

Frequency-dependent tuning of the human vestibular “sixth sense” by transcranial oscillatory currents



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HIGHLIGHTS

- Transcranial oscillatory currents may stimulate the vestibular cortex in the range of its physiological activity (1 or 2 Hz)
- Induced behavioral effects (motion sickness and postural sways) are not due to a peripheral spread of the current towards vestibular receptors.
- Motion sickness represents a previously neglected possible side effect of slow-frequency tACS.

ARTICLE INFO

Article history:

Accepted 12 June 2023

Available online

Keywords:

Transcranial alternating current stimulation
Vestibular cortex
Kinetosis
Motion sickness
Cybersickness

ABSTRACT

Objective: The vestibular cortex is a multisensory associative region that, in neuroimaging investigations, is activated by slow-frequency (1–2 Hz) galvanic stimulation of peripheral receptors. We aimed to directly activate the vestibular cortex with biophysically modeled transcranial oscillatory current stimulation (tACS) in the same frequency range.

Methods: Thirty healthy subjects and one rare patient with chronic bilateral vestibular deafferentation underwent, in a randomized, double-blind, controlled trial, to tACS at slow (1 or 2 Hz) or higher (10 Hz) frequency and sham stimulations, over the Parieto-Insular Vestibular Cortex (PIVC), while standing on a stabilometric platform. Subjective symptoms of motion sickness were scored by Simulator Sickness Questionnaire and subjects' postural sways were monitored on the platform.

Results: tACS at 1 and 2 Hz induced symptoms of motion sickness, oscillopsia and postural instability, that were supported by posturographic sway recordings. Both 10 Hz-tACS and sham stimulation on the vestibular cortex did not affect vestibular function. As these effects persisted in a rare patient with bilateral peripheral vestibular areflexia documented by the absence of the Vestibulo-Ocular Reflex, the possibility of a current spread toward peripheral afferents is unlikely. Conversely, the 10 Hz-tACS significantly reduced his chronic vestibular symptoms in this patient.

Conclusions: Weak electrical oscillations in a frequency range corresponding to the physiological cortical activity of the vestibular system may generate motion sickness and postural sways, both in healthy subjects and in the case of bilateral vestibular deafferentation.

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Significance: This should be taken into account as a new side effect of tACS in future studies addressing cognitive functions. Higher frequencies of stimulation applied to the vestibular cortex may represent a new interventional option to reduce motion sickness in different scenarios.

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1. Introduction

Vestibular information processing is often considered a sixth sense, the one missed by the Greek philosopher Aristotle (Goldberg, 2012). A reason for Aristotle's misconception could be that, unlike other sensory systems, afferent signals from vestibular receptors (otoliths and semicircular canals) usually do not reach a level of consciousness, if not under certain pathological conditions of the inner ear or of the brain.

Indeed, unlike visual, somatosensory, and auditory cortices, the human vestibular cortex is not a single primary sensory area, but rather a multisensory associative region, located in the mid-posterior Sylvian fissure, initially thought to correspond to the monkey's Parieto-Insular Vestibular Cortex (PIVC) (Brandt and Dieterich, 1999) and more recently thought to include also the Posterior Insular Cortex (PIC) (Frank and Greenlee, 2018). The multisensory nature of these vestibular core regions of the temporal supramarginal gyrus, which constantly integrate verticality perception and self-motion, providing an egocentric tridimensional space referencing (Brandt et al., 2014), meanwhile being involved in many high-level cognitive and motor functions (Angelaki and Cullen, 2008), is supported by its cytoarchitecture, whose koniocortical features are not as evident as those of other unimodal primary sensory areas (Eickhoff et al., 2006).

Meta-analytical modeling using activation likelihood estimation for the integration of results of neuroimaging studies based on caloric irrigation of the ear or peripheral galvanic vestibular stimulation (GVS) (zu Eulenburg et al., 2012; Lopez et al., 2012), has shown a widespread cortico-subcortical "vestibular network" integrating vestibular inputs, in which the parietal operculum (and the PIVC-PIC complex in particular) has been found consistently activated. In this context, GVS with alternating, rather than direct, currents at the frequency of 1 Hz or 2 Hz are most effective to elicit subjective sensations of motion perception, coupled with activations in the vestibular network (Stephan et al., 2005).

Based on these findings, we reasoned that perturbing non-invasively, but directly, the vestibular cortex with such slow frequencies at 1 or 2 Hz could overcome either the correlational nature of neuroimaging findings or their intrinsic caveats regarding the vestibular domain [indeed, the mere exposition to static fields of the 3 Tesla magnetic resonance imaging (MRI) scanner elicits nystagmus (Roberts et al., 2011)], meanwhile providing causal evidence on its physiological role.

For these purposes, we used transcranial alternating current stimulation (tACS), biophysically modeled on previous spatial (neuroimaging-derived) and oscillatory findings of the neocortical vestibular representations, in a way that the induced fields could target as much as possible the central core regions of the vestibular network while minimizing stimulation over the rest of the brain. tACS is a non-invasive brain stimulation (NiBS) technique that entrains oscillatory activity of cortical neurons in a frequency-specific manner, thereby modifying the associated behavior (Polanía et al., 2018; Rossi et al., 2022). The working hypothesis was that the slow frequency (1 or 2 Hz) tACS of the vestibular cortex would induce "central" vestibular symptoms by entraining local intrinsic slow frequencies. Indeed, during symptoms of motion sickness, the most frequent vestibular disturbance (Golding and Gresty, 2005), a widespread and progressive increase

of slow-frequency electroencephalographic (EEG) oscillations in the delta range, mainly in temporoparietal and occipital regions, along with symptoms worsening, is described (Krokos and Varshney, 2022; Nürnberger et al., 2021).

2. Methods

2.1. Experiment 1

Thirty (30) healthy subjects (18 males; 29 fully right-handed; mean age: 27 ± 3.7 years; mean education: 17.2 ± 2.7 years) were recruited at the University of Siena. Participants with a history of neurological disorders including epilepsy, migraine, undergoing psychiatric therapy, or presenting symptoms attributable to motion sickness were excluded from the study. Each subject signed a written informed consent before entering the study, which was approved by the Local Ethics Committee, under the code of Brain-sight 21–24.

