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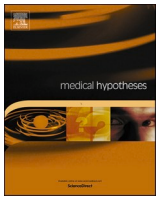

Research Article

Functional seizure therapy via transauricular vagus nerve stimulation

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ABSTRACT

This article explores the potential of transauricular Vagus nerve stimulation (taVNS) in treating Functional Seizures (FS), a condition that significantly burdens healthcare systems. Traditional seizure treatments are ineffective for FS due to its unique pathophysiology, highlighting the urgent need for alternative therapeutic strategies. While invasive VNS has shown promise in improving autonomic balance, its invasive nature poses limitations in FS treatment. taVNS, a non-invasive alternative, enhances parasympathetic tone and reduces sympathetic activity. Additionally, it is hypothesized to modulate interoceptive processing by influencing Heart Rate Evoked Potential and normalizing interoceptive signals. This hypothesis article examines taVNS from a closed-loop perspective, focusing on the controllability and observability of its effects using wearable physiological sensors. It postulates regulating desired therapeutic states through physiological sensor feedback, suggesting the potential for customized, adaptive stimulation in FS treatment. However, rigorous testing of its controller and observer functions will be necessary for optimal clinical translation of adaptive taVNS.

Introduction

Functional Seizure (FS) is a common and disabling neurological condition. It resembles epileptic seizures but does not have the electroencephalographic abnormalities. Hence it is also known as known as Psychogenic nonepileptic seizure (PNES) or Non Epileptic Attack Disorder (NEAD) [1,2]. As a part of the Functional Neurological Disorder (FND) spectrum, it contributes up to a quarter of patients referred to epilepsy centres [3]. FS carry extensive socioeconomic impacts, including direct costs like repeated hospitalizations, medical investigations (often unnecessary), medication, and productivity loss [2]. A primary challenge in FS management is the lack of a universally effective treatment. Traditional anti-epileptic medications do not address the non-electrical disturbance origins of FS [4]. Cognitive Behavioural Therapy (CBT) offers some benefits but is not uniformly effective or universally accessible [5]. Then, auricular acupuncture is well-tolerated in PNES patients and shows similar reductions in event frequency as CBT; however, it also requires expert delivery [6]. This creates a significant gap in FS treatment, particularly in enhancing self-management and reducing recurrent healthcare utilization. Therefore, developing novel treatments for FS is an urgent socioeconomic need with significant public health implications.

Invasive Vagus Nerve Stimulation (VNS), a technique involving the electrical stimulation of the cervical segment of the left vagus nerve through an implantable device, is an established treatment for epilepsy [7]. The effectiveness extends to functional seizures, which may occur alongside epilepsy. Vivas et al found that 63 % patients reported improvement in FS with VNS and 36 % reported an improvement up to 75–100 % [8]. However, the invasive nature, adverse events and cost have precluded the use of invasive VNS in FS.

Transcutaneous auricular vagus nerve stimulation (taVNS) is a non-invasive, low intensity electrical stimulation of the auricular branch of vagus nerve (ABVN) [9]. The modern approach to taVNS was first described by Ventureyra [10], and further bolstered by cadaveric studies [11]. The vagus nerve connects to the central nervous system via the nucleus tractus solitarius (NTS), and then sends direct afferent projections to the parabrachial complex (PB), which in turn projects to the locus coeruleus (LC) and raphe nuclei. Ascending projections from the PB reach higher brain regions including the cerebellum (CB), thalamus (Thal), hypothalamus (Hyp), amygdala (Amg), nucleus basalis (NBM), orbital frontal cortex (OFC), cingulate cortex (Cing), and prefrontal cortex (PFC)[12]. Further studies have shown that taVNS, in addition to

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targeting the parasympathetic nervous system and impacting the sympathetic/parasympathetic balance, activates multiple upstream brain networks involving these areas in the same way as classic VNS [13]. A related study [14] highlights that taVNS mimics invasive VNS by modulating pupil dilation and reducing occipital alpha oscillations, indicating increased arousal and neuromodulatory signaling through the locus coeruleus-noradrenaline (LC-NE) system. This supports the potential of taVNS for both clinical applications and basic neuroscience research in FS.

Current understanding of FS pathophysiology suggest that it is a multi-network brain disorder with alterations seen within and across the limbic/salience network (SN), self-agency/multimodal integration (Interoception and DMN), attentional and central executive network (CEN), and sensorimotor circuits [15]. The central feature is the automatic activation of a "seizure scaffold" in the context of a high-level inhibitory processing dysfunction and elevated autonomic arousal [16]. FS often involve multiple autonomic symptoms which may occur in the absence of subjective fear and has attributed a significant role to parasympathetic/sympathetic imbalance and vagal dysfunction. The inability to effectively cope with and regulate emotional responses can exacerbate this imbalance, leading to the onset of seizures. Studies indicate a reduced resting vagal tone in FS patients compared to healthy controls, with decreased vagal tone observed during FS episodes [17–19], increased arousal pre-seizure and a reduction post-seizure in FS patients [20]; furthermore, a *meta*-analysis reveals heightened resting heart rates in children and adolescents with FND and a tendency towards reduced heart rate variability in FND patients across all ages. Notably, *peri*-ictal heart rate serves as a differentiator between patients with functional and epileptic seizures [21]. In a recent study Ryan et al showed that predictive models with pre-to-post-ictal heart rate change (HR-delta) and post-ictal HR provide the highest diagnostic accuracy for epileptic seizures vs. FS [22].These findings highlight the therapeutic potential of enhancing vagal function through taVNS.

