Transcutaneous Auricular Vagus Nerve Stimulation towards Visually Induced Motion Sickness Reduction: A Pilot Study

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Abstract— **Transcutaneous auricular vagus nerve stimulation (taVNS) is a novel neuromodulation application for vagal afferent stimulation. Owing to its non-invasive nature, taVNS is a potent therapeutic tool for a diverse array of diseases and disorders that ail us. Herein, we investigated taVNS-induced effects on neural activity of participants during visually induced motion sickness. 64-channel electroencephalography (EEG) recordings were obtained from 15 healthy participants in a randomized, within-subjects, cross-over design during sham and taVNS conditions. To assess motion sickness severity, we used the motion sickness assessment questionnaire (MSAQ). We observed that taVNS attenuated theta (4-8 Hz) brain activity in the right frontal, right parietal and occipital cortices when compared to sham condition. The total MSAQ scores, and central, peripheral and sopite MSAQ categorical scores were significantly lower after taVNS compared to sham. These findings reveal for the first time the potential therapeutic role of taVNS toward counter-motion sickness, and suggest that taVNS may be reliable in alleviating symptoms of motion sickness in real-time, non-pharmacologically.**

Clinical relevance— **This suggests taVNS potential to offset motion sickness-induced nausea; which may be of translational value to counter e.g., chemotherapy-induced nausea.**

I. Introduction

Our brains have neural connections to the vagus nerve which transcutaneous auricular vagus nerve stimulation (taVNS) aims to exploit by introducing electrical impulses to modulate brain cortical activity and, potentially, ameliorate disease. In fact, because of this unique entrance into the brain's electrical communication system, taVNS has been explored for refractory epilepsy [1], treatment-resistant depression [2] and post-traumatic stress disorder [3].

While taVNS mechanistic underpinnings remain unclear; neurobiologically, taVNS aims to recruit auricle (e.g., tragus or cymba conchae) sensory receptors and trigger afferent signalling via the auricular branch of the vagus nerve toward the superior (jugular) ganglion. This afferent signalling converges onto a brainstem structure called the nucleus tractus solitarius (NTS) [4], [5]. NTS may then project these sensory signals to other important brain regions including the locus coeruleus; a prominent area of the brain for regulating arousal [6]. Ultimately, taVNS elicits changes to cortical and subcortical brain regions.

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How taVNS influences the physiological response of motion sickness – a syndrome marked by progressive, multi-dimensional symptoms – remains unknown. Currently, ambiguous sensory information provides support for the long-held view that sensory conflict is the cause of motion sickness. The conflicting sensory modalities include the proprioceptive, vestibular and visual systems [7]. Sensory integration of conflicting inputs from these systems at the NTS [8] leads to perturbations in autonomic regulation and brain cortical activity. While symptoms initially present as mild, continued exposure to provocative stimuli bias individuals to experience exacerbated stress, identified by a wide array of symptoms such as drowsiness, eyestrain, sweating, dizziness, pallor and headache etc. A core symptom of motion sickness is nausea, which often precipitates to vomiting.

High levels of motion sickness change brain cerebral activity. In fact, manifold studies have correlated atypical electroencephalogram (EEG) signals with increasing motion sickness. EEG delta (0.5-4 Hz) and theta (4-8 Hz) power in the temporo-frontal brain region was found to increase during the progression of motion sickness [9]. Moreover, [10] show that a virtual reality environment augments delta, theta and alpha (8-12 Hz) power in the parietal and occipital cortices. It emerges that motion sickness has deleterious effects on these slow oscillations of the brain (i.e., delta, theta, alpha) based on the conclusions from literature.

The present paper aims to compare brain cerebral activities of human participants receiving active taVNS in one session and sham in another, to determine whether taVNS influences the progression of motion sickness. To the best of the authors' knowledge, this paper provides the first insights into the non-pharmacological neuromodulatory effect of taVNS toward motion sickness reduction, assessed objectively using EEG, and behaviourally using the motion sickness assessment questionnaire (MSAQ) [11].