Experimental procedure. A double-blind, randomized, cross-over study has been conducted. Data have been collected in a large and low-noise space to minimize the influence of the external environment (Lee et al., 2018). The protocol consisted of five consecutive recording sessions for each participant, who was asked to stand in the center of a stabilometric platform (NeuroCom Smart Equitest system® (Oregon, USA), while wearing the cap for tACS delivery (Fig. 1a). The first session was recorded without stimulation (baseline) while in the following four sessions the tACS was randomly delivered at three different frequencies plus one sham stimulation. Stimulation frequencies were set at 1 Hz, 2 Hz (i.e., those frequencies better eliciting vestibular activation), and 10 Hz. The 1 Hz and 2 Hz stimulations represented the experimental conditions, while the 10 Hz and Sham stimulations represented the control conditions (Fig. 1c). Before recording, each participant was asked to stand in the center of the posturographic platform and to get familiar with it and with the upright, slightly widened-base position – as required by the software – needed to be maintained for the duration of each trial. During the recording, subjects had to maintain the position they assumed at the beginning with their gaze directed toward a fixed point placed at eye level (Lee et al., 2018). Meanwhile, an experimenter was positioned behind the participant in order to prevent a possible fall.

At the end of the recording of each session of stimulation, participants were asked to step off the platform and were given a sufficiently long recovery time before the next session, to prevent possible carry-over effects of stimulation. During the recovery phase, subjects had to answer the Simulator Sickness Questionnaire (Kennedy et al., 1993) (SSQ, originally developed for military flight simulators in the 1990s, regarding the symptoms of motion sickness) and a NiBS side effects questionnaire. Questionnaires were not submitted at the end of the first recording (baseline) because, as an exclusion criterion, study participants had to report no symptoms attributable to a motion sickness in order to be included in the sample. As questionnaires were administered by an experimenter blind to the stimulation type and subjects were blind to the type of stimulation received, the study was double-blind.

Each of the five recording sessions (i.e., Basal, 1 Hz, 2 Hz, 10 Hz, and Sham) included two conditions: condition 1 (eyes-open,

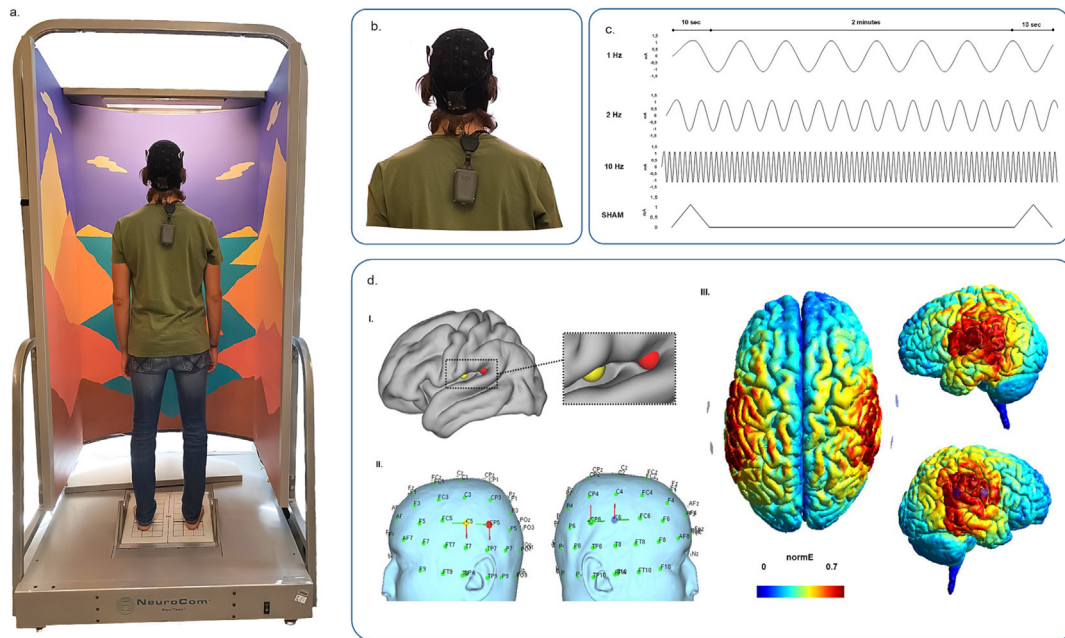


Fig. 1. Experimental procedure. **a. Recording session.** participants were asked to stand in the center of a stabilometric platform (NeuroCom Smart Equitest system® (Oregon, USA) while wearing the cap for transcranial alternating current stimulation (tACS) delivery. The represented person (one of the Authors) gave his permission to be photographed; **b. tACS delivery.** High-definition (HD) tACS was administered through an 8-channel EEG/tCS (electroencephalography and transcranial current stimulation) hybrid neurostimulation system (Starstim8; Neuroelectrics, Barcelona, Spain). The device was connected via Bluetooth to the computer. tACS was randomly delivered at three different frequencies plus one sham stimulation. The person in the photo is the same of Panel a; **c. Stimulation frequencies.** Stimulation frequencies were set at 1 Hz, 2 Hz (i.e., those frequencies better eliciting vestibular activation), and 10 Hz. The 1 Hz and 2 Hz stimulations represented the experimental conditions, while the 10 Hz and Sham stimulations represented the control conditions; **d. Details of biophysical modeling for the tACS montage.** E-field resulting from the tACS montage used during the data collection. **Panel I.** Bilateral parietal-insular-vestibular cortex (PIVC) and the posterior insular cortex (PIC) were chosen as target areas. MNI coordinates of the left PIVC (yellow sphere: $x = -43, y = -14, z = 17$ and the left PIC (red sphere): $x = -42, y = -36, z = 23$. **Panel II.** A tACS montage with 4 electrodes was chosen to reach bilateral PIVC and PIC: C5 (1.15 mA), C6 (-1.15 mA), CP5 (1.35 mA), and CP6 (-1.35 mA). **Panel III.** The figure graphically represents the resulting E-field (NormE) in V/m on a healthy example subject.

motionless visual surrounding, and platform), condition 2 (eyes-closed, motionless visual surrounding, and platform); each condition included 3 trials of 20 seconds, thus 60 seconds per condition and 2 minutes per recording session.

The platform sampled 100 measurements per second (2000 measurements during each trial) for a total of 6000 measurements per condition and 12,000 measurements per recording. On the other hand, brain stimulation was delivered continuously during the 2-minute recording of each session, with 10 seconds of ramp-up/ramp-down. The order of recording conditions (eyes-open/eyes-closed) was randomized among subjects and remained the same for the 5 recordings; the interval between recordings was 15 minutes. Thus, the whole experimental procedure took about 1 hour and 10 minutes per subject.

tACS delivery (Fig. 1b,c). High-definition (HD) tACS was administered through an 8-channel EEG/tCS (transcranial current stimulation) hybrid neurostimulation system (Starstim8; Neuroelectrics, Barcelona, Spain; Fig. 1c). The device was connected via Bluetooth to the computer. Hybrid electrodes (NG Pistim) were used, consisting of an upper part containing the sintered Ag/AgCl core with a diameter of 12 mm, screwed onto a lower base such that a circular area of about 3.14 cm² was covered. The electrodes were placed on a 32-channel neoprene EEG headset, according to the International 10–20 EEG System. The portion of the scalp underneath the electrode was prepared by inserting 15 ml of sterile sodium chloride solution (0.9%) to avoid uncomfortable skin sensations and reduce impedances, which were kept below 20 kOhm. Similarly, sham stimulation has been set with a ramp up/ramp down of 10 seconds during which, intensity and phase angle were the same as real stimulation conditions while frequency was set at 10 Hz.