Another group of evidence supporting the role of taVNS comes from the observed brain network changes. Badran et al demonstrated that taVNS achieved bilateral activation of the ACC and left dorsolateral prefrontal cortex (DLPFC) [12]. In another recent study, using MEG, Keatch et al showed that taVNS stimulation lead to changes in functional connectivity across multiple regions linked to the DMN, SN and the CEN [23]. Previously, increased connectivity between the executive, frontoparietal, sensorimotor and default mode networks in FS was seen [24]. Furthermore, the strength of connectivity correlated to the frequency of seizures [25]. Interestingly, both the Keatch et al [23] and Fang et al [26] established that functional connectivity between the DMN and both the insula and parahippocampus decreased after taVNS. This is a direct opposite action seen in FS and provides a mechanistic plausibility for our hypothesised therapeutic role of taVNS.

Another line of research suggests potential role of taVNS – the relationship between Heartbeat Evoked Potential (HEP) and FS and underscores the importance of interoceptive processes in FND/FS [27]. HEP, an electroencephalogram (EEG) marker of interoceptive processing, reflects the body's perception of internal physiological states. Studies have shown that HEP alterations in FS patients occur prior to seizures, with a notable reduction in HEP amplitude between interictal and preictal states [28]. HEP has been used to assess internally triggered emotional signals, with findings indicating its modulation at specific brain network nodes related to affective-cognitive integration [29]. Additionally, the insula has been shown as the primary source of HEP, an established marker of interoception [30]. Notably, taVNS has demonstrated the ability to modulate HEP, particularly affecting the insula. This modulation extends to frontocentral and centroparietal electrode sites and the insula's connected regions, significant for their roles in the pathogenesis of FND and FS [15,31]. As brainstem and insula receive interoceptive information from the head via the facial and trigeminal cranial nerves from nucleus tractus solitary (NTS) [32]; taVNS, via its direct effect on NTS, can thus be a potential tool to improve the impaired interoception as observed in FS.

The hypothesis

Based on the current scientific literature and methodical efforts for closed loop taVNS for various neurorehabilitation applications [33,34,35], our hypothesis posits that taVNS may offer an effective therapeutic approach for FS via three primary mechanisms:

1. Autonomic Nervous System Regulation: taVNS has the potential to diminish the overactivity of the sympathetic nervous system and enhancing the parasympathetic tone, rebalancing a fundamental aspect of its pathophysiology.
2. Interoceptive Processing Modification: The potential influence of taVNS on the Heart Evoked Potential (HEP) and the insular region of the brain suggests a modulation of interoceptive processing, a key imbalance observed in FS.
3. Neural Network Reorganization: taVNS might alter the neural dynamics involving the Default Mode Network (DMN), Salience Network (SN), and Central Executive Network (CEN), as seen in FS.

Evolution of the hypothesis

Although VNS began as a non-invasive technique in the 1880 s but became primarily invasive in the 20th century that is unsuitable in FS due to risk benefit challenges. The emergence of taVNS marked a new era, offering non-invasive stimulation similar to invasive VNS and then closed-loop taVNS (CL-taVNS) was proposed in 2020, enhancing personalized neuromodulation [34]. Mechanistic understanding of the controllability of the three FS mechanisms stated above using taVNS and observability for the taVNS effects using physiological sensors is vital for closed loop taVNS. Closed loop taVNS may provide individualized dosing by dynamically adjusting stimulation intensity, frequency, or timing to optimize the therapeutic effects while minimizing potential side effects in FS as per control system theory [36,37]. Specifically, brain states in attention and arousal fluctuations have been implicated in FND [38]. A recent study [39] examined changes in resting brain metabolism in patients experiencing their first episode of motor FND and its link to persistent disability after three months. Nineteen patients were recruited and compared to 23 healthy controls using 18F-fluorodeoxyglucose positron emission tomography. Initial findings showed hypometabolism in bilateral frontal regions of patients, which normalized by three months. Improved disability scores were linked to increased activity in the prefrontal dorsolateral cortex, right orbito-frontal cortex, and bilateral frontopolar cortex. Conversely, higher baseline metabolism in the right and left subgenual anterior cingulate cortex was negatively correlated with motor recovery. These results suggest specific brain metabolic markers are associated with motor disability and recovery in FND patients which may be observable using functional near infrared spectroscopy (fNIRS) under neuromodulation using taVNS. We hypothesize that taVNS of the auricular branch of the vagal nerve (ABVN) that connects to the nucleus tractus solitarii (NTS) will be able to regulate autonomic functions and making taVNS applicable from controllability and observability perspective. However, prior literature lacks consensus on which auricular sites are most densely innervated by the ABVN and whether brain regions activated by electrical auricular taVNS depend on specific application parameters [9,40,41]. Here, we hypothesize that the effects of a novel slow bi-polar electrical stimulation (0.1–0.2 Hz) of the taVNS using mastoid electrodes [42] will be observable using functional near infrared spectroscopy (fNIRS) signals modulated via extrinsic peripheral nerves and intrinsic subcortical nerves viz. LC-NE system [43,44,45]. The innervation of cerebral circulation is categorized into intrinsic and extrinsic systems [43]. Intrinsic systems originate within the central nervous system and innervate cerebral parenchymal vessels without exiting the brain. These are not traditionally considered autonomic, though this distinction may change

as understanding improves. Extrinsic systems also start in the central nervous system but exit and have an extra-axial synapse before reaching cerebral pial vessels. The autonomic innervation of cerebral circulation, including sympathetic and parasympathetic nerves, is part of these extrinsic systems.

