap inventory scores in patients with impaired balance or peripheral and central vestibular loss (38,47). Interpretation of results from these studies, although informative, is limited by small sample sizes, lack of randomization, the absence of blinding, and variability in treatment schedules and follow-up (48).

A 26-week study of 44 participants was performed at the University of Wisconsin–Madison, comparing the use of high- or low-frequency TLNS plus PT in an mmTBI population that was greater than or equal to one year from their injury and continued to demonstrate a balance deficit after conventional PT (41). Participants engaged in a two-week in-clinic training program, followed by 12 weeks of at-home progressive training and then a 12-week withdrawal period (no training or TLNS). This study reported significant improvement in both treatment groups from baseline to weeks 2, 5, 14, and 26 for balance (based on sensory organization test [SOT] composite score and DGI). The scores during the withdrawal period demonstrated that the improvements achieved during the 12 weeks of training intervention were sustained. Interestingly, although both groups demonstrated significant

Table 1. A Summary of Endpoints and Measurement.

Primary effectiveness endpoint	The proportion of responders at week 5
Secondary effectiveness endpoint	Increase in SOT from baseline at weeks 2 and 5
Primary safety endpoint	Frequency of falls during the five-week study*
Secondary safety endpoint	Frequency and severity of headaches measured by HDI at baseline and week 5
Other assessments of interest	6MWT distance at baseline, weeks 2 and 5
	DGI at baseline, weeks 2 and 5
	SQI at baseline and week 5
	QoL measure at baseline and week 5
	AEs throughout treatment

*A "fall" was defined as an event where a participant lost balance and fell or would have fallen were it not for external intervention, such as stabilization on the back of a chair or the wall; stabilization to restore balance was not considered to be a fall.
6MWT, six-minute walk test; DGI, dynamic gait index; HDI, headache disability index; QoL, quality of life; SOT, sensory organization test; SQI, sleep quality index.

improvement from baseline, the outcomes between the high- and low-frequency groups were not significantly different.

As described above, promising results have been reported from studies using TLNS plus targeted PT across various neurological conditions; however, many of these investigations are small studies or case reports or had participants with varying neurological conditions. To investigate the role of TLNS plus PT in a well-defined homogeneous population of patients with mmTBI, two studies were designed: the 26-week study noted above (41) and the large, multicenter, double-blind randomized study (NCT02429167) described here. The goal of the latter was to evaluate the safety and effectiveness of TLNS plus targeted PT in people with a chronic balance deficit after an mmTBI who had plateaued with a prior conventional PT program.

MATERIALS AND METHODS

Study Design

This multicenter, double-blind, randomized study (NCT02429167; clinicaltrials.gov) was conducted at seven sites in the United States and Canada from August 2015 to September 2017. Institutional review boards at each site approved the study protocol, and the trial was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonization Harmonized Tripartite Guidelines for Good Clinical Practice (see Supporting Information Methods). All participants provided written consent before participation. Randomization was performed by the sponsor-designated clinical research organization according to generally accepted standards to ensure blinding of the participants and treating clinicians. The participants, TLNS trainers, and investigators were all blinded to treatment group. A blinding assessment was conducted at the end of the study to assess success.

Participants

Participants were eligible if they were aged 18–65 years, had a documented mmTBI diagnosis greater than or equal to one year prior to enrollment, and had a balance deficit with a NeuroCom® SOT composite score ≥16 points below normal (based on normative data). All participants had to have undergone a targeted PT program focused on balance/gait deficit due to TBI and reached a plateau in recovery (according to their healthcare providers). Prior PT varied, and participants were not required to submit specifics of the previous program, only that they had a persisting balance deficit (as described above) after undergoing PT. Enrolled patients also had to have a "negative" neuroradiologic scan and report greater than or equal to one year after their most recent TBI. "Negative" neuroradiologic scans were defined as no evidence of refractory subdural hematomas, tumors, significant anatomical anomalies, or loss of gray matter, per clinical judgment of the neuroradiologist.

Participants were excluded if they had oral health problems, nonremovable metal orthodontic devices, oral cavity piercings that could interfere with TLNS use, chronic infectious disease, uncontrolled hypertension, diabetes, other neurological disorders (not attributed to their primary diagnosis), cancer treatment (other than basal cell carcinoma) within the past year, penetrating injury, craniotomy, or refractory subdural hematoma. Participants with long-term use of psychoactive medications that would compromise the participant's ability to comprehend and perform study activities per investigators and those with pacemakers or elevated cardiovascular risk were also excluded. Individuals with severe symptoms (see Supporting Information Methods) were also excluded. Any changes in medication, either for TBI-related or other symptoms, or any use of other investigational device or medication lesser than or equal to three months prior to enrollment were temporary exclusions and subject to study physician discretion.

Treatment

As previously described (31,49), the TLNS device delivers 19-volt amplitude-controlled, pulse-width modulated, unbalanced biphasic pulses to the anterior superior surface of the tongue through 143 gold-plated electrodes on a polyimide substrate (see Supporting Information Methods). A zero net direct current minimizes the potential for tissue irritation. Participants ($N = 122$) were randomized in a 1:1 ratio to receive TLNS with either high-frequency pulse (HFP) or low-frequency pulse (LFP) stimulation in combination with PT. The HFP emitted triplets of 0.4 μs to 60 μs wide pulses (five ms intervals; 150 pulses/s), and the LFP used a modified stimulus waveform pattern of 12.5 s intervals to each electrode (0.08 pulses/s). The HFP/LFP stimulation ratio is 1875:1. The stimulus intensity on the device was set to a comfortable level according to the feedback provided by each participant and was fixed at this level for the study duration. The sensation of the stimulus has been reported to feel similar to a carbonated beverage, and reports of taste sensations are infrequent (31).

The treatment program consisted of five weeks of training using the TLNS device in 20-minute sessions for 100–120 minutes/day over

two stages. Stage 1 was a two-week in-clinic training during which participants worked with a therapist who was certified in use of the device: twice daily for one-hour sessions to perform the different training modules (two balance, two gait, one warm-up, one movement control exercise, one breathing and awareness training [BAT]), followed by a BAT session completed independently at home. The same regimen was performed in stage 2, with the exclusion of the morning BAT session. Stage 2 was a three-week at-home training program and participants returned to the clinic for weekly supervised training during which the PT program was adjusted. Participants were assessed at baseline and after two and five weeks. All participants followed the same TLNS use and PT regimen; training intensity was customized to the individual's presentation and abilities. Adherence was automatically monitored through the TLNS device by logging usage; these data were downloaded and verified weekly, and compliance rates were determined.

