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A Review of the Evidence and Current Applications of Portable Translingual Neurostimulation Technology

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ABSTRACT

Objectives: Translingual neurostimulation (TLNS) with adjunct physical rehabilitation is used to treat balance and gait deficits in several chronic neurological conditions. The purpose of this review is to summarize and appraise the evidence currently available on the portable TLNS device and to assess its potential clinical application.

Materials and Methods: In this narrative review, MEDLINE, EMBASE, Web of Science, and Google Scholar were searched for primary research investigating the use of portable TLNS devices on any neurologic condition. Data were extracted, reviewed, and appraised with respect to study design, conduct, and reporting.

Results: Five randomized controlled trials (RCTs), three quasi-experimental trials, and seven case reports/series were found. Most studies demonstrated improvements in balance and gait deficits secondary to traumatic brain injury and multiple sclerosis, but evidence is also present to a lesser degree for stroke and balance disorder patients. In these studies, the feasibility and safety of TLNS have been convincingly demonstrated. Functional magnetic resonance studies have also suggested a plausible neuroplastic therapeutic mechanism. However, the efficacy of TLNS remains unclear due to bias and confounding within studies, and heterogeneity of results between studies.

Conclusions: TLNS is a promising treatment modality for various chronic neurological conditions that are often refractory to conventional therapy. However, TLNS technology remains largely investigational as high-quality RCTs are still required to elucidate efficacy, optimal dosages, necessary treatment durations, and treatment durability. Further research to develop an appropriate control group is needed for scientifically valid comparisons of TLNS.

Keywords: Brain injury, cranial nerve stimulation, high-frequency electrical stimulation, low-frequency electrical stimulation, multiple sclerosis (MS), neurostimulation, rehabilitation, stroke

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INTRODUCTION

Neuromodulation has been a therapeutic modality for neurological conditions since the 1950s, often for conditions refractory to conventional therapies (1). Nerve activity is altered through electrical or chemical stimulation targeted to specific neurologic regions. Regions stimulated and their downstream effects vary between neuromodulation modalities. For instance, deep brain stimulation (DBS) was the first U.S. Food and Drug Administration-approved neuromodulation modality and involved surgical implantation of electrodes that stimulate deep structures in the brain to treat Parkinson's disease, essential tremor, dystonia, among other neuropsychiatric disorders (2). Other neuromodulation techniques, including transcranial direct current stimulation and repetitive transcranial magnetic stimulation (rTMS), have since been developed (1). Although each technique has unique benefits and limitations, all work through modulation of large neural networks (3).

In contrast, cranial nerve non-invasive neuromodulation (CN-NINM) is a novel neuromodulation technique that precisely targets cranial nerves. Researchers (Dr. Yuri Danilov, Dr. Mitch Tyler, Dr. Kurt Kaczmarek, and Dr. Paul Bach-y-Rita) at the University of Wisconsin-Madison partnered with Helius Medical to develop the Portable Neuromodulation Stimulator (PoNS) (Helius Medical Technologies, Newton, PA, USA) (4). This $3 \times 3 \times 0.1$ cm (100 g) device was designed to provide portable translingual neurostimulation (TLNS), a form of CN-NINM, alongside physical

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rehabilitation to improve symptoms of chronic neurologic conditions (5). Electrical signals are delivered to the dorsal aspect of the tongue to augment neuroplastic changes that occur with physical rehabilitation. Afferents in the lingual nerve (a branch of the trigeminal nerve carrying tactile sensation) and chorda tympani nerve (a branch of the facial nerve carrying taste and pain) transmit these signals to their respective brainstem nuclei in the dorsal pons. It is hypothesized that subsequent collateral interactions are made with the adjacent vestibular nuclei where many neural circuits involving movement, balance, gait, breathing, and awareness intersect (4). Consequently, clinical outcomes may be improved while retraining these pathways through physical rehabilitation (4). The tongue is used as the stimulatory target because of its high nerve fiber density (the lingual nerve has 10,000–33,000 fibers and each chorda tympani nerve has 3000–5000 fibers) and the controlled environment in the mouth (6).

Past reviews have been published on TLNS; however, none have focused on appraising the current body of evidence and assessing its applications to several neurological conditions (4). Rather, superficial approaches to summarizing evidence were employed and substantially more research is now available (4,7–11). Thus, the purpose of this review is to summarize and appraise the clinical evidence currently available for TLNS and assess its potential clinical applications.

MATERIALS AND METHODS

We did not deem a formal systematic review to be appropriate due to the iterative nature of our research objective, lack of consensus for quantitative outcomes for TLNS, and anticipated heterogeneity of study designs. Therefore, we did not formally perform data synthesis. To obtain a comprehensive, up-to-date, and unbiased survey of literature, multiple databases were searched for all primary research in the English language up to April 30, 2020, investigating the effects of TLNS technology on any neurological condition. Ovid MEDLINE, Ovid EMBASE, Web of Science, and Google Scholar were searched. The following Boolean strategy was used to search each database: ((((“Translingual” AND (“Neuro*” OR “Stimulation”))) OR (“Portable” AND “Neuromodulation” AND “Stimulator”)) OR (“PoNS” AND “Helius”)) OR (“Cranial Nerve” AND “Neuromodulation”). Given the current investigational status of the intervention, conference abstracts, case reports, and case series were included. Animal studies, commentaries, editorials, or review articles were excluded. Additionally, reference and citation lists of all relevant studies were manually searched. Figure 1 illustrates the selection of studies depicted in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram (Fig. 1). Two authors (D.D. and A.L.) independently screened abstracts and full texts, extracted all data, and critically appraised studies using the Cochrane Risk of Bias 2.0 tool for RCTs and the Cochrane Risk of Bias In Non-Randomized Studies of Interventions tool for nonrandomized studies (12,13). The remaining author resolved all disagreements (G.K.).