Hypothesis testing

The randomized controlled trial should be double-blinded, building on a recent pilot study that demonstrated the feasibility of supervised, at-home, self-administered taVNS [46]. To ensure the study focuses on the appropriate patient population and achieves reliable results, specific inclusion and exclusion criteria are proposed.

Inclusion Criteria

Diagnosis of Functional Seizure (FS) Confirmed by a Neurologist: Only patients who have been officially diagnosed with FS by a neurologist are included. This ensures the accuracy and relevance of the diagnosis.

EEG Documentation of Functional Seizures: Participants must have EEG evidence of Functional Seizures. This objective measure verifies the presence of FS.

May Include Patients with Overlapping Motor or Other Functional Neurological Disorders (FND): Patients who have other forms of FND in addition to FS are also considered. This acknowledges the complexity and variability of neurological disorders in affected individuals.

Must Have Experienced Active FS Within the Last 3 to 6 Months: Participants need to have had active FS episodes recently. This criterion ensures that the study targets individuals currently affected by the condition.

Exclusion Criteria

Patients with a Dual Diagnosis of Epilepsy and FND: Those diagnosed with both epilepsy and FND are excluded to prevent confounding effects, as epilepsy requires different management and treatment strategies.

Patients with Active Mental Health Needs, Including Suicidal Tendencies, Active Psychosis, or Severe PTSD: Individuals with severe, active mental health conditions are excluded to ensure their safety and to avoid complications that could interfere with the study outcomes.

To investigate the observability of taVNS effects, we used a wearable Brainpatch™ headset [46], as illustrated in the top panel of Fig. 1. This device delivers a slow bi-polar electrical stimulation at a frequency of 0.1–0.2 Hz via mastoid electrodes [42]. The setup also includes a MyndSens™ multi-distance fNIRS sensor, positioned on the medial Brodmann Area 10 (frontopolar cortex) [47], to measure hemodynamic responses. The photon migration model predicts light travel and absorption in the brain using multi-distance fNIRS from 2 cm to 4 cm. The depth of light penetration depends on the source-detector separation distance and the subject's skull and scalp thickness. Short separation channels within 1 cm of the source provide physiological noise data from superficial layers. Unlike traditional methods, our multi-distance fNIRS model accounts for the brain's complex structure by applying advanced physics principles.

During the experiment, participants wore the Brainpatch™ headset while receiving taVNS. The fNIRS sensor captured changes in oxyhemoglobin and deoxyhemoglobin concentrations at the frontopolar cortex, starting from a pre-stimulation resting-state baseline. We analyzed the collected data using a modal stabilization diagram (stable modes labelled, see middle panel of Fig. 1) [45] to identify stable modes of the hemodynamic responses to the stimulation. This multi-distance fNIRS method enabled to assess the physiological effects of taVNS at various depths of neurovascular tissue (parenchymal capillaries < 0.05 Hz versus pial and penetrating vessels > 0.05 [43] – see top panel of Fig. 1) and explore potential therapeutic implications.

Implications

Spatially resolved depth-sensitive fNIRS measurements [48], unaffected by electrical stimulation (taVNS) artifacts, can be modelled to analyse hemodynamic responses from pial vessels to the capillary bed (see Fig. 1 top panel, picture adapted from [49]). Prior work [50] has shown that increasing the source-detector (SD) separation from 20 to 65 mm leads to a consistent rise in brain tissue sensitivity. Each 10 mm increase in SD separation (up to $\sim$ 45 mm) enhances gray matter sensitivity by an additional 4 %. The hemodynamic response along the vasculature includes the effects of vasomotor, chemical, and metabolic controls, which are prominent during hyper and hypo arousal states [43,44]. Here, it is postulated that orthosympathetic activation influences pial and perforant arteries (above 0.05 Hz), while LC-NE impacts intraparenchymal arterioles and capillaries (below 0.05 Hz). [27]. Notably, frequencies between 0.02 Hz and 0.05 Hz are stable modes for LC-NE vasomotor responses [44,45] which were modulated by slow bipolar electrical stimulation (0.1–0.2 Hz) using mastoid electrodes [42] – see the Fig. 1 middle panel. However, mastoid electrode montage may also activate the greater occipital nerve and its ascending fibers to the locus coeruleus which promotes noradrenaline release [51]. Nevertheless, a synergistic therapeutic effect is postulated based on a common mechanistic underpinning [52] since occipital nerve stimulation has been shown to suppress global pain in fibromyalgia patients [53].

