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Transauricular Vagus Nerve Stimulation (taVNS) enhances Conditioned Pain Modulation (CPM) in healthy subjects: A randomized controlled trial

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Dear Editor,

Vagal Nerve Stimulation is a novel proposed treatment for pain. Originally approved as a cervical implant for epilepsy and depression, non-invasive VNS devices offer greater accessibility, and reduced side effects in comparison to the invasive VNS [1]. Transauricular VNS stimulates the auricular branch of the vagal nerve (ABVN) which is directly connected to the nucleus tractus solitarius (NTS) in the medulla, from where projects to the hypothalamus, thalamus, amygdala, hippocampus, and prefrontal cortex, releasing dopamine, serotonin, and norepinephrine and, consequently, modulating pain response [1].

There is still a lack of evidence regarding the effect of vagal nerve stimulation on pain syndromes, including its mechanistic effects, before auricular vagal stimulation can be used widely in the clinic. A used biomarker for pain control mechanism and predictor of responders to neuromodulation treatments is the Conditioned Pain Modulation (CPM) – a process based on applying controlled stimuli, which can be pressure, heat, or cold sensation, to measure pain response. In brief, CPM measures the efficacy of descending pain pathways when an individual is exposed to a given sensation [2]. To date, only one study that investigated the effect of taVNS on the pain threshold of healthy subjects, finding an increase in mechanical and pressure pain threshold and a decrease of mechanical pain sensitivity; however, CPM was not evaluated [2].

Understanding how taVNS could modulate the endogenous pain system in healthy subjects could bring insights of the application of the technique in pain conditions. So, our study aims to determine the effect of taVNS on CPM, as this tool was shown to be a valid assessment tool to measure pain response.

In this clinical trial (NCT05801809), conducted from May to September 2023, we randomized 44 participants into two groups (allocation ratio 1:1): active taVNS (n = 22, Fig. 1A) and sham taVNS (n = 22). The detailed methodology is described in the Supplementary Material 1. All completed the intervention (Supplementary Fig. S1). Four participants (one in the active and three in the sham group) did not complete the CPM assessment due to personal reasons or time availability. For this outcome, complete and imputed cases were included in the analysis. For the rest of the outcomes, all participants completed the data collection successfully.

The baseline characteristics of the patients in the two groups were balanced in terms of clinical and demographic characteristics (mean age 41.3 years old, 16% women). Supplementary Table S1 sho ws a detailed description of sample characteristics.

Before intervention, there was no significant difference in the scores of pain-60, TSPS, and CPM between taVNS and sham taVNS groups ($p = 0.83$, $p = 0.29$, $p = 0.13$, respectively). After intervention, we found an improvement of CPM efficacy ($p = 0.004$) after active taVNS (CPM change = 0.34; SD = 0.60) compared to sham (CPM change = −0.53; SD = 1.14) (Fig. 1B). From our regression model, we confirmed a statistically significant difference in the change of CPM score between the taVNS and sham taVNS groups (beta coefficient = 0.80; 95% CI: 0.23–1.37; $p = 0.007$), that survived after controlling for age and biological sex (Supplementary Table S2). The effect size (Cohen's d) of this change was 0.97 (95% CI 0.31–1.62), which constitutes a large effect size. Similarly, results did not change after inputting missing CPM values (multiple imputation method).

Furthermore, from our unadjusted and adjusted analyses, no between-group differences were found in pain-60 (unadjusted: $p = 0.58$; adjusted: $p = 0.76$) or TSPS (unadjusted: $p = 0.25$; adjusted: $p = 0.40$) (Supplementary Table S2).

From Bayesian analyses using non-informative priors, we found a 99.99% probability that active taVNS is better than sham for improving CPM in health subjects (Fig. 1C). The regression coefficient was similar to the frequentist approach (Coefficient = 0.80, 95% CrI: 0.25–1.35). This suggests strong evidence in favor of our alternative hypothesis (Bayes' factor of 234.29).

Moreover, we found no effect modification by age group (interaction p-value = 0.46), biological sex (interaction p-value = 0.81), race (white vs. non-white, interaction p-value = 0.63) or adequate mood levels at baseline (interaction p-value = 0.32), suggesting homogenous effects across subgroups.

