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Transcranial Alternating Current Stimulation Reduces Network Hypersynchrony and Persistent Vertigo

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ABSTRACT

Objectives: Persistent oscillating vertigo that occurs after entrainment to periodic motion is known as Mal de Débarquement Syndrome (MdDS). Down-modulation of this oscillating vertigo is associated with reduction in long-range resting-state functional connectivity between fronto-parieto-occipital regions. In order to determine the association between this oscillating vertigo and hypersynchrony as measured by the auditory steady-state response (ASSR), we investigated the differences in ASSR between individuals with MdDS and healthy controls as well as the change in ASSR in individuals with MdDS before and after treatment with transcranial alternating current stimulation (tACS).

Materials and Methods: Individuals with treatment refractory MdDS lasting at least six months received single administrations of fronto-parieto-occipital tACS in an "n-of-1" double-blind randomized design: alpha-frequency in-phase, alpha-frequency antiphase, and gamma frequency antiphase control. The treatment protocol that led to the most acute reduction in symptoms and improved balance was administered for 10–12 sessions given over three days (each session 20-min at 2–4 mA).

Results: Twenty-four individuals with MdDS participated (mean age 53.0 ± 11.8 years [range: 22–66 years, median: 57.0 years]; mean duration of illness 38.6 ± 53.4 months [range: 6–240 months, median: 18.0 months]). Individuals with MdDS had elevated ASSR compared to healthy controls at baseline ($t_{11} = 5.95$, $p < 0.001$). There was a significant decrease in the 40 Hz-ASSR response between responders compared to nonresponders to tACS (*t*-test, $t_{15} = -2.26$, $p = 0.04$). Both in-phase and anti-phase alpha tACS lead to symptom improvement but only antiphase alpha-tACS led to a significant decrease of 40 Hz-ASSR (*t*-test, $t_{12} = -9.6$, $p < 0.001$).

Conclusions: Our findings suggest that tACS has the potential to reduce network-level hypersynchrony and pathological susceptibility to entrainment by sensory input. To the best of our knowledge, this is the first successful demonstration of desynchronization by noninvasive brain stimulation leading to reduced vertigo. Other disease states associated with pathological functional coupling of neuronal networks may similarly benefit from this novel approach.

Keywords: Auditory steady-state response, Mal de Débarquement Syndrome, persistent oscillating vertigo, transcranial alternating current stimulation

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INTRODUCTION

Oscillating stimuli are abundant in our environment from both natural and human-made sources. Sound, motion, light, and electrical signals have the potential to interact with the nervous system through entrainment even when they are not consciously perceived (1).

In particular, exposure to wave motion during water-based travel has been known for centuries to cause postmotion oscillating vertigo, often lasting for months or years (2). This postmotion vertigo usually feels as if one were still on the moving vessel despite being on stable ground. When brief, the phenomenon is well recognized by the term, ''landsickness'' (3). When persistent, this form of oscillating vertigo is known as Mal de Débarquement Syndrome (MdDS), or ''sickness of disembarkation,'' (2,4). Neuroimaging studies in MdDS show that it may be a human model of entrainment to motion that leads to prolonged changes in nervous system function (5,6).

MdDS usually occurs after exposure to low amplitude oscillating motion, such as from water, air, or land-based travel (7). The resulting oscillating vertigo, described as ''rocking,'' ''bobbing,'' or ''swaying,'' only improves with re-exposure to passive motion such as driving in a car or getting back on the initial triggering stimulus (2,4).

The entorhinal cortex has been proposed as an important substrate in the maintenance of persistent MdDS since it is entrainable with periodic stimulation, is functionally connected to a large swath of neocortex, and plays a critical role in updating the hippocampus on environmental features relevant for navigation (8,9). Hypermetabolism of the left entorhinal cortex and altered resting-state functional connectivity between the entorhinal cortex and neocortical areas have been reported in individuals with MdDS (5,6,10). Symptom reduction with repetitive transcranial magnetic stimulation (rTMS) over dorsolateral prefrontal cortex correlates with reduction in functional connectivity between the entorhinal cortex and the posterior parietal sensory association area including the default mode network as well as between front-parieto-occipital networks that may be involved in spatial attention processing (6,10,11).

Individuals with MdDS can experience many symptoms beyond just vertigo, however including headache, visual motion intolerance, fatigue, cognitive slowing, and tinnitus (12). This may be partially explained by the widespread connectivity of the entorhinal cortex with prefrontal and sensory association areas (13,14). The relatively innocuous motion stimuli that trigger MdDS may thus affect widespread brain regions with effects that are measurable in a cross-modal way.

We tested the hypothesis of whether hypersynchrony as measured by the auditory steady-state response (ASSR) in individuals with MdDS correlates with symptom status. The ASSR measures the neural response in the auditory cortex to periodic sound stimuli and represents a measure of stimulus-driven synchronization in cortical networks. ASSR at 40 Hz has been shown to be a potential biomarker for complex cognitive processing, sleep state, and disorders such as bipolar disorder and schizophrenia, and may be thus be used as a general marker of brain synchrony rather than specifically related to the auditory system (15-19).

In order to determine how ASSR relates to symptom state in MdDS, we compared a group of individuals with MdDS to age-matched healthy controls and determined the relationship between ASSR change and modification of the oscillating vertigo perception with transcranial alternating current stimulation (tACS). We applied three different tACS conditions in order to provide physiologically counter-balanced stimulations (antiphase alpha tACS, in-phase alpha tACS, and antiphase gamma tACS). These stimulations were given in randomized order between participants in a double-blind manner with a protocol designed to directly test whether antiphase stimulation at the alpha frequency (vs. gamma) is the critical paradigm to drive symptom related normalization in hypersynchrony. We hypothesized that antiphase alpha-tACS would be the most effective in decreasing auditory hyperexcitability in individuals with MdDS consistent with past studies that showed decreased synchrony in the high-alpha band correlating with MdDS symptom improvement (10). Our findings suggest that MdDS is a multinetwork disorder driven by periodic motion input in which reduction of hypersynchrony with alpha tACS may be a therapeutic option.