Fig. 1 bottom panel shows our overarching hypothesis that taVNS alters functional connectivity in the Default Mode and Salience Networks via the Nucleus Tractus Solitarius (NTS) that needs validation with whole head imaging. By monitoring Salience Network activities through fNIRS-EEG and skin conductance responses, personalized taVNS parameters can be achieved at the point of care. The multi-modal data collected from these wearable sensors can then be used to assess the taVNS effects for testing [54], and ensure that the individual user responds to the taVNS treatment at the point of care settings. Here, fNIRS and EEG (with HEP) are proposed as multi-modal sensor feedback for capturing the taVNS effects on the salience network. This is based on the extensive literature establishing HEP as a biomarker for interoceptive network [27,28,31]. Another strong observability parameter will be the measurement of skin conductance responses (SCR). SCR is an established method of measuring electrodermal activity (EDA), a peripherally expressed index of the autonomic nervous system function, where larger and more numerous SCRs are usually associated with more intense experiences of arousal [55]. Xia et al found that greater SCR reactivity and stronger intrinsic salience network connectivity independently predicted more intense arousal experiences [56]. Additionally, the interaction between SCR reactivity and salience network connectivity demonstrated the complex relationship between central neural circuitry and peripheral autonomic responses in shaping individual differences in arousal experience. Startle stimuli can be used for evoked responses, which acts via periaqueductal gray (PAG) that exhibits extensive connectivity with all brainstem nuclei and cortical/subcortical regions. Therefore, to enhance observability for the closed-loop VNS, it may be necessary to temporally integrate evoked responses with multi-sensor (fNIRS-EEG-SCR) fusion method that can provide predictive coding information about the arousal and brainstem motor network [57] effects in FS. In this line, SCR sensing during startle stimuli is proposed to be fused with the fNIRS-EEG (and HEP) for gaining insights into the impact of stimulation on the salience network and associated arousal responses.

The wearable nature of the proposed sensors, such as the Brainpatch™ headset and MyndSens™ fNIRS sensor (see Fig. 1 top panel), enables real-time, personalized adjustments to taVNS parameters at the point of care. This capability ensures that treatment is tailored to individual responses, enhancing efficacy and minimizing unnecessary