RESULTS

Five randomized-controlled trials (RCTs), three quasi-experimental trials, and seven case reports/series were found (Table 1). For overall risk of bias, two RCTs had “high-risks of bias,” and three RCTs had “some concerns of bias” (Table 2). All three quasi-experimental trials had “serious risks of bias” (Table 3).

Traumatic Brain Injury

Traumatic brain injury (TBI) is a common and debilitating injury. The Centers for Disease Control and Prevention estimates that over five-million people in the United States (US) live with a disability from TBI (14). Despite post-acute rehabilitation, 125,000 new patients per year require assistance with their activities of daily living following their injury (15). The disease burden of TBI in the United States was estimated to be over $221 billion annually in 2009 (16). The long-term sequelae of TBI coupled with the stark economic consequences warrants research into novel therapies such as TLNS.

The earliest study into TLNS on TBI patients was a case series of four patients with chronic balance and gait secondary to moderate TBI (mean time-since-onset: 5.4 years) (17). Subjects received TLNS stimulation along with flexibility and conditioning exercises with a therapist, twice daily, five days/week for two weeks. Compared to baseline, all subjects had clinically significant improvements in their gait (mean improvement in the Dynamic Gait Index [DGI]: +14.8) and balance (mean improvement in the Sensory Organization Test [SOT]: +35.3). Data from select TBI subjects also showed improvements in cognition, eye movement, and synchronization of muscular activity in the left soleus and vastus lateralis (17).

Subsequently, two double-blind RCTs were conducted: TBI-001 and the long-term treatment trial (8,18). TBI-001 was a multicenter RCT (n = 122) conducted in the United States by Helius Medical (8). Patients were included if they had mild-to-moderate TBI (mmTBI) lasting at least one-year and if their age-adjusted SOT scores were <16 points below normal. Patients were randomized to either five-weeks of high-frequency pulse (HFP) or low-frequency pulse (LFP) stimulation in addition to high-volume physical rehabilitation. The pulse frequency was 150 Hz and 0.08 Hz (1875:1 ratio) for HFP and LFP, respectively. Additional waveform parameters of HFP and LFP are illustrated in Figure 2 (19). Both groups observed statistically significant within-group improvements in Dynamic Gait Index (DGI) scores ($p < 0.0001$). Reductions in falls and improvements in the 6-minute walk test (6MWT) were observed in both groups, although no statistical testing was conducted. Seventy-one percent of the HFP and 64% of the LFP group had a clinically significant improvement in balance (defined as ≥15-point increase on SOT), but this between-group difference did not reach statistical significance (p = 0.37). Twenty-two device-related adverse effects (AEs) were reported, all of which were self-limiting. The most common AEs were vomiting (n = 5), nausea (n = 5), and fainting (n = 2) (8). All AEs were reported cumulatively without distinction between groups.

The long-term treatment trial, a single-centered RCT (n = 43), was conducted to investigate extended treatment periods and outcomes following treatment discontinuation (18). The trial involved the same eligibility criteria and pulse frequencies as TBI-001 but participants received an extended treatment period of 14 weeks of either HFP or LFP stimulation with adjunct high-volume physical rehabilitation. Participants then returned to normal activity and were followed for an additional 12 weeks to investigate treatment durability. Both groups demonstrated a >30 point increase in mean SOT scores (minimum clinically significant difference [MCSD] = 8.5 points) and a three point increase in DGI scores (MCSD = 3) (20,21) Furthermore, both groups had

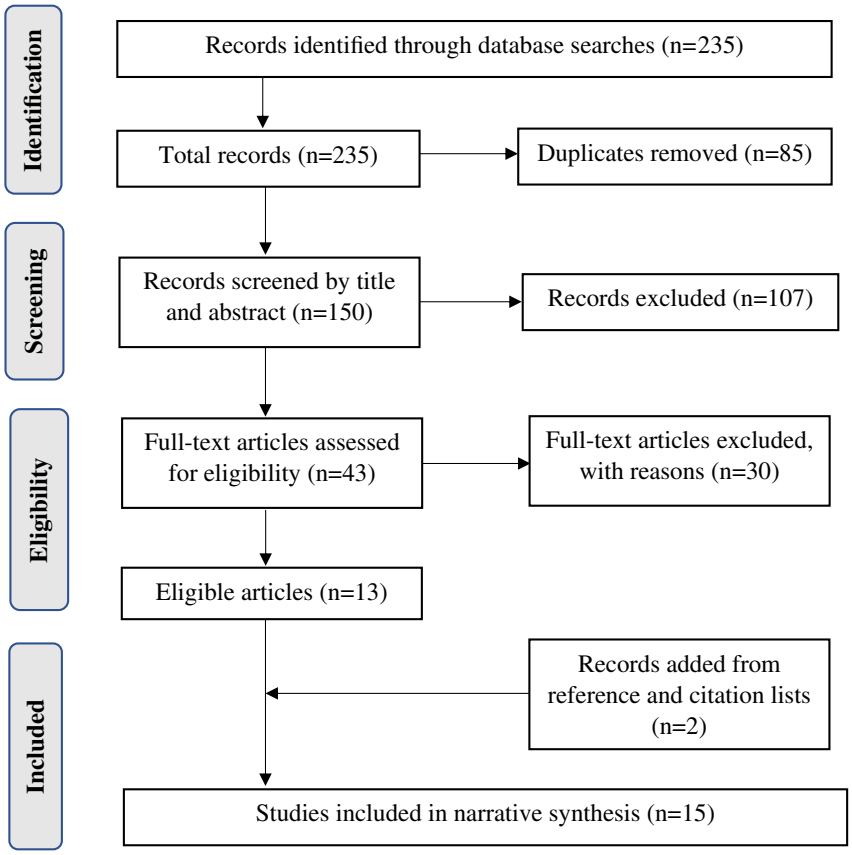


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. [Color figure can be viewed at wileyonlinelibrary.com]

statistically significant improvements from baseline SOT and DGI scores at all trial timepoints (weeks 2, 5, 14, and 24). However, no statistically significant between-group differences were observed. Improvements in SOT and DGI scores were retained at 12 weeks after treatment discontinuation. Fifty-four and 37 total AEs during the treatment period were reported in the HFP and LFP groups, respectively. Of which, eight mild-to-moderate treatment-related AEs were reported among both groups. Only vertigo, pain, and headache were listed as examples of treatment-related AEs. It was not specified if such AEs were self-limited and in which group they occurred in (18).