MATERIALS AND METHODS

Study Design

This study was performed at the Laureate Institute for Brain Research in Tulsa, OK. Study procedures were completed according to Declaration of Helsinki guidelines and approved by Western IRB (www.wirb.com). Participants provided written informed consent and were recruited under ClinicalTrials.gov study (NCT02540616). This study used tACS as a research intervention and was completed between July 2017 and June 2019. Inclusion criteria were as follows: 1) persistent oscillating vertigo that started within 48-hours after disembarking from sea, air, or land based moving vessel; 2) symptom duration of at least six months; and 3) no other cause for symptoms after evaluation by a neurologist or otolaryngologist with appropriate testing to rule out other causes of symptoms. Exclusion criteria were as follows: 1) an unstable medical or psychiatric condition such as a history of bipolar disorder or psychosis; 2) pregnant or planning to become pregnant during study participation; 3) contraindications to receiving tACS in this blinded study included skin disorders (including sunburns on the head) or prior experience with tACS; and 4) an inability to complete all study related testing. All participants remained on their baseline medications with no change in dose for eight weeks prior to data collection.

EEG Recoding and Auditory Task

Electroencephalography (EEG) data were obtained at baseline and after all tACS sessions were completed. EEG was recorded with 128 channels (Brain Products GmbH, Gilching, Germany) at a

sampling rate of 5 kHz. The center 23 electrodes were used for ASSR calculation (Supporting Information Fig. S1). An auditory-click train task was implemented in Presentation (Neurobehavioral Systems, Inc., Berkeley, CA) to obtain the ASSR. The auditory stimuli were delivered binaurally through air-conducting earphone tubes ER·3C (Etymotic Research Inc., Elk Grove Village, IL) at sound pressure level (SPL) of 90 dB. Participants fixated on a crosshair on a computer monitor while listening to 500 msec long click-trains at rates of 10, 20, 30, and 40 Hz. Subsequent click-trains were separated by a jittered interval between 450 msec and 550 msec of silence. The order of the click-train frequencies was pseudo-random and balanced, for a total of 100 click-trains for each frequency and a grand total of 400 click-trains. Synchronization between the auditory stimulus presentation and EEG acquisition was achieved by splitting the stereo output of the sound card into two separate mono outputs. One channel was used for the actual auditory stimuli, while the other channel was recorded with the EEG data. Offline processing was performed in EEGLAB with custom-built scripts in MATLAB R2019a as follows: 1) the data were band-pass filtered from 1 to 50 Hz and down-sampled to 500 Hz; 2) the data were preprocessed by an artifact subspace reconstruction algorithm to identify high-variance data epochs and reconstruct missing data; 3) bad channels that were found in the previous step were interpolated and common average referencing was performed; 4) infomax independent component analysis (ICA) (20) was performed to remove eye blinks, eye movement, muscle activity, and heartbeat artifact; 5) ICA components were visually inspected and noise components were manually selected for rejection. The selection for ICA components were verified by the ICLabel classification (21); and 6) the preprocessed data were epoched from −0.2 to 0.6 sec, resulting in 100 trials of click-trains for each frequency (10, 20, 30, and 40 Hz). Time-frequency analysis was performed using Morlet wavelet transform (seven cycles). Amplitudes and phase information were obtained

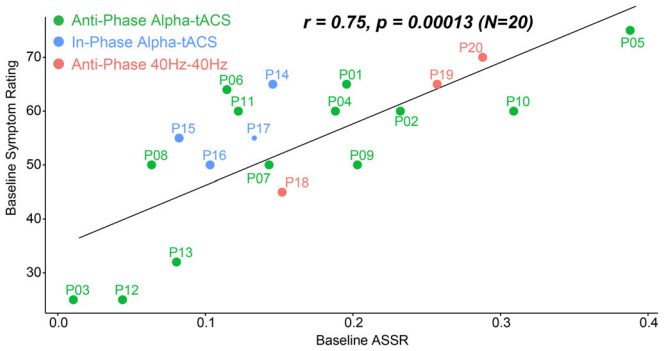

Figure 2. Correlation between symptom rating and ASSR at baseline (day 1). Scatter plot of symptom rating scores and baseline ASSR across all participants for each group (antiphase alpha-tACS: $N = 13$, in-phase alpha-tACS: $N = 4$, antiphase 40 Hz-tACS: $N = 3$). [Color figure can be viewed at wileyonlinelibrary.com]

and intertrial phase coherence (ITPC) of ASSR was computed using the phase information across trials as:

$$\mathrm{ITPC}(c,f,t) = \left| \frac{1}{n} \sum_{e=1}^{n} \frac{X_e(c,f,t)}{|X_e(c,f,t)|} \right|,$$

where $X_e(c, f, t)$ is the spectral estimate of epoch e at channel c, frequency f, and time t (n = total number of epochs). In this report, we only present ITPC of ASSR in response to 40 Hz auditory click trains.

Transcranial Alternating Current Stimulation

We used the XCSITE 100 stimulator (Pulvinar Neuro LLC, Durham, NC) and applied three different tACS conditions: antiphase alpha-tACS and two counter-balanced conditions (in-