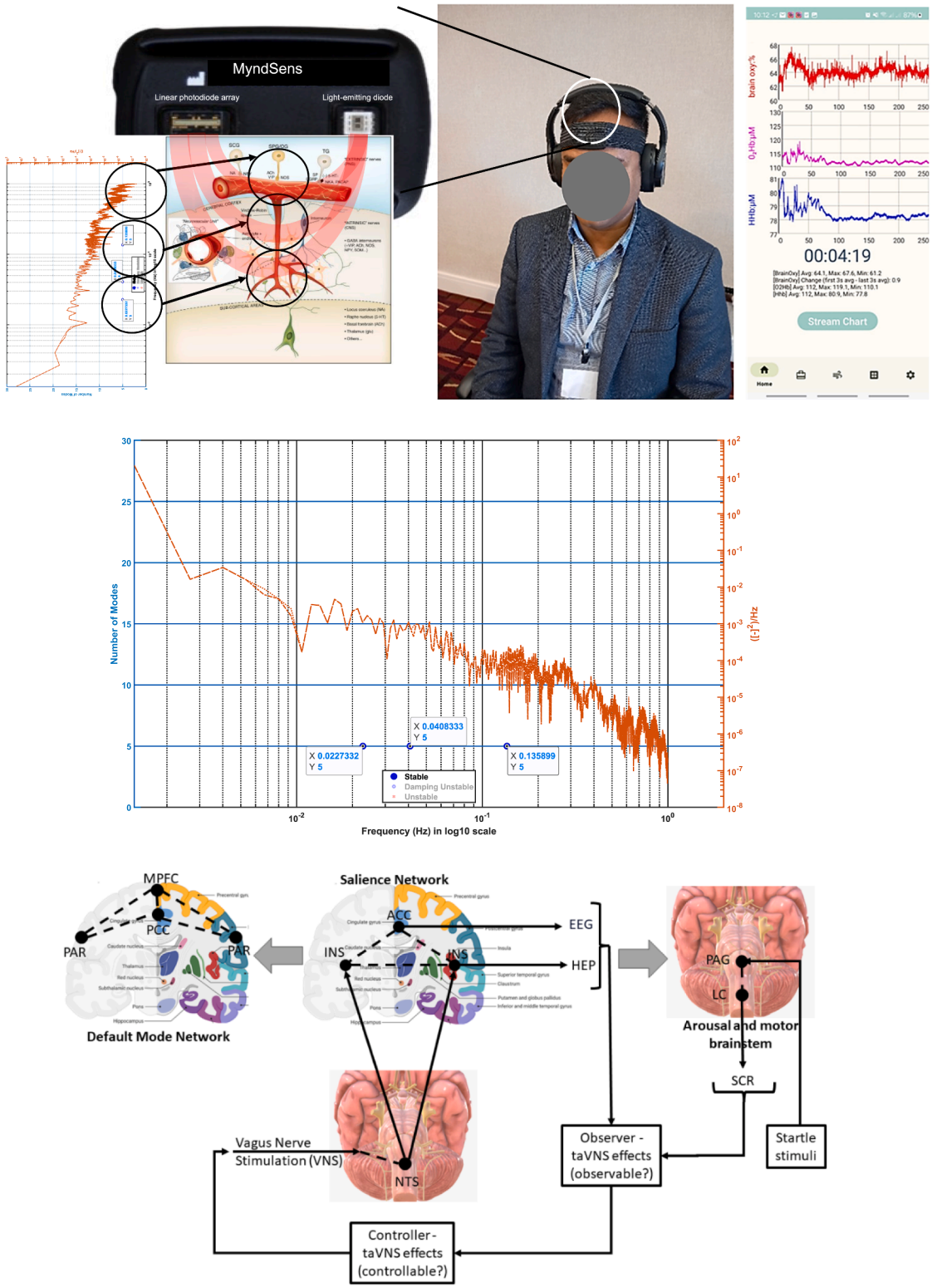

Fig. 1. The top panel shows a point-of-care application using a Brainpatch headset for slow bi-polar electrical stimulation (0.1–0.2 Hz) with mastoid electrodes, and a MyndSens multi-distance fNIRS sensor measuring from pial and penetrating vessels > 0.05 to parenchymal capillaries < 0.05 Hz (picture adapted from [49]). The middle panel depicts stimulation effects on oxyhemoglobin and deoxyhemoglobin concentrations in the frontopolar cortex relative to the pre-stimulation baseline, using a modal stabilization diagram with data-tips labeled stable modes. The bottom panel hypothesizes that taVNS alters functional connectivity via the Nucleus Tractus Solitarius (NTS) in key brain networks (DMN and Salience Network). It suggests individualizing taVNS parameters by electrophysiological monitoring the interaction between Salience Network activity (via EEG-HEP) and skin conductance responses (SCR), linked to arousal mediated by the Periaqueductal Gray (PAG) and Locus Coeruleus (LC). Future studies aim to validate these effects and assess clinical outcomes.

stimulation. Personalized treatment strategies can significantly improve patient outcomes by adapting to the unique physiological and neural profiles of each patient, thereby reducing the frequency and severity of FS episodes. The future integration of fNIRS and EEG (with HEP) as multi-modal sensors to capture the effects of taVNS on the salience network has significant and multifaceted implications for both clinical practice and research. By combining these central neural monitoring methods with the measurement of skin conductance responses (SCR), a future study can provide a comprehensive view of how taVNS affects both brain and autonomic nervous system function. fNIRS offering insights into cerebral blood flow and oxygenation, while EEG, particularly with HEP, capturing neural activity linked to interoception. SCR measures electrodermal activity, reflecting autonomic arousal and providing a peripheral indicator of the autonomic nervous system's response. Together, these methods enable a holistic analysis of the physiological and neural changes induced by taVNS. Then, CL-taVNS systems can adapt to real-time changes, using physiological biomarkers to trigger electrical stimulation, and are being developed for various disease-specific applications [33,34,35]. Here, combining EEG with taVNS [33] after gross artifact removal [58], offers a multi-modal portable, non-invasive solution, with EEG providing real-time electrophysiological markers [59] and taVNS modulating brain activity.

A closed loop taVNS system using prefrontal EEG with fNIRS for adapting stimulation holds promise for therapeutic and supportive applications at the point of care, requiring further research to maximize its potential. For mechanistic understanding and validation of effects, functional connectivity has been explored for predicting individual responses to VNS, and showed that responders exhibited greater connectivity in limbic and sensorimotor networks [60]. As taVNS was observed to modify functional connectivity, particularly those associated with DMN, SN and CEN, this could be explored for validation of the treatment response. Moreover, this whole brain neuroimaging approach allows for the validation of hypotheses regarding taVNS-induced changes in brain connectivity, particularly within the Default Mode Network (DMN) and Salience Network via the Nucleus Tractus Solitarius (NTS). Whole-head imaging techniques can be employed to confirm these mechanistic pathways, providing empirical support for the therapeutic mechanisms of taVNS. Such validation is essential for establishing taVNS as a scientifically grounded treatment option possibly addressing the whole body-brain circuit [61], potentially leading to its broader application and implementation in clinical practice.

This multi-modal approach allows for the development of predictive models for arousal and brainstem motor network modulation using taVNS, which are crucial for mechanistic understanding and treating Functional Seizures (FS). Then, the ability to integrate evoked responses, such as those from startle stimuli, adds another layer of observability, linking peripheral autonomic responses with central neural circuitry. This comprehensive data fusion can reveal complex interactions between the brain and autonomic nervous system, offering predictive insights into individual differences in arousal experiences and the pathophysiology of FS. Furthermore, this multi-modal sensor feedback approach advances neuroscientific research by enabling detailed investigations into the neural mechanisms underlying FS and taVNS. Researchers can explore how changes in prefrontal brain connectivity correlate with clinical outcomes, identifying biomarkers and neural signatures associated with effective treatment responses. This knowledge can drive the development of novel therapeutic strategies, enhancing the overall understanding of FS and improving the quality of life for affected individuals.

Future research should prioritize identifying reliable biomarkers to measure the effects of taVNS in FS patients, potentially through comparative studies of feedback mechanisms like fNIRS, EEG, HEP, and SCR. Developing personalized taVNS treatment protocols tailored to individual patient profiles could enhance therapy effectiveness. Long-term studies are crucial to assess the sustained efficacy and safety of taVNS, helping to understand its long-term benefits and potential side effects. Exploring the integration of taVNS with other therapies, such as Cognitive Behavioral Therapy (CBT), hypnotherapy, or pharmacological treatments, may provide a more comprehensive approach to managing FS. Detailed cost-effectiveness analyses will evaluate the economic benefits of taVNS in reducing FS-related healthcare costs, supporting broader implementation and insurance coverage. Additionally, educational programs are needed to inform patients and healthcare providers about taVNS and ensure the therapy's accessibility to a wider patient population. By pursuing these future directions, the potential of taVNS as a transformative treatment for FS can be fully realized, leading to improved patient outcomes and a reduction in the socioeconomic burden of the disorder.

