Identifying and Engaging Neuronal Oscillations by Transcranial Alternating Current Stimulation in Patients With Chronic Low Back Pain: A Randomized, Crossover, Double-Blind, Sham-Controlled Pilot Study

Sangtae Ahn, Julianna H. Prim, Morgan L. Alexander, Karen L. McCulloch, Flavio Fröhlich

Abstract

Chronic pain is associated with maladaptive reorganization of the central nervous system. Recent studies have suggested that disorganization of large-scale electrical brain activity patterns, such as neuronal network oscillations in the thalamocortical system, plays a key role in the pathophysiology of chronic pain. Yet, little is known about whether and how such network pathologies can be targeted with noninvasive brain stimulation as a nonpharmacological treatment option. We hypothesized that alpha oscillations, a prominent thalamocortical activity pattern in the human brain, are impaired in chronic pain and can be modulated with transcranial alternating current stimulation (tACS). We performed a randomized, crossover, double-blind, sham-controlled study in patients with chronic low back pain (CLBP) to investigate how alpha oscillations relate to pain symptoms for target identification and whether tACS can engage this target and thereby induce pain relief. We used high-density electroencephalography to measure alpha oscillations and found that the oscillation strength in the somatosensory region at baseline before stimulation was negatively correlated with pain symptoms. Stimulation with alpha-tACS compared to sham (placebo) stimulation significantly enhanced alpha oscillations in the somatosensory region. The stimulation-induced increase of alpha oscillations in the somatosensory region was correlated with pain relief. Given these findings of successful target identification and engagement, we propose that modulating alpha oscillations with tACS may represent a target-specific, nonpharmacological treatment approach for CLBP. This trial has been registered in ClinicalTrials.gov (NCT03243084).

Perspective

This study suggests that a rational design of transcranial alternating current stimulation, which is target identification, engagement, and validation, could be a nonpharmacological treatment approach for patients with CLBP.

Key words

Chronic low back pain, electroencephalography, alpha oscillations, transcranial alternating current stimulation

Chronic pain is associated with pathological changes in neuronal activity over somatosensory, insular, cingulate, and prefrontal cortices.46 These brain regions play a fundamental role in the processing of pain.32, 51,57 Several electroencephalography (EEG) and magnetoencephalography (MEG) studies have shown that patients with chronic pain exhibit abnormal neuronal oscillations.43, 55 In particular, pathologically increased theta oscillations (4–8 Hz)34, 48,49, 53,58 have motivated a conceptual framework of thalamocortical dysrhythmia (TCD) in chronic pain.33, 34 Moreover, the peak frequency of neuronal oscillations measured by EEG and MEG appears lower in patients with chronic pain when compared to healthy control participants.48, 49,53, 56,58 Thus, these findings imply that identifying the relationship between neurophysiological changes and pain severity and engaging the identified target could represent a network-level approach to understand a causal role of chronic pain. Yet, little is known about whether and how such network pathologies can be modulated with targeted noninvasive brain stimulation in patients with chronic pain.

Here, we performed a randomized, crossover, double-blind, sham-controlled clinical trial to investigate how noninvasive brain stimulation can target neuronal oscillations in patients with chronic pain. We chose to investigate target identification and engagement of neuronal oscillations in a sample of patients with chronic low back pain (CLBP), which is the single leading cause of disability worldwide.22 We built a model of a bifrontal stimulation-electrode montage to target and modulate the bilateral somatosensory cortex in patients with CLBP because previous studies have shown that abnormal neuronal oscillations in the somatosensory cortex reflect pain perception.13, 20,45, 46,60 In addition, previous brain stimulation approaches, such as deep brain stimulation and repetitive transcranial magnetic stimulation (rTMS), successfully targeted the somatosensory cortex to reduce pain severity.6, 31,47 Inspired by these successful approaches and the fundamental role of somatosensory cortex in pain, we built a model bifrontal montage to target the somatosensory cortex.

We formulated 2 hypotheses in our study. First, patients with CLBP exhibit impaired alpha oscillations. This hypothesis is based on previous findings that pain perception suppresses alpha oscillations23, 24,45 and the suppression is correlated with pain severity.7, 9,25, 40,52 Second, transcranial alternating current stimulation (tACS), which is a noninvasive brain stimulation tool that can modulate neuronal oscillations by applying oscillating electrical currents,21, 54 can enhance alpha oscillations in the somatosensory cortex and thereby induce pain relief. We recorded alpha oscillations by high-density EEG to investigate the hypothesized association of alpha oscillations with pain severity in patients with CLBP and applied 10-Hz tACS based on the identified target region. We assessed pain severity and perceived disability related to CLBP with two self-report rating scales. We found that alpha oscillations in the somatosensory region were negatively correlated with pain severity. Furthermore, 10-Hz tACS applied in the somatosensory region enhanced alpha oscillations and the enhancement correlated with pain relief. Our findings of successful target identification and engagement with tACS suggest that applying noninvasive

brain stimulation to modulate neuronal oscillations may be a nonpharmacological tool to treat CLBP.

Methods

Participants

Both male and female participants (age 18–65) were recruited from local pain and physical therapy clinics in Chapel Hill, NC area. Inclusion criteria consisted of a diagnosis of CBP by a licensed clinician, pain severity ≥3 on a 0–10 numerical pain rating scale,11 and duration of CLBP for at least 6 months (Table 1). All participants signed a consent form. Eligibility of participants was determined by a telephone screening before the first session. Twenty participants participated in 2 sessions (10-Hz tACS and sham) separated by 1 to 3 weeks and intervention sequence was randomized and balanced across all participants. Randomization was performed using sequentially numbered assignment. One of the authors (J.H.P.) generated the random allocation sequence, enrolled all participants, and assigned the participants to the sequence.

Table 1. Demographic Information

	Participants (n = 20)
Gender (M/F)	8/12
BMI	25.9 ± 4.3
Duration of CLBP, mo	84.8 ± 70
DVPRS, baseline	4.4 ± 1.0
ODI, baseline	22.7 ± 11.2
Race (Caucasian/African American)	18/2
Ethnicity (Hispanic/Not Hispanic)	1/19
Education level	
High school or equivalent	3
Associate's or Bachelor's degree	9
Advanced degree	8

NOTE. Data are reported as mean ± SD.

Study Design

We performed a randomized, crossover, double-blind, sham-controlled, clinical trial with 2 stimulation conditions (10-Hz tACS and sham). The study was performed at the University of North Carolina at Chapel Hill (ClinicalTrials.gov, NCT03243084) and approved by the Biomedical Institutional Review Board of the University of North Carolina at Chapel Hill. Behavioral questionnaires were administered before and after the stimulation at each session. All participants completed the Defense and Veterans Pain Rating Scale (DVPRS)8 and Oswestry Disability Index (ODI)18 to assess the severity of chronic low back pain and perceived disability, respectively. The DVPRS comprises a validated numerical rating pain scale (0–10) with detailed verbal descriptions and facial expressions. We used the back pain-specific ODI, which consists of 10 questions pertaining to perception of disability in daily life activities. Although participants completed both self-report measures at the beginning of each session, participants only completed the DVPRS immediately after stimulation. Because the ODI encompasses questions about daily living, the follow-up was taken 2 days after each session for a more valid measure of any disability change. EEG data were recorded from participants with their eyes closed for 2 minutes before the stimulation and with their eyes open before and after the stimulation for 2 minutes. EEG signals were recorded using a 128-channel Geodesic EEG system (EGI Inc, Eugene, OR) at a sampling rate of 1 kHz. Electrode Cz and one electrode between Cz and Pz were used as the reference and as the ground, respectively. Instructions for the tasks were implemented in Presentation (Neurobehavioral Systems, Inc, Berkeley, CA). Participants were instructed by a computer voice to fixate on a crosshair and open their eyes while staying relaxed for the eyes-open condition. Here we report on the primary and secondary outcomes with regard to modulation of alpha oscillations and associated changes in pain symptoms. Results on heart rate variability will be reported elsewhere. The sample size was determined by the amount of funding available for the grant that supported this work. The study was performed between September and December 2017. Twenty of twenty-one participants completed the study after enrolling (1 participant dropped out due to a scheduling conflict). We here report on the 20 study completers. The trial was ended when the target of 20 participants completing both sessions was reached. CONSORT diagram is provided in supplementary materials. The study protocol will be made available in response to written request to the corresponding author (F.F.)