Before intervention, there was no significant difference in the BMIS, VAS mood, or VAS fatigue between taVNS and sham taVNS groups ($p = 0.23$, $p = 0.90$, $p = 0.20$, respectively). After intervention, no between-

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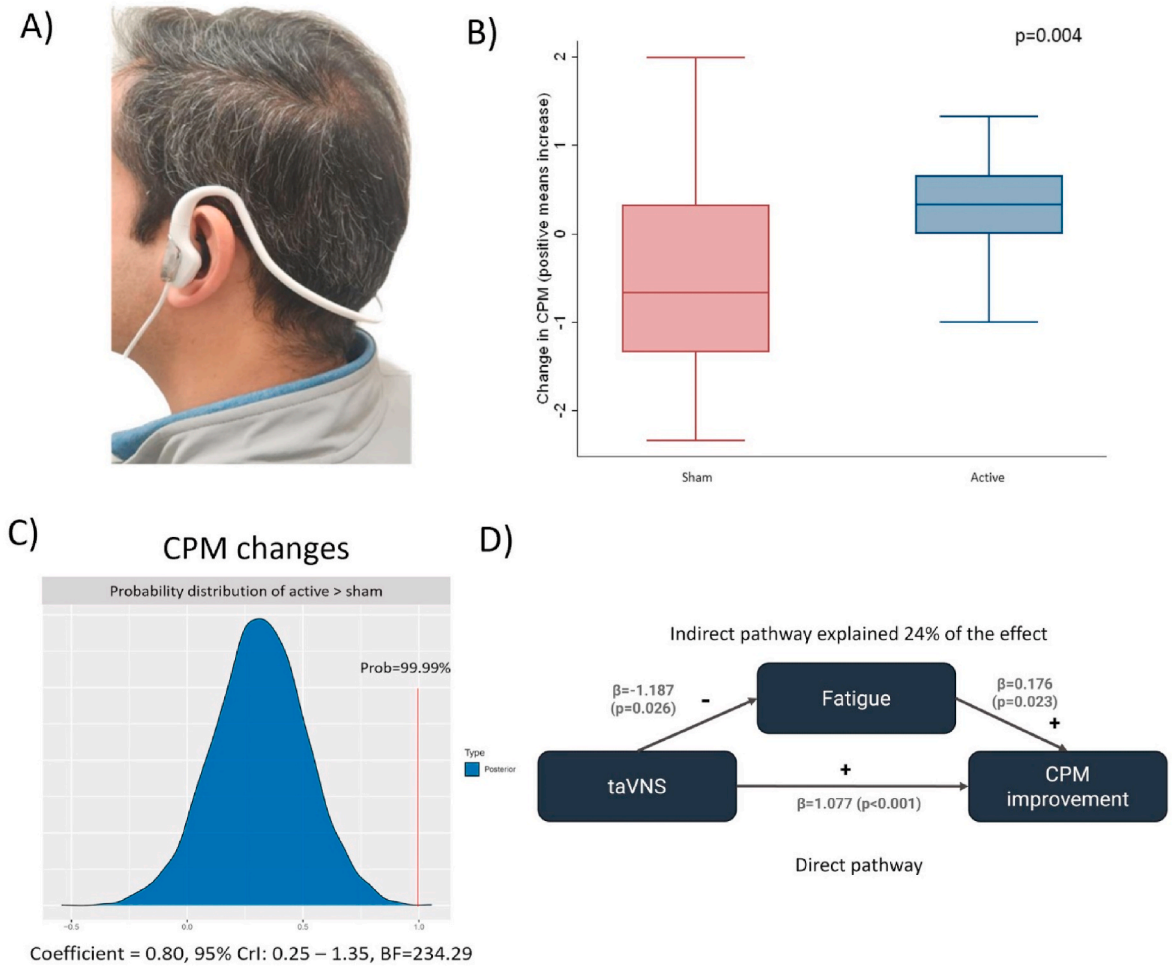

Fig. 1. Fig. 1A. Group comparison of change in CPM scores after intervention active taVNS (n = 22) and sham taVNS (n = 22). Fig. 1B. Posterior probability distribution of our alternative hypothesis (active taVNS > sham taVNS). Fig. 1C. Causal mediation analysis of taVNS effects on CPM improvement. Fig. 1D. Example Setup. A representation of a subject receiving taVNS on both ears.

group differences were found in BMIS (unadjusted: p = 0.17; adjusted: p = 0.16), VAS mood (unadjusted: p = 0.37; adjusted: p = 0.68), or VAS fatigue (unadjusted: p = 0.05; adjusted: p = 0.05) (Supplementary Table S2).

To investigate clinical surrogates of the CPM improvement in our sample, regression analysis adjusted and stratified by the group allocation were implemented. We found that reduction of VAS fatigue (coefficient = −0.39, 95% CI: −0.67 to −0.12; p = 0.007), mood improvement (coefficient = 2.53, 95% CI: 0.55–4.51; p = 0.02), and higher pain-60 (coefficient = 0.16, 95% CI: 0.02–0.31; p = 0.03) were statistically significant correlates of CPM efficacy improvement in the active taVNS group. However, these variables were not significant correlates in the sham taVNS group (VAS fatigue: p = 0.82, BMIS mood score: p = 0.86, and pain-60: p = 0.11).