Conclusion

The integration of fNIRS, EEG (with HEP), and SCR as multi-modal sensors to capture taVNS effects on the salience network represents a significant advancement in both clinical and research domains. This approach offers a comprehensive, real-time, and personalized method for monitoring and treating Functional Seizures (FS), facilitating the development of predictive models and personalized treatment strategies, and supporting the validation of therapeutic mechanisms. Additionally, it propels neuroscientific research, potentially leading to new insights and innovations in the treatment of FS and related conditions.

Here, taVNS emerges as a promising, non-invasive option for targeting FS pathophysiology by influencing the autonomic nervous system, neural network connectivity, and interoceptive processing. The incorporation of control system principles in adaptive closed loop taVNS, using real-time fNIRS, EEG, HEP, and SCR feedback for dynamic stimulation adjustment, could significantly improve treatment precision and effectiveness. However, the optimal observer for taVNS effects in FS remains unknown. Addressing the controllability of autonomic imbalance and neural dysfunctions in FS through taVNS, mechanistic research may substantially reduce healthcare costs, enhance patient quality of life, and contribute to the development of neuromodulatory therapies for FS.

Declarations

Consent statement/Ethical approval: Not required.

Availability of data and materials

Not applicable.

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CRediT authorship contribution statement

Abhijit Das: Writing – review & editing, Resources, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Anirban Dutta:** Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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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References