Studies demonstrated that TLNS together with high-volume physical rehabilitation is a promising treatment modality for balance and gait symptoms secondary to chronic mmTBI. Statistically and clinically significant within-group improvements in gait and balance were achieved after only two weeks of treatment. Despite the large commitment of time, energy, and resources for treatment, the acceptable retention rates speak to the applicability of TLNS. Treatment benefits were retained 12 weeks following discontinuation, which are suggestive of neuroplastic changes. However, both RCTs had biases and confounding introduced by trial design that limits the validity of findings. Both RCTs had an overall "high-risk of bias." The first RCT had a "high-risk of bias" from selective reporting as reported outcomes deviated from the original protocol. The latter RCT had a "high-risk of bias" from missing outcome data as 27% (n = 6) of the HFP group was lost to follow-up compared none in the LFP group. Both RCTs had "some concerns of bias" arising from the randomization process as no information was provided on the allocation concealment process. Furthermore, the efficacy of TLNS remains unclear given the lack of between-group differences for any post-treatment outcome; this raises the concern that LFP stimulation may be conferring a therapeutic effect (22). Additionally, it was impossible to determine the degree to which TLNS or high-volume physical rehabilitation contributed to the observed improvements.

Multiple Sclerosis

Multiple sclerosis (MS) presents with varied symptoms but gait disability is among the most prevalent. At the time of diagnosis, half of patients report at least mild gait disability, but this progresses to 82% by ten-years mark (23). Given that the median survival after disease onset is 41 years, most MS patients develop gait, balance, and mobility issues with time (24). MS research has largely focused on immunomodulating medications, which potentially modify the course of the disease (25). Neuromodulation, such as DBS or functional electrical stimulation (FES), has shown promise in treating MS-related motor deficits. But DBS is limited by its invasive nature and FES is limited to specific gait abnormalities (e.g., foot drop). TLNS represents a safe and noninvasive intervention that, unlike FES, targets larger neural networks to achieve results (4).

The earliest study to test the efficacy of TLNS in a MS population was a double-blind RCT (n = 20) that included all subtypes of MS. (26) Subjects were randomized into the intervention group, which received TLNS using 50 μsec pulses at 200 Hz, or the control group, which received a TLNS device calibrated to produce pulses 1/1000th the intensity of the minimally perceivable level.

Table 1. Characteristics of Included Studies Stratified by Neurological Conditions of Patients.