Biophysical Modeling (Fig. 1d). Electrode location was defined through a software (SimNIBS) that uses a detailed model of an adult brain to predict the current distribution. It realistically calculates the electric field generated by different NiBS methods. The bilateral parietal-insular-vestibular cortex (PIVC) $x = -43, y = -14, z = 17$ (left) and $x = 40, y = -14, z = 18$ (right) and the posterior insular cortex (PIC) $x = -42, y = -36, z = 23$ (left) and $x = 58, y = -34, z = 17$ (right) (Wirth et al., 2018) were the target areas. Based on this model, 4 electrodes were placed at C5 (intensity: 1.15 mA; phase angle: 0°), CP5 (intensity: 1.35 mA; phase angle: 0°), C6 (intensity: 1.15 mA; phase angle: 180°), and CP6 (intensity: 1.35 mA; phase angle: 180°). At the level of CP5, a total of 2.5 mA was delivered in each session.

Subjective sensations to brain stimulation. As abovementioned, study participants underwent a questionnaire on the possible side effects of the tACS. The items investigated were headache, neck pain and scalp pain, burning sensation on the scalp, other sensations under the electrodes (tingling, itching, burning), skin reddening, drowsiness, difficulty in concentrating, perception of phosphenes, or any other.

Primary evaluation criterion - Motion Sickness. The primary criterion of the evaluation was the motion sickness reported subjectively by participants, assessed using the Simulator Sickness Questionnaire (SSQ), which is widely used to quantify motion (or cyber) sickness also during virtual reality experiences. Participants are asked to report the degree of subjective sickness concerning 16 symptoms on a scale from 0 (no perception) to 3 (severe perception) experienced while undergoing stimulation. Based on a large sample of data collected from military pilots, a total score < 5 corresponds to a negligible degree of motion sickness, between 5 and

10 to minimal symptoms, between 10 and 15 significant symptoms, and between 15 and 20 a concerning degree, while a total score > 20 corresponds to a severe degree of motion sickness (Stanney et al., 1997). Furthermore, by grouping ratings for the individual symptoms, three non-mutually exclusive categories representing symptoms of nausea (N), oculomotor disturbance (O), and disorientation (D) have been considered. The same scoring has been used for these subscales as factors, in order to provide scales with similar variability (Kennedy et al., 1993).

Secondary evaluation criterion - Degree of sway. The degree of sway at rest in a standing, stationary and stable position was defined by the center of pressure (COP), recorded using EquiTest, a stabilometric platform capable to quantify postural control in the standing position under static and dynamic conditions. It represents one of the main methods of performing computerized dynamic posturography. This device can measure ground reaction forces and, through these, calculate COP displacements, center of mass (COM) oscillation, equilibrium score (ES), and postural stability index (PSI). In studies of postural control, the change in COP measured through force plates is considered (Lemay et al., 2014; Scoppa et al., 2013). COP represents the position of the vertical ground reaction vector on the force plate (Winter, 1995). As COP reflects the movement of the body to maintain the COG (center of gravity) above the base of the support, its displacement from the equilibrium position is generally larger in magnitude than the displacement of the COG (Prieto et al., 1993). Under static conditions, however, COP coincides with COG. COP is usually measured by the force plate only in conditions 1 and 2. The COP path reflects postural muscle activity aimed at adjusting the position of the center of gravity, whose projection must remain within the base of support to maintain balance. Linear measures such as COP path length or swing range are often used to describe how much COP moves in the anteroposterior (AP) and mediolateral (ML) directions, providing information about the amount of movement (Prieto et al., 1996).

2.2. Data pre-processing

SSQ. Scoring of SSQ has been conducted as reported by (Kennedy et al., 1993). Briefly, the total score is defined by the sum of the 16 items multiplied by a constant scaling factor (3.74). For what concerns the single categories (nausea, oculomotor disturbance, and disorientation) the sum of the specific items' ratings were multiplied by a constant scale factor as follows: (i) nausea: items (1, 6, 7, 8, 9, 15, 16) \times 9.54; (ii) oculomotor disturbance: items (1, 2, 3, 4, 5, 9, 11) \times 7.58; (iii) disorientation: items (5, 8, 10, 11, 12, 13, 14) \times 13.92 (see Annex 1, Supplemental Materials).

Stabilometric examination data. The stabilometric platform, NeuroCom Smart Equitest system[®], only allowed us to record 3 trials of 20 s each per condition (eyes open and eyes closed). For each condition, the 3 trials of 20 seconds each were grouped together and the first 10 seconds were discarded for two reasons: first, to avoid errors due to the initial assumption of the balanced posture (Mezzarane and Kohn, 2007); second, to exclude measurements recorded during ramp-up phase of the stimulation. Thus, we kept for the analysis 50 sec of recording, that is 5000 measurements per condition (eyes open, eyes closed), per recording. COP \times and y coordinates were extracted from the platform for each measurement, corresponding to the participant's AP and ML axes, respectively (Verbecque et al., 2016; Wälchli et al., 2018). From the AP and ML components of the COP trajectory, the "sway path" parameter corresponding to the total length of the COP trajectory was obtained (McCamley et al., 2022). Through the sum of the distances between consecutive points in the COP path, the total length of the COP path (total excursion, TOTEX), corresponding to the total sway path, was obtained (Prieto et al., 1996).ce:display>

$$TOTEX = \sum_{n=1}^{N-1} [(AP[n+1] - AP[n])^2 + (ML[n+1] - ML[n])^2]^{1/2}$$

2.3. Statistical analysis

For both SSQ and stabilometric examinations, outcomes were analyzed using IBM SPSS statistics 26 Windows software. A p-value < 0.05 was considered significant. The level of significance in multiple comparisons was Bonferroni corrected.

SSQ. The Shapiro-Wilk test was used to check the normality of the data. A non-normal distribution was found for 2 Hz pacing ($W_{(30)} = 0.811$, $p < .001$), 10 Hz pacing ($W_{(30)} = 0.817$, $p < .001$) and Sham ($W_{(30)} = 0.625$, $p < .001$). Mauchly's test was used to check the sphericity of the data. A violation of the assumption of sphericity was found ($\chi^2_{(5)} = 311.352$, $p = .045$), so the Greenhouse-Geisser correction was performed ($p < .001$). Considering these results, Friedman's nonparametric test for repeated trials was used.