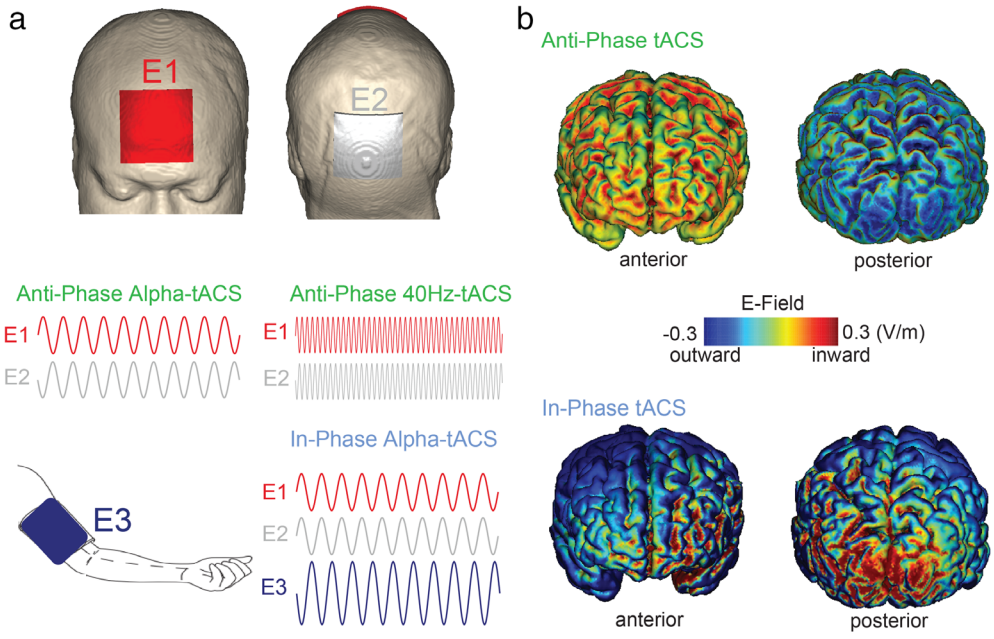

Figure 1. Stimulation montage, waveforms, and electric field distribution. (a) Stimulation montage and waveforms for antiphase alpha-tACS, in-phase alpha-tACS, and antiphase 40 Hz-tACS. Electrodes E1 and E2 deliver antiphase waveforms (1 mA zero-to-peak sine-wave) at alpha and 40 Hz frequency. For in-phase alpha-tACS, electrodes E1 and E2 deliver in-phase waveforms (2 mA zero-to-peak sine-wave) and electrode E3 on the left upper arm were used as a return electrode. (b) Electric field distribution of inward/outward electric field for antiphase tACS (top) and in-phase tACS (bottom) at the peak of the tACS waveform. [Color figure can be viewed at wileyonlinelibrary.com]

phase alpha-tACS and anti-phase gamma [40 Hz] tACS). For antiphase alpha-tACS, we applied two electrodes (10 × 10 cm) on the frontal and parieto-occipital regions (Fig. 1a) at 10 Hz, at the individual alpha frequency (IAF), or slightly above the IAF by rounding up to the nearest 0.5 Hz (IAF+) based on stimulation capabilities at the time (the current device capabilities now allow stimulation control within 0.1 Hz). For the antiphase 40 Hz-tACS control, the electrode configuration was the same as the antiphase alpha-tACS configuration. The return electrode was placed on the left upper arm for the in-phase condition (Fig. 1a). A split electrode was used to divide the current going to the head so that current was delivered evenly between the frontal and parieto-occipital electrodes (Supporting Information Fig. S2). The stimulations were given for 20 min at 1 mA zero-to-peak intensity for anti-phase and 2 mA zero-to-peak for in-phase stimulation conditions including 30-sec of ramp-up and ramp-down periods. Twelve individuals were stimulated at 10 Hz, six at their IAF, and six at IAF+ (0.1–0.4 Hz above IAF). These different frequencies were investigated to determine whether the IAF could be an important variable in treatment outcome. Electric field distributions at the peak of the stimulated waveforms were calculated for antiphase (Fig. 1b, top) and in-phase (Fig. 1b, bottom) tACS conditions, respectively (tES Lab 2.0, Neurophet Inc., Seoul, South Korea) using a T1-weighted MRI template from the human connectome project. The MRI data were segmented by eight tissues (cerebrum gray matter, cerebrum white matter, cerebellar gray matter, cerebellar white matter, ventricles, CSF, skull, and skin) and each tissue was assigned isotropic conductivity values. We used the finite element method with tetrahedron volume meshes. The number of tetrahedron mesh was about 4.3 million and the quasi-static Maxwell's equation was used.

The participants were given one session each of these three conditions in randomized order. Three conditions can be permuted into six different orders (1-2-3, 3-2-1, 2-3-1, etc.). Each order of stimulation was given to four participants culminating in a study group of 24 participants. The stimulation order for any individual participant was determined at the start of the study (July 2017) by a research coordinator who was not involved in the data analysis. The Principal Investigator of the study and the data analyst were unaware of which stimulation protocol each participant received until the study was unblinded at study completion (June 2019).

During the stimulation sessions, the participants were seated in a back supported chair and were facing a window. Stimulation sessions were performed with eyes closed but enough sunlight penetrated the eyelids that the phosphenes induced by the stimulations reduced the differences in phosphene perception across the three conditions. An active control (gamma frequency) was used explicitly in order to control for phosphene perception but at a frequency too high for entrainment. Participants were assessed for change in intensity of the oscillating vertigo for 60-min after each session before proceeding to the next condition. They chose the condition that most significantly reduced their symptoms or did not make their symptoms worse. Only treatment conditions that improved or did not worsen symptom

Table 1. Participant Identification, Protocol Choice, Alpha Stimulation Category, Change in Symptoms, and Change in ASSR.

Subject ID	Protocol	Group assignment	Baseline VAS	VAS change	Baseline ASSR	ASSR change
P01	Antiphase	10	65	−20	0.195705	−0.14957
P02	Antiphase	10	60	−10	0.23212	−0.13212
P03	Antiphase	10	25	−20	0.010437	−0.12201
P04	Antiphase	10	60	−30	0.188099	−0.1881
P05	Antiphase	10	75	−5	0.387894	−0.08789
P06	Antiphase	10	64	−4	0.114569	−0.11457
P07	Antiphase	IAF+	50	−10	0.143137	−0.10314
P08	Antiphase	IAF+	50	−25	0.063531	−0.15635
P09	Antiphase	IAF	50	−15	0.203097	−0.1031
P10	Antiphase	IAF	60	−5	0.308926	−0.10893
P11	Antiphase	IAF+	60	−25	0.122317	−0.12232
P12	Antiphase	IAF	25	7.5	0.043786	−0.01044
P13	Antiphase	IAF	32	4	0.08037	−0.08037
Mean			52.0	−12.1	0.161076	−0.113762
s.d.			15.7	11.6	0.107437	0.042633
P14	In-phase	10	65	−20	0.145705	−0.04448
P15	In-phase	IAF+	55	−45	0.08212	0.005635
P16	In-phase	IAF+	50	−20	0.103137	0.030967
P17	In-phase	IAF	55	−10	0.133137	0.051881
DM1*	In-phase	10	45	−5	na	na
DM2*	In-phase	10	80	−30	na	na
DM3*	In-phase	IAF	30	5	na	na
Mean			54.3	−17.9	0.116025	0.011001
s.d.			15.7	16.5	0.028806	0.041540
P18	40 Hz	10	45	−10	0.152007	0.025705
P19	40 Hz	10	65	−5	0.25705	0.081879
P20	40 Hz	10	70	0	0.287894	0.070893
DM4*	40 Hz	IAF+	65	10	na	na
Mean			61.3	−1.3	0.232317	0.059492
s.d.			11.1	8.5	0.071240	0.029772

*DM = Data missing for ASSR.