tACS

We applied 3 carbon-silicone electrodes to the scalp with Ten20 conductive paste (Bio-Medical Instruments, Clinton Township, MI) and used the XCSITE 100 stimulator (Pulvinar Neuro LLC, Chapel Hill, NC) to administer tACS. Five-digit codes were used to ensure blinding of the study coordinators with regard to the stimulation conditions. The XCSITE 100 device does not display any information that would provide insights into whether verum or sham stimulation is applied. Two of the three electrodes (5 × 5 cm each) were placed at F3 and F4 according to 10-20 international coordinate system and these 2 electrodes were connected together for 10-Hz tACS. The other electrode (5 × 7 cm) was placed at Pz as a “return” electrode. Stimulation montage and

modeling of electric field distribution were calculated with the tES LAB 1.0 software (Neurophet Inc, Seoul, South Korea) as depicted in Fig 1. In this software, we used a T1-weighted MRI (adult male) from the human connectome project.14 The MRI data were segmented by 8 tissues (cerebrum gray matter, cerebrum white matter, cerebellar gray matter, cerebellar white matter, ventricles, cerebrospinal fluid, skull and skin) and each tissue was assigned isotropic conductivity values.29 To obtain electric field distributions, we used the finite element method with tetrahedron volume meshes. The number of tetrahedron mesh was ~4.3 million and the quasi-static Maxwell's equation was used. The 2 electrodes placed at the frontal lobe delivered an in-phase sinusoidal waveform with 1 mA amplitude each (zero-to-peak). Stimulation duration was 40 minutes for both conditions. Verum stimulation delivered 40 minutes of 10-Hz tACS with 10 seconds of ramp-up and ramp-down. Sham stimulation delivered 10 seconds of ramp-up, followed by 60 seconds of 10-Hz tACS, followed by 10 seconds of ramp-down for a total of 80 seconds. The choice of such an “active sham” is an established strategy to enhance blinding of the participants to the stimulation condition. To confirm successful blinding, participants were asked to fill out a questionnaire how sure they were of receiving stimulation on a visual analog scale (0–100) after each stimulation session. We found no significant difference of the visual analogue scale between the 2 stimulation conditions (P = .1555, Wilcoxon signed rank test; supplementary Fig 1). On average, the stimulation sessions were spaced by 14.4 ± 6.5 days. During the stimulation, all participants were seated comfortably and watched Reefscapes (Undersea Productions, Queensland, Australia) that displays tropical fish underwater scenes to minimize the phosphenes induced by stimulation. Participants were asked to stay relaxed, watch the video, and keep their eyes open.

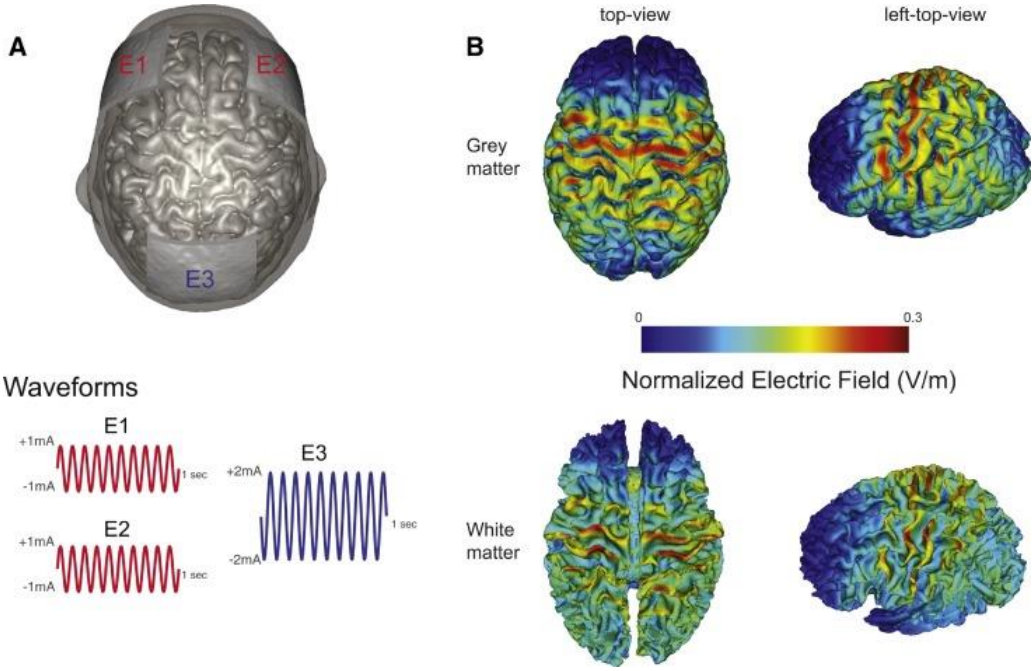


Figure 1. Stimulation montage, waveforms, and distributions of electric field in the brain. (A) Electrodes E1 and E2 delivered in-phase 10-Hz tACS with 1mA amplitude (zero-to-peak). Electrode E3 was used as the return electrode. (B) Normalized electric field distribution (V/m) by bifrontal 10-Hz tACS (top-view and left-top-view) in grey and white matter.

EEG Analysis and Statistical Testing

Off-line processing was performed by EEGLAB,12 FieldTrip,42 and custom-built scripts in MATLAB. First, all data were downsampled to 250 Hz with anti-aliasing filtering and bandpass filtered from 1 to 50 Hz. Second, the data were preprocessed by an artifact subspace reconstruction algorithm39 to remove high-variance and reconstruct missing data. Briefly, the algorithm first finds a minute of data that represents clean EEG as a baseline. Then, principle component analysis is applied to the whole data set with a sliding window to find the subspaces in which there is activity that is more than 5 standard deviations away from the baseline EEG. Once the function has identified the outlier subspaces, it treats them as missing data and reconstructs their content using a mixing matrix that is calculated from the clean data. Third, bad channels that were found in the previous step were interpolated and common average referencing was performed. Fourth and lastly, infomax independent component analysis26 was performed to remove eye blinking, eye movement, muscle activity, heartbeats, and channel noise. All independent component analysis components were visually inspected and components were manually selected for rejection. These initial preprocessing steps were carried out on the full EEG dataset before unblinding of the study.

Resting-state EEG data were epoched into 2-second windows. Each epoch was visually inspected in the temporal domain and bad epochs that contained abnormal spikes or high-frequency noise were removed. Power spectral density (PSD) was computed by Welch's method with a 2-second window and a 12.5% overlap resulting in a PSD with 0.5-Hz frequency bins. Individual alpha frequency (IAF), which we defined as the frequency of peak power in the occipital alpha (8–12 Hz) from eyes-closed EEG data, was selected for each participant. The power of the alpha oscillations was obtained by averaging of the PSD around the IAF ($IAF-1Hz \leq IAF \leq IAF+1Hz$) and the alpha oscillations were normalized by the average of all electrodes to minimize the intersubject variability of alpha oscillations.1, 2 Thirty-eight electrodes outside of the scalp were excluded and the remaining 90 electrodes inside of the scalp were used for topographical representation.

For statistical testing, we used a linear mixed-model analysis with fixed factors of “condition” (tACS and sham), “session” (session1, session2), and “sequence” (tACS-sham, sham-tACS), with random factor “participant” written in R (R Foundation for Statistical Computing, Vienna, Austria). We assumed that no carryover effect was observed because there were sufficient washout periods between the 2 sessions and outlasting treatment effects of stimulation are negligible. Kenward–Roger approximations were used to perform F-tests for each factor and interaction and obtain P values. Post hoc statistical tests were performed using student's t-test across participants at each electrode and it was corrected by false discovery rate (FDR).5 Changes of measured values over sessions were quantified with a modulation index (MI):

$$MI(a,b)=(a-b) / (a+b).$$

Changes in spatially-normalized alpha oscillations were calculated by $MI(Alpha_{after}, Alpha_{before})$. In contrast, changes in DVPRS and ODI were calculated by $MI(DVPRS_{before}, DVPRS_{after})$ and $MI(ODI_{before}, ODI_{after})$, respectively. Given the non-normal distribution of the modulation indices for the assessments, we also performed exploratory analysis using the Wilcoxon signed rank test.