Study	Publication type	Design and sample size	Participants	Intervention*	Control	Outcome measures	Timing of assessments†
Traumatic brain injury							
Danilov et al. (17)	Conference proceeding	Case series; four total	Chronic moderate TBI, >5-years postinjury	Perceivable TLNS + "flexibility and conditioning exercises, and CN-NINM training"; two sessions/day, five days/week, for two weeks	N/A	DGI, BRBNT, electromyogram, SOT	Outcomes reassessed after completion of intervention; no follow-up
Ptito et al. (8)	Journal publication	RCT; 122 total; 59 in intervention group, 63 in control group	Chronic mild-to-moderate TBI, >1-year post-injury	High-frequency perceivable TLNS + balance, gait, and movement training; three sessions/day for five-weeks	Low-frequency perceivable TLNS + balance, gait, and movement training; 3 sessions/day for 5-weeks	6MWT, DGI, fall frequency, HDI, QLMI, SOT, SQI	Outcomes reassessed after 2 and 5 weeks of intervention; no follow-up
Tyler et al. (18)	Journal publication	RCT; 44 total; 22 in intervention group, 22 in control group	Chronic mild-to-moderate TBI, >1-year post-injury	High-frequency perceivable TLNS + balance, gait, and movement training; three sessions/day for 14-weeks	Low-frequency perceivable TLNS + balance, gait, and movement training; three sessions/day for 14-weeks	6MWT, BSI-18, DGI, HDI, NSI, PSQI, SOT	Outcomes reassessed after 2, 5, and 14 weeks of intervention; 12 weeks of follow-up
Multiple sclerosis							
Tyler et al. (26)	Journal publication	RCT; 20 total; 10 in intervention group, 10 in control group	MS, all subtypes	Perceivable TLNS + balance, gait, and relaxation training; two sessions/day for 14-weeks	Non-perceivable TLNS + balance, gait, and relaxation training; two to three sessions/day for 14-weeks	DGI	Outcomes reassessed after 2, 6, 10, and 14 weeks of intervention; no follow-up
Leonard et al. (7)	Journal publication	RCT; 14 total; seven in intervention group, seven in control group	MS, all subtypes	Perceivable TLNS + balance, gait, motor control, and breathing and awareness training; three sessions/day for 14-weeks	Nonperceivable TLNS + balance, gait, motor control, and breathing and awareness training; two to three sessions/day for 14-weeks	CFI for MS, BAI, BDI-II, DGI, fMRI, neuropsychological outcomes, MFS, MS impairment scale, SOT	Outcomes reassessed after 2, 4, 6, 8, 10, 12, and 14 weeks of intervention; no follow-up
Stroke							
Danilov (36)	Conference proceeding	Case report; one total	Chronic stroke, four-years post-injury	Perceivable TLNS + "flexibility and conditioning exercises, and CN-NINM training"; two sessions/day, five days/week, for 13-months	N/A	9-hole peg, abilhand, box and block, DGI, SOT, RBANS, SIS, TUG, VNG	Outcomes reassessed regularly during 13 months of intervention, although specific timing not indicated; no follow-up
Galea et al. (9)	Journal publication	RCT; ten total; five in intervention group, five in control group	Subacute stroke, one-week to one-month post-injury	Perceivable TLNS + balance and gait training; two sessions/day for two weeks	Balance and gait training; two sessions/day for two weeks	CogLog, DASS, gait tests, miniBEST, posturography	Outcomes reassessed after completion of intervention; no follow-up
Balance disorders							
Wildenberg et al. (41,42)	Journal publication	Quasi-experimental trial; 21 total; 12 balance disorder subjects, nine healthy subjects	Chronic balance disorders subjects and healthy subjects	Perceivable TLNS delivered to balance subjects for nine total sessions over five-days	No intervention given to healthy controls	ABC, DGI, DHI, fMRI, posturography, self-perception of impairment	Outcomes reassessed after completion of intervention; no follow-up
Wildenberg et al. (40)	Journal publication	Quasi-experimental trial; 18 total; nine balance disorder subjects, nine healthy subjects	Chronic balance disorders subjects and healthy subjects	Perceivable TLNS delivered to balance subjects for 19 total sessions over ten days	No intervention given to healthy controls	fMRI, SOT	Outcomes reassessed after completion of intervention; no follow-up
Other neurological disorders							
Ignatova et al. (10)	Journal publication	Quasi-experimental trial; 134 total; 94 in intervention group, 40 in control group	Pediatric spastic diplegia	Perceivable TLNS + classes of massage, simulation training, hydrotherapy, mechanotherapy, and therapeutic gymnastics; frequency unclear‡	Classes of massage, simulation training, hydrotherapy, mechanotherapy, and therapeutic gymnastics; frequency unclear‡	Ashworth scale, FMS	Outcomes reassessed after completion of intervention; no follow-up
Kondratyeva et al. (11)	Conference proceeding	Case series; 70 total	Ataxia post-resection of large and giant vestibular schwannomas	TLNS (unclear if perceivable); rehabilitation protocol unclear; one session/day for ten days	N/A	Ataxia standing and walking scores, Karnovsky scale	Outcomes reassessed after completion of intervention; no follow-up
Chisholm et al. (46)	Journal publication	Case report; two total	Motor incomplete spinal cord injury (ASIA C), >9.5 years post-injury	Perceivable TLNS + balance and gait, training; five sessions/week for 24-weeks	N/A	6MWT, 10MWT, ABC, FIM, IPAQ, LSQ, SCI-FAP, SCIM, static balance test	Outcomes reassessed after 12 and 24 weeks of intervention; no follow-up
Verbny et al. (47)	Conference proceeding	Case report; one total	Parkinson's disease, six-years since diagnosis	TLNS (unclear if perceivable); protocol aside from "physical and cognitive exercises" unclear; 4-months	N/A	Nystagmus tests, dynamic eye tests	Outcomes reassessed after completion of intervention; no follow-up
Lizama et al. (48)	Journal publication	Case report; one total	Balance and gait deficits three months post-resection of fourth ventricle ependynoma	Perceivable TLNS; two sessions/day for two weeks	N/A	Instrumented gait assessment, miniBEST, posturography	Outcomes reassessed after completion of intervention; no follow-up
Bastani et al. (49)	Journal publication	Case report; one total	Cerebellar degeneration, 20 years since diagnosis	Perceivable TLNS; two sessions/day for two weeks	N/A	CogLog, DASS, instrumented gait assessment, miniBEST, posturography	Outcomes reassessed after completion of intervention; no follow-up

Abbreviations: ABC, Activities-Specific Balance Confidence; BAI, Beck Anxiety Inventory; BRBNT, BDI-II, Beck Depression Brief Repeatable Battery of Neuropsychological Tests; BSI-18, Brief Symptom Inventory 18; CFI, cognitive function inventory; CN-NINM, cranial nerve noninvasive neuromodulation; CogLog, Cognitive Log; DASS, Depression Anxiety Stress Scale; DGI, Dynamic Gait Index; fMRI, functional magnetic resonance imaging; FIM, Functional Independence Measure; HDI, Headache Disability Index; IPAQ, Impact on Participation and Autonomy Questionnaire; LSQ, Life Satisfaction Questionnaire; MFS, modified fatigue scale; miniBEST, Mini Balance Evaluation Systems Test; MS, multiple sclerosis; N/A, not applicable; NSI, Neurobehavioral PSQI, Pittsburgh Sleep Quality Index; QLMI, Quality of Life Measure Index; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RCT, randomized controlled trial; SCI-FAP, Spinal Cord Injury-Functional Ambulation Profile; Spinal Cord Independence Measure, SCIM; SIS, Stroke Impact Scale; SOT, Sensory Organization; SQI, Sleep Quality Index; TBI, traumatic brain injury; Test; TLNS, translingual neurostimulation; Symptom Inventory; Inventory-II; TUG, Timed Up and Go; VNG, video nystagmography; 6MWT, 6-meter walk test; 10MWT, 10-meter walk test.

*Data extracted for TLNS frequency and intensity; and rehabilitation type, dosage, and frequency, if possible.

†Timing assessments may vary based on specific outcome measurement.

‡Unclear if TLNS and classes occurred over ten days, or ten-times daily.

Table 2. Risk of Bias Assessments of Randomized Controlled Trials Using Risk of Bias 2.0 Tool (RoB 2.0).