Stabilometric examination. The Shapiro-Wilk test was used to check the normality of the data. A non-normal distribution was found for Baseline ($W_{(31)} = 0.890$, $p = .004$), 1 Hz pacing ($W_{(31)} = 0.741$, $p < .001$), 2 Hz pacing ($W_{(31)} = 0.702$, $p < .001$), 10 Hz pacing ($W_{(31)} = 0.786$, $p < .001$) and Sham ($W_{(31)} = 0.780$, $p < .001$). For this reason, the data were transformed into natural logarithms, outliers have been checked and removed according to Tukey's method, and the Mixed Model test was used. Raw data were then still used for graphical representation only.

Finally, the two-tailed Spearman's test was carried out to evaluate a possible correlation between motion sickness and the degree of sway path. The Passing-Bablok regression analysis (Passing and Bablok, 1983) has been performed in case of positive correlation to determine if motion sickness predicts sway path degree. For the correlation analyses, the questionnaire's total score and subscores and the single eyes-open and eyes-closed conditions of the stabilometric platform recording were considered. For both correlation and regression analysis, the difference between active stimulation condition and baseline has been considered.

2.4. Experiment 2

A second experiment was performed to exclude that tACS effects could be due to a peripheral spread of the stimulation activating vestibular receptors of the inner ear. A rare patient (male, 71 years old) suffering from bilateral vestibular loss received tACS in the same set of experiment 1. The patient has been affected by severe progressive idiopathic vestibular loss since 2003. At the time of the experiment, the patient reported severe ataxia and oscillopsia while walking. The bi-thermal caloric stimulation showed no response bilaterally, cervical and ocular vestibular evoked myogenic potentials were absent bilaterally and the video head impulse test demonstrated a Vestibular Ocular reflex (VOR) gain < 0.3 on all semicircular canals with overt and covert saccades. Therefore, the patient was virtually deafferented in the vestibular domain. The experimental procedure, evaluation criteria, setting, and tACS delivery were exactly comparable to the ones used for healthy subjects. Differently, even though the patient did not refer symptoms while standing motionless, we still evaluated motion sickness by SSQ during baseline condition on the platform.

In addition, the patient underwent tACS over the mastoids (by positioning only two electrodes at TP9 and TP10), at 1 Hz and 2 Hz frequencies (Stephan et al., 2005), in order to test whether peripheral stimulation elicited vestibular symptoms, including nystagmus (Curthoys and MacDougall, 2012), despite the documented deafferentation. In this case, the patient did not stand on

the platform for safety reasons (i.e., possible fall), so we collected only subjective sickness by SSQ.

3. Results

3.1. Experiment 1. Motion sickness

SSQ total score. Friedman's test showed a significant effect of stimulation frequency on the total score ($\chi^2_{(3)} = 38.847$, $p < .001$; Fig. 2a). Multiple comparisons showed a Bonferroni-corrected significant increase of SSQ ratings during 2 Hz-tACS versus Sham condition ($p < .001$), during 1 Hz-tACS versus Sham condition ($p < .001$), and during 1 Hz-tACS versus 10 Hz-tACS condition ($p = .008$). A significant increase of the SSQ emerged also during 2 Hz-tACS versus 10 Hz-tACS condition (uncorrected $p = .0147$) and during 10 Hz-tACS versus Sham condition (uncorrected $p = .0147$), but these differences did not survive after the Bonferroni correction.

Nausea Sub-Score. Friedman's test showed a significant effect of stimulation frequency ($\chi^2_{(3)} = 27.746$, $p < .001$; Fig. 2b). Multiple comparisons showed a significant Bonferroni-corrected increase of nausea subscore during 2 Hz-tACS ($p = .002$) and 1 Hz-tACS ($p = .002$) versus the Sham condition.

Oculomotor Disorder Sub-Score. Friedman's test showed a significant effect of stimulation frequency on the oculomotor score ($\chi^2_{(3)} = 21.314$, $p < .001$; Fig. 2b). Furthermore, multiple comparisons (Bonferroni-corrected) showed a significant increase in this score during 1 Hz-tACS versus Sham conditions ($p = .001$). Also, a significant increase of oculomotor complaints emerged during 2 Hz-tACS versus Sham condition (uncorrected $p = .036$) and during 10 Hz-tACS versus Sham condition (uncorrected $p = .012$), which did not survive if Bonferroni corrected.

Disorientation Sub-Score. Friedman's test showed a significant effect of stimulation frequency on the disorientation score ($\chi^2_{(3)} = 52.402$, $p < .001$; Fig. 2b). Multiple comparisons (Bonferroni-corrected) showed a significant increase of this score during 2 Hz-tACS ($p < .001$) and during 1 Hz-tACS ($p < .001$) versus Sham condition, during 2 Hz-tACS versus 10 Hz-tACS condition ($p = .003$) and 1 Hz-tACS versus 10 Hz-tACS condition ($p < .001$).

3.2. Experiment 1. Sway path

Total Sway-Path. Linear Mixed Model test showed a significant effect of stimulation frequency on the total score ($F_{(4; 109,185)} = 7.927$, $p < .001$; Fig. 3a). Multiple comparisons (Bonferroni-corrected) showed that low frequencies of stimulation at 1 and 2 Hz induced a significant increase of postural sway versus Baseline, 10 Hz tACS and versus Sham condition. More in detail, 1 Hz-tACS versus Baseline ($p = .004$), 2 Hz-tACS versus Baseline ($p = .043$), 1 Hz-tACS versus 10 Hz-tACS condition ($p < .001$), 1 Hz-tACS versus Sham condition ($p = .017$), 2 Hz-tACS versus 10 Hz-tACS condition ($p = .002$).

Sway-Path EO (eyes-open). Linear Mixed Model test showed a significant effect of stimulation frequency on postural sway during eyes open condition ($F_{(4; 104,953)} = 7.404$, $p < .001$; Fig. 3b). Multiple comparisons (Bonferroni-corrected) showed a significant increase of postural sway versus Sham condition during 2 Hz-tACS ($p = .045$) and 1 Hz-tACS ($p < .001$); a significant increase was observed also during 1 Hz-tACS versus 10 Hz-tACS condition ($p = .002$) and between the 1 Hz-tACS condition and Baseline ($p = .002$).

Sway-Path EC (eyes-closed). Linear Mixed Model test showed a significant effect of stimulation frequency on postural sway during eyes open condition ($F_{(4; 106,269)} = 5.478$, $p < .001$; Fig. 3c). Multiple comparisons (Bonferroni-corrected) showed a significant increase of postural sway during 2 Hz-tACS versus 10 Hz-tACS condition

($p = .008$), during 1 Hz-tACS ($p = .047$) and 2 Hz-tACS ($p = .001$) versus Baseline.