Results

Pain Assessments and Endogenous Alpha Oscillations

We first examined how endogenous alpha oscillations were correlated with CLBP severity measured by the DVPRS and ODI, ie, target identification. Baseline spatially-normalized alpha oscillations were calculated from 2-minute eyes-open data at the first study session regardless of the stimulation condition for that session. We calculated the Spearman's rho between the baseline alpha oscillations and the assessments across all participants at each scalp EEG channel. We found significant negative correlations over the bilateral and left somatosensory region for the DVPRS and ODI, respectively (Fig 2A). The black dots represent EEG channels with statistically significant correlations ($P < .05$, FDR-corrected). Negative correlations indicate endogenous alpha oscillations were lower for patients with higher pain severity (DVPRS) and higher perceived disability (ODI). Given the similarity in the topographic distribution of these correlations, we confirmed that the DVPRS and ODI scores were positively correlated ($r = .6375$, $P = .0025$; Fig 2B). These results suggest that reduced endogenous alpha oscillations could represent the severity of CLBP and its impact on the perceived disability.

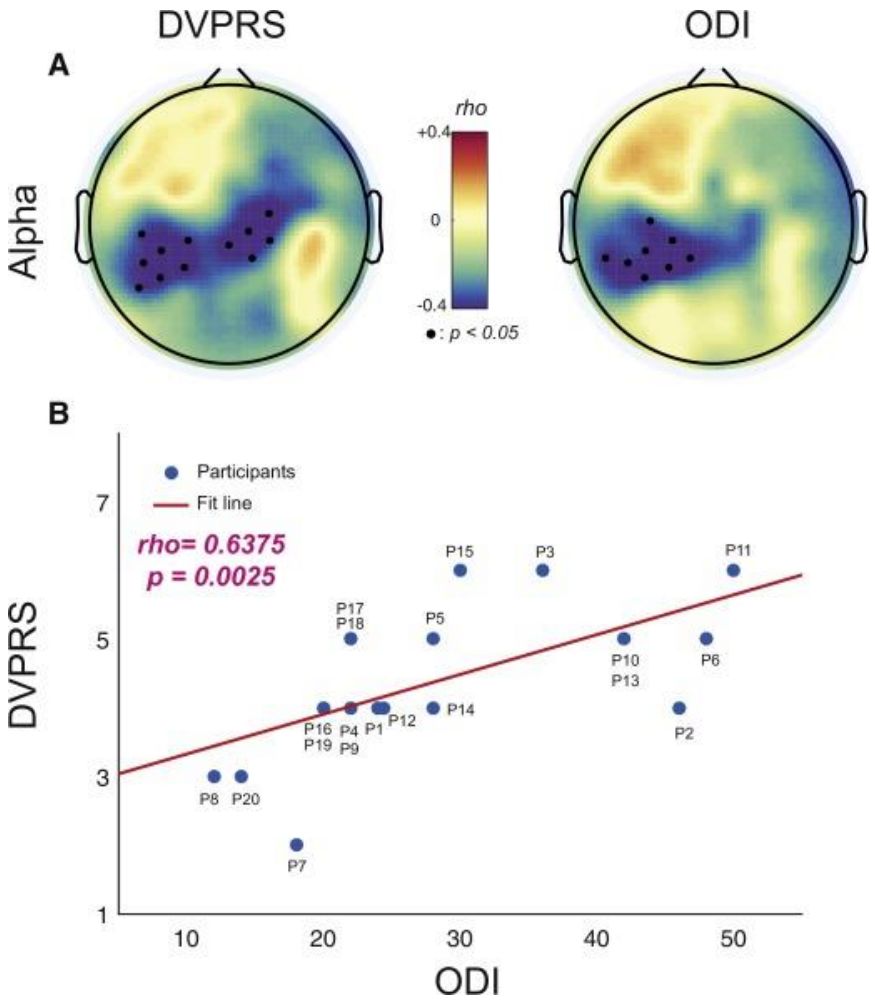


Figure 2. Correlations between baseline alpha oscillations and clinical assessments(DVPRS and ODI). (**A**) Topographical distribution for DVPRS and ODI. Small black dots represent EEG channels with statistical significance ($P < .05$, FDR-corrected). (**B**) Scatter plot for correlated ODI and DVPRS (rho = .6375, $P = .0025$).

Enhanced Alpha Oscillations by 10-Hz tACS

Our finding that a reduction in alpha oscillations is associated with pain severity in CLBP suggests that tACS could restore these pathological reduced oscillations. Thus, we next examined modulation, ie, target engagement, of endogenous alpha oscillations by 40 minutes of bifrontal 10-Hz tACS and sham stimulation. Changes in spatially-normalized alpha oscillations from eyes-open data for 2 minutes were obtained immediately before and after stimulation for conditions. The increase in alpha oscillations was significantly higher in the 10-Hz tACS condition (Fig 3, left) compared to the sham condition (Fig 3, middle; $F1,18 = 6.5$, $P = .02$). The black dots in the topographic map (Fig 3, right) represent the location of EEG channels with statistically significant differences in modulation of alpha oscillation between 10-Hz tACS and sham, ($P < .05$, FDR-corrected). These results suggest that 10-Hz tACS selectively enhanced endogenous alpha oscillations over the somatosensory region in patients with CLBP.

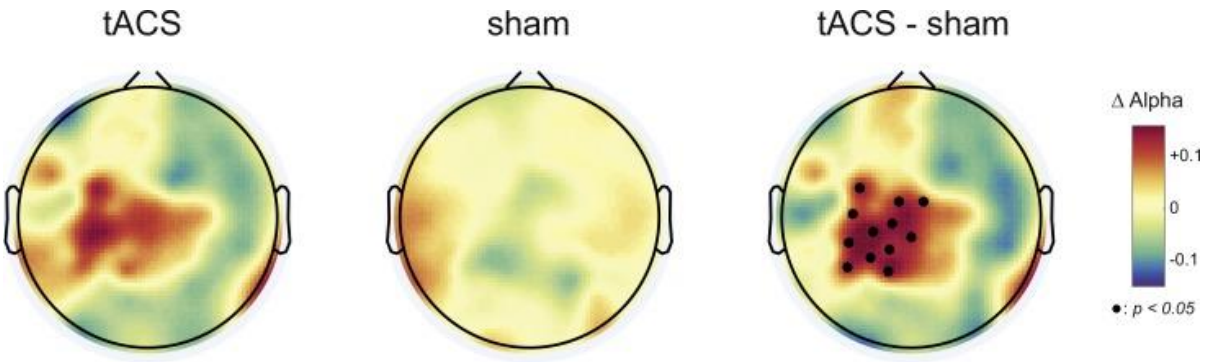


Figure 3. Averaged topographical distribution of changes in spatially-normalized alpha oscillations for tACS (left), sham (middle), and the difference (right). Individual alpha frequency was used (IAF ± 1 Hz) and small black dots represent EEG channels with statistical significance ($P < .05$, FDR-corrected).

Changes in Pain Assessments and Alpha Oscillations

Given the correlation between a reduction of alpha oscillations and pain severity, we next asked whether the stimulation-induced changes in alpha oscillations modulated pain severity. We examined how enhanced alpha oscillations by 10-Hz tACS were correlated with changes in pain severity. We calculated the Spearman's rho between changes in spatially-normalized alpha oscillations, $MI(Alpha_{after}, Alpha_{before})$, and the 2 assessments $MI(DVPRS_{before}, DVPRS_{after})$, $MI(ODI_{before}, ODI_{after})$ for each stimulation condition at each EEG channel. We found significant positive correlations over the somatosensory and frontal regions for the DVPRS in the 10-Hz tACS condition (Fig 4, top row). The black dots in the topographic map represent statistically significant EEG channels ($P < .05$, FDR-corrected). In contrast, no significant correlations were obtained in the sham condition for the DVPRS. Similarly, for the ODI, we found significant positive correlations over the left somatosensory and frontal regions ($P < .05$, FDR-corrected) in the 10-Hz tACS condition and no significant correlations in the sham condition. Thus, increasing alpha oscillations reduced pain severity and perceived disability, which suggests a causal of pathological reduced alpha oscillations in CLBP.