Figure 1. CONSORT flow diagram. HFP, high-frequency pulse; LFP, low-frequency pulse; PT, physical therapy.

Endpoints

A summary of endpoints and measurements is shown in Table 1. The primary efficacy endpoint was the proportion of SOT responders (defined by an improvement in SOT composite score of ≥15 points) after five weeks of treatment. An increase of greater than or equal to eight points in SOT composite score is considered to be clinically significant (50). There were two secondary efficacy endpoints: change in SOT composite score from baseline to the end of in-clinic training (week 2) and to the end of at-home training (week 5). The primary safety endpoint was the frequency of falls, as recorded by the participant on an electronic case report form (eCRF), which was filled out either at/near the time of each clinic visit or when test results were received; data were de-identified on the eCRF. The secondary safety endpoint was the frequency of headaches at baseline and after five weeks of treatment, measured by the headache disability index (HDI). Additional outcomes of interest were the six-minute walk test (6MWT), DGI, quality of life measure index (QLMI), and sleep quality index (SQI). The incidence of adverse events (AEs) were collected throughout the study, assessed and recorded at each study center visit. Severe AEs are those that are usually incapacitating and prevented the participant from performing normal daily activities; they typically required a systemic drug or other treatment. A serious AE was defined as any reaction that is life-threatening at the time of the event or that results in death, hospitalization, or significant/persistent disability.

Data Analysis

The intent-to-treat population, the primary population for efficacy analyses, included all participants who were randomized into HFP or LFP treatment groups (see Supporting Information Methods). The safety population included all participants receiving greater than or equal to one treatment in either group.

Given reports of positive responses to both high- and low-level stimulation in vagus nerve studies (51,52), transcutaneous electrical nerve stimulation (TENS) (53–56), and transcranial magnetic stimulation (57,58), it was considered possible that both the HFP and LFP treatment groups would respond to TLNS treatment in this study. If there was no significant between-group difference for the primary efficacy endpoint, the two treatment arms were to be pooled for preplanned statistical analyses of the primary and secondary efficacy endpoints.
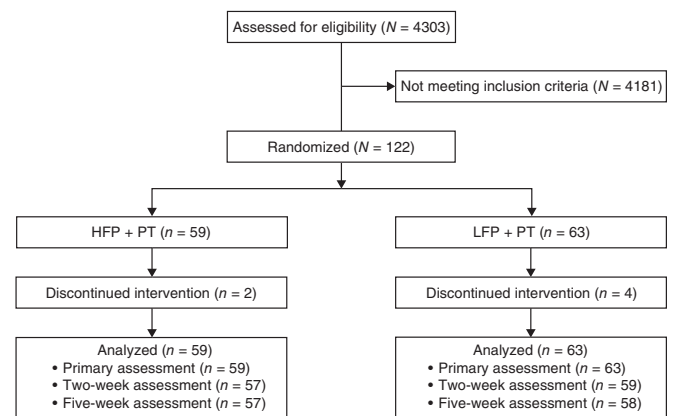
One interim effectiveness analysis was planned for when 30 participants in each study arm had completed the five-week treatment and was conducted by an unmasked independent statistician. If the results were significantly higher in the HFP + PT than in the LFP + PT group ($p \leq 0.005$), the study would be terminated. If $p > 0.005$, the study would be continued until all participants had been enrolled.

A post hoc statistical analysis of additional variables of interest (i.e., 6MWT, QLMI, SQI) was conducted. Least squares mean values were determined at baseline and at week 5 for each measure in each treatment group. The difference in these values was calculated along with a p value to assess significance between the two time points. A score decrease in HDI or SQI or a score increase in QLMI was considered a clinical improvement.

To evaluate the effect of different covariables on changes in SOT composite score, two post hoc analyses were performed: a logistic regression analysis of 88 covariates (see Supporting Information Methods) and a multivariate logistic regression analysis (MVA). Covariates in the MVA included age, sex, body mass index, prior PT duration, time since TBI, baseline 6MWT distance, and baseline postconcussion total score.

Sample Size Determination

Determination of sample size was based on results from a small pilot study of participants who received HFP + PT. There were no available data to predict the magnitude of the difference between results for the HFP + PT and LFP + PT groups when this randomized study began; therefore, it was assumed that 90% of patients in the HFP + PT group and 60% of those in the LFP + PT group would be responders. Under these assumptions, a two-group continuity-corrected χ^2 test with a 0.05 two-sided significance level indicated that 90% power to detect a between-group difference in responder rate for the HFP + PT and LFP + PT groups could be achieved with a sample size of 49 in each arm. The target enrollment for each arm was set at 60 to account for a projected 20% dropout rate.

RESULTS

A total of 4303 participants from across seven sites in the United States and Canada were screened via phone interview followed by 210 live screens. Inclusion criteria were met by

Table 2. Patient Demographic and Clinical Characteristics.

Characteristics	HFP + PT (n = 59)	LFP + PT (n = 63)
Mean age, years (range)	48.9 (21–63)	43.8 (18–64)
Male, n (%)	16 (27)	23 (37)
Female, n (%)	43 (73)	40 (63)
Race, total population (N = 122), n (%)		
African American/Black	6 (5)	
American Indian/Alaskan Native	1 (<1)	
Asian	3 (2)	
Native Hawaiian/Pacific Islander	2 (2)	
White	110 (90)	

HFP, high-frequency pulse; LFP, low-frequency pulse; PT, physical therapy.