Study*	Randomization process	Deviations from intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Ptito et al. (8)	Some concerns No information on allocation concealment and between-group baseline values for outcome measures were not provided	Low risk "Participants, TLNS trainers, and investigators were all blinded to treatment group" and intention-to-treat analysis was performed	Some concerns Two dropouts in HFP group and five dropouts in LFP group. Dropouts were unexplained, but unlikely to be related to assignment to intervention	Low risk Outcomes were measured appropriately and in the same manner for all participants. Outcome assessors were unaware of participant intervention status	High risk The protocol was retrospectively registered. Additionally, the statistical tests and assumptions used were not reported in neither the study nor the protocol	High risk
Tyler et a. (18)	Some concerns No information on allocation concealment. Between-group baseline values for outcome measures were largely balanced	Low risk "Double blinded" and intention-to-treat analysis was performed	High risk Six dropouts only in the HFP group. Dropouts were unexplained and unbalanced between groups	Low risk Outcomes were measured appropriately and in the same manner for all participants. Unclear if outcome assessors were blinded, but potential knowledge of intervention status would likely not have affected outcome measurement	Low risk The protocol was prospectively registered. Additionally, results were unlikely to be selected from multiple outcome measurements or multiple analyses of data	High risk
Tyler et al. (26)	Some concerns No information on allocation concealment. Between-group baseline values for outcome measures were largely balanced	Low risk "Double blinded" and no dropouts	Low risk No dropouts	Low risk Outcomes were measured appropriately and in the same manner for all participants. Unclear if outcome assessors were blinded, but potential knowledge of intervention status would likely not have affected outcome measurement	Some concerns No protocol was available. Additionally, results were unlikely to be selected from multiple outcome measurements or multiple analyses of data	Some concerns
Leonard et al. (7)	Some concerns No information on allocation concealment. Between-group baseline values for outcome measures were largely balanced	Low risk Participant blinding status was not reported. Therapists and other research personnel were blinded. There were no deviations from the intended intervention due to the trial context.	Low risk No dropouts	Low risk Outcomes were measured appropriately and in the same manner for all participants. Unclear if outcome assessors were blinded, but potential knowledge of intervention status would likely not have affected outcome measurement	Some concerns No protocol was available. Additionally, results were unlikely to be selected from multiple outcome measurements	Some concerns
Galea et al. (9)	Low risk Adequate allocation sequence concealment and allocation sequence generation. Baseline differences were not analyzed	Low risk Participant and provider blinding status was not reported. There were no deviations from the intended intervention due to the trial context	Low risk No dropouts	Low risk Outcomes were measured appropriately and in the same manner for all participants. Outcome assessors were unaware of participant intervention status	Some concerns The protocol was retrospectively registered. Additionally, results were unlikely to be selected from multiple outcome measurements or multiple analyses of data	Some concerns

Abbreviations: HFP, high-frequency pulse; LFP, low-frequency pulse; TLNS, translingual neurostimulation.
*Risk of bias assessments were completed for every outcome per study. However, no differences in risk of bias assessments were observed between outcomes.

Table 3. Risk of Bias Assessments of Non-randomized Controlled Trials Using the Risk of Bias in Non-randomized Studies – of Interventions Tool (ROBINS-I).

Study*	Confounding	Selection of participants	Intervention measurement	Departure from intervention	Missing data	Measurement of outcomes	Selection of reported results	Overall
	Serious	Low	Low	Low	Low	Low	Low	
Wildenberg et al. (41,42)	Control group was healthy subjects rather than balance disordered patients without TLNS	Broad inclusion of all balance disordered subjects	Only intervention group received TLNS	No deviation from intended protocol	One subject in intervention group did not complete pre-intervention assessment. But unlikely to affect overall result	Same assessment tools applied to both groups. Data collection unlikely to be affected by absence of blinding	All results reported	Serious
	Serious	Low	Low	Low	Low	Low	Low	
Wildenberg et al. (40)	Control group was healthy subjects rather than balance disordered patients without TLNS	Broad inclusion of all balance disordered subjects	Only intervention group received TLNS	No deviation from intended protocol	Data unavailable for one subject. But unlikely to affect overall result	Same assessment tools applied to both groups. Data collection unlikely to be affected by absence of blinding	All results reported	Serious
	Serious	Low	Low	Low	No information	Moderate	Serious	
Ignatova et al. (10)	Allocation to intervention *vs.* control arm dependent on patients' rehab program	No selection criteria were applied	TLNS rehabilitation only occurred in intervention arm	No deviation from intended protocol	Patient flow through study, including lost to follow-up, was not given	Same assessment tools applied to both groups. No mention of tester blinding	No mention of patient demographic or study flow	Serious

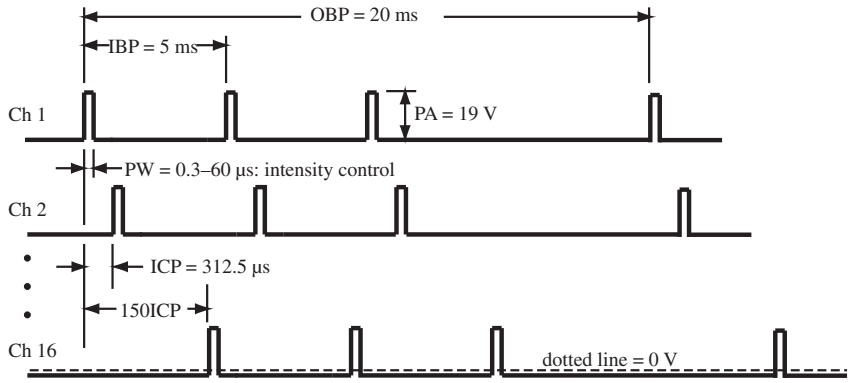
Abbreviation: TLNS, translingual neurostimulation.
*Risk of bias assessments were completed for every outcome per study. However, no differences in risk of bias assessments were observed between outcomes.

Both groups received high-volume physical rehabilitation and were treated for 14 weeks. The intervention group had statistically and clinically significant improvements in DGI scores observed in weeks 6, 10, and 14 compared to baseline ($p < 0.05$). This was not observed in the control group. By weeks 10 and 14, the intervention group had significantly higher DGI scores compared to the control group ($p < 0.05$ and $p < 0.005$, respectively). The primary AEs of TLNS use was transient head/jaw ache in 25% of subjects (distribution between intervention and control group was not described) and increased salivary production in all subjects. Both resolved following improved education around proper device usage.