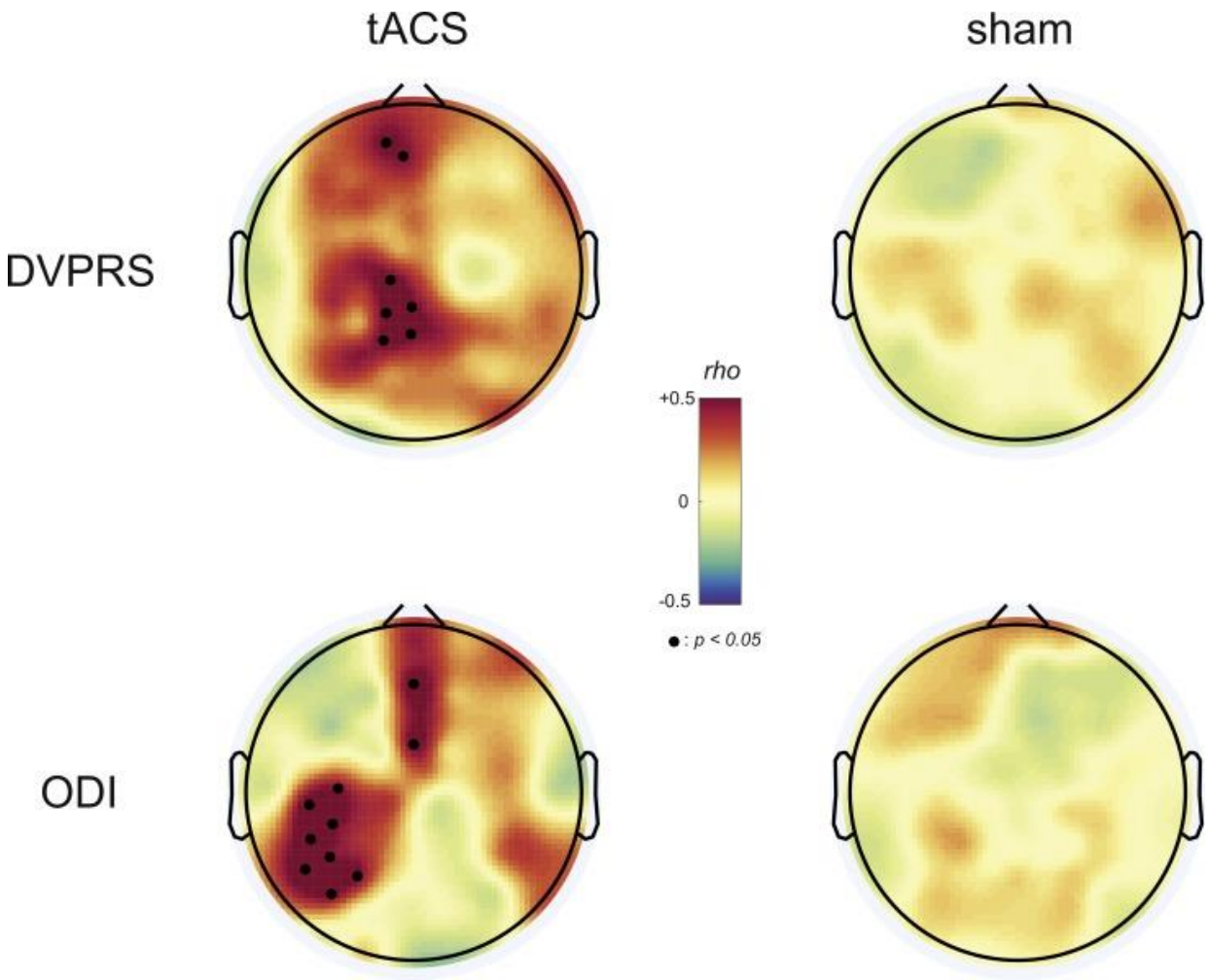


Figure 4. Topographical distribution of correlations between enhanced alpha oscillations and pain symptom changes. Small black dot represent EEG channels with statistical significance (P < .05, FDR-corrected).

Clinical Improvement of CLBP

As secondary outcome, we determined the improvement in the DVPRS and ODI scores independent of the neurophysiological changes. We calculated changes of the 2 assessments (DVPRS and ODI) by using the modulation indices *MI* ($DVPRS_{after}$, $DVPRS_{before}$) and *MI* (ODI_{after}, ODI_{before}) across the stimulation conditions. Statistical testing with a linear mixed model and Kenward–Roger approximations revealed no significant effect for the simulation conditions, ($F_{1,18} = 1.13$, $P = .3$). However, the DVPRS and ODI data were not normally distributed as determined by the Kolmogorov–Smirnov tests for the null hypothesis that the data comes from a standard normal distribution ($P = .005$). We thus performed exploratory analysis with the Wilcoxon signed rank test, a nonparametric test for non-normally distributed data. We found a significant effect only for change in DVPRS ($P = .0488$; Fig 5A) and not a change in ODI ($P = .17$; Fig 5B).

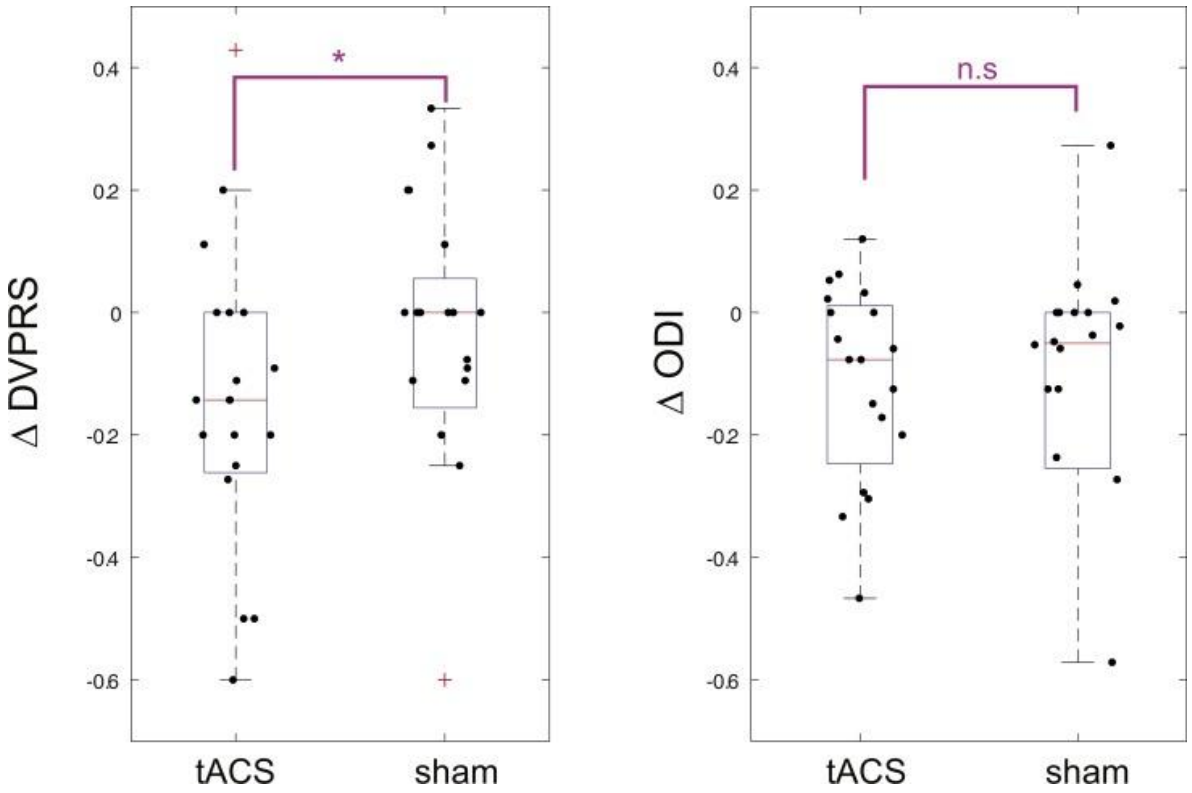


Figure 5. Changes in pain assessments (DVPRS and ODI) under stimulation conditions (tACS and sham). Statistical significance was assessed with the nonparametric Wilcoxon signed rank test (*$P < .05$). Red symbol indicates an outlier.

Discussion

Previous studies have shown that patients with chronic pain exhibit abnormal neuronal oscillations.46 In particular, alpha oscillations have been hypothesized to be involved in chronic pain.9, 25,45, 52 Yet, to our knowledge we are the first to examine whether noninvasive brain stimulation can enhance alpha oscillations and thereby improve symptoms of chronic pain. We performed a randomized, crossover, double-blind, sham-controlled clinical trial to examine the association between endogenous alpha oscillations and pain severity in patients with CLBP and the modulation of alpha oscillations by 10-Hz tACS. We found that endogenous alpha oscillations in the somatosensory region were negatively correlated with pain severity measured by the assessments for back pain (DVPRS) and perceived disability due to back pain (ODI). Bifrontal 10-Hz tACS targeting the somatosensory region successfully enhanced alpha oscillations compared to sham stimulation. Further, we found that changes of pain relief were correlated with changes of endogenous alpha oscillations in the frontal and somatosensory regions. Our findings of successful target identification and engagement of alpha oscillations by 10-Hz tACS for patients with CLBP demonstrate the potential of tACS for treating pain by modulating neuronal oscillations.