Figure 4. Mean increase in DGI score from baseline. The mean DGI score at weeks 2 and 5 was calculated for both the HFP + PT and LFP + PT treatment arms. *$p < 0.0001$ vs baseline. DGI, dynamic gait index; HFP, high-frequency pulse; LFP, low-frequency pulse; PT, physical therapy.
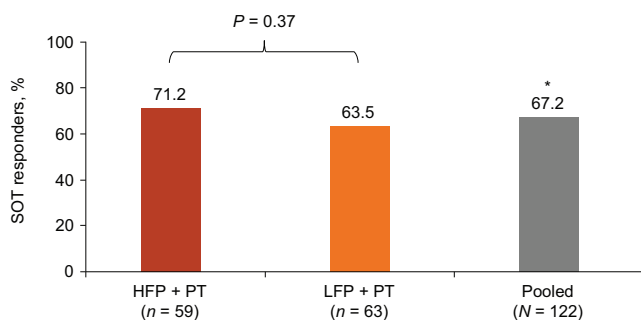

Figure 2. SOT responders at five weeks. SOT responder rate in the HFP + PT, LFP + PT, and pooled groups at five weeks. Responders were defined as participants who had an improvement of ≥15 points in SOT score from baseline. *$p < 0.0005$ vs baseline. HFP, high-frequency pulse; LFP, low-frequency pulse; PT, physical therapy; SOT, sensory organization test.

122 participants, who were randomized into two TLNS treatment groups: HFP + PT (n = 59) and LFP + PT (n = 63; Fig. 1). The median time from the qualifying injury to enrollment in the overall population was 5.7 years (range, 1–33 years). Prior to study entry, participants underwent a mean 8.8 months (range, 1–60 months) of outpatient PT for TBI-related symptoms. Rehabilitation programs varied in their inclusion of components such as
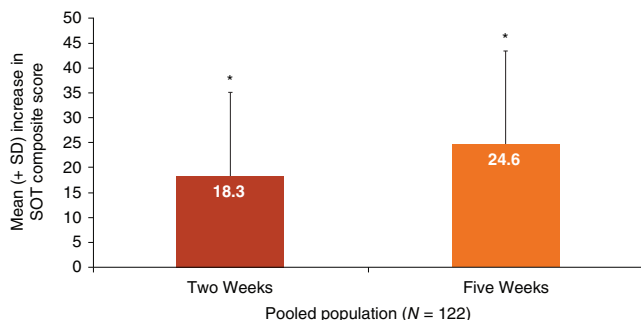

Figure 3. Mean increase in SOT composite score from baseline in the pooled population (HFP + PT and LFP + PT). Mean changes (+SD) from baseline to weeks 2 and 5 in SOT composite score for the pooled group. *$p < 0.0005$ vs baseline. HFP, high-frequency pulse; LFP, low-frequency pulse; SD, standard deviation; SOT, sensory organization test.
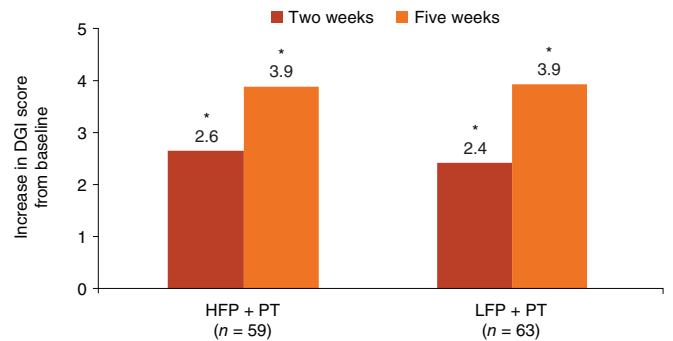
exercise, balance training, gait training, vestibular therapy, work adaptations, ocular training, and neuromuscular reeducation. Detailed demographic characteristics of study participants are summarized in Table 2. At the study start, participants had common ongoing symptoms that included headache/migraine (n = 74), dizziness (n = 45), fatigue (n = 40), and concentration/memory difficulties (n = 29). A total of 115 participants had data available at the five-week assessment. Overall compliance measured by the TLNS device was a mean of 94% across weeks 2 through 5 of the study.

Efficacy Endpoints

The proportion of participants who were SOT responders was significant in both HFP + PT (71.2%, n = 42) and LFP + PT (63.5%, n = 40) groups compared with baseline ($p < 0.0005$). There was no significant difference between the responder rates for the HFP + PT and LFP + PT groups ($p = 0.37$). In accordance with the predefined statistical analysis plan, the two treatment groups were pooled, which resulted in an overall responder rate of 67.2% (n = 82) compared with baseline ($p < 0.0005$; Fig. 2).

Results for the combined HFP + PT and LFP + PT populations indicated a clinically and statistically significant improvement in mean SOT composite scores from baseline to two and five weeks of treatment (Fig. 3). Mean SOT composite score ($\pm$ standard deviation) for the pooled population was 18.3 ± 16.8 points ($p < 0.0005$) at two weeks and 24.6 ± 18.8 points ($p < 0.0005$) at five weeks. Mean DGI scores in both treatment groups were significantly increased from baseline at weeks 2 and 5 ($p < 0.0001$; Fig. 4).

The change in least squares mean values of the 6MWT, QLMI, and SQI from baseline to week 5 was measured (Supplemental Table 1). HDI and SQI scores significantly decreased and QLMI scores significantly increased from baseline to week 5 in both treatment groups.

A post hoc logistic regression analysis identified seven covariates with potential to predict an SOT response. No logistic regression estimates were >1.0, and most odds ratio CIs contained 1.0 (Supplemental Table 2). An MVA was also performed. This analysis showed that the variables (i.e., age, sex, body mass index, baseline 6MWT distance, and baseline postconcussion total score), including time since TBI, had little or no predictive power for those who responded to treatment
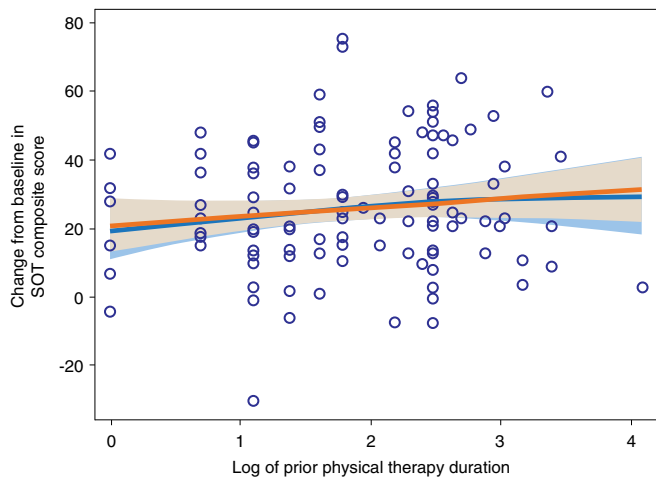
Figure 5. Change in SOT composite score from baseline over the duration of prior PT. The pooled population of HFP + PT and LFP + PT groups were analyzed through linear regression analysis (orange line) and locally weighted scatter plot smoothing (LOESS; blue line). The corresponding shaded areas represent confidence bands for the linear regression and LOESS lines; fit of the solid line within the associated confidence band suggests there is no likely relationship between the observed change in SOT composite score from baseline and the duration of prior PT. LOESS, locally weighted scatterplot smoothing; PT, physical therapy; SOT, sensory organization test.

