Short communication

Alpha-tACS effect on inhibitory control and feasibility of administration in community outpatient substance use treatment

Stacey B. Daughtersa,⁎, Jennifer Y. Yi⁎, Rachel D. Phillipsa, Regina M. Carelli⁎, Flavio Fröhlichb,c,d,e,f,g

a Department of Psychology & Neuroscience, University of North Carolina, Chapel Hill, NC, 27516, USA
b Department of Psychology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
c Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
d Department of Neurology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
e Department of Biomedical Engineering, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
f Carolina Center for Neurostimulation, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
g Neuroscience Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA

ARTICLE INFO

Keywords:
- Substance use disorder
- Transcranial alternating current stimulation
- Inhibitory control
- Alpha oscillations

ABSTRACT

Background: Deficits in inhibitory control (IC) and distress tolerance (DT) are associated with substance use disorders (SUD) and post-treatment return to substance use. Transcranial alternating current stimulation (tACS) modulates the neural oscillations that are associated with the cognitive and affective mechanisms contributing to IC and DT. The aims of the current study were to examine the feasibility and acceptability of administering tACS in a community-based SUD treatment setting, and to test the effect of alpha-tACS on IC and DT.

Method: A double-blind, randomized, active sham-controlled trial of treatment-seeking adults with a SUD (N = 30, Meanage = 43.2 ± 9.8 years, 70.0% male). Participants attended two sessions and completed computerized inhibitory control and distress tolerance tasks while receiving tACS targeting the bilateral dorsolateral prefrontal cortex (DLPFC). Participants received sham-tACS and were then randomized to receive sham-, alpha-, or gamma-tACS within 2–3 days.

Results: Treatment retention was 87%. Participant self-reported belief of having received tACS and mean side effect intensity ratings did not differ across conditions, with all side effect ratings in the absent to mild range. There was a large (d = 0.83) and significant effect of alpha-tACS on inhibitory control compared to sham-tACS (β = 1.78, SE = 0.65, 95% CI: 0.41, 3.14, p < 0.01). There were no significant effects of condition on distress tolerance.

Conclusions: To our knowledge, this is the first study of tACS in adults with a SUD. Our findings provide preliminary evidence for recruitment, retention, and administration feasibility of tACS in a community-based substance use treatment program and a beneficial effect of alpha-tACS on inhibitory control.

1. Introduction

Disruptions in inhibitory control (IC), the ability to inhibit a prepotent response (Luijten et al., 2014), and distress tolerance (DT), the ability to persist in goal-directed behavior during negative affective states (Daughters et al., 2005), are associated with greater substance use frequency and poorer substance use treatment response (Ali et al., 2013a, 2013b; Billieux et al., 2010; Brown et al., 2009; Reese et al., 2019a; Strong, 2012; Tull et al., 2013), highlighting the value of developing and testing interventions that target these mechanisms in the context of SUD treatment.

IC and DT deficits are characterized by altered neural activation in the prefrontal cortex (PFC) among individuals with SUD. Both IC and DT are associated with lower neural activation in the dorsolateral prefrontal cortex (DLPFC) and DT is associated with functional connectivity between the DLPFC and anterior cingulate cortex (ACC)/ventromedial prefrontal cortex (vmPFC) (Daughters et al., 2017; Hester et al., 2004; Kaufman et al., 2003). Cortical oscillations reflect neural activation patterns and play a causal role in cognitive processing (Hellrich and Knight, 2016) by synchronization of brain areas (Fries, 2005). Oscillations in the alpha frequency band (8–12 Hz) represent an active mechanism for top-down modulation of cortical activity and is

⁎ Corresponding author.
E-mail address: daughter@unc.edu (S.B. Daughters).

https://doi.org/10.1016/j.drugalcdep.2020.108132
Received 4 March 2020; Received in revised form 26 May 2020; Accepted 10 June 2020
Available online 18 June 2020
0376-8716/ © 2020 Elsevier B.V. All rights reserved.
associated with selective engagement and disengagement of cognitive resources as a function of behavioral demands (Jensen and Mazaheri, 2010; Borghini et al., 2018). In prefrontal regions, alpha oscillations contribute to inhibitory processes (Klimesch, 2012) and goal-directed behavior (Knyazev, 2007) in healthy controls and adults with SUD (Pandey et al., 2016). Although non-invasive brain stimulation targeting the DLPCF in SUD has been associated with improvement in clinical outcomes such as craving and substance use (Coles et al., 2018; Ekhtiari et al., 2019), the findings remain inconclusive and stimulation that directly targets alpha oscillations has yet to be investigated. A test of the effect of non-invasive brain stimulation on IC and DT may provide thus clarity on the mechanisms contributing to improved clinical response.