3.3. Experiment 1. Correlation analysis

Spearman's test between SSQ total score and total sway path for each active stimulation condition (1 Hz, 2 Hz, and 10 Hz-tACS) showed no significant correlation. Taking into account the sub-scores of SSQ and the two recording conditions (eyes-open and eyes-closed), a significant positive correlation has been found when considering the difference between 1 Hz tACS and baseline, between the eyes-open condition and the total SSQ score ($r_{(30)} = 0.47$, $p = .009$; Fig. 4a); more in detail, there was a significant positive correlation when considering the 1 Hz-tACS condition between the eyes-open condition and the nausea subcategory ($r_{(30)} = 0.45$, $p = .012$; Fig. 4b), the oculomotor disturbance subcategory ($r_{(30)} = 0.43$, $p = .017$; Fig. 4c) and the disorientation subcategory ($r_{(30)} = 0.50$, $p = .005$; Fig. 4d).

According to Passing-Bablok analysis, the overall regression was statistically significant ($R^2 = 0.18$; $F_{(1,28)} = 6.17$; $p = .02$), suggesting that total SSQ score predicted the sway path degree, ($\beta = 0.004$), 95% CI [0.0007, 0.0075] (Fig. 4a). When considering sub-scores of the SSQ, the regression was still significant for nausea ($R^2 = 0.19$; $F_{(1,28)} = 6.78$; $p = .014$) and for disorientation ($R^2 = 0.2$; $F_{(1,28)} = 6.96$; $p = .013$), suggesting their contribution to predict the sway path degree [nausea: ($\beta = 0.005$), 95% CI: 0.001, 0.0088 (Fig. 4b); [disorientation ($\beta = 0.003$), 95% CI: 0.0007, 0.006 (Fig. 4d)]. On the other hand, the oculomotor disturbance did not predict sway path degree, as the regression was not significant [$R^2 = 0.11$; $F_{(1,28)} = 3.35$; $p = .07$], ($\beta = 0.005$), 95% CI: 0.0005, 0.009] (Fig. 4c).

Reported side effects. Besides the described vestibular symptoms, no other significant side effects of tACS were reported, except for phosphenes during the 10 Hz stimulation condition in 25 subjects (83.3%), who described phosphenes as slight or mild. This perception may explain the high scores observed in the disorientation subscore of the SSQ (Fig. 2b). No clinically evident nystagmus was evoked in any stimulation conditions.

3.4. Experiment 2. Vestibular deafferentation patient

As a single case study, we did not conduct a statistical analysis of the patient's data but the results are worth mentioning (Fig. 5).

For what concerns motion sickness (Fig. 5a), ratings from SSQ as reported by the patient are shown. During baseline, 10 Hz-tACS, and sham conditions, the patient reported no symptoms while with 1 Hz-tACS and 2 Hz-tACS, the patient displayed symptoms suggestive of motion sickness, especially for disorientation subscore (Fig. 5b). These results have been recorded also when 2 Hz-tACS and 1 Hz-tACS were applied on mastoids, but in these cases, symptoms have been considered much less severe (total score: 1 Hz-tACS = 22 against 1 Hz-tACS on mastoids = 3.74; Fig. 5b).

Differently from healthy subjects, the patient's sway path (Fig. 5c) during baseline was similar to the one recorded during 1 Hz-tACS and not so different from the one recorded during 2 Hz-tACS, while 10 Hz-tACS lead to a drastic decrease in his sway path. These results are more evident in the eyes-closed condition (Fig. 5e) than in the eyes-open one (Fig. 5d).

4. Discussion

Results demonstrate how the human vestibular cortex can be effectively stimulated by weak, almost imperceptible, transcranial oscillatory potentials, tuning our so-called "sixth sense" in a frequency-specific manner, resulting in subjective symptoms of