[1] Hallett M, Aybek S, Dworetzky BA, McWhirter L, Staab JP, Stone J. Functional neurological disorder: new subtypes and shared mechanisms. Lancet Neurol 2022; 21:537–50.
[2] O'Mahony B, Yogarajah M. The Economic Cost of Functional Neurological Disorders: A Systematic Review (P14–11.009). Neurology 2023:100.
[3] Bodde NM, Brooks JL, Baker GA, Boon PA, Hendriksen JG, Aldenkamp AP. Psychogenic non-epileptic seizures—diagnostic issues: a critical review. Clin Neurol Neurosurg 2009;111:1–9.
[4] Perez DL. The CODES trial for dissociative seizures: a landmark study and inflection point. Lancet Psychiatry 2020;7:464–5.
[5] Goldstein LH, Robinson EJ, Mellers JDC, Stone J, Carson A, Reuber M, et al. Cognitive behavioural therapy for adults with dissociative seizures (CODES): a pragmatic, multicentre, randomised controlled trial. Lancet Psychiatry 2020;7: 491–505.
[6] Maa E, Applegate M, Keniston A. Auricular acupuncture for the treatment of nonepileptic seizures: A pilot study. Epilepsy Behav 2020;111:107329. https://doi.org/10.1016/j.yebeh.2020.107329.
[7] George MS, Nahas Z, Bohning DE, Lomarev M, Denslow S, Osenbach R, et al. Vagus nerve stimulation: a new form of therapeutic brain stimulation. CNS Spectr 2000;5: 43–52.
[8] Vivas AC, Reitano CJ, Waseem H, Benbadis SR, Vale FL. An analysis of quality of life (QOL) in patients with epilepsy and comorbid psychogenic nonepileptic seizures (PNES) after vagus nerve stimulation (VNS). Epilepsy Behav 2017;73: 208–13.
[9] Butt MF, Albusoda A, Farmer AD, Aziz Q. The anatomical basis for transcutaneous auricular vagus nerve stimulation. J Anat 2020;236:588–611.
[10] Ventureyra EC. Transcutaneous vagus nerve stimulation for partial onset seizure therapy: a new concept. Childs Nerv Syst 2000;16:101–2.
[11] Peuker ET, Filler TJ. The nerve supply of the human auricle. Clin Anat 2002;15: 35–7.
[12] Badran BW, Dowdle LT, Mithoefer OJ, LaBate NT, Coatsworth J, Brown JC, et al. Neurophysiologic effects of transcutaneous auricular vagus nerve stimulation (taVNS) via electrical stimulation of the tragus: a concurrent taVNS/fMRI study and review. Brain Stimulat 2018;11:492–500.
[13] Tan C, Qiao M, Ma Y, Luo Y, Fang J, Yang Y. The efficacy and safety of transcutaneous auricular vagus nerve stimulation in the treatment of depressive disorder: A systematic review and meta-analysis of randomized controlled trials. J Affect Disord 2023.
[14] Sharon O, Fahoum F, Nir Y. Transcutaneous vagus nerve stimulation in humans induces pupil dilation and attenuates alpha oscillations. J Neurosci 2021;41: 320–30. https://doi.org/10.1523/JNEUROSCI.1361-20.2020.
[15] Perez DL, Nicholson TR, Asadi-Pooya AA, Bègue I, Butler M, Carson AJ, et al. Neuroimaging in functional neurological disorder: state of the field and research Agenda. Neuroimage Clin 2021;30:102623.
[16] Brown RJ, Reuber M. Towards an integrative theory of psychogenic non-epileptic seizures (PNES. Clin Psychol Rev 2016;47:55–70.
[17] Bakvis P, Roelofs K, Kuyk J, Edelbroek PM, Swinkels WA, Spinhoven P. Trauma, stress, and preconscious threat processing in patients with psychogenic nonepileptic seizures. Epilepsia 2009;50:1001–11.
[18] Ponnusamy A, Marques JL, Reuber M. Heart rate variability measures as biomarkers in patients with psychogenic nonepileptic seizures: potential and limitations. Epilepsy Behav 2011;22:685–91.
[19] Ponnusamy A, Marques JL, Reuber M. Comparison of heart rate variability parameters during complex partial seizures and psychogenic nonepileptic seizures. Epilepsia 2012;53:1314–21.
[20] van der Kruijs SJ, Vonck KE, Langereis GR, Feijs LM, Bodde NM, Lazeron RH, et al. Autonomic nervous system functioning associated with psychogenic nonepileptic seizures: analysis of heart rate variability. Epilepsy Behav 2016;54:14–9.
[21] Paredes-Echeverri S, Maggio J, Bègue I, Pick S, Nicholson TR, Perez DL. Autonomic, endocrine, and inflammation profiles in functional neurological disorder: a systematic review and meta-analysis. J Neuropsychiatry Clin Neurosci 2022;34:30–43.
[22] Ryan JM, Wagner KT, Yerram S, Concannon C, Lin JX, Rooney P, et al. Heart rate and autonomic biomarkers distinguish convulsive epileptic vs. functional or dissociative seizures. Seizure Eur J Epilepsy 2023;111:178–86.
[23] Keatch C, Lambert E, Kameneva T, Woods W. Functional connectivity analysis of transcutaneous vagus nerve stimulation (tVNS) using magnetoencephalography (MEG). IEEE Trans Neural Syst Rehabil Eng 2023.
[24] van der Kruijs SJ, Bodde NM, Vaessen MJ, Lazeron RH, Vonck K, Boon P, et al. Functional connectivity of dissociation in patients with psychogenic non-epileptic seizures. J Neurol Neurosurg Psychiatry 2011.
[25] Kruijs SJ, Jagannathan SR, Bodde NM, Besseling RM, Lazeron RH, Vonck KE, et al. Resting-state networks and dissociation in psychogenic non-epileptic seizures. J Psychiatr Res 2014;54:126–33.
[26] Fang J, Rong P, Hong Y, Fan Y, Liu J, Wang H, et al. Transcutaneous vagus nerve stimulation modulates default mode network in major depressive disorder. Biol Psychiatry 2016;79:266–73.
[27] Al E, Iliopoulos F, Forschack N, Nierhaus T, Grund M, Motyka P, et al. Heart–brain interactions shape somatosensory perception and evoked potentials. Proc Natl Acad Sci 2020;117:10575–84.
[28] Elkommos S, Martin-Lopez D, Koreki A, Jolliffe C, Kandasamy R, Mula M, et al. Changes in the heartbeat-evoked potential are associated with functional seizures. J Neurol Neurosurg Psychiatry 2023.
[29] Couto B, Adolfi F, Velasquez M, Mesow M, Feinstein J, Canales-Johnson A, et al. Heart evoked potential triggers brain responses to natural affective scenes: a preliminary study. Auton Neurosci 2015;193:132–7.
[30] Park H-D, Bernasconi F, Salomon R, Tallon-Baudry C, Spinelli L, Seeck M, et al. Neural sources and underlying mechanisms of neural responses to heartbeats, and their role in bodily self-consciousness: an intracranial EEG study. Cereb Cortex 2018;28:2351–64.
[31] Poppa T, Benschop L, Horczak P, Vanderhasselt M-A, Carrette E, Bechara A, et al. Auricular transcutaneous vagus nerve stimulation modulates the heart-evoked potential. Brain Stimulat 2022;15:260–9.
[32] Fermin AS, Friston K, Yamawaki S. An insula hierarchical network architecture for active interoceptive inference. R Soc Open Sci 2022;9:220226.
[33] Ruhnau P, Zaehle T. Transcranial auricular vagus nerve stimulation (taVNS) and Ear-EEG: potential for closed-loop portable non-invasive brain stimulation. Front Hum Neurosci 2021;15. https://doi.org/10.3389/fnhum.2021.699473.
[34] Yu Y, Ling J, Yu L, Liu P, Jiang M. Closed-loop transcutaneous auricular vagal nerve stimulation: current situation and future possibilities. Front Hum Neurosci 2022;15:785620. https://doi.org/10.3389/fnhum.2021.785620.
[35] Xiao X-Z, Li R, Xu C, Liang S, Yang M, Zhong H, et al. Closed-loop transcutaneous auricular vagus nerve stimulation (taVNS) for the improvement of upper extremity motor function in stroke patients: a study protocol. Front Neurol 2024;15. https://doi.org/10.3389/fneur.2024.1379451.
[36] Ogata K. Modern control engineering fifth edition. 2010.
[37] Dutta A. Bidirectional interactions between neuronal and hemodynamic responses to transcranial direct current stimulation (tDCS): challenges for brain-state dependent tDCS. Front Syst Neurosci 2015;9:107.
[38] Voon V, Cavanna AE, Coburn K, Sampson S, Reeve A, LaFrance Jr WC, et al. Functional neuroanatomy and neurophysiology of functional neurological disorders (conversion disorder). J Neuropsychiatry Clin Neurosci 2016;28:168–90.
[39] Conejero I, Collombier L, Lopez-Castroman J, Mura T, Alonso S, Olié E, et al. Association between brain metabolism and clinical course of motor functional neurological disorders. Brain J Neurol 2022;145:3264–73. https://doi.org/10.1093/brain/awac146.
[40] Chen Y, Yang H, Wang F, Lu X, Hu L. Modulatory effects of transcutaneous auricular vagus nerve stimulation (taVNS) on attentional processes. Gen Psychiatry 2023;36:e101176.
[41] Verma N, Mudge JD, Kasole M, Chen RC, Blanz SL, Trevathan JK, et al. Auricular vagus neuromodulation—a systematic review on quality of evidence and clinical effects. Front Neurosci 2021;15:664740. https://doi.org/10.3389/fnins.2021.664740.
[42] Tukaiev S, Pravda O, Vysokov N, Tarasenko A, Toleukhanov D, Komarenko V, et al. Non-invasive vagus nerve stimulation attenuates the burnout. Eur Psychiatry 2022; 65:S734. https://doi.org/10.1192/j.eurpsy.2022.1896.
[43] Goadsby PJ. Chapter 16 - Autonomic nervous system control of the cerebral circulation. In: Buijs RM, Swaab DF, Eds. Handb. Clin. Neurol., vol. 117, Elsevier; 2013, p. 193–201. doi: 10.1016/B978-0-444-53491-0.00016-X.
[44] Iadecola C. Intrinsic and Extrinsic Neural Regulation of the Cerebral Circulation. In: Schmiedek P, Einhäupl K, Kirsch C-M, editors. Stimul. Cereb. Blood Flow, Berlin, Heidelberg: Springer; 1992, p. 19–36. doi: 10.1007/978-3-642-77102-6_3.
[45] Stefanski M, Arora Y, Cheung M, Dutta A. Modal analysis of cerebrovascular effects for digital health integration of neurostimulation therapies—a review of technology concepts. Brain Sci 2024;14:591. https://doi.org/10.3390/brainsci14060591.
[46] Tarasenko A, Guazzotti S, Minot T, Oganesyan M, Vysokov N. Determination of the effects of transcutaneous auricular vagus nerve stimulation on the heart rate variability using a machine learning pipeline. Bioelectricity 2022;4:168–77. https://doi.org/10.1089/bioe.2021.0033.
[47] Peng K, Steele SC, Becerra L, Borsook D. Brodmann area 10: collating, integrating and high level processing of nociception and pain. Prog Neurobiol 2018;161:1–22. https://doi.org/10.1016/j.pneurobio.2017.11.004.
[48] Veesa JD, Dehghani H. Functional near infrared spectroscopy using spatially resolved data to account for tissue scattering: a numerical study and arm-cuff experiment. J Biophotonics 2019;12:e201900064.
[49] Hamel E. Perivascular nerves and the regulation of cerebrovascular tone. J Appl Physiol Bethesda Md 1985;2006(100):1059–64. https://doi.org/10.1152/japplphysiol.00954.2005.
[50] Strangman GE, Li Z, Zhang Q. Depth sensitivity and source-detector separations for near infrared spectroscopy based on the colin27 brain template. PLoS One 2013;8: e66319.
[51] Vanneste S, Mohan A, Yoo HB, Huang Y, Luckey AM, McLeod SL, et al. The peripheral effect of direct current stimulation on brain circuits involving memory. Sci. Adv. 2020;6:eaax9538. doi: 10.1126/sciadv.aax9538.