Transcranial alternating current stimulation (tACS) is a form of non-invasive brain stimulation that modulates neural oscillations in humans by application of weak electric current to the scalp (Antal and Paulus, 2013). The underlying neurobiological mechanism of tACS is the remarkable susceptibility of neural oscillations to low-amplitude rhythmic electric fields (Fröhlich and McCormick, 2010). The oscillation modulation by tACS enhances information transfer throughout anatomically and functionally connected regions, in turn, improving cognitive processes (Battleday et al., 2014; Fröhlich et al., 2015; Herrmann et al., 2013). A unique strength of tACS is the targeted, frequency-specific stimulation of endogenous cortical oscillations (Ali et al., 2015a, 2015b; Herrmann et al., 2013; Tavakoli and Yun, 2017). Alpha-tACS is designed to modulate alpha oscillations by applying a 10 Hz stimulation current waveform and has demonstrated feasibility and efficacy in clinical populations relative to gamma-tACS (stimulation at a control frequency in the gamma band) and sham-tACS in major depressive disorder (Alexander et al., 2019). Alpha-tACS was also found to enhance top-down control of auditory networks and thereby reduce auditory hallucinations in schizophrenia (Ahn et al., 2019) and reduce pathological hyperexcitability in sensory-motor cortex in patients with chronic pain (Ahn et al., 2018). Thus, augmenting top-down control to increase IC and DT in substance use disorder represents a promising approach with significant clinical potential. Yet, tACS has not yet been investigated for SUD.

The aims of the current study were to test the (1) feasibility and acceptability of recruitment, retention, and administration of tACS in a community substance use treatment program, and (2) effect of alpha-tACS targeting the bilateral DLPCF on IC and DT compared to two comparison conditions, among treatment-seeking adults with a SUD. It was hypothesized that participants randomized to receive alpha-tACS would demonstrate significantly greater IC and DT compared to those randomized to the comparison conditions.

2. Method

2.1. Participants

Study participants (N = 30; 70.0 % male; 63.3 % White/Caucasian, 26.7 % Black/African American; Mean age = 43.2 ± 7.74 years; Mean education level = 12.7 ± 3.6 years) were recruited at community-based SUD treatment centers via announcements and fliers. Inclusion criteria were age 18–55 years, current DSM-5 SUD (American Psychiatric Association [APA], 2013), and ability to read English at a fifth grade reading level (Word Reading Subtest of the Wide Range Achievement Test – Revised [WRAT-R]; Jastak and Wilkinson, 1984)). Exclusion criteria were current DSM-5 psychotic disorder (APA, 2013) and electrical stimulation safety contraindications including current use of antiepileptic medications or benzodiazepines, history of significant head or traumatic brain injury, prior brain surgery, brain devices or implants, electroconvulsive therapy (ECT) within the past six months, or pregnancy/nursing. The study was approved by the University of North Carolina at Chapel Hill Institutional Review Board and participant safety was monitored by the North Carolina Translation and Clinical Sciences Institute Data and Safety Monitoring Board.

2.2. Study design and procedure

This was a pre-registered (ClinicalTrials.gov NCT03122587) double-blind, randomized, active sham-controlled trial with three tACS conditions (sham-, alpha-, and gamma-tACS). Participants received sham-tACS at session 1 (S1) and were randomized to receive the experimental tACS condition within 2–3 days at session 2 (S2). The primary outcome variables, inhibitory control and distress tolerance, were assessed at S1 and S2. Randomization was stratified based on number of days abstinent at S1 (< 30, 30–90, > 90 days), and occurred prior to the S1 assessment of IC and DT. Thirty-eight participants were randomized and completed S1, 33 (87 %) completed S2, and 30 (80 %; n = 10 in each condition) had complete data for inclusion in study analyses (see Consort Diagram, Figure S1).