II. Methods

A. Participants

All experiments were conducted at the University of Kent (with ethical approved ref: CREAG015-12-2021) in adherence with the Declaration of Helsinki guidelines and regulations for human research. A total of 15 healthy volunteers (12 female, mean age $\pm$ S.D. 28.2 $\pm$ 7.0 years, age range = 21-49 years) were retained for this study after data for one participant was excluded due to loss of follow-up. Participants had normal or corrected-to-normal vision, provided written informed consent, and received an Amazon

gift voucher (£30) for participation. All participants were neurotypical and not on any medication.

B. Experimental Setup and Protocol

After random assignment to initial taVNS or sham conditions, the protocol involved sequenced structured tasks (i.e., pre-MSAQ, Baseline, Nauseogenic visual stimulus, Recovery, post-MSAQ) for both conditions and at follow-up, which took place after a washout period of minimum 1 week (Fig. 1). A nauseogenic visual stimulus (visual display of stripes circularly shifting at 62.5°/s) was developed to induce motion sickness. Stimulus presentation was performed using Psychophysics Toolbox Version 3 running on MATLAB (The MathWorks, Inc., Natick, MA, USA). During stimulus presentation participants provided nausea intensity ratings using the scale ($0 \rightarrow$ "no nausea"; $1 \rightarrow$ "mild"; $2 \rightarrow$ "moderate"; and $3 \rightarrow$ "strong") by pressing on a keypad. The MSAQ comprises 16 symptoms which can be subdivided into 4 dimensions (Gastrointestinal, Central, Peripheral, Sopite) where each symptom is assessed on a nine-point scale with ($1 \rightarrow$ 'not at all') and ($9 \rightarrow$ 'severely').

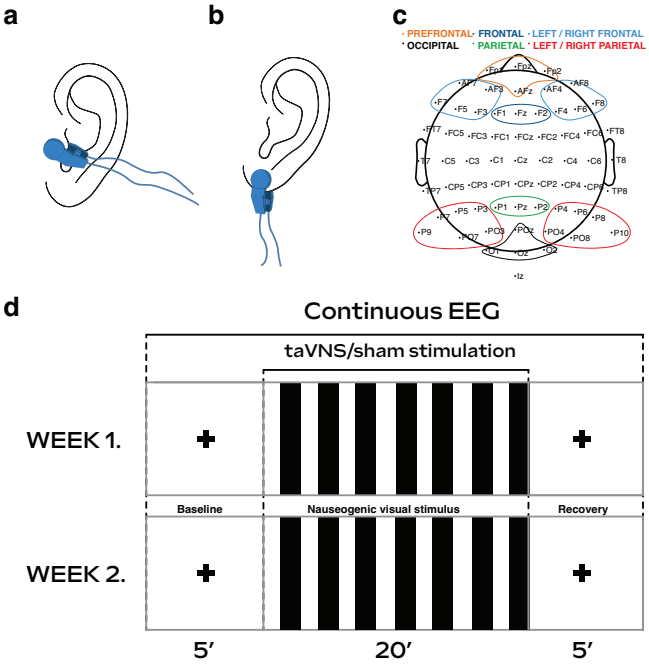

Fig. 1. Experimental schematics. **(a)** The electrode was clipped to the left tragus during taVNS condition. **(b)** And clipped to the left earlobe during sham condition. **(c)** 64-channel electroencephalography (EEG) electrode locations and regions of interest. **(d)** Participants underwent a baseline, nauseogenic visual stimulation and recovery section, respectively on both week 1 (first visit) and week 2 (follow-up visit), separated by 1 week. Continuous 64-channel EEG data were recorded from beginning of baseline to end of recovery. Participants were randomly assigned to receive taVNS or sham in week 1 (first visit) and to receive the opposite treatment on follow-up.