[52] Teodoro T, Edwards MJ, Isaacs JD. A unifying theory for cognitive abnormalities in functional neurological disorders, fibromyalgia and chronic fatigue syndrome: systematic review. J Neurol Neurosurg Psychiatry 2018;89:1308–19.
[53] De Ridder D, Vanneste S. Occipital nerve field transcranial direct current stimulation normalizes imbalance between pain detecting and pain inhibitory pathways in fibromyalgia. Neurother J Am Soc Exp Neurother 2017;14:484–501. https://doi.org/10.1007/s13311-016-0493-8.
[54] Tiefenbach J, Cox ER, Paterson M, Iannoukos D, Scott S, Hoeritzauer I, et al. Testing the 'seizure scaffold': What can experimental simulation tell us about functional seizures? Epilepsy Behav 2020;113. https://doi.org/10.1016/j.yebeh.2020.107518.
[55] Boucsein W, Fowles DC, Grimnes S, Ben-Shakhar G, Roth WT, Dawson ME, et al. Society for psychophysiological research ad hoc committee on electrodermal measures. Publication recommendations for electrodermal measurements. Psychophysiology 2012;49:1017–34.
[56] Xia C, Touroutoglou A, Quigley KS, Feldman Barrett L, Dickerson BC. Salience network connectivity modulates skin conductance responses in predicting arousal experience. J Cogn Neurosci 2017;29:827–36.
[57] Singh K, Cauzzo S, García-Gomar MG, Stauder M, Vanello N, Passino C, et al. Functional connectome of arousal and motor brainstem nuclei in living humans by 7 Tesla resting-state fMRI. Neuroimage 2022;249:118865.
[58] Kohli S, Casson AJ. Removal of gross artifacts of transcranial alternating current stimulation in simultaneous EEG monitoring. Sensors 2019;19:190. https://doi.org/10.3390/s19010190.
[59] Banellis L, Cruse D. Skipping a Beat: Heartbeat-Evoked Potentials Reflect Predictions during Interoceptive-Exteroceptive Integration. Cereb Cortex Commun 2020;1:tgaa060. doi: 10.1093/texcom/tgaa060.
[60] Mithani K, Wong SM, Mikhail M, Pourmotabbed H, Pang E, Sharma R, et al. Somatosensory evoked fields predict response to vagus nerve stimulation. NeuroImage Clin 2020;26:102205.
[61] Jin H, Li M, Jeong E, Castro-Martinez F, Zuker CS. A body–brain circuit that regulates body inflammatory responses. Nature 2024:1–9. https://doi.org/10.1038/s41586-024-07469-y.