We also conducted a causal mediation analysis to explore possible underlying mechanisms by which an indirect pathway—mood, fatigue, or pain-60—could explain the effects of taVNS on CPM changes. The causal mediation analysis suggested that changes in fatigue mediated the effects of taVNS (Fig. 1D). The indirect pathway (coefficient = −0.209, p = 0.02) via fatigue reduction explained 24% of the total effect (coefficient = 0.86, p = 0.007). Mood improvement and increase in pain-60 were not significant mediators.

No severe or unexpected adverse events were reported. Only one subject in the active group reported minor tingling behind the left ear at the beginning of the stimulation that resolved within the next 5 min. The subject did not ask to stop stimulation and the session was completed as planned. No differences between groups were found (active taVNS: 0.04%, sham taVNS: 0%, p = 0.31).

This study showed that taVNS is able to decrease sensitivity to thermically evoked pain in healthy subjects. Studies using fMRI showed that taVNS leads to a significant response in downstream targets of vagal afferents, such as the NST, the subthalamic nucleus, locus coeruleus, and both dorsal and median raphe nuclei compared to the control condition. Additionally, noradrenaline (NE), serotonin (5-HT), and dopamine (DA) are key neurotransmitters related to the neurophysiological impact of taVNS over the afferent pathway of the vagus nerve [3–5]. Previous trials with healthy subjects indicate that the activation of NTS, LC, and the dorsal raphe nuclei (DRN) has an impact on the limbic and the brain reward systems [6,7]. Also, Badran et al. demonstrated that taVNS can activate the anterior cingulate cortex (ACC), which is involved in cognition and emotional processing. All those previous findings potentially explain the effects of improving mood and the perception of fatigue in patients after the session of vagus stimulation.

The assessment and treatment of chronic pain must take into consideration its multifaceted nature. Psychological variables can significantly impact how a person perceives pain and reacts to it emotionally and behaviourally. Chronic pain and fatigue are prevalent, concerning, and often coexisting symptoms. The clinical burden and the "clinical problem" are that these symptoms are linked to a lower quality of life and greater expenses when they are "persistent" or "unexplained." In addition, they present a diagnostic challenge and have a major effect on indirect costs and healthcare utilization [8]. In this scenario, an

intervention that can reduce the central sensitization of a noxious stimulus, mediated by modulating the fatigue levels has promising applications in several chronic pain conditions.

The mechanisms underlying fatigue in chronic pain conditions are unclear. Immune dysregulation and autonomic dysfunction have been linked. For example, autonomic dysfunction symptoms are prevalent and linked to elevated levels of fatigue and disease activation. It is important to note that there is a complicated interaction between systemic proinflammatory cytokines and fatigue, and more research is needed to determine how tVNS, fatigue, and inflammatory cytokines are related [9].

Improvement of fatigue through stimulating the vagus nerve was reported in previous studies with patients with systemic lupus erythematosus (SLE), and primary Sjogren's Syndrome [10]. Our recently metanalysis agrees with the anti-inflammatory response, showing modulation of IL-1b and IL-10. Future research on patients with chronic pain may focus on the potential analgesic effects of taVNS in clinical settings.

Our results showed that one session of taVNS is capable of increasing CPM in healthy subjects. These results were confirmed by frequentist and Bayesian approaches. Moreover, the analysis demonstrated a significant correlation between VAS fatigue and mood with CPM improvement in the taVNS group. Fatigue reduction was a mediator of the taVNS. Taken together, our finding suggests a salutogenic effect in the pain processing system associated with taVNS. However, future RCTs using taVNS in patients with chronic pain are still needed to establish the analgesic effects of taVNS for clinical populations.

CRediT authorship contribution statement

Kevin Pacheco-Barrios: Conceptualization, Formal analysis, Investigation, Supervision, Writing – original draft, Writing – review & editing. **Anna Carolyna Gianlorenco:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Lucas Camargo:** Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Maria Fernanda Andrade:** Methodology, Writing – original draft, Writing – review & editing. **Hyuk Choi:** Conceptualization, Validation, Writing – original draft, Writing – review & editing. **Jae-Jun Song:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Felipe Fregni:** Conceptualization, Methodology, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: H.C. and J.S. are directly associated with Neurive Co, a company developing neuromodulation technologies, such as taVNS, to treat common brain diseases. Neurive funds research at the Spaulding Neuromodulation Center. F.F. is a consultant for Neurive.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.03.006.

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