Evaluating a novel Transcutaneous Auricular Vagus Nerve Stimulation control condition

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Abstract

Objective: Transcutaneous auricular vagus nerve stimulation (taVNS) is being actively explored as a therapeutic option for multiple conditions. Current blinding strategies employed in the literature are variable, and non-optimal due to perception confounds. Additional strategies are needed. We assessed the blinding integrity of taVNS when used with a novel sham waveform.
Methods: Ten healthy subjects (mean age: 36.6 ± 11.3 y) completed a randomized, double-blind, parallel study. taVNS was delivered while participants performed tasks mimicking upper limb rehabilitative training. The intervention consisted of 6, thirty-minute sessions over 2 weeks. The blinding assessment was performed after the last session.
Results: Majority of the participants (n=6) were unsure of their stimulation allocation. The binomial test indicated no evidence of systematic unblinding based on guessing alone. Bang's blinding index was -0.20 and -0.60 for the active and sham groups, respectively.
Discussion: This study's sham taVNS protocol indicates satisfactory participant blinding. Testing on larger samples and clinical populations is advocated to further demonstrate utility.

Keywords: transcutaneous auricular vagus nerve stimulation, taVNS, blinding, stroke, motor activated auricular vagus nerve stimulation, tVNS.

1. Introduction

Implanted vagus nerve stimulation (VNS) involves a cuff electrode, typically placed around the left cervical vagus nerve, that delivers electrical impulses to modulate vagal activity. It is a well-established neuromodulatory technique, clinically approved in the United States for treating depression and epilepsy. VNS has also been shown to enhance neuroplasticity, accelerate neural activity restoration, and activate motor learning-related neurocircuitry in animal models and humans [1–4]. Clinical trials on paired VNS showed that it significantly boosts motor learning when delivered synchronously with motor rehabilitation, nearly doubling the effectiveness of conventional post-stroke motor rehabilitation [5–7].This trial led VNS to be the first FDA-approved neuromodulation method for post-stroke rehabilitation.

A non-invasive option to stimulate the vagus nerve, known as transcutaneous auricular vagus nerve stimulation (taVNS), has gained traction in the past two decades [8] and achieved its first FDA approval in 2021 for opioid withdrawal relief [9]. The intervention uses surface electrodes applied to specific anatomical landmarks in the ear, usually the cymba concha and tragus, to activate underlying efferent fibers of the auricular branch of the vagus nerve, which project through the subcutaneous tissue of the external ear. taVNS has several advantages over the implanted approach, including noninvasiveness, cost, and the potential for remote-supervised administration [10].

A recent study tested the effects of taVNS combined with motor rehabilitation tasks. One trial arm received taVNS in response to motor activity detected by electromyography (EMG) while the other arm received unpaired stimulation [11]. Both groups improved in motor function, but the group that received paired stimulation experienced approximately double the effect size of the un-paired taVNS group, even though the paired group received significantly less stimulation overall. These findings suggest that closed-loop stimulation by pairing the stimuli with movement may make treatment more effective. Yet, the absence of a sham arm leaves open the possibility that non-specific factors contributed to the observed improvements, underscoring the need for carefully designed blinding strategies to establish true efficacy

Most of the blinding strategies established for other brain stimulation modalities are difficult to implement in taVNS. For example, rTMS sham protocols use a clicking sound of the coil to mimic the active stimulation, but taVNS operates silently, making such strategies inapplicable. In implanted VNS, the stimulation is generally subsensory, so a robust blinding is possible [6]. Additionally, habituation-based methods commonly applied in transcranial electrical stimulation [12] are not suitable, as taVNS is typically delivered with suprasensory pulses. Topical anesthetic to mask sensation pain or during treatment as used in some settings [13–15] is not possible in taVNS as it could block the sensory nerve transmission, compromising the stimulation efficacy As a result, taVNS studies often rely on suboptimal blinding methods, such as positioning electrodes at alternate anatomical targets [16]. However, this approach is inherently limited, as it depends on participants' unfamiliarity with correct electrode placement and compromises the experimenter blind. Other strategies include the use of identical clamps with three tips, which allow activation of two skin points depending on allocation to active or sham stimulation [17], or using same

anatomical sites but applying stimulation at a different frequency [18]. Although these approaches address some challenges of blinding, they still require careful validation to ensure that stimulation at an alternative anatomical site or frequency does not inadvertently produce therapeutic effects. An additional confound with using different frequencies is the application of different stimulation intensities (linked to individual perceptual threshold) as noted in Bauer et al., 2016. Passive control, in which electrodes are applied at the active sites, but no stimulation is delivered, also has limited utility, as it fails to mimic the sensory feedback due to stimulation[16], which may enable the participant to guess group allocation, thereby invalidating the blind.