Table 3. TLNS Device-Related AEs.

TLNS-related AEs with >1 episode*	Number of episodes
Burning sensation on the tongue	6
Tongue tingling	4
Sore tongue	3
Decrease in tongue sensation	2

*All device-related AEs were mild in severity.
AE, adverse event; TLNS, translingual neurostimulation.

(Supplemental Table 3). The duration of prior PT also did not have any predictive power for improvement in SOT composite score (Fig. 5).

Safety

Both the HFP + PT and LFP + PT groups had a reduction in the number of falls from baseline (Fig. 6a) and a reduction in HDI scores from baseline (Fig. 6b) over the course of treatment.

A total of 841 AEs were reported, 279 of which were device related. Twenty-two AEs across 12 participants were deemed "definitely" related to the TLNS device and were all considered mild (Table 3). There were 24 severe treatment-related AEs reported across nine participants during the study; these AEs resolved, and each participant continued in the study. None of these severe AEs was considered related to the device. The most common severe AEs were multiple episodes of vomiting ($n = 5$), nausea ($n = 5$), fainting ($n = 2$), and worsening of nausea ($n = 2$). No serious AEs were reported.
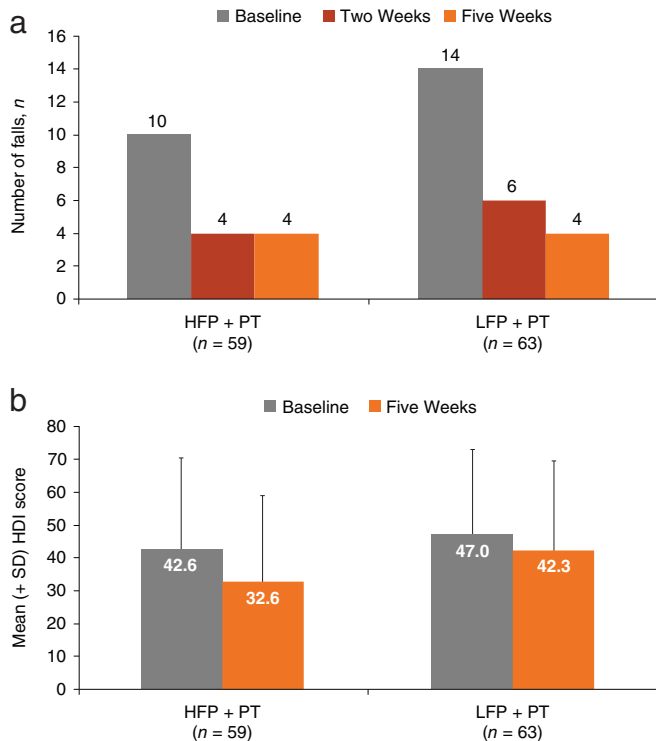
DISCUSSION

This study is the largest multisite randomized trial in patients with a chronic balance deficit after mmTBI who had plateaued on their previous rehabilitation program. Results from this study indicate that TLNS plus targeted PT with either HFP or LFP stimulation had a significant benefit in this population. Improvements from baseline in both the SOT composite score and DGI from both groups were statistically significant and clinically meaningful, defined as a minimal eight-point increase in the SOT composite score and a minimal 2.9-point increase in DGI score, respectively (59,60). Responder analysis in this study used 15 points as a cutoff threshold to demonstrate improvement in the SOT, almost double what has been demonstrated to be a clinically meaningful change (50,59).

The statistical analysis plan stipulated that if the results for the two groups were not statistically different, they would be pooled for analysis. The responder rate for the pooled group significantly improved from baseline (67.2%, $p < 0.0005$). Furthermore, the combined analysis showed that the use of TLNS + PT resulted in significant improvements in SOT composite scores after two and five weeks of treatment (both $p < 0.0005$).

The lack of significant difference for SOT composite scores between the dosage groups was, in part, attributed to high response rates occurring in both the LFP + PT group (63.5%) as well as the HFP + PT group (71.2%). At the time of study development, there were no previous data for participants with LFP stimulation (the 26-week study [41] had just been initiated), and three potential outcomes were considered for group comparison in this

Figure 6. Reduction in falls and in HDI scores from baseline. Reduction in total number of falls (a) and changes in mean HDI (+ SD) scores (b) from baseline and at five weeks were calculated for each treatment arm. HDI, headache disability index; HFP, high-frequency pulse; LFP, low-frequency pulse; PT, physical therapy; SD, standard deviation.

study: neither group responded, one responded significantly better than the other, or the groups produced comparable responses. Having a treatment arm with a low-level stimulation would be preferred to a placebo device without stimulation, as a device with no perceived stimulus may unblind a participant as being in the control group. However, although a low-level stimulation group is necessary in neurostimulation studies, positive responses in this group may limit the statistical superiority of high-level stimulation (29).

After this study protocol was developed and registered, investigations with other neurostimulation devices reported difficulties with low, minimally perceived sham stimulation and little or no difference in treatment effect between high- and low-frequency stimulation (52–58,61). These findings parallel the positive results observed with the LFP + PT group and suggest that neural activity and clinical responses may still occur despite stimulation parameters being considerably lower than the hypothesized active treatment. Future research will help assess the dosing parameters of TLNS, the degree to which PT contributes to the outcomes, and long-term benefits of the treatment.