C. Electrical Stimulation

Non-invasive taVNS was applied using the EM6300A TENS (Med-Fit UK Ltd, Stockport, UK) device; a battery driven medical vagus nerve stimulator with electrodes that can be clipped onto the ear (e.g., tragus or earlobe; Fig. 1a,b). Stimulation was administered as asymmetric biphasic square-wave pulses at 1.0 mA current intensity, pulse width of 200 µs, delivered at 20 Hz (frequency rationale based on previous findings by other authors e.g., [3]).

D. Data Acquisition, Processing and Analysis

EEG data were acquired using a 64-channel BioSemi ActiveTwo system (BioSemi B. V., Amsterdam, Netherlands) at 256 Hz sampling rate. Electrode placement conformed to the international 10-20 system. EEG signal processing was performed using custom-written MATLAB scripts incorporating EEGLAB subroutines [12]. A Butterworth bandpass filter was applied at 2-20 Hz. To classify bad channels, a threshold measure of (spectrum = 3 S.D., probability = 3 S.D., and kurtosis = 5 S.D.) was applied. The detected bad channels were visually inspected before being marked for removal. Further, any bad data segments were removed. Then, independent component analysis (ICA) EEG data decomposition was applied and components showing eye blinks, saccades and other non-brain artifacts were removed. The clean EEG time series was obtained by back-projection of neuronal sources obtained after running ICA. Then a common average referencing (CAR) was performed. Spherical interpolation was performed for any removed noisy channels.

Further analysis was based on epochs selected from high nausea sections based on participant subjective ratings. We believe this is where motion sickness would be more concentrated after gradual buildup during nauseogenic visual stimulation. Our brain regions of interest were the frontal, parietal and occipital regions at theta and alpha frequency bands (Fig. 1c). To perform EEG spectral decomposition, we utilized the multitaper spectral analysis on epochs of 300s baseline and 300s stimulus. Power normalization was performed using a decibel (dB) transformation

$$dB\ power = 10 * \log_{10}\left(\frac{Power_{stimulus}}{Power_{baseline}}\right), \qquad (1)$$

where "stimulus" denotes condition types (i.e., taVNS vs. sham), and "baseline" denotes epochs prior to stimulus onset.

E. Statistical Analysis

All statistics were computed using MATLAB. Data are presented as mean $\pm$ standard error of the mean (SEM). Paired-sample tests were used to compare brain activity (Student's t-test) and MSAQ scores (Wilcoxon signed rank test). Effect sizes were computed using Cohen's d (unbiased estimate) and Cliff's Delta for brain activity and MSAQ scores respectively. Descriptors for Cohen's d are ($d < 0.2 \rightarrow$ 'negligible'; $d < 0.5 \rightarrow$ 'small'; $d < 0.8 \rightarrow$ 'medium'; $d \geq 0.8 \rightarrow$ 'large') [13] and those for Cliff's Delta are ($|\delta| < 0.147 \rightarrow$ 'negligible'; $|\delta| < 0.33 \rightarrow$ 'small'; $|\delta| < 0.474 \rightarrow$ 'medium', $|\delta| \geq 0.474 \rightarrow$ 'large') [14]. Non-parametric cluster-based permutation tests [15] were used for time-frequency matrices between conditions. 1000 random permutations were performed to generate a null-hypothesis t-value distribution at ($p < 0.05$) where at each iteration

extracting the maximum cluster mean of the t-values. Then cluster-correction was applied by discarding any clusters in the real tmap that had voxels lower than 95% of null-distribution. Fig. 3 shows brain voxels that are significant. Spearman correlation was used for computing the relationship between brain activity and MSAQ scores. All statistical tests were two-tailed at ($p < 0.05$).

III. Results

Compared to sham, taVNS conditions reduced EEG theta spectral power at right frontal ($t_{(14)} = 2.32$, $p = 0.0360$, $d = 0.7$), right parietal ($t_{(14)} = 2.37$, $p = 0.0328$, $d = 0.5$) and occipital ($t_{(14)} = 2.22$, $p = 0.0434$, $d = 0.7$) brain cortical regions (Fig. 2). Fig. 3 displays the difference in time-frequency power between taVNS and sham conditions. Statistically significant clusters found via permutation statistics, and corrected for multiple comparisons, are marked with black contours. The two pronounced temporal clusters (Fig. 3) are around (35.5-39.5 s, $p = 0.0061$; 143.5-150.5 s, $p = 0.0072$). Fig. 4 displays a time-frequency power representation for one example participant for both sham (top panel) and taVNS (bottom panel) condition.