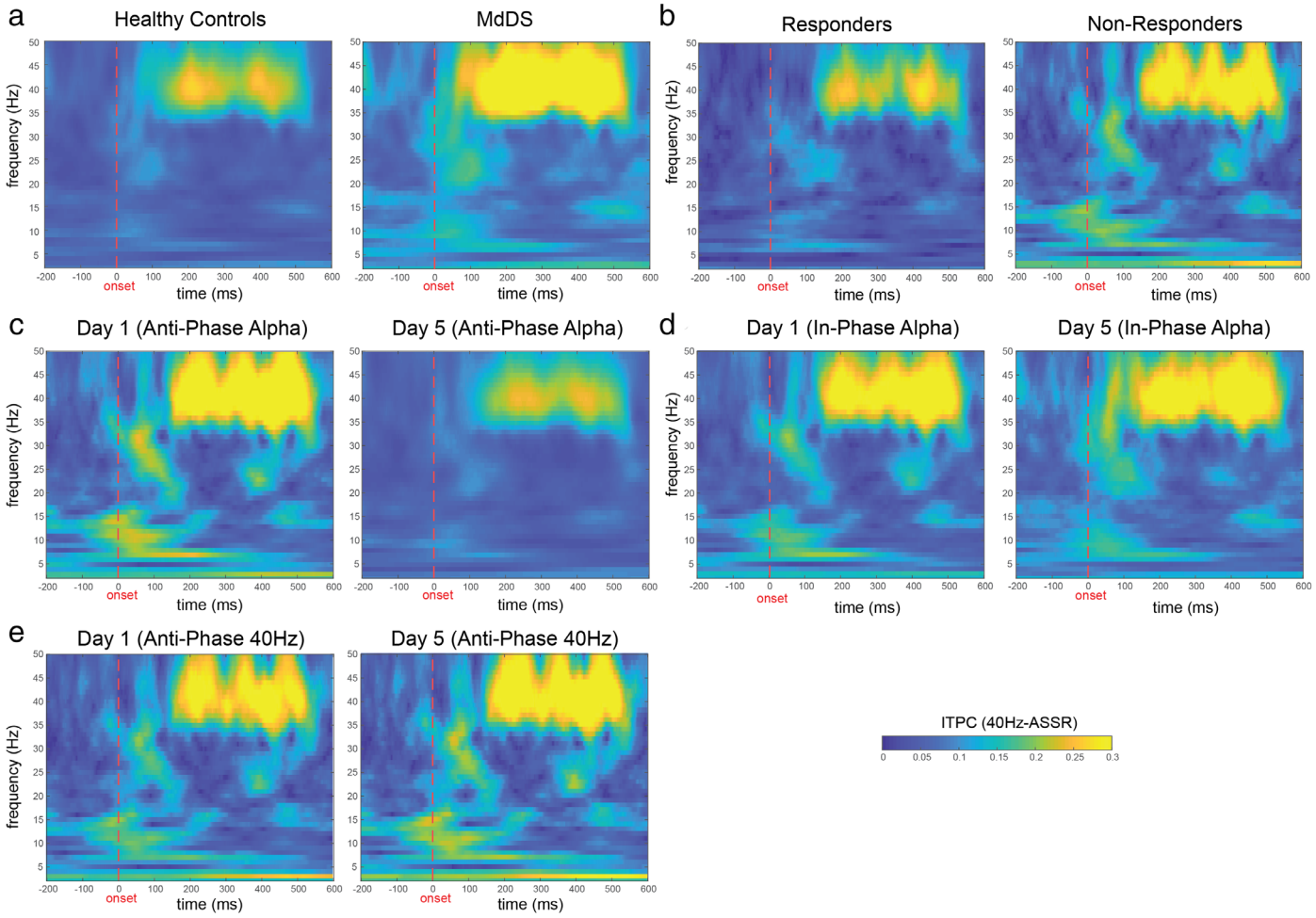

Figure 3. ASSR in participants with MdDS and healthy controls, treatment response, and treatment allocation by response to tACS. (a) A comparison of 40 Hz-ASSR in participants with MdDS and healthy participants at baseline. Intertrial phase coherence (ITPC) was used to quantify 40 Hz-ASSR. (b) ITPC of 40 Hz-ASSR in responders and nonresponders after 10–12 sessions of tACS. (c–e) ITPC pretreatment and posttreatment (after 10–12 sessions of tACS) in the antiphase alpha-tACS (c), in-phase alpha-tACS (d), and antiphase 40 Hz-tACS (e) groups, respectively. [Color figure can be viewed at wileyonlinelibrary.com]

severity were repeated the next day. If the participant was not sure about the best condition, two conditions could be repeated the following day but in the reverse order in which they were administered on the test day. Therefore, some participants received two-fewer "stacked" treatment sessions than others. Each participant thus received 10–12 sessions of 20-min of tACS over three days, with all sessions given in the mornings and a 60-min rest period in between sessions.

Participants rated symptoms on a 100-point visual analog scale (VAS) of symptom severity in which 0 reflected no oscillating vertigo and 100 reflected symptoms so severe that standing was not possible. On this 100-point VAS, a decrease of ≥10 was considered to be a response and a decrease of <10 was considered to be a nonresponse, consistent with prior studies showing that this is the difference that participants found to be meaningful (22,23).