Placebo effect, Hawthorne effect, and nonspecific attention and care should be discussed here as they are often recognized as factors that may impact the outcomes of neurological disorders in response to treatments (62). In fact, a heightened placebo effect is often recognized with medical devices (63). Studies with TENS reported 40%–60% placebo response rates (64–66), which challenge the accurate interpretation of the efficacy of TENS treatment. Placebo effect influences the statistical power of a study because of the elevated baseline measurement; therefore, sufficient trial sample size calculated according to realistic estimates of the differences between the expected effects of the treatment and control arms is always recommended (67). The sample size was powered by the statistical assumption that 90% of patients in the HFP + PT group and 60% of those in the LFP + PT group would be responders.

Placebo effect may also result from a favorable view of one's disease condition. By believing that the post-TBI symptoms are transient or improving, patients may put forth greater effort in therapy and continue social activities or form expectations based on experiences/knowledge of previous treatment with a similar device (63). In this study, all participants had chronic post-TBI symptoms that had not completely resolved with prior PT. Yet, with TLNS plus targeted PT, many participants had highly meaningful improvements in balance and gait. In addition, an assessment was conducted at the end of the study and demonstrated adequate blinding. Furthermore, in animal studies, in which "participant" expectations regarding potential treatment benefit are unlikely to influence study results, trigeminal nerve stimulation of different electrical intensities positively impacted outcomes with stroke, TBI, and hemorrhagic shock and hypoxia in rats, with seemingly little difference between different-intensity groups (68,69). In summary, the placebo effect in this study, if any, was likely negligible.

Additionally, it is improbable that the significant benefits observed in both groups in this study were associated with spontaneous recovery. Study participants plateaued on a previous PT program and had a long interval between their most recent TBI and study enrollment (a mean interval of 5.7 years for the total population); because PT is based on individual response, there was variance in the amount of time patients participated in their respective therapeutic programs. Given the significant outcomes presented here and the lack of improvement in participants in the lengthy period prior to study enrollment, we speculate that PT enhanced with TLNS contributed to the clinically meaningful benefits in both groups; although the degree of individual contribution of TLNS or PT to the participant remains to be determined in future investigations.

Another point of discussion pertains to whether the effects of physiotherapy without TLNS can be estimated. Because patients had failed to achieve normal balance in previous PT programs, it would have been difficult to justify enrolling a sufficient number of participants for a PT alone arm; therefore, to estimate the effect of PT alone, results from the present study were compared to those in a study by Badke et al. (see Supporting Information Additional Efficacy Analyses), in which participants were treated with vestibular therapy alone (70). The goal of this comparison was to estimate the difference in observed improvement in SOT scores between a combination of TLNS plus targeted PT and PT alone. In the study by Badke et al., participants with central or peripheral vestibular dysfunction, as well as with balance dysfunction due to central nervous system pathology, were enrolled (70). They received vestibular therapy similar in duration and intensity to the PT received in the present TLNS study. The analysis showed that the magnitude of SOT improvement achieved in the present study was significantly higher than those reported by Badke et al. Although the intervention used in the latter study by Badke et al. was specifically vestibular rehabilitation, this treatment approach is used often for balance therapy (71) and is considered a reasonable approximation of the PT-only approach.

In the Badke et al. study, results were not statistically different before and after therapy (70): an average increase of 6.4 ± 3.8 in the SOT composite score was observed for the peripheral group and 11.2 ± 9.9 for the mixed/central group. In contrast, in our TLNS study, the SOT composite score was increased by 26.5 ± 20.8 in the HFP + PT group and by 22.9 ± 16.5 in the LFP + PT group. Statistically significant differences in the improvement of SOT composite scores were observed for both HFP + PT ($p = 0.0026$) and LFP + PT ($p = 0.0133$) groups when compared with Badke's treatment group. In support of this analysis, systematic reviews of the effectiveness of PT put forth limited evidence of the positive effects of exercise intervention alone for the improvement of balance and gait in patients after TBI (13,72). Furthermore, the independent therapeutic effect of TLNS has been observed in patients with MS at various stages. In a pilot study by Leonard et al., participants either received TLNS treatment similar to the HFP + PT group described here or received PT in combination with a placebo device (control group) with no perceptible stimulation (43). Results showed significant improvements in SOT score from baseline to week 14 in the HFP + PT group but not in the control group.

To analyze the potential association between certain baseline patient characteristics and study outcomes, two post hoc statistical analyses were conducted. Results indicated that there was no single variable with large predictive value for SOT response in either treatment group; in addition, previous PT duration seems to have the weakest explanatory power for the response observed.

TBI treatment efficacy and its variability is another point that merits discussion. Investigation of TBI treatment efficacy in clinical trials is hindered, in part, by recruitment of a heterogeneous population that includes participants with various TBI severity classifications and diverse levels of function (72). Additionally, TBI studies often report on treatment of acute and chronic TBI symptoms (72). Strict enrollment criteria were used for this study to provide a more homogeneous population of participants who had a clearly defined functional level. Importantly, this study included participants suffering from persistent symptoms, which is a population believed to be less likely to fully recover and who

are often underrepresented in TBI studies (73). Although this inclusion did result in several screened patients being ineligible for this study, over 100 participants were enrolled and treated. Hopefully, this study will lay the groundwork for additional investigations with this treatment modality, which can possibly include a broader population of patients with TBI or other neurological deficits associated with balance impairment.

Of additional note, in this study, there were two times more female than male participants. In the general population, men typically experience TBIs at an incidence rate 1.4-times that of women (74); however, for sports-related concussions specifically, when comparing the same sport, women tend to have a higher incidence of concussion injury and related symptoms than men, and these symptoms are more severe and have a longer duration than those in men (75). Although the reason for this difference is not entirely known, the recruitment method, participant availability, or the fact that women may be more likely than men to seek medical care may have played a role.

Finally, secondary outcome analysis indicated decreases in falls from baseline for both treatment groups and reductions in the frequency of headaches, as measured with the HDI at the end of weeks 2 and 5 of treatment. TLNS plus targeted PT also exhibited an acceptable overall safety profile with no apparent differences between the HFP + PT and LFP + PT groups. No serious AEs were observed. Most of the AEs reported were not device related and were consistent with a post-TBI balance disorder or resulted from the sensation of the stimulation. Further studies are warranted to assess outcomes with long-term follow-up.