Therefore, the objective of the present study is to determine whether a novel sham waveform could provide effective blinding during taVNS, tested while participants performed a motor task.

2. Methods

2.1 Study Design

The double-blind study was approved by the WCG IRB (protocol #20226394) in accordance with the Declaration of Helsinki. We recruited 11 healthy subjects (2 female; age 36.6 ± 11.3 years). Participants provided written informed consent, and were screened for contraindications to taVNS. Subjects were taVNS naïve- i.e., never received taVNS before. One subject withdrew prior to randomization due to concerns regarding the prospect of completing six sessions paired with the planned tasks. Of the remaining ten subjects, 50% (5) were allocated to receive active stimulation and 50% (5) were allocated to receive sham.

2.2 Titration

Electrodes were placed on the cymba concha and tragus. Perceptual threshold (PT) for each participant was obtained using a staircase procedure, which involves delivering a short stimulation at increasing intensities and recording the minimum intensity that the subject first reports a sensation/perception. Then, the current was increased and delivered at a decreasing intensity until the stimulation was no longer sensed. The **Table** below lists the individual PT of the 10 subjects and the corresponding stimulation intensity.

Subject number	Perceptual threshold (mA)	Stimulation Intensity
1	0.20	0.40
2	0.40	0.80
3	0.30	0.60
4	0.78	1.56
5	0.53	1.06
6	0.21	0.42

7	0.30	0.60
8	0.55	1.10
9	0.20	0.40
10	0.40	0.80

Table: Individual perceptual threshold (PT) and stimulation intensity values. PT testing was performed using a staircase procedure and performed on the first visit. Individual stimulation intensity was set to twice the PT and kept constant throughout for the subsequent six visits. Stimulation intensity was set to double PT.

2.3 Active and Sham Parameters

Parameters for the active stimulation group replicated the taVNS study by Badran et al. 2023. Specifically, six 30 minute sessions were delivered over 2 weeks. Stimulation was delivered at double the subject's PT with a 30-second ramp up at the beginning and a 30-second ramp down at the end. Stimulation was delivered as trains of monophasic pulses at 25 Hz with a pulse width of 500 microseconds. Each train was 5 seconds with intervals of 5 seconds between each train (5 sec ON / 5 sec OFF). In total, subjects in the active arm received 22,500 pulses.

For sham stimulation, we employed a novel sham procedure. An existing taVNS stimulator (Soterix Medical, Woodbridge, NJ) was customized to allow generating this novel sham waveform At the beginning of the session, the current ramped up for 30 seconds to the desired current limit (2x PT) and then back down for 30 seconds. The up/down ramping was then repeated every 10 minutes to make it less likely for subjects to correctly ascertain that they were only receiving sham. The pulse width, frequency, train duration, and interval were the same in the sham group as for the active group, resulting in a total of 2,250 pulses delivered to each subject in the sham group. **Figure 1** illustrates the current waveform used for active and sham stimulation. In addition to being quantitatively fewer, because the sham waveform never maintained the target current but instead ramped up and down, the *mean* intensity of the pulses was approximately half that of the active group. The participant and the experimenter were blind to the stimulation assignment.

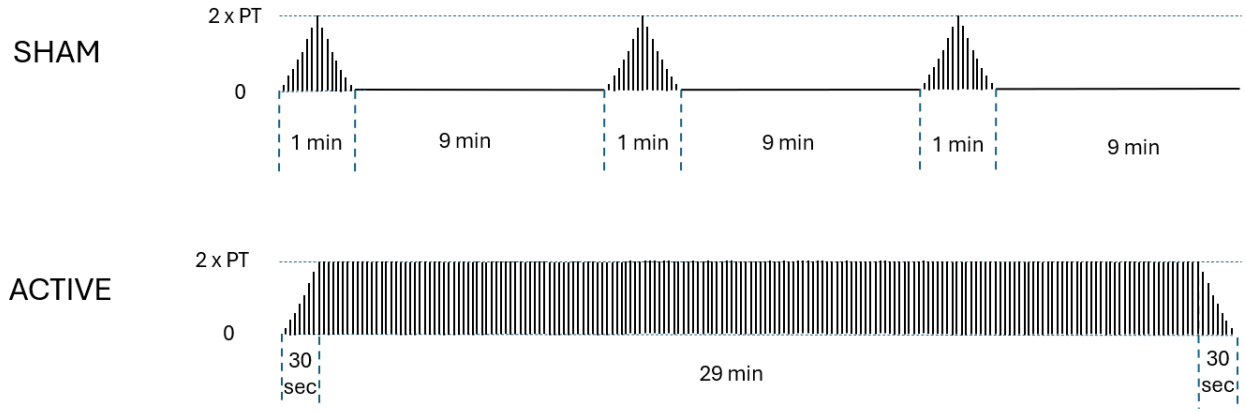

Figure 1: **Illustrations of the sham and active stimulation waveforms used for this study.** In both cases, stimulation ramped up to twice the individual-specific perceptual threshold (PT). Stimulation was delivered as trains of monophasic pulses (25 Hz, 500 µs pulse width) with each train 5 seconds long and an inter-train interval of 5 seconds.