Table I shows a summary of differences in motion sickness severity between sham and taVNS conditions. Overall, participants exhibited reduced symptomatology. For the taVNS condition, decreases in occipital theta brain activity significantly correlated with improvements in Peripheral dimension symptom scores ($rho_{spearman} = 0.52$, $p = 0.0462$). As shown in Table II, there was a moderate but non-significant correlation between right parietal cortical activity with MSAQ Peripheral scores.

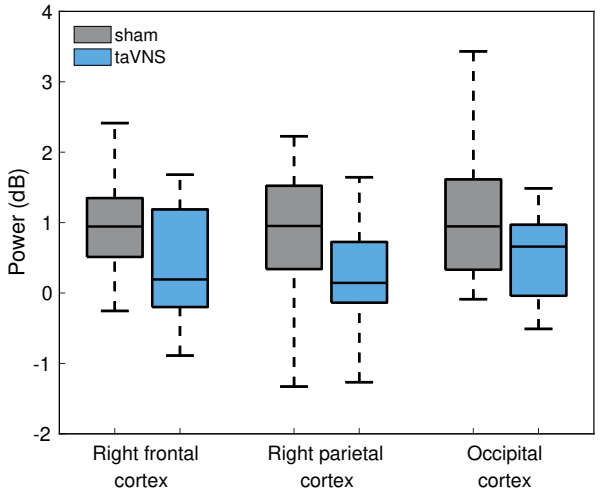

Fig. 2. EEG theta power comparisons for sham and taVNS conditions for all participants at the right frontal, right parietal and occipital cortices.

IV. Discussion

In this study, we have demonstrated the first insights of taVNS potential in eliciting motion sickness mitigating effects by examining brain cerebral activity. Our findings show that taVNS decreased neural activity in the theta spectral band from the right frontal, right parietal and occipital cortices during motion sickness-induced nausea. Previous research has consistently shown increased brain cortical activity in the frontal, parietal and occipital cortices during the experience of motion sickness [9], [10], [16], [17]. Our data indicate how stimulating the vagus nerve leads to a diminution of motion sickness-related brain activity in these aforementioned cortices. Others have shown that non-invasive stimulation of the vagus nerve can lead to theta activity reductions [18], [19]. A possible explanation for this finding is that taVNS may be forming an auriculo-vagal afferent pathway [20] by which the NTS receives afferent sensory input from vagal stimulation, and projects it to higher order brain structures via vagal cortical pathways [21]. The frontal electrode region described here reside over an aspect of the right dorsolateral prefrontal cortex (DLPFC); an area typically targeted by transcranial magnetic stimulation (TMS). While TMS activates the DLPFC directly, we surmise here that taVNS may be linking to DLPFC indirectly.

Based on the long-held belief that motion sickness arises due to sensory-conflict, research has consistently reported

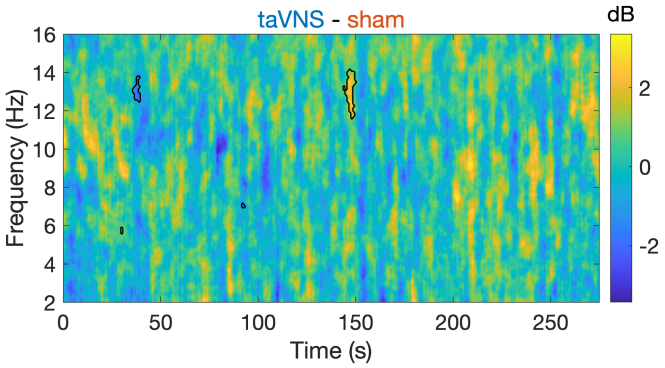

Fig. 3. Time-frequency difference between sham and taVNS conditions across regions of interest for all participants. Black contours denote significant temporal clusters after a two-sided non-parametric permutation test with cluster-correction.