2.3. Electrode montage and tACS paradigm

Two electrodes (5 × 5 cm) were placed over F3 and F4 (corresponding to the left and right DLPCF, respectively), and a third return/reference electrode (5 × 7 cm) over Cz. The Pulvinar Neuro XCSITE 100 stimulator (Chapel Hill, NC) delivered a 2 mA peak-to-peak amplitude current between the F3/F4 (2 mA peak-to-peak at each electrode) and Cz (4 mA peak-to-peak) sites. All conditions used a ramping up and out procedure (60 s each) to reduce and equate skin sensations at stimulation onset. Alpha-tACS stimulation was set to 10 Hz, gamma-tACS to 40 Hz, and sham-tACS consisted of ramping up and out at 10 Hz for a total of 120 s of stimulation. Total stimulation time was 40 min, inclusive of the ramping up and out procedure and study tasks (Go/No Go and PASAT-C). Each stimulation session was recorded as applied waveforms and subsequently verified.

2.4. Study measures

Participants reported sociodemographic information, severity of nicotine dependence (Fagerstrom Test for Cigarette Dependence [FTCD]; Heatherton et al., 1991), stimulation side effects (Adverse Effects Stimulation Questionnaire [AESQ]; Mellin et al., 2018) and their belief of whether they received active tACS. Trained interviewers assessed for DSM-5 psychotic disorder and SUD (Mini International Neuropsychiatric Interview [MINI] 7.0; Sheehan et al., 1998) and the number of days abstinent from substance use (Timeline Followback [TLFB]; Sobell and Sobell, 1990).

Inhibitory control (IC) was assessed with the computerized Go/No-Go task (Altamirano et al., 2011) and measured by calculating d-prime (z(hit rate) – z(false alarm rate)), reflecting how well individuals discriminated and correctly responded to Go (X) and No-Go (Y) stimuli (Schulz et al., 2007; Wikens, 2002). Distress tolerance was assessed with the computerized Paced Auditory Serial Addition Task (PASAT-C; Lejuez et al., 2003; Reese et al., 2019b), a working memory task that is titrated in real time to participant skill level, increases in difficulty over time, and results in forced failure and negative feedback (i.e., explosion sound) for missed or incorrect responses. Participants have the option to quit the task at any point during the final round. Distress tolerance is measured as latency until task termination (quitting the task) during the final round, with a maximum duration of 15 min. A composite measure of affective distress is calculated at pre-task and prior to the final round from participants self-reported anxiety, frustration, irritability, difficulty concentrating, and physical discomfort (0 none to 100 [extreme]). Motivation to perform well on the task was self-reported (0 not at all to 10 [extremely]) upon task completion and prior to the participant receiving performance feedback.
Table 1
TACS condition effects.