2.4 Procedures for taVNS Paired with a Motor Task

Stimulation sites were exfoliated with NuPrep Skin Prep gel (Weaver & Company, Houston, TX) by gentle rubbing at each site for ~15 seconds. The gel was subsequently wiped off with a cleansing wipe. This served the purpose of not only removing any oils or grime from the exposed skin but also facilitated proper contact impedance with the adhesive-based hydrogel electrodes (RELI-stick, Soterix Medical, Woodbridge, NJ). During the stimulation session, participants engaged in jigsaw puzzles and scissor-cutting exercises. These tasks served a dual purpose: they replicated the motor activated auricular vagus nerve stimulation (MAAVNS) protocol (Badran 2023), which combines taVNS with post-stroke motor rehabilitation, and provided a distraction to reduce participants' focus on the electrical stimulation, thereby minimizing the likelihood of successful identification of whether they received active or sham stimulation. Participants were further encouraged to complete their assigned task (e.g., finishing the puzzle) within the session, thereby sustaining attention and reinforcing engagement with the activity rather than the stimulation. **Figure 2** illustrates participants performing a motor task while receiving taVNS. For both the active and sham groups, stimulation was initiated approximately 30 seconds after task onset, once participants were sufficiently engaged, to reduce awareness of the stimulation further. After each session, participants were asked to rate the task's difficulty, indicate whether it caused any anxiety (i.e. with respect to task progress), and provide their opinion on whether the procedure might be useful for post-rehabilitation patients. These questions were designed to further distract participants from the stimulation and put emphasis on the task.

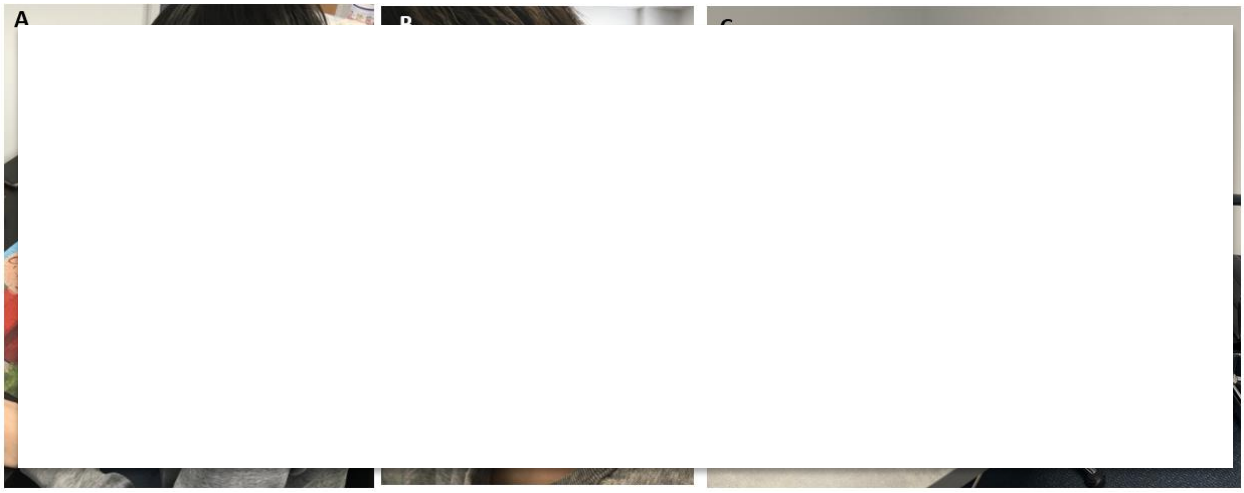

Figure 2: **Active or sham taVNS was delivered for 30 minutes while subjects engaged in motor tasks**. The tasks were similar to those done during post-stroke motor rehabilitation. The tasks included putting together a jigsaw puzzle (A) and scissors cutting (C). The electrode locations are shown in (B). For all tasks, the stimulation device was kept behind and away from the participant to prevent any potential distraction.

2.5 Blinding Questionnaire

To evaluate the success of participant blinding, we administered a structured post-intervention questionnaire adapted from Flanagan et al. 2019[19], which asked participants to indicate whether they believed they received active stimulation, sham stimulation, or were unsure. Participants who

answered active or sham were then asked to rate their confidence in this belief on a 5-point Likert scale.