TABLE I
A summary of the MSAQ results. Data are mean ± SEM.

MSAQ metrics	sham	taVNS	*p*-value	Cliff's δ
Total	18.0 ± 2.6	8.3 ± 1.9	7.1e-06	0.30
Gastrointestinal	17.4 ± 6.5	10.2 ± 5.8	0.3125	0.20
Central	18.2 ± 4.1	8.3 ± 3.3	0.0032	0.26
Peripheral	15.3 ± 3.1	7.1 ± 2.5	0.0012	0.24
Sopite	17.9 ± 3.0	8.3 ± 2.1	1.1e-04	0.28

TABLE II
Spearman Correlation between brain activity and MSAQ.

	Right frontal cortex	Right parietal cortex	Occipital cortex
Total	0.07	0.13	0.34
Gastrointestinal	0.06	0.22	0.06
Central	-0.22	-0.01	0.23
Peripheral	0.28	0.41	0.52*
Sopite	-0.22	-0.14	0.20

* Statistically significant correlations ($p < 0.05$).

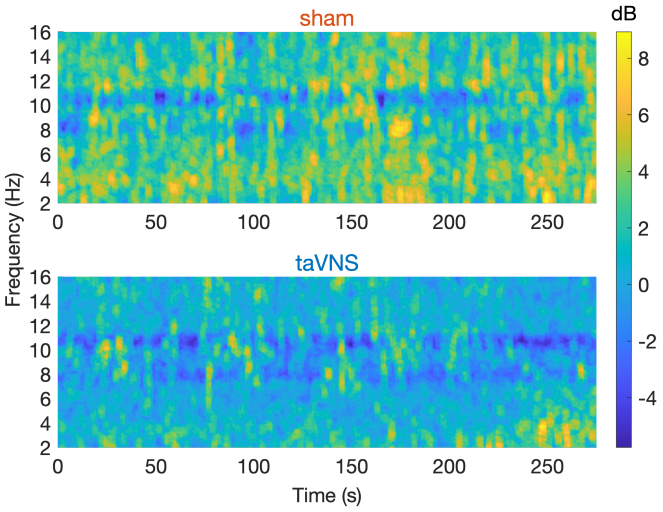

Fig. 4. Time-frequency power during the sham (top panel) and taVNS (bottom panel) conditions for one example participant.

increased theta brain activity in the parietal and occipital cortices during increasing motion sickness severity [10], [17]. In our study, we observed that taVNS was able to decrease theta activity in these regions compared to sham. We have long known the role of the parietal cortex in spatial awareness, and that of the occipital cortex in visual input integration. Thus our findings suggest that during sham condition, illusory motion from the nauseogenic visual stimulus may be causing participants to experience e.g., 'disorientation', 'dizziness' and 'spinning-like sensation'; symptoms that are symbolic of the MSAQ Central dimension and were markedly higher during sham condition (Table I). During taVNS, participants showed improvements in symptom scores as spatial and visual information is properly integrated. Recent evidence [22], [23] shows that motion sickness can be alleviated by reduction of brain activity in the regions described here.

Our results suggest that taVNS elicits malaise mitigating effects in response to nauseogenic visual stimulus in humans. The present findings advance our understanding of taVNS potential in mitigating ailments such as motion sickness that negatively influence the physiology and cortical activity of individuals, and thus could pave the way for novel neurorehabilitation interventions exploiting taVNS. While the present study has focused on motion sickness, cerebral activity at frequencies examined here may be useful in understanding and treating other conditions.

This pilot study on taVNS towards ameliorating motion sickness has limitations that should be addressed in future studies; the small sample size, and the lack of any stimulation during the sham condition.

In summary, this work demonstrates that electrical stimulation at the tragus can alleviate motion sickness. One implication is that taVNS may have potential to be translated to address other sources of nausea.

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