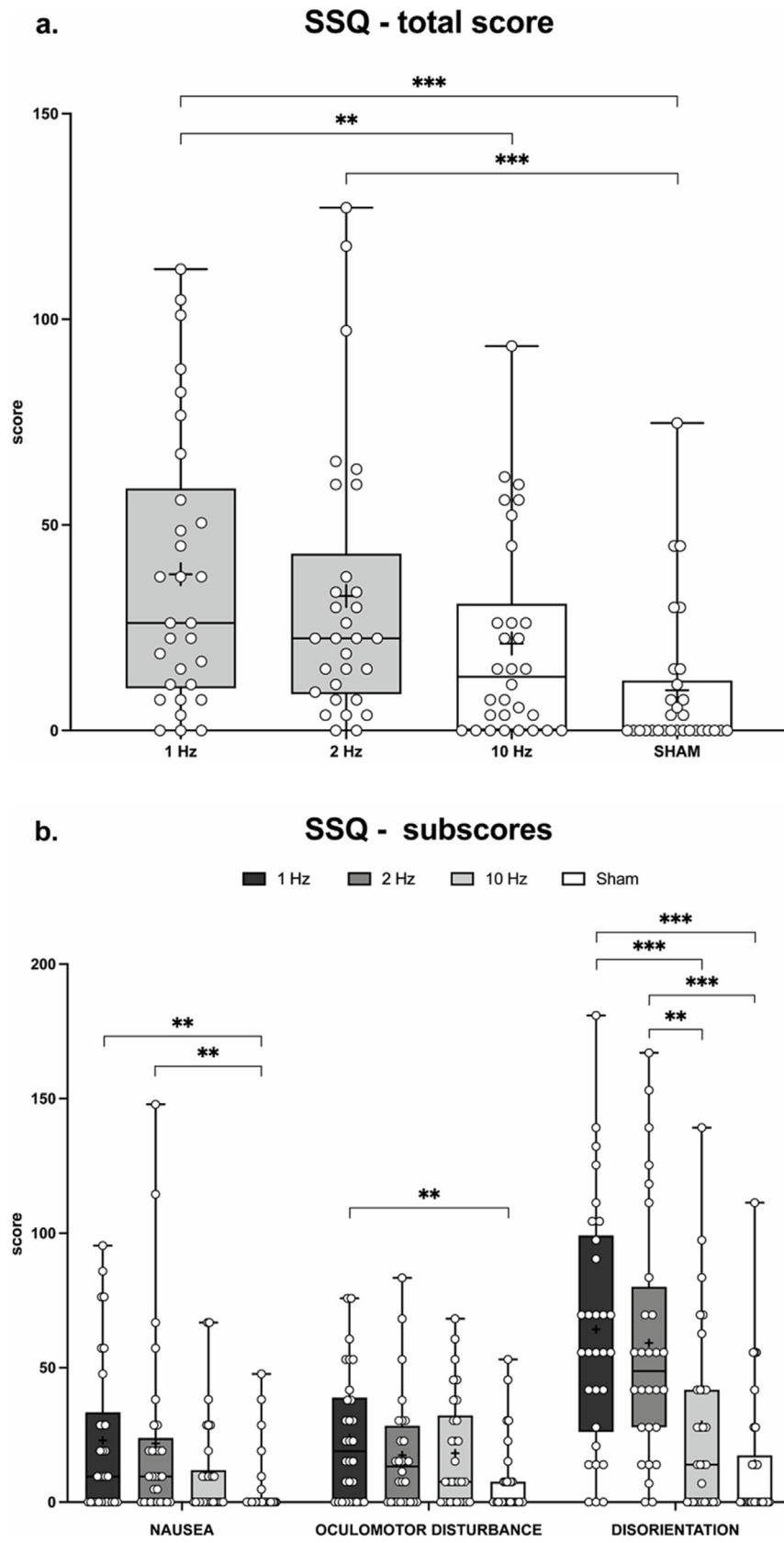


Fig. 2. Motion sickness in healthy subjects. Simulator Sickness Questionnaire (SSQ) outcomes regarding total score (a) and each subscore addressing nausea, oculomotor disturbance, and disorientation (b). Ratings > 20 at the total score must be considered severe symptomatology (Kennedy et al., 1993). Legend: + refers to the mean; * refers to $p < .05$; ** refers to $p < .01$; *** refers to $p < .001$.

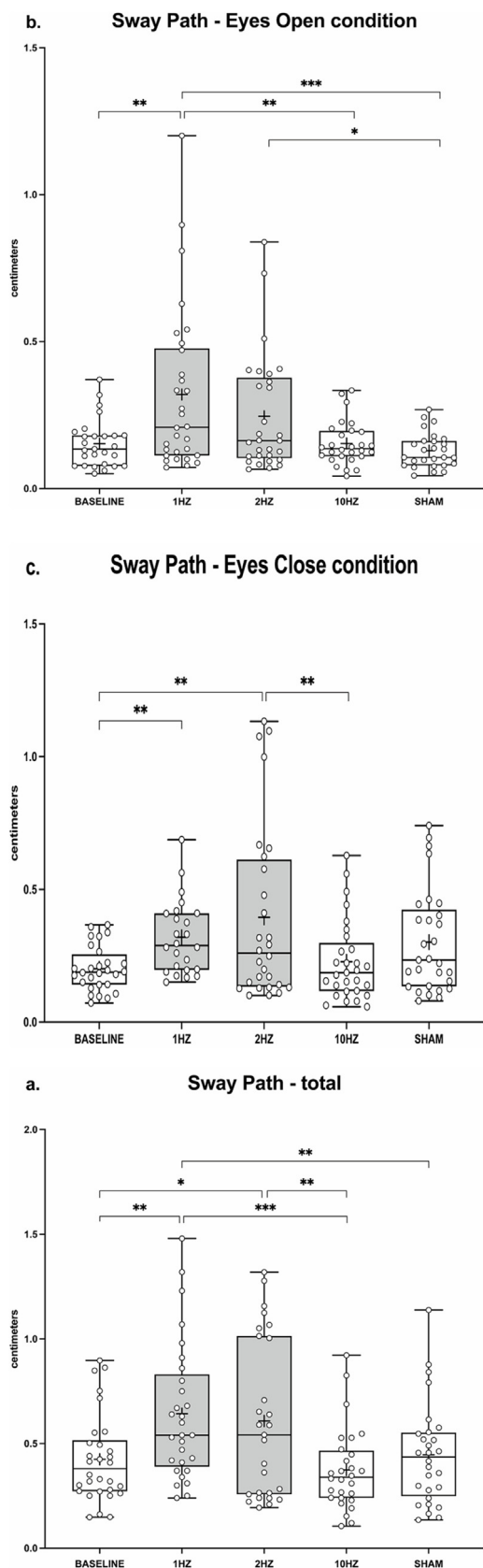


Fig. 3. Sway Path in healthy subjects. Sway Path (in centimeters) as calculated by Neurocom Smart EquiTest stabilometric platform outcomes during transcranial alternating current stimulation (tACS). Significant sway path increase is shown in 1 Hz-tACS and 2 Hz-tACS conditions compared to baseline and control conditions (sham and 10 Hz-tACS). These results are visible either when considering eyes-open (b) and eyes-closed (c) conditions separately or together (a). **Legend:** + refers to the mean; * refers to $p < .05$; ** refers to $p < .01$; *** refers to $p < .001$.

motion sickness and objectively measurable postural sways. The effects of the central vestibular stimulation seem quite robust, considering that the recruited subjects denied ever having suffered from vestibular symptoms related to motion sickness. Results also support, in an original way, some physiological aspects of the vestibular processing, as the central role played by low-frequency oscillations in generating motion sickness symptoms (Krokos and Varshney, 2022; Nürnberg et al., 2021) and postural sway. However, this aspect will need full confirmatory evidence by showing 1 or 2 Hz tACS entrained congruent EEG changes in this sense. Results in the patient also strongly suggest that the vestibular behavioral and posturographic changes are central in origin, as they take place even in the patient with bilateral vestibular deafferentation, as confirmed by the absence of the VOR and of the effects of the bi-thermal stimulation. In the patient, tACS at 1 and 2 Hz applied directly on mastoids did not produce significant motion sickness (Fig. 5a).

These results should be also considered among new potential side effects of low-frequency tACS in future studies, as motion sickness is currently not listed in the most recently updated guidelines (Antal et al., 2017).

Following the pioneering Penfield’s observations (Penfield, 1957) in awake humans undergoing brain surgery, who described vestibular sensations during electrical stimulation of a deep region of the exposed neocortex located in the lateral sulcus around the superior temporal gyrus, only a few studies have previously attempted to target the human vestibular cortex by NiBS (using Transcranial Magnetic Stimulation or Transcranial Direct Current Stimulation): most of them were aimed to disclose the causal role of different neocortical regions thought to belong to the vestibular cortex, as the temporoparietal junction (TPJ) (Fiori et al., 2015; Santos-Pontelli et al., 2016) the supramarginal gyrus (Kheradmand et al., 2015) or the dorsal (Willacker et al., 2019) or posterior (Young et al., 2020) parietal cortex in the representation of subjective verticality (or sense of upright), including postural adaptations. Other physiological questions addressed by NiBS in the vestibular domain were self-motion duration (Seemungal et al., 2009), its role in motor control (Reichenbach et al., 2016), influence on the vestibular-ocular reflex (Arshad et al., 2014), and temporal/spatial perception (Dalong et al., 2021). However, none of these studies was based on tACS at different frequencies.