Responses were analyzed using multiple strategies. First, a binomial test assessed whether participants guessed their group assignment (active vs. sham) at a rate significantly greater than chance. “Unsure” responses were excluded from this analysis. Second, we computed the Bang’s Blinding Index (BI) separately for active and sham groups, treating “unsure” responses as indicative of successful blinding. BI values range from –1 to +1, where 0 indicates perfect blinding, positive values reflect unblinding in the expected direction, and negative values suggest incorrect guessing.

3. Results

All 10 participants (n=5 in the active group and n=5 in the sham group) completed the post-intervention blinding questionnaire. When asked to guess their group assignment, 4 participants provided a definitive guess (“active” or “sham”), while 6 responded “unsure.”

Participant Guess Accuracy

Among the 4 participants who made a guess, 3 correctly identified their group assignment. A binomial test indicated that this proportion (75%) was not significantly greater than chance ($p = 0.31$), suggesting no evidence of systematic unblinding based on guessing alone.

Bang’s Blinding Index (BI)

To account for “unsure” responses, we computed the Bang’s BI separately by group. BI values were:

- Active group: BI = –0.20 (n=5), indicating moderate blinding with slight bias toward incorrect guessing or uncertainty.
- Sham group: BI = –0.60 (n=5), indicating strong blinding, with most participants either unsure or incorrectly identifying their condition.

These values reflect effective blinding across both groups, with the sham group exhibiting stronger blinding integrity.

Confidence Ratings and Guess Accuracy

Confidence scores were available for four participants with definitive guesses. The mean confidence rating among those who guessed correctly was 4.67, compared to 3.00 among those who guessed incorrectly.

4. Discussion

The goal of a gold standard blinding is to ensure that neither the participant nor the experimenter know the stimulation condition allocation. This minimizes bias and ensures that the observed effects are truly due to the intervention rather than expectations, belief, or psychological influences. Therefore, blinding strategies strive to mimic the active stimulation to the extent possible (i.e., same device, sensory feedback, electrodes/placement, and procedures) while not producing a therapeutic effect. This is especially important in taVNS, where stimulation often produces perceptible sensations that can compromise blinding. Despite this, few taVNS studies formally assess blinding integrity, leaving a critical gap in the evidence base. The lack of a universally accepted blinding strategy in taVNS is further compounded due to the numerous stimulation parameters available (ie., intensity, frequency, pulse width, train duration, inter-train interval) unlike other modalities [12,20] .

We demonstrate here the utility of a waveform that is predicated on mimicking all stimulation parameters but restricting delivery to specific instants. The inherent assumption being that intermittent stimulation would trick the participants in thinking that they are receiving continuous stimulation while being engrossed in their task. Additionally, the substantially reduced number of pulses delivered (a tenth) and at reduced intensity, is unlikely to produce a lasting change in excitability / plasticity. These assumptions would, however, need testing in clinical populations. We note that a similar blinding strategy was employed in a large tDCS depression study and while blinding was effective, no antidepressant difference was found between the active and sham arms [21]. Further, the study authors could not discount that sham tDCS was biologically active.

So, while taVNS needs some active control throughout, this serves as a cautionary note. This study has several limitations. First, the sample size was small, limiting the generalizability of the findings. Second, we did not formally assess the integrity of the experimenter's blinding. Third, the study was conducted in healthy controls, who may exhibit different sensory thresholds compared to clinical populations. Nevertheless, we speculate that blinding performance may in fact be enhanced in clinical cohorts, owing to differences in expectations, pre-existing conditions, and sensory experiences. For example, a participant recovering from stroke is likely to concentrate on the rehabilitation tasks rather than the precise sensations of stimulation, and the presence of baseline symptoms may further obscure distinctions between active and sham conditions.

In summary, our results indicate satisfactory participant blinding at study end in a small pool of healthy subjects performing tasks mimicking upper limb rehabilitative training paired with tAVNS. The direct extrapolation of the outcomes of our trial to other situations (clinical populations, individuals with previous experience with taVNS, trials involving fewer stimulation sessions, and different electrode sites) must be performed with care. Nonetheless, we present a promising strategy that serves as a stepping stone for future investigation.

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Authorship statement:
Mr. Valter and Drs. Datta and Badran designed the study. Mr. Valter, Mr. Turnquist, Mr. Nazim and Dr. Datta planned the study procedures. Mr. Valter and Mr. Nazim performed the data collection. Mr. Valter and Drs. Pilloni and Datta performed data analysis and interpretation. Mr. Valter and Dr. Datta prepared the manuscript draft with important intellectual input from Drs. Kimberley, Badran, and Charvet. Mr. Valter and Drs. Pilloni and Datta had complete access to the study data. All authors approved the final manuscript.

Conflict of Interest Statement:
YV, GT, KN, and AD are employees of Soterix Medical, Inc. The remaining authors have nothing to disclose.

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