RESULTS

Participant Characteristics

Twenty-four individuals with MdDS (23 women, one man) were recruited. Mean age at the time of the study was 53.0 ± 11.8 years (range: 22–66 years, median: 57.0 years); mean duration of illness = 38.6 ± 53.4 months (range: 6–240 months, median: 18.0 months). Triggers included water-based travel (e.g., boat or cruise) in 15, air-travel in 9, and land-based travel in 1. One individual had overlapping triggers and was counted in both the water and air groups. Of the 24 participants, 13 chose antiphase alpha-tACS, 7 chose in-phase alpha-tACS, and 4 chose antiphase 40 Hz-tACS. Complete sets of pretreatment and posttreatment EEG data were available for 13 antiphase alpha-tACS, 4 in-phase alpha-tACS, and 3 anti-phase 40 Hz-tACS because some data were lost due to either poor EEG quality or auditory equipment malfunction. Six healthy women were recruited as control participants. Mean age was 45.3 ± 6.7 years (range 36–54 years, median: 45.5 years). Unpaired *t*-test with MdDS group, $p = 0.140$.

ASSR Calculation

To identify how auditory responses differed in participants with MdDS and healthy controls, we computed intertrial phase coherence (ITPC) as a measure of ASSR in response to 40 Hz auditory click-trains (40 Hz-ASSR). We observed a positive correlation between baseline symptom severity and the 40-Hz ASSR ($r = 0.75$, $p = 0.0013$, $N = 20$) (Fig. 2) (Table 1). Concurrently, we found that participants with MdDS showed elevated 40 Hz-ASSR compared to the healthy controls (Fig. 3a; Welch's *t*-test, $t_{11} = 5.95$, $p < 0.001$).

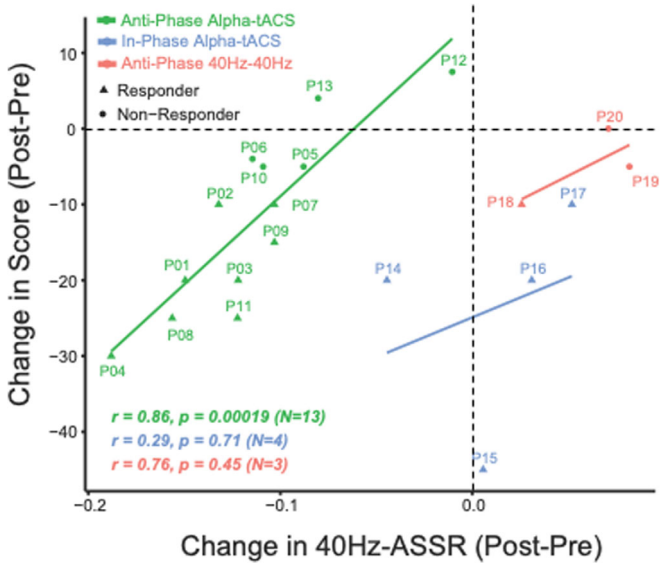

Figure 4. Correlation between symptom rating change and ASSR change. Scatter plot of changes in symptom rating scores and changes in ITPC across all participants for each group (antiphase alpha-tACS: $N = 13$, in-phase alpha-tACS: $N = 4$, antiphase 40 Hz-tACS: $N = 3$). Colored lines indicate a least-squares fit line to the scatter plot for each group. The zero reference is highlighted by dotted lines. [Color figure can be viewed at wileyonlinelibrary.com]

Table 2. Change in VAS After tACS Relative to the IAF.

	Assigned group	*N*	Mean VAS Change ± s.d.
Group 1	10 Hz	12	−13.25 ± 10.38
Group 2	IAF	6	−2.25 ± 9.131
Group 3	IAF+	6	−19.17 ± 18.28
Post hoc Tukey HSD			
Group 1 to group 2 Q = 2.36, $p = 0.2391$			
Group 2 to group 3 Q = 3.64, $p = 0.0450$			
Group 1 to group 3 Q = 1.27, $p = 0.6466$			
	Stimulation relative to IAF	*N*	
Group 1	0 Hz	8	−5.44 ± 10.08
Group 2	0.1–1.3 Hz	11	−21.27 ± 11.99
Group 3	>1.3 Hz	5	−2.00 ± 7.58
Post hoc Tukey HSD			
Group 1 to group 2 Q = 4.00, $p = 0.0263$			
Group 2 to group 3 Q = 4.86, $p = 0.0067$			
Group 1 to group 3 Q = 0.87, $p = 0.8145$			

Of the three groups, 8 of 13 in the antiphase alpha (data available for 13), four of seven in the in-phase alpha (data available for four), and one of four in the 40-Hz control (data available for three) were considered to be responders when using a criterion of ten points or more decrease in symptom severity on the VAS. We found a significant difference in changes of the 40 Hz-ASSR response between responders and non-responders across all groups (Fig. 3b; Welch's *t*-test, $t_{15} = -2.26$, $p = 0.04$). In the subgroup analysis, we found that only the antiphase alpha-tACS group showed a significant difference of 40 Hz-ASSR post-treatment compared to pretreatment (Fig. 3c, Welch's *t*-test, $t_{12} = -9.6$, $p < 0.001$). The counter-balanced tACS conditions did not show such a significant difference (Fig. 3d, in-phase alpha-tACS, $p > 0.05$, Fig. 3e, antiphase 40 Hz-tACS, $p > 0.05$). These calculations were repeated for the 10 Hz stimulation frequency, but there were no activations (Supporting Information Fig. S3).

To investigate the relationship between changes in symptom rating scores and changes in 40 Hz-ASSR on an individual level, we computed the Pearson correlation coefficient between ASSR and symptom rating and found a significant positive correlation for the anti-phase alpha-tACS group but not for the other groups Fig. 4 (antiphase alpha-tACS: $r = 0.86$, $p = 0.00019$, $N = 13$; in-phase alpha-tACS: $r = 0.29$, $p = 0.71$, $N = 4$; antiphase 40 Hz-tACS: $r = 0.76$, $p = 0.45$, $N = 3$) (Table 1).

