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Letter to the Editor

Neural Correlates of taVNS: Scalp EEG and insular sEEG heartbeat evoked potentials modulation in an Epileptic patient case study

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Dear Editor,

Transcutaneous auricular vagus nerve stimulation (taVNS), introduced by, (Ventureyra, 2000) emerged as a promising non-invasive neuromodulation method for treating various neurological and psychiatric disorders (Gerges et al., 2024). Despite its potential, the lack of reliable neurophysiological biomarkers limits the clinical efficacy and precise targeting of taVNS to the vagal pathway (Burger et al., 2020). Heartbeat-Evoked Potentials (HEPs), neural responses time-locked to cardiac events, are gaining interest as a biomarker reflecting brain–heart interactions mediated through interoceptive processing pathways (Yuan et al., 2007), primarily involving the insula and anterior cingulate cortex (Park et al., 2018). Previous research has shown that taVNS can diminish scalp-level HEP amplitude in frontocentral regions (Poppa et al., 2022) based on pooled cohort-level analyses. Yet, no study has performed direct measurements to correlate these findings empirically. Heart Rate Variability (HRV)—commonly proposed as a physiological marker of vagal activity—has been debated with recent *meta*-analysis (Wolf et al., 2021) questioning HRV's specificity as a biomarker of effective vagal activation by taVNS.

We present a detailed case study exploring, for the first time, the simultaneous impact of taVNS on scalp and invasive stereo-electroencephalography (sEEG)-derived HEPs, complemented by inter-trial coherence (ITC) analysis on a 36-year-old female patient with refractory epilepsy undergoing pre-surgical evaluation at Saint-Luc University Hospital, UCLouvain–Brussels, Belgium. Ethical approval and informed consent were obtained (reference: B403201630289). The clinical context enabled us to register scalp EEG concomitantly with sEEG electrodes directly from the insular cortex and surrounding regions, which play pivotal roles in interoceptive processing and autonomic regulation.

Our experimental design incorporated three distinct conditions: baseline (no stimulation), active taVNS (applied to the cymba conchae region), and sham stimulation (applied to the earlobe). Stimulations were administered using a Cerbomed Nemos device, configured with a stimulation frequency of 25 Hz, pulse width of 250 μs, and stimulation cycle of 30 s On / 30 s Off. Each stimulation condition was recorded on separate days to eliminate residual and carry-over effects. EEG data were simultaneously captured from 19 scalp electrodes and 76 invasive sEEG contacts, alongside concurrent ECG, allowing the synchronization to heartbeats. Statistical comparisons used ANOVA and t-tests.

Our analysis focused on EEG epochs ranging from −500 ms to + 500 ms around ECG R-peaks, emphasizing the 200–400 ms post-R-peak interval—an established temporal window for interoceptive neural responses. EEG and sEEG data were band-pass filtered (1–30 Hz), artifact rejection was performed, and visual confirmation was employed to ensure the correct root mean squared error semi-automated approach on eliminated trials over superimposed trials, eliminating 8 out of 580 baseline epochs, 45 out of 821 taVNS epochs, and 48 out of 616 Sham epochs. Retained epochs were time-averaged by stimulation condition for each scalp and sEEG electrode. The results showed significant modulation of scalp-derived HEP amplitudes in frontocentral and left temporal electrodes under active taVNS conditions compared to sham stimulation. Notably, taVNS reduced scalp-level amplitudes of the HEP while sham increased HEP amplitudes ($p = 0.018$ for the region of interest of electrodes Fp1, Fp2, F3, Pz, and F7). Intracranial sEEG data provided critical validation of scalp-level observations, revealing distinct polarity reversals around cardiac events within the anterior short gyrus of the insula, indicating a local cortical generation rather than passive volume conduction. Scalp and insular HEPs are shown in Fig. 1. Moreover, active taVNS significantly decreased ITC values (baseline: 0.040 vs. taVNS: 0.032; $p = 0.023$), indicating reduced neural synchronization and a less consistent cortical response to cardiac inputs. Conversely, sham stimulation produced no significant ITC modulation (baseline: 0.042 vs. sham: 0.035; $p = 0.101$), further supporting the specificity of taVNS-induced neural desynchronization. HRV Root Mean Square of Successive Differences (RMSSD) analyses revealed a non-specific increase under both taVNS and sham conditions. Additional anatomical details and analyses can be found as supplementary material.