CONCLUSIONS

The results of this large multisite randomized clinical trial indicate that the combination of TLNS plus targeted PT is a promising and safe treatment for participants with a chronic balance deficit following an mmTBI who have plateaued on previous PT. Participants in both the HFP + PT and LFP + PT groups had significant and clinically meaningful improvements in SOT and DGI scores over time. Reductions in the number of falls and headaches and improved sleep quality were also reported. TLNS plus targeted PT was well tolerated with no serious AEs.

Acknowledgments

Authorship Statement

Robert Folmer, Kenton Gregory, Linda Papa, Alain Ptito, Vivek Prabhakran, Michael Yochelson, and William Walker were primary investigators of the study; Kim Skinner served as the licensed physical therapist and translingual neurostimulation (TLNS) treatment expert; all authors contributed to the interpretation of the data and the development of the manuscript. All authors approved the final version of the manuscript.

REFERENCES

1. Centers for Disease Control and Prevention. Traumatic brain injury in the United States. 2015. https://www.cdc.gov/traumaticbraininjury/pdf/TBI_Report_to_Congress_Epi_and_Rehab-a.pdf.
2. Department of Veterans Affairs, Department of Defense. VA/DoD Clinical practice guideline for the management of concussion-mild traumatic brain injury. V2.0. 2016. https://www.healthquality.va.gov/guidelines/Rehab/mtbi/mTBICPGFullCPG50821816.pdf.
3. Rau C, Wu S, Chen Y et al. Effect of age on Glasgow coma scale in patients with moderate and severe traumatic brain injury: an approach with propensity score-matched population. Int J Environ Res Public Health 2017;14:1378.
4. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. Lancet 1974;2:81–84.
5. Palmer CS, Gabbe BJ, Cameron PA. Defining major trauma using the 2008 abbreviated injury scale. Injury 2016;47:109–115.
6. Malec JF, Brown AW, Leibson CL. The Mayo classification system for traumatic brain injury. J Neurotrauma 2007;24:1417–1429.
7. Li M, Zhao Z, Yu G, Zhang J. Epidemiology of traumatic brain injury over the world: a systematic review. Austin Neurol Neurosci 2016;1:1007.
8. Centers for Disease Control and Prevention. Traumatic brain injury and concussion. 2017. https://www.cdc.gov/traumaticbraininjury/severe.html.
9. Polinder S, Cnossen MC, Real RGL et al. A multidimensional approach to post-concussion symptoms in mild traumatic brain injury. Front Neurol 2018;9:1113.
10. Kleffelgaard I, Roe C, Soberg HL, Bergland A. Associations among self-reported balance problems, post-concussion symptoms and performance-based tests: a longitudinal follow-up study. Disabil Rehabil 2012;34:788–794.
11. Selassie AW, Zaloshnja E, Langlois JA, Miller T, Jones P, Steiner C. Incidence of long-term disability following traumatic brain injury hospitalization, United States, 2003. J Head Trauma Rehabil 2008;23:123–131.
12. GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: a systematic analysis for the global burden of disease study 2016. Lancet Neurol 2019;18:56–87.
13. Murray DA, Meldrum D, Lennon O. Can vestibular rehabilitation exercises help patients with concussion? A systematic review of efficacy, prescription and progression patterns. Br J Sports Med 2017;51:442–451.
14. Bagalman E. Health care for veterans: traumatic brain injury. Washington, DC: Congressional Research Service, 2015. https://digitalcommons.ilr.cornell.edu/key_workplace/1401/.
15. Peterson M, Greenwald BD. Balance problems after traumatic brain injury. Arch Phys Med Rehabil 2015;96:379–380.
16. Thurman D, Guerrero J. Trends in hospitalization associated with traumatic brain injury. JAMA 1999;282:954–957.
17. Kontos AP, Elbin RJ, Lau B et al. Posttraumatic migraine as a predictor of recovery and cognitive impairment after sport-related concussion. Am J Sports Med 2013;41:1497–1504.
18. Smith C, Gentleman SM, Leclercq PD et al. The neuroinflammatory response in humans after traumatic brain injury. Neuropathol Appl Neurobiol 2013;39:654–666.
19. Marshall S, Bayley M, McCullagh S, Velikonja D, Berrigan L. Clinical practice guidelines for mild traumatic brain injury and persistent symptoms. Can Fam Physician 2012;58:257–267.
20. Pogoda TK, Hendricks AM, Iverson KM et al. Multisensory impairment reported by veterans with and without mild traumatic brain injury history. J Rehabil Res Dev 2012;49:971–984.
21. Hillier SL, Sharpe MH, Metzer J. Outcomes 5 years post-traumatic brain injury (with further reference to neurophysical impairment and disability). Brain Inj 1997;11:661–675.
22. Chamelian L, Feinstein A. Outcome after mild to moderate traumatic brain injury: the role of dizziness. Arch Phys Med Rehabil 2004;85:1662–1666.
23. Thornton M, Marshall S, McComas J, Finestone H, McCormick A, Sveistrup H. Benefits of activity and virtual reality based balance exercise programmes for adults with traumatic brain injury: perceptions of participants and their caregivers. Brain Inj 2005;19:989–1000.

24. Benson BW, Meeuwisse WH, Rizos J, Kang J, Burke CJ. A prospective study of concussions among National Hockey League players during regular season games: the NHL-NHLPA concussion program. *CMAJ* 2011;183:905–911.

25. Kerr ZY, Zuckerman SL, Wasserman EB, Covassin T, Djoko A, Dompier TP. Concussion symptoms and return to play time in youth, high school, and college American football athletes. *JAMA Pediatr* 2016;170:647–653.

26. Deer TR, Mekhail N, Petersen E. The appropriate use of neurostimulation: stimulation of the intracranial and extracranial space and head for chronic pain. Neuromodulation appropriateness consensus committee. *Neuromodulation* 2014; 17:551–570.

27. Penning S, Schoenen J. A survey on migraine attack treatment with the CEFALY® device in regular users. *Acta Neurol Belg* 2017;117:547–549.