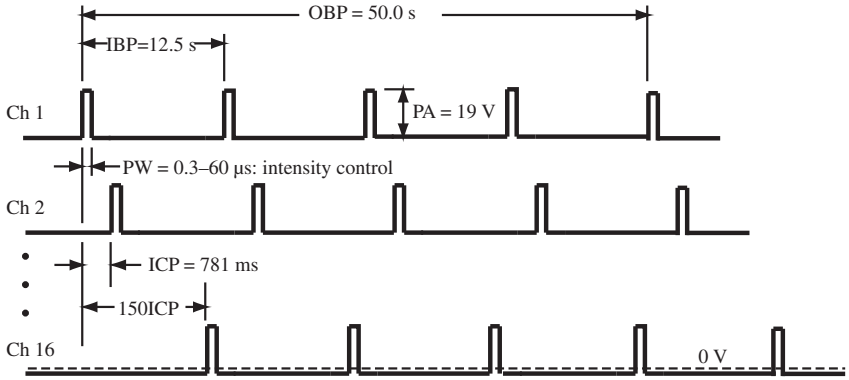
The second study was a pilot RCT ($n = 14$) involving blinding of just the research personnel (7). Electrostimulation intensities and physical rehabilitation protocols were similar to the earlier aforementioned study, but three domains were tested: balance, gait, and cognition. With respect to balance, within-group SOT scores were significantly higher postintervention in the intervention group ($p < 0.001$) but not the control group ($p = 0.06$). TLNS was significantly associated with SOT improvement ($p = 0.015$). With respect to gait, both the intervention and the control group demonstrated improvement in DGI scores, but between-group differences were not statistically significant. Both groups demonstrated significant improvement in cognition using the COGMED system ($p < 0.0001$). However, no statistically significant between-group differences were observed. There was no mention of AEs in this study.

Both the intervention and control group received functional magnetic resonance imaging (fMRI), but neuronal activity was only significantly increased in the dorsolateral prefrontal cortex (DLPFC) and dorsal anterior cingulate cortex (dACC) post-TLNS in the intervention group. No changes on fMRI were observed pre- and post-TLNS in the control group. The DLPFC is associated with working memory and processing verbal/spatial information while the dACC is associated with decision-making (27,28). TLNS was thought to have the greatest impact on augmenting balance and gait through targets in the brainstem, but these fMRI results suggest that TLNS confers neuroplastic changes in regions distant to the brainstem to affect cognition.

Although both studies demonstrate feasibility, the efficacy of TLNS remains inconclusive. The DGI was the only assessment used across both studies but a between-group difference was only observed by Tyler et al. (26) In terms of internal validity, both RCTs had an overall risk of bias score of "some concerns." Specifically, both RCTs had "some concerns of bias" from the randomization process as no information was provided on the allocation concealment process. Both RCTs also had "some concerns of bias" from selective reporting as no protocols were available. Moreover, it is important to note these two studies utilized variations in pulse intensity to generate an intervention and control group, which is an alternative to the variations in pulse frequency used in the TBI studies. There is empiric evidence confirming the lack of therapeutic effect of low frequency TLNS and, based on studies of other neurostimulation modalities, it may be reasonable to assume intensity adjustments can also generate a non-therapeutic control group (22,29). Future research into treatment parameters of TLNS should attempt to provide empiric evidence supporting the lack of therapeutic benefit of sub-perceptible TLNS and examine treatment durability after intervention cessation. Finally, the generalizability of both studies was limited by small sample sizes despite their inclusion of all MS subtypes. The natural history of MS varies between subtypes making low powered rehabilitation



(a) Normal "Active" waveform



(b) "Placebo Low" waveform

Figure 2. Idealized stimulation waveforms: (a) "Normal" or "High-Frequency Pulse" waveform eliciting buzz sensation, and (b) "Placebo Low" or "Low-Frequency Pulse" waveform which is perceivable to subjects as discrete pulses but which has much lower pulse rate. Ch, channel; IBP, Inner Burst Period; ICP, Inner-Channel Period; OBP, Outer Burst Period; PA, Pulse Amplitude; PW, Pulse Width. Figure re-used in accordance with the Attribution Creative Commons BY License.

research challenging as some subtypes benefit substantially more from rehabilitation than others (30). Larger studies will improve generalizability and allow for subgroup analysis based on MS subtype.

Stroke

Worldwide, stroke is the second leading cause of disability and mortality (31). Motor deficits represent the most common disability post-stroke, afflicting upward of 72–77% of stroke survivors (32). Motor deficits affecting balance, posture, and gait are particularly devasting as they reduce the ambulation and cardiovascular fitness of survivors, which in turn is associated with increased falls risk, depression, and health-care expenditure (33). Conventional physical rehabilitation post-stroke is the mainstay of treatment. However, only 65% of stroke survivors see any improvements in motor deficits with therapy (34). This leaves 35% of survivors seeing no improvement.

DBS and rTMS have been successful in treating post-stroke tremor, dyskinesia, and dystonia (2,35). However, evidence for these modalities to augment balance and gait rehabilitation remains limited. The superficial placement of electrodes in rTMS may limit how targeted the intervention can be. The surgical placement of electrodes in DBS presents certain risks that limit the patient population this intervention may be applicable to. TLNS may represent a targeted and noninvasive intervention that may augment balance and gait rehabilitation (4).

The earliest study of TLNS on stroke survivors was a case report of an 80-year-old female four years poststroke (36). The subject presented with deficits in balance, gait, cognition, eye movements, and right arm function that all persisted despite conventional physical rehabilitation. After 13 months of training with TLNS, which consisted of twice-daily flexibility and conditioning sessions occurring five times per week, the subject demonstrated improvements in mobility and a decreased falls risk (36). The subject's gait improved 48% (16–23 on the DGI) and mobility improved by 31% (timed-up-and-go reduced from 15.6 to 10.7 sec). Subsequently, a pilot RCT (n = 10) was conducted on both ischemic and hemorrhagic stroke survivors, 7–30 days post-stroke (9). Patients were randomized to two-weeks of TLNS-augmented balance and gait rehabilitation or rehabilitation alone. Significant between-group differences were observed for Balance Evaluation Systems Test (BEST) scores (p = 0.032); this was the first demonstration of TLNS efficacy on stroke survivors. However, no significant between-group differences were observed for posture, walking, or mobility. All participants using TLNS completed the

intervention without issue, except two participants experienced isolated AEs including one episode of dizziness and one episode of temple pain; both self-resolved before the end of the testing period.