TCD has been proposed as a framework for understanding underlying mechanisms of chronic neurogenic pain.34 In agreement with this the framework, increased theta oscillations and slowing of the dominant spectral peak were consistently observed in previous studies.48, 49,53, 56 A decreased inhibition of the thalamus seems to be linked to increased theta oscillations in patients with chronic neurogenic pain. However, a study failed to replicate these findings in patients with CLBP.50 In this study, they recruited patients with CLBP (duration of illness at least 1 year) and compared them with age- and sex-matched healthy participants. The authors did not find any significant difference in terms of increased theta oscillations and peak shift to lower frequency and concluded that differing pain locations may have caused the discrepancy. Interestingly, none of the patients with chronic neurogenic pain suffered from low back pain in previous studies that tested the TCD hypothesis.48, 49,53, 56 In contrast, our study focused on the strength of the alpha oscillation motivated by the inverse correlation between neuronal activity and alpha oscillation power. We hypothesized that alpha oscillations are reduced in CLBP because of disinhibition associated with pathologically increased cortical excitation in chronic pain,62 which indicates dysfunction of inhibitory neurotransmitters.61 Testing the TCD was not a goal of this study and thus a direct comparison of the results is not possible. Instead, our findings may represent a fundamental neurophysiological correlate of pain symptoms in patients with CLBP. In the view of translation to a population with neuropathic pain using our approach, theta oscillations may be targeted by theta-tACS. However, identifying the relationship between theta oscillations and pain intensity should be performed first to target and modulate abnormal theta oscillations. Once the relationship is consistent across patients with neuropathic pain, detailed spatial targeting can be applied based on the identified target region.

Inspired by a previous study,19 which found the relationship between peak alpha frequency and pain sensitivity, we investigated this relationship in our data. We found no significant correlation between peak alpha frequency and the 2 pain assessments (DVPRS and ODI) at baseline (Supplementary Fig 2). This discrepancy may come from a differing population of participants because our study population consisted of patients with CLBP. In addition, patients with long-term chronic pain may exhibit some degree of depression as a comorbidity15 thus we assessed Hamilton Depression Rating Scale (HAM-D) from all participants to investigate a relationship between pain severity and depression level. We found no significant correlation between HAM-D scores and the 2 pain assessments (DVPRS and ODI) at baseline (Supplementary Fig 3). We only assessed HAM-D at baseline because tracking depression level was not a goal of this study. This relationship needs to be investigated further in a larger sample with multiple assessments.

Deep brain stimulation that stimulates periventricular/periaqueductal gray matter, internal capsule, and sensory thalamus has shown promising improvement of pain relief.6, 47 Because of substantial risks of surgical implantation of electrodes in the brain, noninvasive brain stimulation techniques including rTMS have been investigated for the treatment chronic pain.28, 31,44 Similar to our study, these studies considered chronic pain as a disorder associated with reorganization of the central nervous system.17 The first rTMS study showed that 10-Hz rTMS

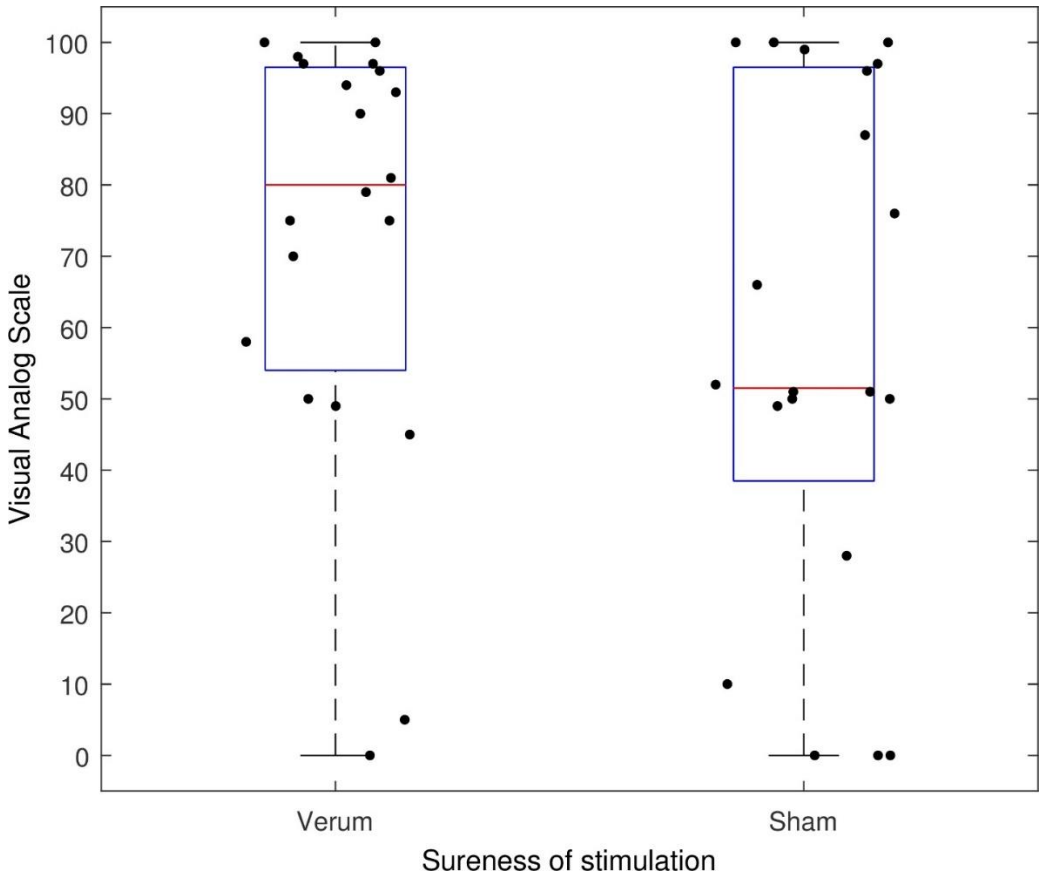
for 20 minutes applied to the motor cortex decreased pain severity in a sham-controlled clinical trial.30 A study with 1Hz-rTMS on the right somatosensory area also reduced pain compared to 20Hz-rTMS and sham.16 Although these rTMS studies showed a substantial reduction in pain, several similar studies failed to replicate these findings. One study with 20-Hz rTMS found no significant differences between real and sham groups28 and another double-blind, sham-controlled clinical trial with 1-Hz and 20-Hz rTMS found no significant treatment effects compared to sham stimulation.3 Recent meta-analysis showed that rTMS for treating pain does not achieve the minimum clinically important difference threshold of 15% or greater.41 In addition to rTMS, transcranial direct current stimulation (tDCS) has also been investigated. A recent meta-analysis found similar heterogeneity of outcomes for the tDCS studies.41

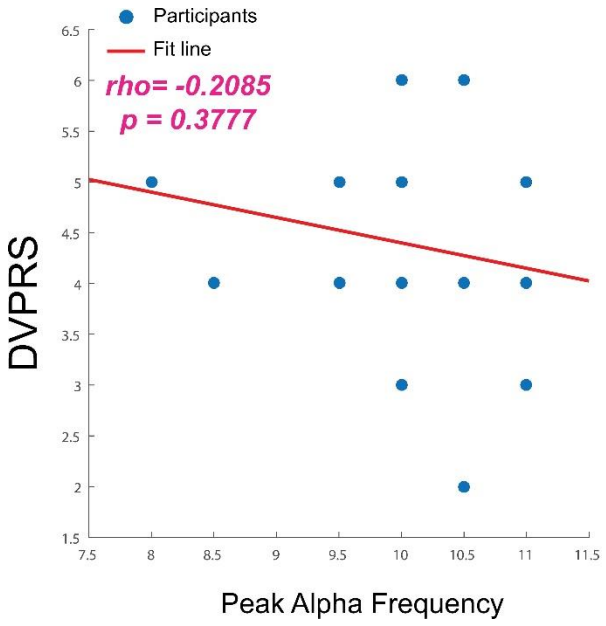
It is of note that alpha oscillations have been investigated in depth in the context of pain stimuli in healthy control participants. Most of these studies have provided evidence for pain perception in presence of suppression of alpha oscillations for phasic pain.23, 36,38, 45 Likewise, longer-lasting tonic pain, which may represent a precursor to chronic pain, suppressed alpha oscillations.13, 24,40, 52 In addition, pain severity and alpha oscillations were negatively correlated.40, 52 These studies are correlational in nature but a recent tACS study with behavioral outcome measures provided the first evidence for a causal role of alpha oscillation in pain processing4 albeit no confirmatory neurophysiological measurements were performed. Our study differed in scope and question since we examined target engagement of tACS by EEG and examined the causal role of alpha oscillations in the context of chronic pain. Such a target-specific approach with EEG may provide a new insight to understand mechanisms of chronic pain.