28. Schoenen J, Vandersmissen B, Schoenen J et al. Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. *Neurology* 2013;80:697–704.

29. Tassorelli C, Grazzi L, de Tommaso M et al. Noninvasive vagus nerve stimulation as acute therapy for migraine: the randomized PRESTO study. *Neurology* 2018;91: e364–e373.

30. Villamar MF, Portilla AS, Fregni F, Zafonte R. Noninvasive brain stimulation to modulate neuroplasticity in traumatic brain injury. *Neuromodulation* 2012;15: 326–338.

31. Danilov Y, Kaczmarek K, Skinner K, Tyler M. Cranial nerve noninvasive neuromodulation: new approach to neurorehabilitation. In: Kobeissey FH, editor. *Brain neurotrauma: molecular, neuropsychological, and rehabilitation aspects*. Boca Raton, FL: CRC Press, 2015; p. 605–628.

32. Kaczmarek KA. The portable neuromodulation stimulator (PoNS) for neurorehabilitation. *Scientia Iranica D* 2017;24:3171–3180.

33. Ptito M, Moesgaard SM, Gjedde A, Kupers R. Cross-modal plasticity revealed by electrotactile stimulation of the tongue in the congenitally blind. *Brain* 2005;128: 606–614.

34. Wildenberg JC, Tyler ME, Danilov YP, Kaczmarek KA, Meyerand ME. Sustained cortical and subcortical neuromodulation induced by electrical tongue stimulation. *Brain Imaging Behav* 2010;4:199–211.

35. Kandel ER, Schwartz JH, Jessell TM. *Principles of neural science*. 3rd ed. New York, NY: Elsevier, 1991;p. 691–692.

36. Frehlick Z, Lakhani B, Fickling SD. Human translingual neurostimulation alters resting brain activity in high-density EEG. *J Neuroeng Rehabil* 2019;16:60.

37. Wildenberg JC, Tyler ME, Danilov YP, Kaczmarek KA, Meyerand ME. High-resolution fMRI detects neuromodulation of individual brainstem nuclei by electrical tongue stimulation in balance-impaired individuals. *Neuroimage* 2011;56: 2129–2137.

38. Wildenberg JC, Tyler ME, Danilov YP, Kaczmarek KA, Meyerand ME. Electrical tongue stimulation normalized activity within the motion-sensitive brain network in balance-impaired subjects as revealed by group independent component analysis. *Brain Connect* 2011;1:255–265.

39. Wildenberg JC, Tyler ME, Danilov YP, Kaczmarek KA, Meyerand ME. Altered connectivity of the balance processing network after tongue stimulation in balance-impaired individuals. *Brain Connect* 2013;3:87–97.

40. Ignatova TS, Kolbin VE, Scherbak SG et al. Translingual neurostimulation in treatment of children with cerebral palsy in the late residual stage. Case study. In: Proceedings of the 11th International Joint Conference on Biomedical Engineering Systems and Technologies (Vol. 4). Setúbal, Portugal: SciTePress, 2018:332–337. https://doi.org/10.5220/0006732403320337.

41. Tyler M, Skinner K, Prabhakaran V, Kaczmarek K, Danilov Y. Translingual neurostimulation for the treatment of chronic symptoms due to mild-to-moderate traumatic brain injury. *Arch Rehabil Res Clin Transl* 2019;1:100026.

42. Bastani A, Cofré Lizama EL, Zoghi M et al. The combined effect of cranial-nerve non-invasive neuromodulation with high-intensity physiotherapy on gait and balance in a patient with cerebellar degeneration: a case report. *Cerebellum Ataxias* 2018;5:6.

43. Leonard G, Lapierre Y, Chen JK et al. Noninvasive tongue stimulation combined with intensive cognitive and physical rehabilitation induces neuroplastic changes in patients with multiple sclerosis: a multimodal neuroimaging study. *Mult Scler J Exp Transl Clin* 2017;3:2055217317690561.

44. Tyler ME, Kaczmarek KA, Rust KL, Subbotin AM, Skinner KL, Danilov YP. Non-invasive neuromodulation to improve gait in chronic multiple sclerosis: a randomized double blind controlled pilot trial. *J Neuroeng Rehabil* 2014;11:79.

45. Chisholm AE, Malik RN, Blouin JS, Borisoff J, Forwell S, Lam T. Feasibility of sensory tongue stimulation combined with task-specific therapy in people with spinal cord injury: a case study. *J Neuroeng Rehabil* 2014;11:96.

46. Galea MP, Cofré Lizama LE, Bastani A, Panisset MG, Khan F. Cranial nerve non-invasive neuromodulation improves gait and balance in stroke survivors: a pilot randomized controlled trial. *Brain Stimul* 2017;10:1133–1135.

47. Danilov YP, Tyler ME, Skinner KL, Hogle RA, Bach-y-Rita P. Efficacy and electrotactile vestibular substitution in patients with peripheral and central vestibular loss. *J Vestib Res* 2007;17:119–130.

48. Papa L, LaMee A, Tan CN, Hill-Pryor C. Systematic review and meta-analysis of noninvasive cranial nerve neuromodulation for nervous system disorders. *Arch Phys Med Rehabil* 2014;95:2435–2443.

49. Danilov Y, Paltin D. Translingual neurostimulation (TLNS): a novel approach to neurorehabilitation. *Phys Med Rehabil Int* 2017;4:1117.

50. Broglio SP, Ferrara MS, Sopiarz K, Kelly MS. Reliable change of the sensory organization test. *Clin J Sport Med* 2008;18:148–154.

51. Silberstein SD, Mechtler LL, Kudrow DB et al. Non-invasive vagus nerve stimulation for the acute treatment of cluster headache: findings from the randomized, double-blind, sham-controlled ACT1 study. *Headache* 2016;56: 1317–1332.

52. Goadsby PJ, de Coo IF, Silver N et al. Non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: a randomized, double-blind, sham-controlled ACT2 study. *Cephalalgia* 2018;38:959–969.

53. Desantana JM, Sluka KA, Lauretti GR. High and low frequency TENS reduce postoperative pain intensity after laparoscopic tubal ligation: a randomized controlled trial. *Clin J Pain* 2009;25:12–19.