<table>
<thead>
<tr>
<th>Perception/Received Active TACS</th>
<th>n</th>
<th>Sham-tTACS (n=10)</th>
<th>Alpha-tTACS (n=10)</th>
<th>Gamma-tTACS (n=10)</th>
<th>Alpha vs. Sham</th>
<th>Gamma vs. Sham</th>
<th>Alpha vs. Gamma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes, No/Don’t Know</td>
<td>5, 5</td>
<td>6, 4</td>
<td>7, 3</td>
<td>0.63, 0.10±0.16</td>
<td>0.73, 0.27±1.99</td>
<td>0.57, 0.08±3.89</td>
<td></td>
</tr>
<tr>
<td>Side Effects</td>
<td>Mean ± SD</td>
<td>1.16 ± 0.16</td>
<td>1.48 ± 0.35</td>
<td>1.51 ± 0.40</td>
<td>0.67 ± 0.22</td>
<td>0.12 ± 0.07</td>
<td>0.00 ± 0.14</td>
</tr>
<tr>
<td>AESQ Total Score</td>
<td>1.16 ± 0.16</td>
<td>1.48 ± 0.35</td>
<td>1.51 ± 0.40</td>
<td>0.67 ± 0.22</td>
<td>0.12 ± 0.07</td>
<td>0.00 ± 0.14</td>
<td></td>
</tr>
<tr>
<td>Inhibitory Control (IC)</td>
<td>Go/NoGo d-prime</td>
<td>−0.62 ± 2.03</td>
<td>0.94 ± 1.72</td>
<td>−0.32 ± 1.89</td>
<td>1.78 ± 0.65±**</td>
<td>0.25 ± 0.35</td>
<td>−1.32 ± 0.66</td>
</tr>
<tr>
<td>Distress Tolerance (DT)</td>
<td>A Latency to quit PASAT-C (min)</td>
<td>0.39 ± 2.84</td>
<td>0.60 ± 3.17</td>
<td>−1.43 ± 3.02</td>
<td>0.05 ± 0.17</td>
<td>0.07</td>
<td>−0.26 ± 0.21</td>
</tr>
</tbody>
</table>

Note: *All models control for session 1 values; †† Scale included 1=Yes, 2=No, 3=Don’t know but only 1 participant rated No (alpha-tTACS) so this item was combined with Don’t Know; AESQ = Adverse Effects Stimulation Questionnaire (1 = absent, 2 = mild, 3 = moderate, and 4 = severe); min = minutes; Δ = change from session 1, β = Unstandardized Beta; SE = Standard Error; d = Cohen’s d effect size. *p < 0.01.

3.2. Identification of covariates

Participant substance use characteristics are reported for each condition in Table S1. There were no significant differences across conditions in the number of days abstinent from alcohol or drug use (M ± SD = 59.9 ± 27.4), DSM-V SUDs including alcohol (n = 18), cocaine (n = 15), opiate (n = 8), cannabis (n = 7), or the total number of SUDs (M ± SD = 2.7 ± 1.5). The alpha-tTACS condition reported a higher level of cigarette dependence (FTCD; M ± SD = 3.2 ± 2.6) than the sham-tTACS condition (F(1,18) = 5.60, p < .05), yet FTCD score was unrelated to S1 IC (r = 0.09, p = 0.64) or DT (r = -0.04, p = 0.85), and therefore not included as a covariate. There were no significant associations between participant characteristics or condition with S1 DT or IC task performance.

3.3. Effect of tTACS on inhibitory control and distress tolerance

The inhibitory control alpha-tTACS vs. sham-tTACS model was significant (Table S1, Fig. 1), with participants in the alpha-tTACS condition demonstrating significantly greater IC than sham-tTACS (Cohen’s d = 0.83; β = 1.78, SE = 0.65, 95% CI: 0.41, 3.14). There were no additional condition effects on IC.

A 2 (pre-, post-task) x 3 (condition) repeated measures ANOVA confirmed a significant increase in self-reported distress during the DT task for S1 [F(1,27) = 27.9, p < 0.001] and S2 [F(1,27) = 29.4, p < 0.001], with no significant time by condition interactions. DT was calculated as a change score (session 1 DT subtracted from session 2 DT) due to the non-normality (positive skew) of the data (Castro-Schilo and Grimm, 2018). There were no condition effects on DT.

4. Discussion

The current study tested the feasibility and acceptability of administering transcranial alternating current stimulation (tTACS) at a community substance use treatment program, and the effect of alpha-tTACS targeting the bilateral dorsolateral prefrontal cortex (DLPFC) on inhibitory control (IC) and distress tolerance (DT), among treatment-seeking adults with substance use disorder (SUD).

In support of feasibility and acceptability, retention was high (87%) and there was no effect of active tTACS on retention, self-reported side effect intensity, or successful blinding. Low self-reported intensity of stimulation side effects support previous reports suggesting transcranial electric stimulation (tES) may be a better tolerated approach compared to transcranial magnetic stimulation (TMS) as tACS and tDCS produce less acoustic noise and side effects (e.g., skin sensations, muscle twitching) than tTMS (Antal and Paulus, 2013). There were no serious adverse events, which is consistent with other tTACS studies (Matsumoto...
and Ugawa, 2017). Participant sociodemographic and substance use characteristics were not associated with retention, suggesting that tACS may be feasible across substance use diagnoses and current length of abstinence.