By applying frequency-specific oscillatory potentials transcranially, we causally confirmed, in a new way, the role of the PIVC in controlling some aspects of vestibular function. Indeed, 1 and 2 Hz-tACS were the most effective in inducing transient subjective sensations of vestibular dysfunction, consistently among subjects, that positively correlated with the sway path increase as measured by posturography (Experiment 1, Fig. 4). Alternatively, it would be possible that tACS disturbed multisensory integration for vestibular function (Brandt and Dieterich, 1999), which could result in disturbed postural balance and subjective sensations. 1 or 2 Hz-tACS (Figs. 2 and 3) were the most effective (versus Sham and 10 Hz) in inducing symptoms suggestive of motion sickness, likely through entrainment of local oscillations, according to the notion that neural correlates of these symptoms appear to take place mainly in temporoparietal and occipital regions as a widespread and progressive increase of slow-frequency EEG oscillations in the delta range, as long as motion sickness increases (Krokos and Varshney, 2022; Nürnberg et al., 2021).

It is worth noting that an increase of delta (i.e., 1–4 Hz) and theta oscillatory EEG activity in the core vestibular PIVC network (and frontal regions), with right hemispheric dominance in right-handers, is thought to represent an oscillatory EEG signature of ego-motion related vestibular stimulation (Ertl et al., 2021), thus suggesting that these slow frequencies could be relevant for sensations of self-motion perception: we causally confirmed this

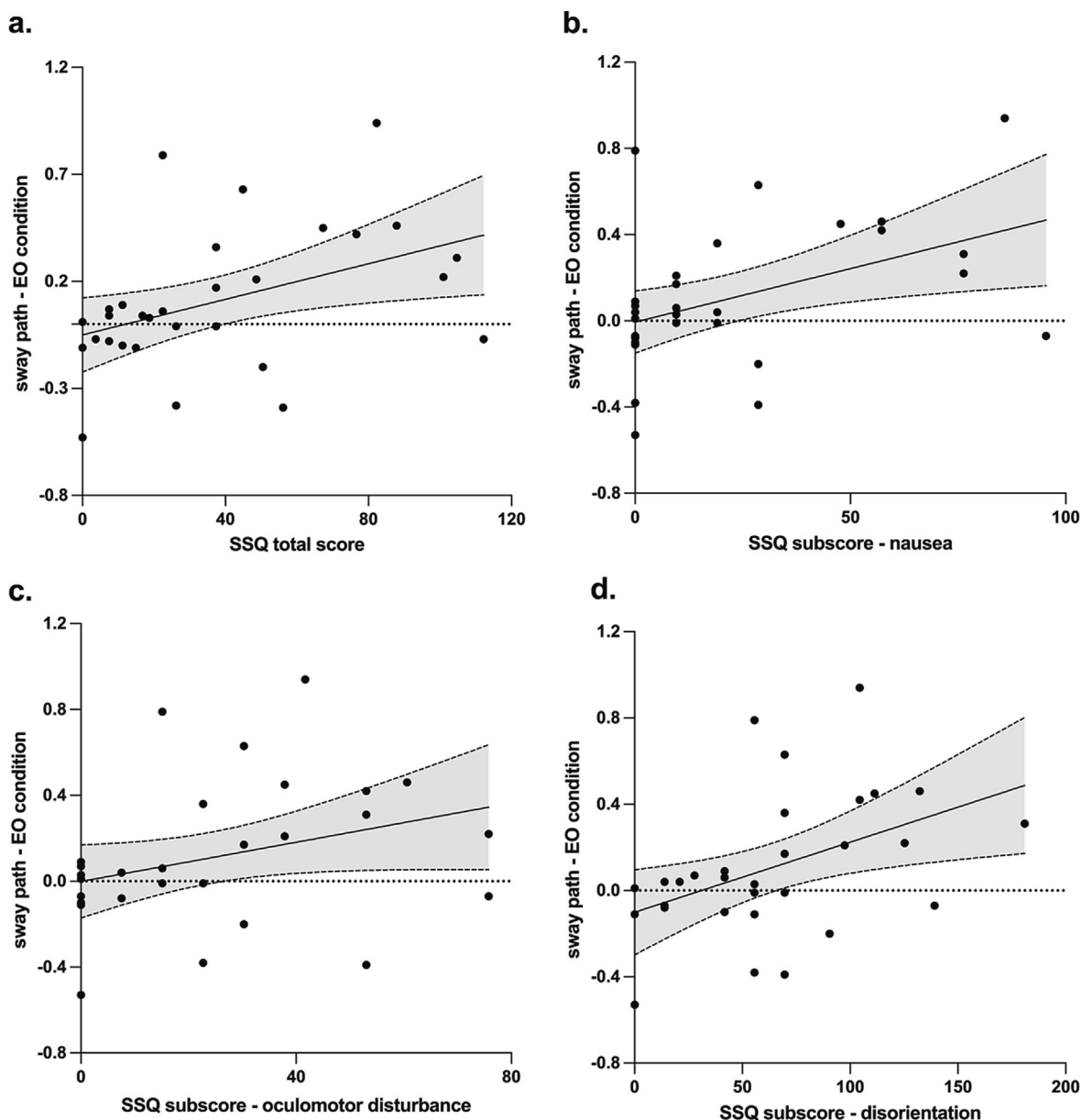


Fig. 4. Correlation analysis and Passing-Bablok regression analysis. A positive correlation has been found when considering the difference between 1 Hz tACS and baseline, between the eyes-open (EO) condition and the total Simulator Sickness Questionnaire (SSQ) score ($r_{(30)} = 0.47$, $p = .009$; **panel a**); more in detail, there was a significant positive correlation between the eyes-open condition and the nausea subcategory ($r_{(30)} = 0.45$, $p = .012$; **panel b**), the oculomotor disturbance subcategory ($r_{(30)} = 0.43$, $p = .017$; **panel c**) and the disorientation subcategory ($r_{(30)} = 0.50$, $p = .005$; **panel d**). Furthermore, by Passing-Bablok regression analysis, motion sickness was found to significantly predict sway path during eyes open condition for what concern the total score: $y = 0.004X - 0.05$; $R^2 = 0.18$; $p = .02$ (**panel a**), the nausea sub-score: $y = 0.005X - 0.005$; $R^2 = 0.2$; $p = .01$ (**panel b**) and disorientation sub-score $y = 0.003X - 0.1$; $R^2 = 0.19$; $p = .01$ (**panel d**). On the other hand, the oculomotor disturbance sub-score was not found to predict sway path during eyes open condition: $y = 0.004X - 0.001$; $R^2 = 0.11$; $p = .78$ (**panel c**). **Legend:** ——— refers to 95% CI.

hypothesis showing that slow frequency tACS, likely through entrainment (Polanía et al., 2018; Rossi et al., 2022), increases this sensation. However, we applied only bilateral stimulation of the vestibular cortex in the current study, so we did not address whether such a right vestibular dominance for right-handers could emerge also using a perturbational approach with tACS.

Since these frequencies are also the most effective in activating the vestibular cortex when used to stimulate vestibular receptors with galvanic stimulation (Stephan et al., 2005), it might be argued that a peripheral spread of current could have participated in inducing transient vestibular dysfunction. Control experiments carried out in the patient with vestibular areflexia confirmed that the above-reported effects were triggered by true cortical stimulation rather than current spread to vestibular peripheral afferents.