54. Hamza MA, White PF, Ahmed HE, Ghoname EA. Effect of the frequency of transcutaneous electrical nerve stimulation on the postoperative opioid analgesic requirement and recovery profile. *Anesthesiology* 1999;91:1232–1238.

55. Köke AJ, Schouten JS, Lamerichs-Geelen MJ et al. Pain reducing effect of three types of transcutaneous electrical nerve stimulation in patients with chronic pain: a randomized crossover trial. *Pain* 2004;108:36–42.

56. Bergeron-Vézina K, Corriveau H, Martel M, Harvey MP, Léonard G. High- and low-frequency transcutaneous electrical nerve stimulation does not reduce experimental pain in elderly individuals. *Pain* 2015;156:2093–2099.

57. Yan T, Xie Q, Zheng Z, Zou K, Wang L. Different frequency repetitive transcranial magnetic stimulation (rTMS) for posttraumatic stress disorder (PTSD): a systematic review and meta-analysis. *J Psychiatr Res* 2017;89:125–135.

58. Zhou DD, Wang W, Wang GM, Li DQ, Kuang L. An updated meta-analysis: short-term therapeutic effects of repeated transcranial magnetic stimulation in treating obsessive-compulsive disorder. *J Affect Disord* 2017;215: 187–196.

59. Wrisley DM, Stephens MJ, Mosley S, Wojnowski A, Duffy J, Burkard R. Learning effects of repetitive administrations of the sensory organization test in healthy young adults. *Arch Phys Med Rehabil* 2007;88:1049–1054.

60. Romero S, Bishop MD, Velozo CA, Light K. Minimum detectable change of the Berg balance scale and dynamic gait index in older persons at risk for falling. *J Geriatr Phys Ther* 2011;34:131–137.

61. Aaronson ST, Carpenter LL, Conway CR et al. Vagus nerve stimulation therapy randomized to different amounts of electrical charge for treatment-resistant depression: acute and chronic effects. *Brain Stimul* 2013;6:631–640.

62. Oken BS. Placebo effects: clinical aspects and neurobiology. *Brain* 2008;131: 2812–2823.

63. Polich G, Laccarino MA, Kaptchuck T et al. Placebo effects in traumatic brain injury. *J Neurotrauma* 2018;35:1–8.

64. Langley GB, Sheppeard H, Johnson M, Wigley RD. The analgesic effects of transcutaneous electrical nerve stimulation and placebo in chronic pain patients: a double-blind non-crossover comparison. *Rheumatol Int* 1984;4:119–123.

65. Deyo RA, Walsh NE, Martin DC, Schoenfeld LS, Ramamurthy S. A controlled trial of transcutaneous electrical nerve stimulation (TENS) and exercise for chronic low back pain. *N Engl J Med* 1990;322:1627–1634.

66. Hughes SC, Dailey PA, Partridge C. Transcutaneous electrical nerve stimulation for labor analgesia. *Anesth Analg* 1988;67:S99–S104.

67. Kaptchuk EJ, Goldman P, Stone DA et al. Do medical devices have enhanced placebo effects? *J Clin Epidemiol* 2000;53:786–792.

68. Shiflett JM, Parent AD, Britz GW, Golanov EV. Forehead stimulation decreases volume of the infarction triggered by permanent occlusion of middle cerebral artery in rats. *J Neurol Stroke* 2015;2:00067.

69. Chiluwal A, Narayan RK, Chaung W et al. Neuroprotective effects of trigeminal nerve stimulation in severe traumatic brain injury. *Sci Rep* 2017;7:6792.

70. Badke MB, Shea TA, Miedaner JA, Grove CR. Outcomes after rehabilitation for adults with balance dysfunction. *Arch Phys Med Rehabil* 2004;85:227–233.

71. Han BI, Song HS, Kim JS. Vestibular rehabilitation therapy: review of indications, mechanisms, and key exercises. *J Clin Neurol* 2011;7:184–196.

72. Bland DC, Zampieri C, Damiano DL. Effectiveness of physical therapy for improving gait and balance in individuals with traumatic brain injury: a systematic review. *Brain Inj* 2011;25:664–679.

73. Katz DI, Cohen SI, Alexander MP. Mild traumatic brain injury. In: Grafman J, Salazar AM, editors. *Traumatic brain injury, part I*. Edinburgh, UK: Elsevier, 2015; p. 131–156.

74. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Traumatic brain injury in the United States: emergency department visits, hospitalizations and death 2002-2006. Atlanta (GA) 2010. https://www.cdc.gov/traumaticbraininjury/pdf/blue_book.pdf.

75. Harmon KG, Drezner JA, Gammons M et al. American Medical Society for Sports Medicine position statement on concussion in sport. *Br J Sports Med* 2013;47: 15–26.

SUPPORTING INFORMATION

Additional supporting information may be found online in the supporting information tab for this article.

COMMENT

In the universe of neuromodulation, there is an undisputable growth of interest toward less invasive and non-invasive approaches as seen in myriad of applications of percutaneous and transcutaneous stimulation targeting somatic nerves in the trunk and extremities, trigeminal nerve in the head and face, and vagus nerve in the neck, earlobe, etc. The authors of this study used a different stimulation target – the patient's tongue – to improve balance in patients suffering from long-lasting deficits after traumatic brain injury. This approach has already been shown beneficial in a pilot study of the same patient category as well as in patients with multiple sclerosis, post-stroke deficits, cerebral palsy, cerebellar degeneration and spinal cord injury.

Based on results of the study, it appears that translingual neurostimulation (TLNS) with a proprietary device in combination with physical therapy improves patients' functionality in a majority of treated subjects, and this effect occurs with very different stimulation settings, including 150 impulses per second and 0.08 pulses per second (one every 12.5 seconds), delivered over 20-minute-long sessions several times a day for a total of 5 weeks.

The results are indeed impressive – and one may hope that with proper regulatory approval this approach will become widely used, resulting in meaningful improvement in mobility and overall functional status in patients with balance disorders of various etiologies. Although this study had relatively narrow inclusion criteria – reflected at a low rate of qualification for study participation among patients screened for enrollment – it is conceivable that this approach would be of value in a much wider population of patients.

Konstantin Slavin, MD
Chicago, IL, USA