Vagal stimulation has been linked to cardiovascular modulation, affecting heart rate, HRV, and blood pressure (De Couck et al., 2017). Reasonably, HRV changes have been proposed as a biomarker for vagal nerve activation as it enhances parasympathetic activity and modestly reduces heart rate. Intermittent taVNS has proven effective in enhancing

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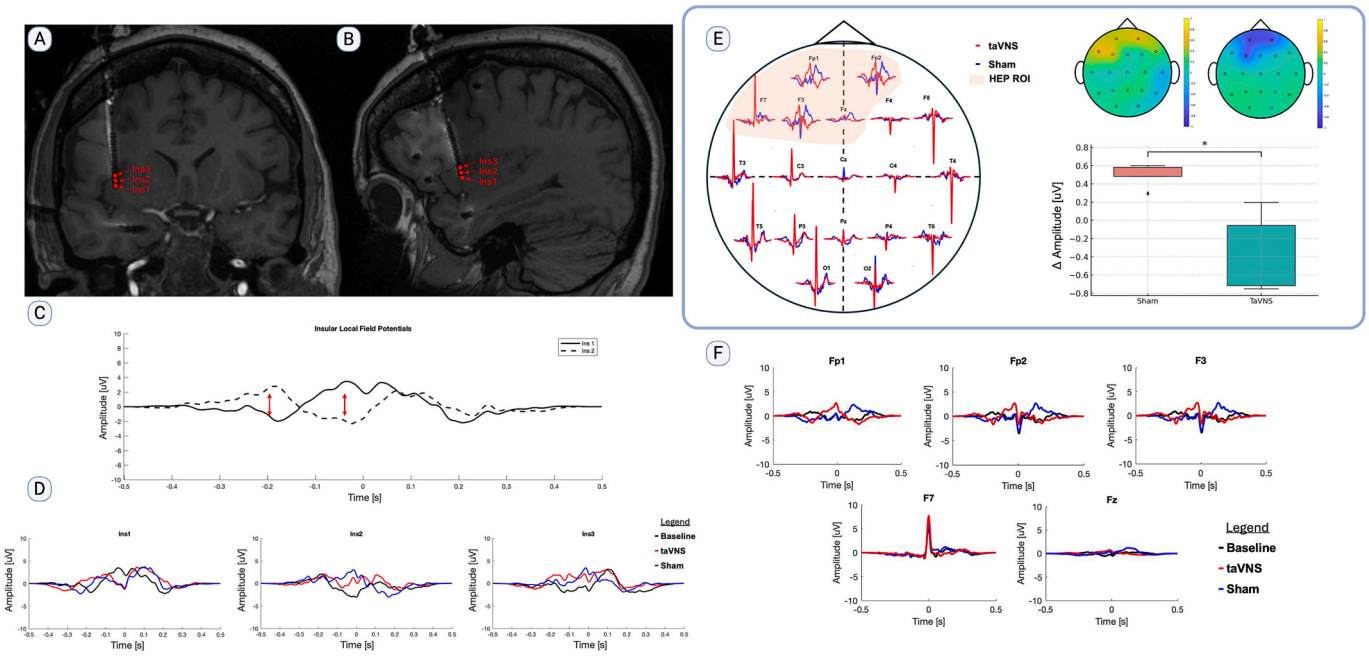

Fig. 1. Post-implantation reconstructed 3D T1w imaging of the insular electrode seen in the coronal plane **(A)** and the sagittal plane **(B)**. Contact Ins1 is the deepest. Ins1, Ins2, and Ins3 electrodes are located in the anterior short gyrus of the insula. **(C)** Representative averaged local field potentials from two insular electrodes, Ins1 (solid) and Ins2 (dashed), representing the HEP waveform aligned to the cardiac R-peak (t = 0). Red arrows highlight polarity reversal differences between the two adjacent insular recording sites. **(D)** Heart-evoked potentials (HEPs) from three insular electrodes (Ins1, Ins2, and Ins3) across Baseline (black), taVNS (red), and Sham (blue) conditions. Waveforms are time-locked to the R-peak (t = 0) and spatially distinct patterns of insular response to heartbeats. **(E)** Topographical mapping of HEP waveforms over scalp electrode locations. Cardiac Field Artifacts (CFA) can be observed aligned with R-peak centered at 0 ms where positive R-peaks are located from the left occipital and reversing polarity towards the right frontal. HEP early and late modulations can be seen after R-peaks, with stimulation-dependent differences being located over the frontocentral and temporal-left side. Topographical difference map between Sham and baseline condition and taVNS and baseline condition for average HEP waveform between + 200 ms and + 400 ms. Boxplot of the averaged amplitude of electrodes Fp1, Fp2, F3, Pz, and F7 within the temporal region of + 200 ms and + 400 ms. TaVNS stimulation produces a decreased amplitude in frontocentral and temporal-frontal left-side electrodes, while Sham produces an increased amplitude over the same period. The color scale represents the voltage amplitude difference from the stimulation condition against baseline in ± 1 μV range. **(F)** Comparison of HEP waveforms between key frontocentral and temporal left locations. Baseline HEP waveforms are presented in black, under taVNS stimulation condition in red, and earlobe Sham stimulation in blue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