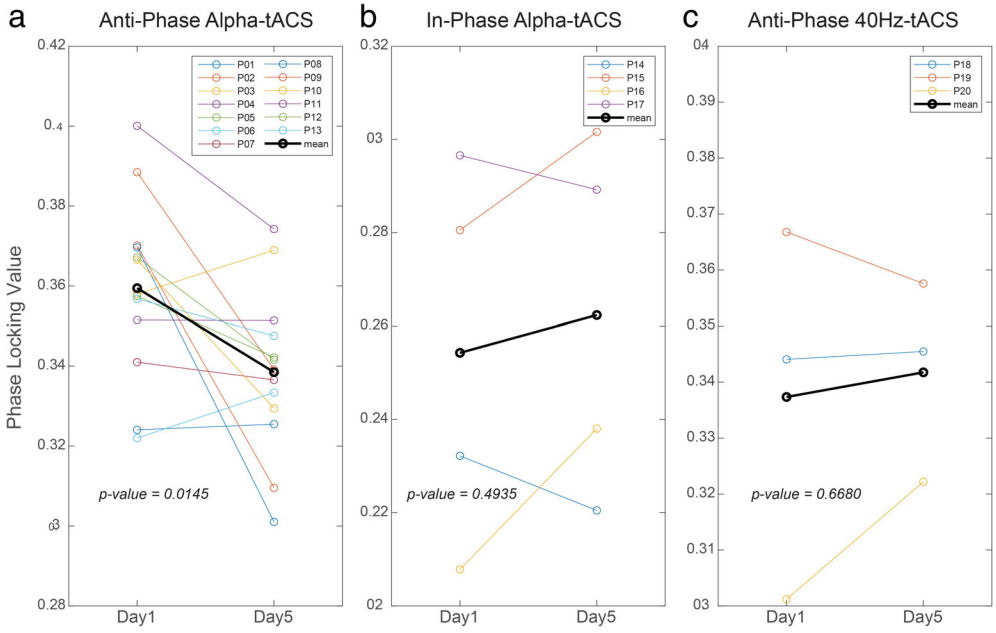

Figure 5. Change of the phase locking value between frontal and parieto-occipital regions in the alpha-frequency band for (a) antiphase alpha-tACS, (b) in-phase alpha-tACS, and (c) antiphase 40 Hz-tACS from day 1 to day 5. [Color figure can be viewed at wileyonlinelibrary.com]

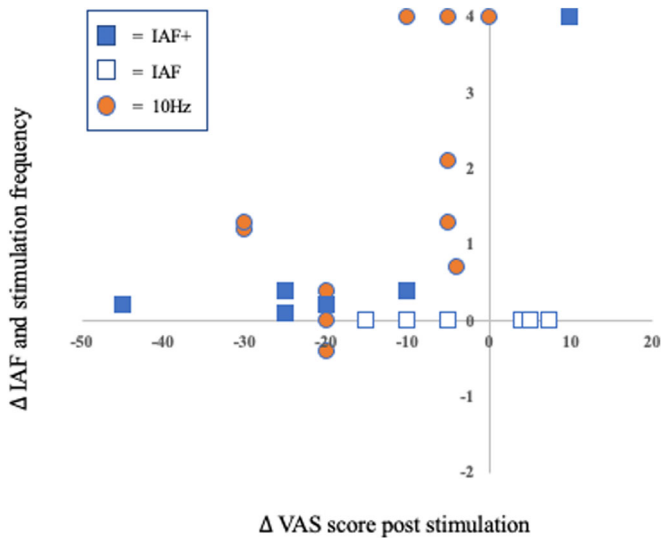

Figure 6. Correlation between change in VAS scores and difference in treatment stimulation frequencies relative to the participant's IAF at Oz. [Color figure can be viewed at wileyonlinelibrary.com]

Phase Synchrony

In order to determine whether tACS changed the pattern of synchrony between frontal and parieto-occipital regions, we computed the phase locking value (PLV) as a measure of synchronization between these regions in the alpha band. We used ten frontal and ten parieto-occipital EEG channels during the task period (0–500 msec) and averaged PLV from each channel-pair. We found a significant reduction in the PLV values in the antiphase tACS condition only ($p = 0.0145$) (Fig. 5).

Response Related to Stimulation Frequency

Twelve individuals were treated with an initial strategy of using a standard 10 Hz stimulation frequency, six were treated at their IAF, and six were treated at IAF+. The differences across groups for VAS change trended toward significance $F_{2,21} = 2.87$, $p = 0.0785$ with the greatest decrease in VAS occurring in the group assigned to the IAF+ strategy (Table 2). Post hoc Tukey HSD test indicated that the only significant difference between the three groups was between the IAF and IAF+ groups.

Because 10 Hz could fall at, above, or below the participant's IAF, we recalculated how participants were treated relative to their IAF regardless of the group to which they were initially assigned. In most cases, 10 Hz was above and near the IAF. However, in one case, it was below and, in one case, it was 2.1 Hz above. Figure 6 shows the distribution of symptom responses relative to the difference between the stimulated frequency and the IAF frequency at Oz. The "4" value reflects the participants who chose the 40 Hz antiphase protocol. Changes in VAS responses relative to their IAF are presented in Table 2. The differences across groups for VAS change were significant $F_{2,21} = 7.90$, $p < 0.0027$ with post hoc Tukey HSD test indicating that the differences were significant between the group treated at 0.1–1.3 Hz above the IAF (group 2) and the other two groups.

DISCUSSION

We investigated whether the persistent oscillating vertigo perception in individuals with MdDS could be modulated with tACS and result in a change in synchrony as measured by ASSR. We found elevated ASSR in participants with MdDS compared to healthy controls at baseline and higher levels of ASSR in individuals with higher symptoms. By applying fronto-parieto-occipital alpha-tACS to suppress the oscillation perception, we found that ASSR was also suppressed. The degree to which the ASSR was suppressed was a function of the response to treatment; individuals with MdDS who had greater reduction in motion perception also had greater reduction in ASSR. The most effective paradigm to achieve this suppression was anti-phase alpha tACS, but in-phase tACS could also suppress the vertigo in some individuals. In some individuals, in-phase stimulation was more effective than antiphase stimulation though leading to a smaller decrease in the ASSR response. Given the differences in e-field patterns generated by in-phase vs. antiphase stimulation and differences in long-range transduction time, in-phase stimulation could theoretically lead to desynchronization in some individuals.