Current evidence suggests the feasibility of TLNS within a subacute stroke population with clinically meaningful and statistically significant improvement in balance (9). Despite demonstrating between-group differences for BEST scores, this estimate of efficacy is limited by "some concerns of bias" from a retrospective protocol registration, a small sample size, and the lack of a sham TLNS intervention. Additionally, several aspects limit the external validity of the results. First, incomplete data precluded meaningful statistical analysis of between-group differences for cognition and depression outcomes. Second, the Canadian Occupational Performance Measures was a planned secondary outcome, but this pilot failed to report results. Lastly, this study treated and followed subjects for only two weeks. The effects of TLNS remain unstudied using the conventional 14-week treatment period and the long-term retention of these benefits remains unclear.

Balance Disorders

Chronic balance disorder is a group of disorders with varying etiology but in all cases, the risk of falls is significantly increased leading to physical disability, impacts on mental health, and increased caregiver and healthcare systems reliance (37). Electrostimulation of the tongue is not a novel concept for treating balance disorders. In vestibular substitution studies, head position data are conveyed through the tongue to replace the information lost due to vestibular dysfunction (38). However, Danilov et al. found that the improvements in balance persisted even after discontinuation of vestibular substitution (39). This suggested that the stimuli, independent of biofeedback, was capable of inducing neuroplastic changes; this was later supported by fMRI studies (40–42). Therefore, TLNS differs in that no exogenous stimuli are provided. The mechanism is not to replace loss vestibular information but rather to amplify neuroplastic changes that occur with rehabilitation in the brainstem and cerebellum.

Two quasi-experimental trials (n = 12, n = 9) applied TLNS to patients with a broad range of chronic balance disorders (central/peripheral vestibular disorder, migraine-related disorder, traumatic brain injury, Meniere's disease, spinocerebellar/cerebellar ataxia, gentamycin ototoxicity, and cerebellar infarction) and compared them to healthy controls (40–42). Both studies used similar methodology in which a cohort of patients with balance disorders and a cohort of healthy controls were both exposed to balance-invoking visual stimulation, fMRI, and tests of balance, gait, and disability. However, only patients with balance disorders received 10 days of TLNS alongside simple balance exercises, after which the same visual stimuli, fMRI, and testing were conducted again. Significant improvements in gait (measured using the DGI; $p < 0.005$), balance (measured using the SOT; $p = 0.026$), posture (measured using accelerometers; $p < 0.005$), and in self-perceived disability (measured using the Dizziness Handicap Inventory; $p < 0.0005$) were observed pre- and post-intervention. In fact, postintervention posture scores in the balance disorder group were not significantly different than the scores of healthy controls. There was no mention of AEs in either study.

fMRI data suggest that TLNS-augmented balance training led to a significant increase in trigeminal nuclei activity when patients received balance-invoking stimuli (42). The trigeminal nuclei does not process balance information, but rather the effects of neuromodulation are transmitted through the nuclei to adjacent structures including the vestibular nuclei to affect change (43). Subsequent fMRI studies report that neuroplastic change did not exclusively occur in the brainstem's trigeminal nuclei but also in distant cortical and subcortical structures (41). Subcortical structures, such as the globus pallidus and thalamus, served to process and transmit this information to cortical structures. TLNS-augmented balance training resulted in alterations to nonspatially related cortical structures consisting of the visual processing centers (visual association cortex) and vestibular processing centers (multisensory corticovestibular system and vestibular nuclei); these functionally related cortical structures form a functional network. According to the reciprocal inhibitory visual-vestibular interaction theory, motion information derived from the visual system will inhibit incoming information from the vestibular system, and vice versa, to protect the brain from incongruent stimuli (44). It appears that this network displays excessive activity in balance disorder and treatment with TLNS normalizes this network by dampening reciprocal inhibition (41). Interestingly, the multisensory corticovestibular system is located in the superior temporal sulci, which is distant from the trigeminal nuclei where TLNS is known to affect the most change. TLNS-augmented training has been shown to improve balance and gait, through targets in the brainstem and pons, but it is also observed to improve cognition and emotion (4,7). Network activation observed in both studies confirms the mechanism identified in previous studies through which TLNS can impart neuroplastic changes to areas not spatially related to the trigeminal nuclei (45).

Both studies demonstrated clinical and self-perceived improvements in balance and gait in balance disorder participants (40–42). Additionally, both studies used fMRI with independent component analysis to determine the structures and networks that were augmented with TLNS. Both studies had serious concerns for risk of bias (40–42). The clinical testing (i.e., balance, gait, and posture) of both studies used a within-subject design, which increased risk of bias. However, the fMRI component of both studies compared imaging findings of balance-disordered patients who completed TLNS and rehabilitation with healthy controls who completed neither. The lack of matched balance-disordered controls, in addition to not accounting for the role of rehabilitation alone, leads to a serious concern for confounding. Future studies should use balance-disordered controls and account for the role of rehabilitation alone in fMRI findings. Nevertheless, functional imaging is a powerful tool that can be leveraged to validate this network modulation pattern hypothesis in other patient populations and to discover new networks.