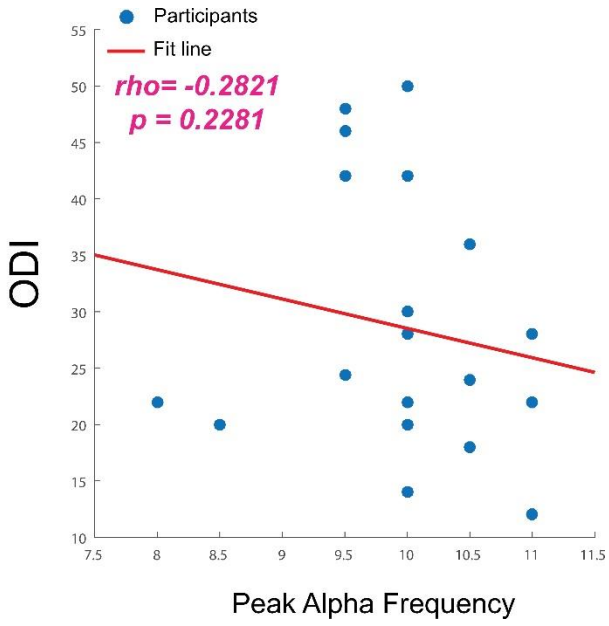
As any scientific study, our study has several limitations. First, we found a significant reduction for DVPRS only on exploratory analysis and none for ODI. One possible reason for this is that post-stimulation ODI was measured 2 days after each session because we hypothesized that a single session of tACS may not change disability. It is of note that our study was designed as a target engagement study with physiological changes including the alpha oscillation as primary outcome rather than treating chronic pain by a single session of tACS. The study was not designed or powered to detect meaningful clinical difference. Importantly, a treatment protocol would consist of repeated application of 10-Hz tACS as in our recent treatment clinical trial for auditory hallucinations in schizophrenia.37 In a follow-up study, we plan to investigate the treatment effect with lager sample size and more refined target engagement strategies such as individual alpha frequency.27, 54,59 Second, even though brain stimulation approaches have been used widely to modulate cortical excitability and treat patients, inter- and intra-individual variability for effects still exist.10, 35 Individualizing stimulation parameters with precise modeling of electric current density may be one approach to minimize variability. In our study, likewise, we fixed stimulation intensity and montage across all participants without individualization. In a follow-up study, individualization of stimulation parameters should be considered as well as multisession stimulation.

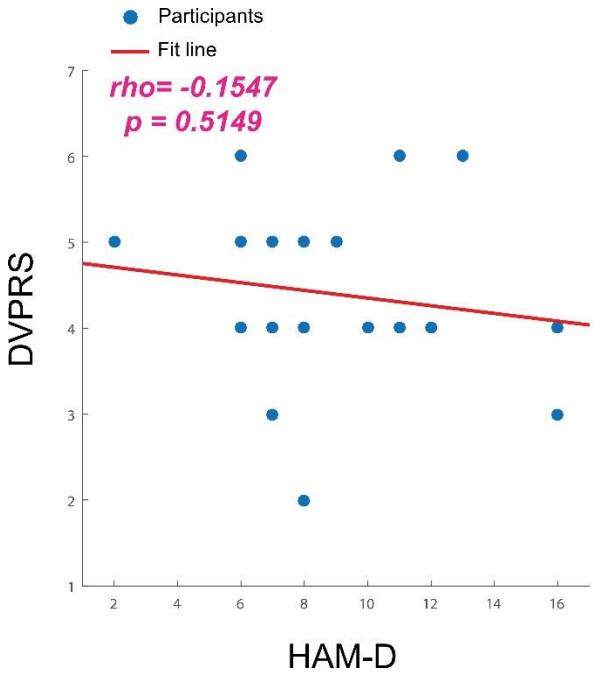
In summary, we report on the first study of target identification and engagement with high-density EEG and tACS for patients with CLBP. Our findings suggest a causal role of alpha oscillations in patients with CLBP. Targeting and modulating neuronal oscillations represents a promising strategy to understand the interaction between pain symptoms and brain oscillations. Potentially, such a target-specific approach to modulate pathologically impaired oscillations with tACS may provide therapeutic benefit for other disorders associated with brain network pathologies.