Our study investigated ASSR changes after several tACS sessions in individuals with a clinical syndrome, pointing to plastic reorganization of the underlying brain networks by tACS and a potential therapeutic role (24). In addition to our study, another group has recently shown that in-phase alpha-tACS reduces the ASSR, though this study was performed in healthy controls (25). Despite the differences in experimental design, two groups have now independently found successful target engagement of the ASSR by alpha-tACS.

Further applications of ASSR to other clinical syndromes are needed in order to determine whether ASSR desynchronization is a marker of treatment by tACS and the degree to which it correlates with symptom status. Hypersynchrony has been proposed as a pathological signature of brain disorders including depression, epilepsy, and Parkinson's disease with one hypothesis suggesting that long-range hypersynchrony limits the expression of intrinsic brain rhythms (26-29). The reduction of this hypersynchrony through brain stimulation methods may be able to return regional functioning back to a native state.

In a subanalysis, we found that setting the stimulation frequency at slightly above the IAF was more effective than stimulating at the IAF. In general, the best responses were observed when the stimulating frequency was just above the IAF. The mechanism of the treatment effect could involve entrainment of the latent rhythm as well as spike-timing related changes in neuronal plasticity, both being influenced by staying within the "Arnold tongue," of entrainment frequencies (30-32). A further area of study would involve titrating the difference between the IAF and the stimulation settings to optimize the outcome.

This study has some limitations. Due to the rarity of MdDS, the overall number of participants in the study was limited. Recruitment took two years, comparable to prior noninvasive brain stimulation studies in MdDS (22,23,33). In addition, the number of participants in the comparison groups was reduced due to data loss. Most of the relationship between symptom reduction and ASSR reduction was found in the antiphase alpha-tACS group since this was the paradigm chosen by most participants. Though this general trend was noted in all groups, it was only statistically significant in the antiphase alpha-tACS group due to the higher number of participants. The healthy control group was small and somewhat younger than the MdDS group. Although these were not statistically significant differences, a higher number of participants in all of the groups might have led to a greater ability to detect smaller degrees of differences, particularly in the in-phase alpha-tACS group.

Second, though the montages were the same across stimulation sessions, the electric field distributions for the antiphase and in-phase conditions were not equivalent, indicating that the effects of

stimulation could not simply be attributed to a synchronizing or desynchronizing effect under the electrodes but could be due to more global effects induced by antiphase stimulation. Even though the induced electric field distribution modeling did not indicate how stimulation modulates synchronization of the brain, more sophisticated simulations in future studies would attempt to create similar electric field distributions between conditions.

Finally, nonspecific effects from peripheral nerve stimulation are possible in transcranial electrical stimulation and can confound treatment responses by adding sensory contamination and by acting as entry points for neuromodulating effects (34). While the 40 Hz control condition did not yield significant clinical effects, bottom-up effects from cutaneous nerves that are frequency dependent are potential concerns with all transcranial stimulation studies (35).

CONCLUSION

The findings from this study indicate that successful reduction of oscillating vertigo with tACS by driving long-range desynchronization correlates with a reduction in the ASSR with the strongest correlation observed with anti-phase tACS. Because in-phase tACS was more effective in some participants, however, n-of-1 studies could be efficient methods to understanding how stimulation parameters can be tailored to targeted physiological parameters. Some of these involve optimizing stimulation frequency relative to the IAF. These data show evidence for symptom severity-related hypersynchrony reversed with tACS in a disorder initially triggered by entrainment to oscillating motion. To the best of our knowledge, this is the first demonstration of how tACS may be used to improve clinical symptoms by reducing pathological oscillatory coupling in brain networks. While the generalizability of these data to other brain disorders is unknown, a similar approach may be effective in other conditions marked by pathological functional coupling.

DATA AVAILABILITY

The source data may be requested through a collaborative agreement with the authors after primary analyses have been completed.

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Authorship Statements

Dr. Ahn wrote the initial draft, analyzed the data, prepared figures, and responded to the reviewers. Ms. Gleghorn and Mr. Doudican were involved in recruitment, data collection, and revision of the manuscript. Dr. Frohlich was involved in study design, design of the ASSR task, and revision of the manuscript. Dr. Cha was involved in study design, recruitment, data collection, revision of manuscript, and responding to reviewers. All authors approved the final version of the manuscript.