HRV at low current intensities (e.g., 2 mA) and brief pulse durations (e.g., 100 μs) when applied to cymba conchae, fossa triangularis, and inner tragus (Machetanz et al., 2021). However, since taVNS stimulates non-cardiac fibers and operates through a complex network of brain regions and nuclei, its impact on HR and HRV may not be direct, as non-vagal sham stimulations also modulate HRV (Wolf et al., 2021). Alternative biomarkers based on the influence of taVNS on the noradrenergic system are thought to be more specific (Burger et al., 2020). While taVNS and cVNS modalities aim to modulate vagal activity, variations in therapeutic outcomes suggest a different nerve fiber population activation. The different fiber composition at the stimulation auricular target region, might explain why their effects on cardiovascular parameters and other biomarkers diverge. Aβ-fibers activation seems consistently involved in therapeutic effects, which are notably less abundant in the Auricular Branch of the Vagus Nerve (ABVN) than in the cervical vagus nerve (Hilz, 2022), implying that a biomarker for assessing an effective vagal pathway stimulation remains crucial.

Recent studies, including (Poppa et al., 2022), explored the effects of taVNS on HEP. Their EEG analyses revealed a taVNS-induced reduction in HEP amplitude at frontocentral and centroparietal electrodes, and source localization identified taVNS effects in the insula, operculum, somatosensory cortex, and prefrontal regions, corroborating the insular role as a key HEP generator, aligning with findings from intracranial studies (Park et al., 2018). Our findings align with these studies, demonstrating that taVNS modulates central neural processes, supporting HEP modulation as a coherent model of vagally-driven interoceptive network activation.

In conclusion, our findings offer evidence advocating for HEP modulation as a promising and reliable biomarker for assessing central neural effects induced by taVNS. Establishing a robust, non-invasive biomarker can significantly enhance therapeutic outcomes, optimize stimulation protocols, and advance clinical non-invasive neuromodulation strategies.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2025.04.013.

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Enrique Germany Morrison[a,b,*], Manon Dumoulin[a], Vincent Joris[a,c], Roberto Santalucia[a,e], Venethia Danthine[a], Inci Cakiroglu[a,b], Giulia Liberati[a,d], Antoine Nonclercq[f], Riëm El Tahry[a,b,g]

[a] *Institute of Neuroscience (IoNS), Université Catholique de Louvain, Brussels, Belgium*

[b] *Walloon Excellence in Life Sciences and Biotechnology (WELBIO) Department, WEL Research Institute, Wavre, Belgium*

[c] *Department of Neurosurgery, Cliniques Universitaires Saint-Luc, Brussels, Belgium*

[d] *Psychological Sciences Research Institute (IPSY), Université Catholique de Louvain, Louvain-la-Neuve, Belgium*

[e] *Department of Child Neurology, Cliniques Universitaires Saint-Luc, Brussels, Belgium*

[f] *BEAMS Department, Université libre de Bruxelles (ULB), Brussels, Belgium*

[g] *Center for Refractory Epilepsy, Department of Neurology, Cliniques Universitaires Saint-Luc, Brussels, Belgium*

[*] Corresponding author at: Institute of Neuroscience, Université Catholique de Louvain (UCLouvain), Avenue Emmanuel Mounier 53/B1.53.05, 1200, Brussels, Belgium.

E-mail address: enrique.germany@uclouvain.be (E. Germany Morrison).