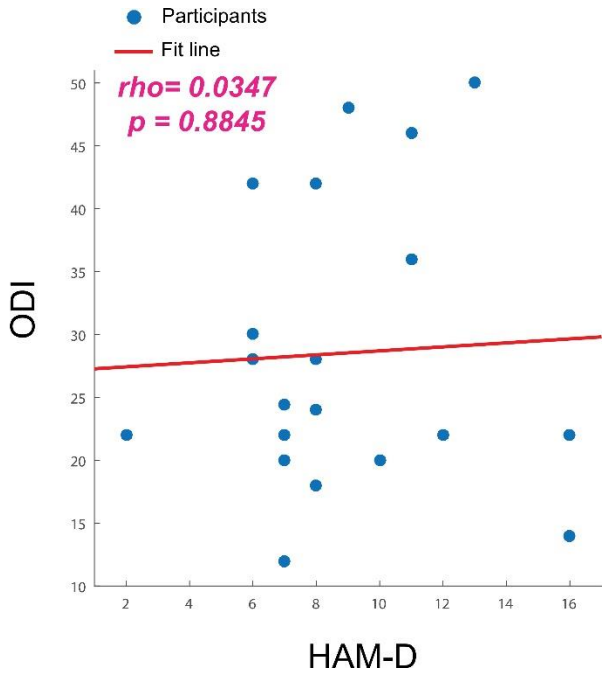
Appendix. Supplementary data





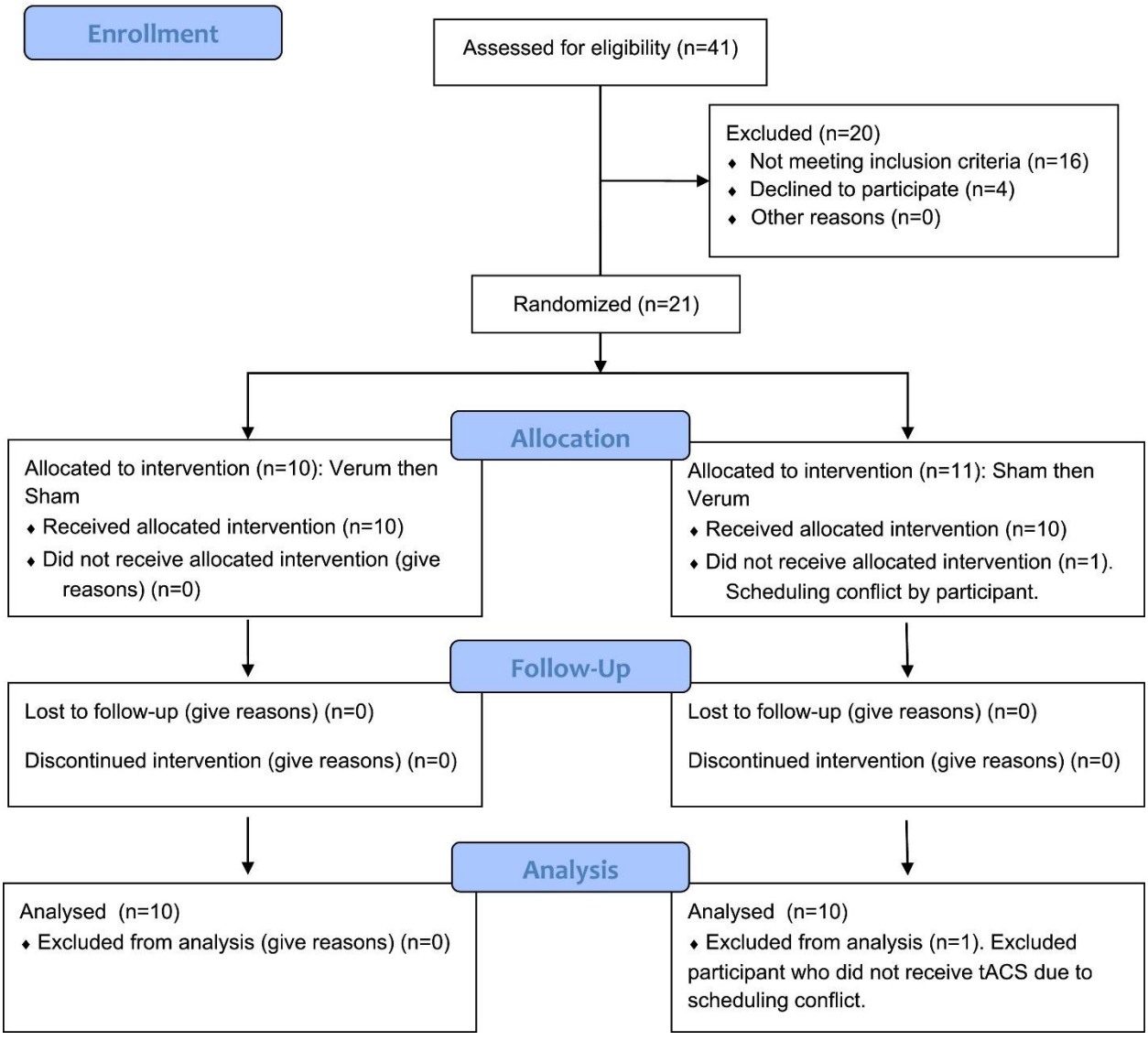



Participants
Fit line
rho= -0.1547
p = 0.5149
DVPRS
HAM-D


Participants
Fit line
rho= 0.0347
p = 0.8845
ODI
HAM-D

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



Acknowledgements

S.A. and J.H.P. contributed equally to this work.

Supported by the National Institute of Mental Health of the National Institutes of Health under Award Numbers R01MH111889 and R01MH101547, North Carolina Translational and Clinical Sciences Institute under Award Number NC TraCS 2KR941707, and Research Electronic Data Capture (REDCap). We gratefully acknowledge the help and support from the Carolina Center for Neurostimulation. The authors specially thank Donghyeon Kim (Neurophet, Inc) for providing valuable feedback on our stimulation montage and modeling of electric field distribution.

F.F. is the lead inventor of IP filed by UNC. The clinical studies performed in the Frohlich Laboratory have received a designation as conflict of interest with administrative considerations. F.F. is the founder, CSO, and majority owner of Pulvinar Neuro, LLC, a company that markets research tDCS and tACS devices. F.F. has received research funding from the National Institute of Health, the Brain Behavior Foundation, the Foundation of Hope, the Human Frontier Science Program, Tal Medical, and individual donations. F.F. is an adjunct professor in Neurology at the Insel Hospital of the University of Bern, Switzerland. F.F. receives royalties for his textbook Network Neuroscience published by Academic Press.

S.A., J.H.P, M.L.A, and K.L.M. have no conflicts of interest to declare.

References

1 S Ahn, M Ahn, H Cho, S Chan Jun**Achieving a hybrid brain–computer interface with tactile selective attention and motor imagery.** J Neural Eng, 11 (2014), Article 066004

2 S Ahn, T Nguyen, H Jang, JG Kim, SC Jun**Exploring neuro-physiological correlates of drivers' mental fatigue caused by sleep deprivation using simultaneous EEG, ECG, and fNIRS data.** Front Hum Neurosci, 10 (2016), p. 219

3 N André-Obadia, R Peyron, P Mertens, F Mauguière, B Laurent, L Garcia-Larrea**Transcranial magnetic stimulation for pain control: Double-blind study of different frequencies against placebo, and correlation with motor cortex stimulation efficacy**. Clin Neurophysiol, 117 (2006), pp. 1536-1544

4 LJ Arendsen, S Hugh-Jones, DM Lloyd**Transcranial alternating current stimulation at alpha frequency reduces pain when the intensity of pain is uncertain.** J Pain, 19 (2018), pp. 807-818

5 Y Benjamini, Y Hochberg**Controlling the false discovery rate: A practical and powerful approach to multiple testing.** J R Stat Soc Ser B, 57 (1995), pp. 289-300

6 RG Bittar, I Kar-Purkayastha, SL Owen, RE Bear, A Green, S Wang, TZ Aziz**Deep brain stimulation for pain relief: A meta-analysis.** J Clin Neurosci, 12 (2005), pp. 515-519

7 P Boord, PJ Siddall, Y Tran, D Herbert, J Middleton, A Craig**Electroencephalographic slowing and reduced reactivity in neuropathic pain following spinal cord injury.** Spinal Cord, 46 (2008), pp. 118-123

8 CC Buckenmaier, KT Galloway, RC Polomano, M McDuffie, N Kwon, RM Gallagher**Preliminary Validation of the Defense and Veterans Pain Rating Scale (DVPRS) in a military population.** Pain Med, 14 (2013), pp. 110-123

9 D Camfferman, GL Moseley, K Gertz, MW Pettet, MP Jensen**Waking EEG cortical markers of chronic pain and sleepiness.** Pain Med, 18 (2017), pp. 1921-1931

10 T Chew, K-A Ho, CK Loo**Inter- and intra-individual variability in response to transcranial direct current stimulation (tDCS) at varying current intensities**. Brain Stimul, 8 (2015), pp. 1130-1137

11 JD Childs, SR Piva, JM Fritz**Responsiveness of the numeric pain rating scale in patients with low back pain**. Spine, 30 (2005), pp. 1331-1334

12 A Delorme, S Makeig**EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis**. J Neurosci Methods, 134 (2004), pp. 9-21

13 R Dowman, D Rissacher, S Schuckers**EEG indices of tonic pain-related activity in the somatosensory cortices.** Clin Neurophysiol, 119 (2008), pp. 1201-1212

14 DC Van Essen, SM Smith, DM Barch, TEJ Behrens, E Yacoub, K Ugurbil**The WU-Minn Human Connectome Project: An overview.** Neuroimage, 80 (2013), pp. 62-79

15 DA Fishbain, R Cutler, HL Rosomoff, RS Rosomoff**Chronic pain-associated depression: Antecedent or consequence of chronic pain?.** A review. Clin J Pain, 13 (1997), pp. 116-137

16 F Fregni, D DaSilva, K Potvin, C Ramos-Estebanez, D Cohen, A Pascual-Leone, SDFreedman**Treatment of chronic visceral pain with brain stimulation.** Ann Neurol, 58 (2005), pp. 971-972

17 F Fregni, S Freedman, A Pascual-Leone**Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques.** Lancet Neurol, 6 (2007), pp. 188-191

18 JM Fritz, JJ Irrgang**A Comparison of a Modified Oswestry Low Back Pain Disability Questionnaire and the Quebec Back Pain Disability Scale.** Phys Ther, 81 (2001), pp. 776-788

19 AJ Furman, TJ Meeker, JC Rietschel, S Yoo, J Muthulingam, M Prokhorenko, MLKeaser, RN Goodman, A Mazaheri, DA Seminowicz**Cerebral peak alpha frequency predicts individual differences in pain sensitivity.** Neuroimage, 167 (2018), pp. 203-210

20 J Gross, A Schnitzler, L Timmermann, M Ploner**Gamma oscillations in human primary somatosensory cortex reflect pain perception.** PLoS Biol, 5 (2007), p. e133

21 RF Helfrich, TR Schneider, S Rach, SA Trautmann-Lengsfeld, AK Engel, CS Herrmann, G Ruffini, PC Miranda, F Wendling**Entrainment of brain oscillations by transcranial alternating current stimulation.** Curr Biol, 24 (2014), pp. 333-339

22 D Hoy, L March, P Brooks, F Blyth, A Woolf, C Bain, G Williams, E Smith, T Vos, JBarendregt, C Murray, R Burstein, R Buchbinder**The global burden of low back pain: Estimates from the Global Burden of Disease 2010 study.** Ann Rheum Dis, 73 (2014), pp. 968-974

23 L Hu, W Peng, E Valentini, Z Zhang, Y Hu**Functional features of nociceptive-induced suppression of alpha band electroencephalographic oscillations.** J Pain, 14 (2013), pp. 89-99

24 C Huishi Zhang, A Sohrabpour, Y Lu, B He**Spectral and spatial changes of brain rhythmic activity in response to the sustained thermal pain stimulation.** Hum Brain Mapp, 37 (2016), pp. 2976-2991