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REFERENCES

1. Thut G, Schyns PG, Gross J. Entrainment of perceptually relevant brain oscillations by non-invasive rhythmic stimulation of the human brain. *Front Psychol* 2011;2:170.
2. Cha YH. Mal de debarquement. *Semin Neurol* 2009;29:520–527.
3. Hain TC, Cherchi M. Mal de debarquement syndrome. *Handb Clin Neurol* 2016; 137:391–395.
4. Brown JJ, Baloh RW. Persistent mal de debarquement syndrome: a motion-induced subjective disorder of balance. *Am J Otolaryngol* 1987;8:219–222.
5. Cha YH, Chakrapani S, Craig A, Baloh RW. Metabolic and functional connectivity changes in mal de debarquement syndrome. *PLoS One* 2012;7:e49560.
6. Yuan H, Shou G, Gleghorn D, Ding L, Cha YH. Resting state functional connectivity signature of treatment effects of repetitive transcranial magnetic stimulation in mal de debarquement syndrome. *Brain Connect* 2017;7:617–626.
7. Cha YH, Cui YY, Baloh RW. Comprehensive clinical profile of mal de Debarquement syndrome. *Front Neurol* 2018;9:261.
8. Fransen E, Tahvildari B, Egorov AV, Hasselmo ME, Alonso AA. Mechanism of graded persistent cellular activity of entorhinal cortex layer v neurons. *Neuron* 2006;49:735–746.
9. Nilssen ES, Doan TP, Nigro MJ, Ohara S, Witter MP. Neurons and networks in the entorhinal cortex: a reappraisal of the lateral and medial entorhinal subdivisions mediating parallel cortical pathways. *Hippocampus* 2019;29:1238–1254.
10. Cha YH, Shou G, Gleghorn D, Doudican BC, Yuan H, Ding L. Electrophysiological signatures of intrinsic functional connectivity related to rTMS treatment for mal de debarquement syndrome. *Brain Topogr* 2018;31:1047–1058.
11. Ding L, Shou G, Yuan H, Urbano D, Cha YH. Lasting modulation effects of rTMS on neural activity and connectivity as revealed by resting-state EEG. *IEEE Trans Biomed Eng* 2014;61:2070–2080.
12. Cha YH, Brodsky J, Ishiyama G, Sabatti C, Baloh RW. Clinical features and associated syndromes of mal de debarquement. *J Neurol* 2008;255:1038–1044.
13. Insausti R. Comparative anatomy of the entorhinal cortex and hippocampus in mammals. *Hippocampus* 1993;3:19–26.
14. Takeyama H, Matsumoto R, Usami K et al. Human entorhinal cortex electrical stimulation evoked short-latency potentials in the broad neocortical regions: evidence from cortico-cortical evoked potential recordings. *Brain Behav* 2019;9: e01366.
15. Saupe K, Widmann A, Bendixen A, Muller MM, Schroger E. Effects of intermodal attention on the auditory steady-state response and the event-related potential. *Psychophysiology* 2009;46:321–327.
16. Rass O, Krishnan G, Brenner CA et al. Auditory steady state response in bipolar disorder: relation to clinical state, cognitive performance, medication status, and substance disorders. *Bipolar Disord* 2010;12:793–803.
17. Rass O, Forsyth JK, Krishnan GP et al. Auditory steady state response in the schizophrenia, first-degree relatives and schizotypal personality disorder. *Schizophr Res* 2012;136:143–149.
18. Khuwaja GA, Haghighi SJ, Hatzinakos D. 40-Hz ASSR fusion classification system for observing sleep patterns. *EURASIP J Bioinform Syst Biol* 2015;2015:2.
19. Parciauskaite V, Voicikas A, Jurkuvenas V et al. 40-Hz auditory steady-state responses and the complex information processing: an exploratory study in healthy young males. *PLoS One.* 2019;14:e0223127.
20. Jung TP, Makeig S, Humphries C et al. Removing electroencephalographic artifacts by blind source separation. *Psychophysiology* 2000;37:163–178.
21. Pion-Tonachini L, Kreutz-Delgado K, Makeig S. The ICLabel dataset of electroencephalographic (EEG) independent component (IC) features. *Data Brief* 2019;25: 104101.
22. Cha YH, Deblieck C, Wu AD. Double-blind sham-controlled crossover trial of repetitive transcranial magnetic stimulation for mal de debarquement syndrome. *Otol Neurotol* 2016;37:805–812.
23. Cha YH, Gleghorn D, Doudican B. Occipital and cerebellar theta burst stimulation for mal de debarquement syndrome. *Otol Neurotol* 2019;40:e928–e937.
24. Riddle J, McPherson T, Atkins AK, Walker CP, Ahn S, Frohlich F. Brain-derived neurotrophic factor (BDNF) polymorphism may influence the efficacy of tACS to modulate neural oscillations. *Brain Stimul* 2020;13:998–999.
25. Hyvarinen P, Choi D, Demarchi G, Aarnisalo AA, Weisz N. tACS-mediated modulation of the auditory steady-state response as seen with MEG. *Hear Res* 2018;364: 90–95.

26. Uhlhaas PJ, Singer W. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. *Neuron* 2006;52:155–168.
27. Leuchter AF, Cook IA, Jin Y, Phillips B. The relationship between brain oscillatory activity and therapeutic effectiveness of transcranial magnetic stimulation in the treatment of major depressive disorder. *Front Hum Neurosci* 2013;7:37.
28. Jiruska P, de Curtis M, Jefferys JG, Schevon CA, Schiff SJ, Schindler K. Synchronization and desynchronization in epilepsy: controversies and hypotheses. *J Physiol* 2013;591:787–797.
29. Heinrichs-Graham E, Kurz MJ, Becker KM, Santamaria PM, Gendelman HE, Wilson TW. Hypersynchrony despite pathologically reduced beta oscillations in patients with Parkinson's disease: a pharmaco-magnetoencephalography study. *J Neurophysiol* 2014;112:1739–1747.
30. Vossen A, Gross J, Thut G. Alpha power increase after transcranial alternating current stimulation at alpha frequency (alpha-tACS) reflects plastic changes rather than entrainment. *Brain Stimul* 2015;8:499–508.
31. Zauner A, Fellinger R, Gross J et al. Alpha entrainment is responsible for the attentional blink phenomenon. *Neuroimage* 2012;63:674–686.
32. Notbohm A, Kurths J, Herrmann CS. Modification of brain oscillations via rhythmic light stimulation provides evidence for entrainment but not for superposition of event-related responses. *Front Hum Neurosci* 2016;10:10.
33. Cha YH, Urbano D, Pariseau N. Randomized single blind sham controlled trial of adjunctive home-based tDCS after rTMS for mal de debarquement syndrome: safety, efficacy, and participant satisfaction assessment. *Brain Stimul* 2016;9:537–544.
34. Vanneste S, Mohan A, Yoo HB et al. The peripheral effect of direct current stimulation on brain circuits involving memory. *Sci Adv* 2020;6:eaax9538.
35. Asamoah B, Khatoun A, Mc Laughlin M. tACS motor system effects can be caused by transcutaneous stimulation of peripheral nerves. *Nat Commun* 2019;10:266.

SUPPORTING INFORMATION

Additional supporting information may be found online in the supporting information tab for this article.

COMMENT

This is an excellent piece that uses a unique patient population to answer an important question that will help inform future transcranial alternating current stimulation (tACS) experimental approaches and treatments.

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