Other Neurological Conditions

TLNS has been investigated in other neurological conditions but the evidence is limited to a quasi-experimental trial and five case reports/series, each describing a different condition. Many of these investigations are presented in conference proceedings and details regarding methodology are unreported. First, a quasi-experimental trial (n = 134) investigated a ten days course of TLNS-augmented rehabilitation versus rehabilitation alone in children with spastic diplegia (mean age: 8, standard deviation: 0.3) (10). Statistically significant within-group improvements in both hand and leg spasticity (measured using the Ashworth scale) were observed in both groups but the improvements in leg spasticity of the TLNS-augmented group was significantly greater ($p < 0.001$). Similarly, statistically significant within-group

improvements in mobility (measured using the functional motor scale) were observed but no between-group differences were found. However, there were serious concerns for risk of bias in this study as a result of patient allocation and outcome reporting. Patients were allocated to the TLNS group and the rehabilitation alone group based on their prescribed rehabilitation plans; patients were prescribed plans based on the severity of their condition. Second, the baseline clinical demographic characteristics of patients and patient flow was unreported in this study. Thus, these findings of within-group improvements should be interpreted with caution.

In the first case series, 70 patients with ataxia following resection of large and giant vestibular schwannomas received an intensive ten session TLNS intervention (11). The authors reported improvements in walking and standing but details regarding methodology and results were unreported in this conference proceeding. In a separate case report, two participants with motor spinal cord injuries that were refractory to conventional rehabilitation demonstrated improvements in balance and gait. Improvements were sustained throughout 14 weeks of TLNS-augmented rehabilitation (46). Both participants, who at baseline were reliant on power wheelchairs, were able to complete the majority (83% and 100%) of the intervention, demonstrating feasibility. In a third case report, a participant with six years of advanced Parkinson's demonstrated improvements in balance, gait, and oculomotor function after four months of TLNS-augmented rehabilitation (47). The fourth case featured a participant with deficits in posture and gait after undergoing a fourth ventricle ependymoma resection three months prior (48). Following two-weeks of TLNS-augmented rehabilitation, the participant demonstrated improvements in postural stability, gait, and a near perfect score on the BEST (20/28 pre-test vs. 27/28 post-test). The final case is of a participant with a 20-year history of progressive spinocerebellar ataxia of unreported etiology who demonstrated improvements in balance and gait after two weeks of TLNS-augmented rehabilitation (49). Most gains in gait were from increased range of motion in the arms/trunk and increased left-to-right symmetry of stride length and velocity.

Across all cases, subjects could complete most of the intervention, including a 12-week home component in the spinal cord injury report. No AEs were reported except for excess salivary production. Although RCT evidence is absent among these populations, many of the participants recruited into these case studies have completed years of physical rehabilitation prior to enrolment without significant gains. These studies, by no means, demonstrate conclusive evidence of TLNS efficacy. Rather, they suggest that TLNS can be feasibly and safely tested in a diverse population, often with refractory neurological conditions, to fill the high demand for effective treatment in this patient population.

CONCLUSIONS AND FUTURE DIRECTIONS

Overall, TLNS research demonstrated a promising therapeutic device that can be feasibly and safely tested on diverse neurological conditions. In 2019, Canada was the first country to approve TLNS to treat chronic balance deficits secondary to mmTBI (50). In 2020, Canada approved its use in MS patients with gait deficits (50). However, approval was largely based on product safety rather than efficacy. Clinicians must cautiously counsel patients about TLNS as patients with chronic illnesses often consider treatment modalities that advertise symptom relief, despite large financial costs and the absence of strong evidence (51).

TLNS has been studied to varying degrees to treat symptoms secondary to stroke, balance disorders, and other neurodegenerative disorders. Thus far, research has been limited small case studies and series, which has demonstrated feasibility and safety in diverse patient populations. The next step must be to produce high-quality RCTs to further elucidate efficacy, optimal dosages, necessary treatment duration, and treatment durability. It is also important to acknowledge the difficulties in finding an appropriate control group when testing TLNS; this is a common issue when investigating nonpharmacologic interventions. For instance, comparisons between any device to physical rehabilitation alone fail to control for placebo effects, while comparisons between any device to a sham device may underestimate the true effect if the sham is active. Further amendments to the TLNS control conditions are necessary to achieve optimal comparisons of efficacy. Otherwise, treatment benefits may be attributed to other factors including placebo effect, increased volume and intensity of physical rehabilitation, or synergistic combinations of the above.

Considering the vital role of physical rehabilitation, it is imperative that protocols are transparently reported. Protocols vary greatly among published studies and are often not transparently reported. Studies should also specify the exact parameters of the pulse-width, frequency, and intensity to improve reproducibility. Adequate reporting of interventions will ensure reproducibility of future trials and allow for a better understanding of TLNS.

Authorship Statement

Dion Diep and Gordon Ko were responsible for the study conception and design. Dion Diep and Andrew Lam were responsible for data extraction and validation, and data analysis and interpretation. All authors provided a critical review, drafted the manuscript, and approved the final manuscript. Gordon Ko is the guarantor.

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COMMENTS

This field is just beginning to be noticed by patients, therapists and researchers so I expect it will be cited going forward.

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This interesting access to central neural processing for treatment of gait and balance is certainly worthwhile for further investigation. The authors have presented a very helpful introduction to this specific application. More importantly, when compared to other

attempts to access the central nervous system for therapeutic neuromodulation (i.e., vagus, sphenopalatine, and auditory routes) it points out the possibilities for many further applications to treat disease processes less invasively and with specific targets. This review inspires creativity for similar efforts in other disease states.

It will be important in the future to discern the differences in sub-perception and sensory-based therapies for translingual stimulation. The remarkably rich sensory neuron density of the tongue may demonstrate responsiveness to higher frequencies and variable waveforms (e.g., sinusoidal, burst-forms, kHz frequencies, etc.) to determine other specific central targets which might be suitable for peripheral modulation.

This is an exciting area for further research and the authors have done a fine job of introducing the neuromodulation community to this approach.

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The authors provide a detailed summary of available research results for the use of TLNS as a non-invasive form of neuromodulation and its potential benefits as an adjunct to rehabilitation. Importantly, they recognize the difficulty in creating adequate control group methodologies in studies of non-pharmacological therapies.

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