25 MP Jensen, LH Sherlin, KJ Gertz, AL Braden, AE Kupper, A Gianas, JD Howe, SHakimian**Brain EEG activity correlates of chronic pain in persons with spinal cord injury: clinical implications.** Spinal Cord, 51 (2013), pp. 55-58

26 T-P Jung, S Makeig, C Humphries, T-W Lee, MJ McKeown, V Iragui, TJ Sejnowski**Removing electroencephalographic artifacts by blind source separation.** Psychophysiology, 37 (2000), pp. 163-178

27 FH Kasten, CS Herrmann**Transcranial alternating current stimulation (tACS) enhances mental rotation performance during and after stimulation.** Front Hum Neurosci, 11 (2017), p. 2

28 EM Khedr, H Kotb, NF Kamel, MA Ahmed, R Sadek, JC Rothwell**Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain.** J Neurol Neurosurg Psychiatry, 76 (2005), pp. 833-838

29 D Kim, H Seo, H-I Kim, SC Jun, J Baron**Computational study on subdural cortical stimulation: The influence of the head geometry, anisotropic conductivity, and electrode configuration.** PLoS One, 9 (2014), Article e108028

30 J Lefaucheur, X Drouot, J Nguyen**Interventional neurophysiology for pain control: Duration of pain relief following repetitive transcranial magnetic stimulation of the motor cortex.** Neurophysiol Clin Neurophysiol, 31 (2001), pp. 247-252

31 RJ Leo, T Latif**Repetitive transcranial magnetic stimulation (rTMS) in experimentally induced and chronic neuropathic pain: A review.** J Pain, 8 (2007), pp. 453-459

32 MD Lieberman, NI Eisenberger**The dorsal anterior cingulate cortex is selective for pain: Results from large-scale reverse inference.** Proc Natl Acad Sci U S A, 112 (2015), pp. 15250-15255

33 R Llinás, FJ Urbano, E Leznik, RR Ramírez, HJF van Marle**Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect.** Trends Neurosci, 28 (2005), pp. 325-333

34 RR Llinás, U Ribary, D Jeanmonod, E Kronberg, PP Mitra**Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography.** Proc Natl Acad Sci, 96 (1999), pp. 15222-15227

35 V López-Alonso, B Cheeran, D Río-Rodríguez, M Fernández-del-Olmo**Inter-individual variability in response to non-invasive brain stimulation paradigms.** Brain Stimul, 7 (2014), pp. 372-380

36 ES May, M Butz, N Kahlbrock, N Hoogenboom, M Brenner, A Schnitzler**Pre- and post-stimulus alpha activity shows differential modulation with spatial attention during the processing of pain.** Neuroimage, 62 (2012), pp. 1965-1974

37 JM Mellin, S Alagapan, C Lustenberger, CE Lugo, ML Alexander, JH Gilmore, LFJarskog, F Fröhlich**Randomized trial of transcranial alternating current stimulation for treatment of auditory hallucinations in schizophrenia.** Eur Psychiatry, 51 (2018), pp. 25-33

38 A Mouraux, J Guérit**Plaghki L: Non-phase locked electroencephalogram (EEG) responses to CO_2 laser skin stimulations may reflect central interactions between A∂- and C-fibre afferent volleys.** Clin Neurophysiol, 114 (2003), pp. 710-722

39 T Mullen, C Kothe, YM Chi, A Ojeda, T Kerth, S Makeig, G Cauwenberghs, J Tzyy-Ping**Real-time modeling and 3D visualization of source dynamics and connectivity using wearable EEG.** Conf Proc IEEE Eng Med Biol Soc (2013), pp. 2184-2187

40 R-R Nir, A Sinai, R Moont, E Harari, D Yarnitsky**Tonic pain and continuous EEG: Prediction of subjective pain perception by alpha-1 power during stimulation and at rest.** Clin Neurophysiol, 123 (2012), pp. 605-612

41 NE O'Connell, L Marston, S Spencer, LH DeSouza, BM Wand**Non-invasive brain stimulation techniques for chronic pain.** Cochrane Database Syst Rev, 4 (2018), Article CD008208

42 R Oostenveld, P Fries, E Maris, J-M Schoffelen**FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data.** Comput Intell Neurosci, 2011 (2010), Article e156869

43 ES Pinheiro, FC de Queirós, P Montoya, CL Santos, MA do Nascimento, CH Ito, MSilva, DB Nunes Santos, S Benevides, JGV Miranda, KN Sá, AF Baptista**Electroencephalographic patterns in chronic pain: A systematic review of the literature.** PLoS One, 11 (2016), Article e0149085

44 B Pleger, F Janssen, P Schwenkreis, B Völker, C Maier, M Tegenthoff**Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I.** Neurosci Lett, 356 (2004), pp. 87-90

45 M Ploner, J Gross, L Timmermann, B Pollok, A Schnitzler**Pain suppresses spontaneous brain rhythms.** Cereb Cortex, 16 (2006), pp. 537-540

46 M Ploner, C Sorg, J Gross**Brain rhythms of pain.** Trends Cogn Sci, 21 (2017), pp. 100-110

47 D Rasche, PC Rinaldi, RF Young, VM Tronnier**Deep brain stimulation for the treatment of various chronic pain syndromes.** Neurosurg Focus, 21 (2006), pp. 1-8

48 J Sarnthein, D Jeanmonod**High thalamocortical theta coherence in patients with neurogenic pain.** Neuroimage, 39 (2008), pp. 1910-1917

49 J Sarnthein, J Stern, C Aufenberg, V Rousson, D Jeanmonod**Increased EEG power and slowed dominant frequency in patients with neurogenic pain.** Brain, 129 (2006), pp. 55-64

50 S Schmidt, JR Naranjo, C Brenneisen, J Gundlach, C Schultz, H Kaube, T Hinterberger, D Jeanmonod**Pain ratings, psychological functioning and quantitative EEG in a controlled study of chronic back pain patients.** PLoS One, 7 (2012), p. e31138

51 AR Segerdahl, M Mezue, TW Okell, JT Farrar, I Tracey**The dorsal posterior insula subserves a fundamental role in human pain.** Nat Neurosci, 18 (2015), pp. 499-500

52 S Shao, K Shen, K Yu, EPV Wilder-Smith, X Li**Frequency-domain EEG source analysis for acute tonic cold pain perception.** Clin Neurophysiol, 123 (2012), pp. 2042-2049

53 J Stern, D Jeanmonod, J Sarnthein**Persistent EEG overactivation in the cortical pain matrix of neurogenic pain patients.** Neuroimage, 31 (2006), pp. 721-731

54 A Vossen, J Gross, G Thut**Alpha power increase after transcranial alternating current stimulation at alpha frequency (α-tACS) reflects plastic changes rather than entrainment.** Brain Stimul, 8 (2015), pp. 499-508

55 M De Vries, O Wilder-Smith, M Jongsma, E Van den Broeke, M Arns, H Van Goor, CVan Rijn**Altered resting state EEG in chronic pancreatitis patients: Toward a marker for chronic pain.** J Pain Res, 6 (2013), p. 815

56 A Vuckovic, MA Hasan, M Fraser, BA Conway, B Nasseroleslami, DB Allan**Dynamic oscillatory signatures of central neuropathic pain in spinal cord injury.** J Pain, 15 (2014), pp. 645-655

57 TD Wager, LY Atlas, MM Botvinick, LJ Chang, RC Coghill, KD Davis, GD Iannetti, RAPoldrack, AJ Shackman, T Yarkoni**Pain in the ACC?.** Proc Natl Acad Sci U S A, 113 (2016), pp. E2474-E2475

58 KD Walton, M Dubois, RR Llinás**Abnormal thalamocortical activity in patients with complex regional pain syndrome (CRPS) type I.** Pain, 150 (2010), pp. 41-51

59 T Zaehle, S Rach, CS Herrmann, M Schurmann, L Marshall**Transcranial alternating current stimulation enhances individual alpha activity in human EEG.** PLoS One, 5 (2010), p. e13766

60 ZG Zhang, L Hu, YS Hung, A Mouraux, GD Iannetti**Gamma-band oscillations in the primary somatosensory cortex: A direct and obligatory correlate of subjective pain intensity.** J Neurosci, 32 (2012), pp. 7429-7438

61 M Zhuo**Canadian Association of Neuroscience Review: Cellular and synaptic insights into physiological and pathological pain. EJLB-CIHR Michael Smith Chair in Neurosciences and Mental Health lecture.** Can J Neurol Sci, 32 (2005), pp. 27-36

62 M Zhuo**Cortical excitation and chronic pain**. Trends Neurosci, 31 (2008), pp. 199-207