As expected, alpha-tACS had a large and statistically significant effect on IC compared to sham-tACS and although not reaching statistical significance, a medium to large effect compared to gamma-tACS. This prediction was based on findings that tACS entrains oscillatory activity, thereby enhancing information transfer and processing speed (Antal and Paulus, 2013), and that alpha oscillations are an established marker of IC (Jensen and Mazaheri, 2010; Knyazev, 2007). Further, alcohol use disorder (AUD) is associated with lower alpha power in frontal regions during inhibitory control relative to healthy controls (Kaufman et al., 2003; Pandey et al., 2016). Despite the important role of IC in SUD and substance use treatment response (Lubman et al., 2004; Luijten et al., 2014), interventions for IC have yet to establish empirical support (Alom et al., 2016; Sofuoglu et al., 2013). The current findings suggest that further research testing the effect of alpha-tACS on IC is warranted. If fruitful, alpha-tACS administered concurrently with empirically supported behavioral treatment programs for SUD may be a promising treatment approach to improve SUD outcomes.

Contrary to expectation, alpha-tACS did not have a significant effect on DT. The prediction that alpha-tACS would have a significantly positive effect on DT was based on theory and reports implicating cognitive control networks on DT (e.g., Reese et al., 2019b). However, it is possible that alternative oscillation frequencies may be implicated in distress tolerance. For instance, theta and delta oscillations are also implicated in emotion regulation and motivational processes, respectively (Knyazev, 2007). Although expanding the investigating of oscillations implicated in DT to alternative frequencies is warranted, we also recommend the replication of the current study with methodological adjustments. A ceiling effect was observed for DT, such that fifty-five percent of the sample persisted for the entire duration of the task during both session 1 and session 2. Although our analytic approach accounted for this positive skew, our findings may not be reliable given the inability to measure change in over half of the sample. As such, future work replicating these findings is encouraged prior to rejecting an effect of alpha-tACS on DT.

A number of limitations are of note. The sample included patients enrolled in intensive outpatient substance use treatment with varying lengths of completed abstinence, limiting the generalizability of our findings to other treatment settings. The study was not powered to detect effects warranting the interpretation of effect size estimates in the current study and replication in future research. These findings are also limited to the effect of a single administration of tACS during task performance, thus it is also important for future work to focus on rational design (Kurmann et al., 2018) for experimental parameters, such as individualized frequency stimulation, dose, and duration to achieve durable modulation of circuit dynamics that outlast the duration of the stimulation (Ektiari et al., 2019; Herrmann et al., 2013). Recent studies in other psychiatric illnesses support such long-term effects of tACS in response to stimulation paradigms that include multiple, daily stimulation sessions (Ahn et al., 2019; Alexander et al., 2019). Intriguingly, persistent changes in alpha oscillations by alpha-tACS have been shown to depend on a common polymorphism in the gene that encodes brain-derived neurotrophic factor (Riddle et al., 2020), a protein involved in synaptic plasticity. Despite these limitations, this study contributes novel findings on the feasibility and acceptability of administering tACS onsite at a community-based substance use treatment program and the effect of alpha-tACS on IC, setting the stage for future research.

Contributors

SBD, RMC, FF, and JYY developed study concept and methodology.

JYY and RDP collected the data. SBD and JYY analyzed the data and drafted the manuscript. All authors provided input on manuscript drafts and approved the final version of the manuscript.

Role of funding source

Nothing declared.

Declaration of Competing Interest

FF is the founder, majority owner, and chief scientific offer of Pulvnar Neuro. The company played no role in the design, execution, or analysis of this study. FF did not have access to any of the data and was not involved in the analysis.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2020.108132.

References

Daughters, S.B., Ross, T.J., Bell, R.P., Yi, J.Y., Ryan, J., Stein, E.A., 2017. Distress tolerance among substance users is associated with functional connectivity between

4