A higher frequency of cortical stimulation (10 Hz) did not produce any vestibular sensation while behavioral results are similar to Sham stimulation, both in total scores (Fig. 2a) and subscores of the SSQ (Fig. 2b), with no sway path changes (Fig. 3), with exception of a non-significant reduction of postural oscillations versus Sham and Baseline during Eyes Closed Condition (Fig. 3c). That 10 Hz was not effective at all in healthy subjects is not surprising, as only subjects with no motion sickness (or kinetosis) symptoms at the moment of evaluation were included in the current study.

However, in the areflexic patient, the 10 Hz tACS transiently reduced his chronic symptoms and signs of vestibular dysfunction (Fig. 5), especially during the eyes closed condition, when posture corrections cannot be supported by visual inputs: despite preliminary because of the single case, this observation opens the future

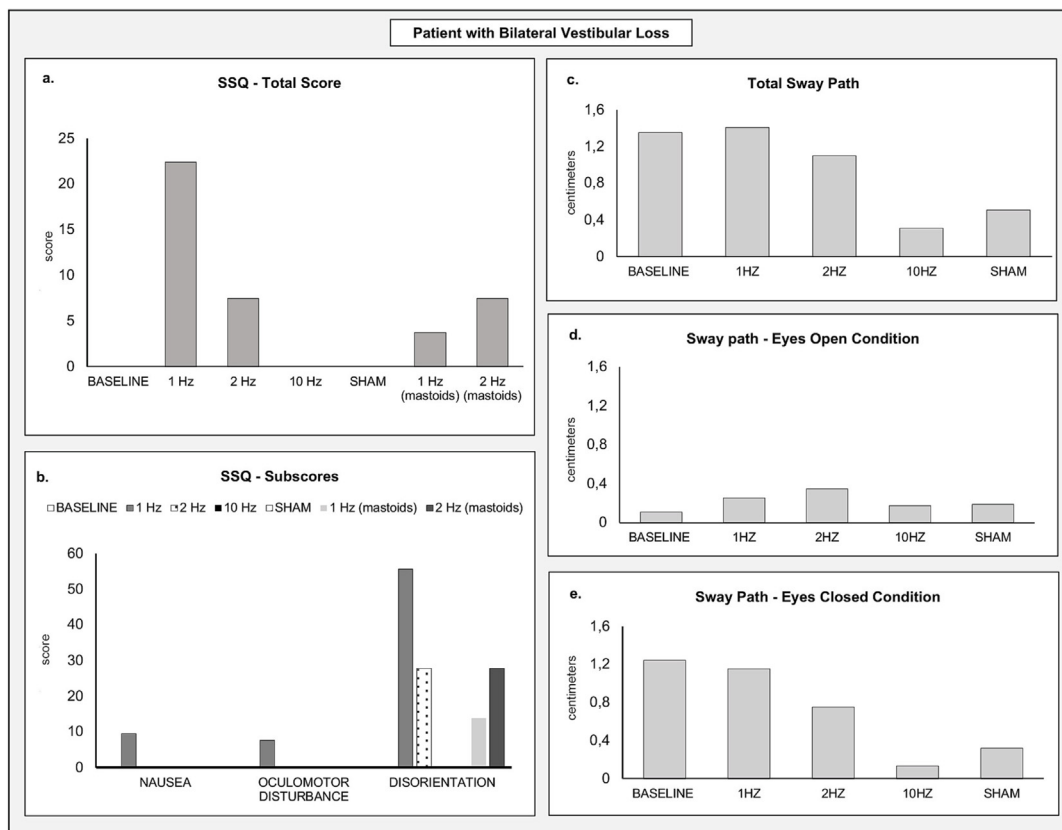


Fig. 5. Motion sickness and sway path in a patient with bilateral vestibular loss. Simulator Sickness Questionnaire (SSQ) outcomes regarding total score (a) and each subscore of nausea, oculomotor disturbance, and disorientation (b). Ratings > 20 must be considered severe symptomatology (Kennedy et al., 1993). Note that, despite bilateral vestibular deafferentation, transcranial alternating current stimulation (tACS) at 1 Hz drastically increased symptoms of motion sickness. The other panels summarize Sway Path (in centimeters) changes, as calculated by Neurocom Smart EquiTest stabilometric platform outcomes. Here is reported the total sway path (c) as well as eyes-open (d) and eyes-closed (e) conditions separately. The total sway path is relatively high in the baseline condition and it is maintained during 1 Hz-tACS and 2 Hz-tACS conditions while it was reduced during 10 Hz-tACS in the eyes-closed condition. Also, the eyes-closed condition seems characterized by a higher level of sway path compared to the eyes-open condition.

possibility to use these higher frequencies of stimulation to reduce vestibular symptoms, such as those related to cybersickness during virtual reality experiences (Benelli et al., submitted) or motion sickness, as recently suggested by the application of frontal-occipital 10 Hz-tACS for alleviating the symptoms of kinetosis (called “oscillating vertigo” or “mal de débarquement syndrome”) that may follow a prolonged exposition of the body to oscillations during the sea or air travels (Cha et al., 2022).

5. Conclusions

Despite some limitations considered in the body of the discussion, current results show how the human vestibular system can be tuned by weak electrical oscillations in a frequency range corresponding to the physiological cortical activity of the system itself. The increase of these oscillations is responsible for motion sickness symptoms and detectable postural sways in healthy subjects and in case of bilateral vestibular deafferentation. This should be taken

into account as a new side effect of tACS in future studies addressing cognitive functions. Higher frequencies of stimulation applied to the vestibular cortex may represent a new interventional option to reduce symptoms of motion sickness in different scenarios.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships with other people or organizations that could inappropriately influence their work.

Acknowledgments

The research has received partial funding from the European Commission H2020 Framework Programme under Grant No. 101017727 of the project “EXPERIENCE”.

Annex 1

SIMULATOR SICKNESS QUESTIONNAIRE (SSQ)
SIMPTOMS

1	General discomfort	0 1 2 3
2	Fatigue	0 1 2 3
3	Headache	0 1 2 3
4	Eyestrain	0 1 2 3
5	Difficulty focusing	0 1 2 3
6	Increased salivation	0 1 2 3
7	Sweating	0 1 2 3
8	Nausea	0 1 2 3
9	Difficulty concentrating	0 1 2 3
10	Fullness of head	0 1 2 3
11	Blurred vision	0 1 2 3
12	Dizzy (eyes open)	0 1 2 3
13	Dizzy (eyes closed)	0 1 2 3
14	Vertigo	0 1 2 3
15	Stomach awareness	0 1 2 3
16	Burping	0 1 2 3

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