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Transcranial Direct Current Stimulation for the Reduction of Alcohol Craving

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by

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DEDICATION

I dedicate this work to my parents, Gary L. Rudder, M.D., and Margaret L. Rudder, for a lifetime of support, encouragement, and love.

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ABSTRACT

Background: Craving is implicated the maintenance of alcohol abuse and dependence as well as relapse during attempts at recovery. An early investigation by Boggio et al. (2008b) demonstrated that transcranial direct current stimulation (tDCS) applied over dorsolateral prefrontal cortex (DLPFC) was effective in reducing craving among individuals with alcohol dependence. The present study is the first to continue to explore the potential of tDCS to manipulate craving in the context of alcohol use and abuse. *Methods:* 18 adult participants completed assessments of alcohol abuse severity, and of alcohol craving and mood before and after transcranial stimulation. Active and sham tDCS of DLPFC was utilized in two separate experimental sessions. The protocol was revised midway through the study to include potential induction of craving through the visual presentation of alcohol cues.

Results: Within the revised protocol, a comparison of pre- to post-stimulation difference scores for active versus sham stimulation produced a reduction in craving that approached significance ($p = .06$). A comparison of pre- to post-stimulation scores for active stimulation produced a significant reduction in craving ($p = .03$), whereas a comparison of pre- to post-stimulation scores for sham stimulation was nonsignificant ($p = .42$). A significant linear relationship existed between response to active stimulation and both alcohol abuse severity and retrospective accounts of alcohol craving. *Conclusions:* The findings showed that tDCS applied to the DLPFC may be effective in reducing alcohol craving among individuals with alcohol use disorders who experience frequent or intense cravings. The use of minimum cutoff scores on assessments of alcohol abuse severity and alcohol craving may aid in identifying individuals who would benefit from tDCS treatment. Additional research may demonstrate the utility of noninvasive brain stimulation in clinical alcohol abuse treatment settings.

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Introduction

The prevalence of alcohol abuse and dependence is relatively high. It is estimated that 17.8% of the U.S. population meets the DSM-IV diagnostic criteria for alcohol abuse during their lifetime, with another 12.5% meeting the criteria for alcohol dependence during their lifetime (Hasin, Stinson, Ogburn, & Grant, 2007). Excessive alcohol consumption is the third leading cause of preventable death in the United States (Bird, Choudhry, Molina, & Kovacs, 2009). Many pharmacological treatment options target alcohol craving. However, these medications often entail unpleasant side effects and may cause adverse reactions.

Craving can play a critical role in the development and maintenance of alcohol dependence, and has been implicated in relapse (Drummond, 2001; Tiffany & Conklin, 2000). The International Classification of Diseases defines craving as a strong desire or compulsion to take to take a psychoactive drug and includes it as an optional diagnostic criterion for addiction (WHO, 1992). There previously was some lack of consensus regarding the role of craving in the maintenance of alcohol dependence, as evidenced by the fact that craving is not included in the diagnostic criteria for alcoholism in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (APA, 2000). However, craving will be added to the list of diagnostic criteria for substance use disorders in the DSM-5 (APA, 2013). Many clinicians and researchers assert that the reduction or elimination of cravings is a worthwhile target in the treatment of addiction. This has led to numerous pharmacological interventions, including naltrexone, acamprosate, gamma-hydroxybutryric acid (GHB), baclofen, topiramate, and selective serotonin reuptake inhibitors (SSRIs), particularly fluoexitine (Addolorato, Abenavoli,

Leggio, & Gasbarrini, 2005). Unfortunately, drug therapies can entail numerous adverse reactions, ranging from minor side effects such as dry mouth (National Library of Medicine, 2009) and constipation (National Library of Medicine, 2012), to more serious side effects such as confusion and hallucinations (National Library of Medicine, 2009), to extremely serious side adverse reactions such as coma and even death (LeTourneau, Hagg, & Smith, 2008). Therefore, a non-pharmacological intervention for the reduction of craving in alcohol users would be a valuable addition to the treatment arsenal for addiction.

Transcranial Direct Current Stimulation: A Non-pharmacological Method to Modulate Brain Function

Transcranial direct current stimulation (tDCS) is the application of a weak electrical current (1 to 2mA) to the scalp in order to modulate the activity of neurons in the brain. Researchers are exploring the use of tDCS to enhance a variety of brain functions, such as visuomotor skills (Antal, Begemeier, Nitsche, & Paulus, 2008; Antal et al., 2004; Antal, Nitsche, Kruse, Hoffmann, & Paulus, 2004), declarative and working memory (Elmer, Burkard, Renz, Meyer, & Jancke, 2009; Fregni, et al., 2005; Javadi & Walsh, 2012; Loo et al., 2012; Marshall, Mölle, Hallschmid, & Born, 2004; Ohn et al., 2008; Tseng, 2012), attention (Coffman, Trumbo, & Clark, 2012; Jacobson, Goren, Lavidor, & Levy, 2012; Kang, Kim, & Paik, 2012; Stone & Tesche, 2009) and accelerated learning (Clark et al., 2012, Cohen, Soskic, Luculano, Kanai, & Walsh, 2010; Galea & Celnik, 2009; Flöel, Rösser, Michka, Knecht, & Breitenstein, 2008). TDCS also is being investigated in numerous clinical applications, including tinnitus (Frank et all,

2012; Fregni et al., 2006b), fibromyalgia (Fregni et al., 2006a, Roizenblatt et al., 2007), depression (Bikson et al., 2008; Boggio et al., 2008a; Loo & Mitchell, 2005; Loo et al., 2012; Murphy, Boggio, & Fregni, 2009; Palm et al., 2012; Schutter & van Honk, 2005), Alzheimer's disease (Boggio et al., 2009a; Ferrucci et al., 2008), and stroke (Celnik, Vandermeeren, Dimyan, & Cohen, 2009; Edwards et al., 2009; Hesse et al., 2007; Hummel et al., 2005; Jo et al., 2009).

Advantages of tDCS

Transcranial direct current stimulation (tDCS) has several features that are attractive for both clinical and basic research studies. It is inexpensive, noninvasive, and considered to be "low risk." The stimulation current is generated by a 9 volt battery, which is delivered via sponge electrodes applied to the scalp. A fraction of the current passes into the brain, inducing a change in the excitability of neuronal tissue (Berlim, Neto, & Turecki, 2009). Additional advantages include its portability and ease of use (Fregni, Boggio, Nitsche, & Pascual-Leone, 2005; Nitsche et al., 2003). Importantly, both transcranial magnetic stimulation (TMS) and tDCS can be used to identify brain regions or networks that are critical for a behavior or function, with the distinct advantage that participants can serve as their own controls via the use of sham stimulation (for a discussion relevant to tDCS, see Gandiga, Hummel, & Cohen, 2006).

The behavioral effects of single tDCS sessions tend to be short-lived, persisting for a maximum of about 30 minutes (Stagg & Nitsche, 2011). However, the duration of brain activity modulation varies with the duration of stimulation, and changes can continue beyond the period of stimulation (Javadi & Walsh, 2011; Nitsche & Paulus,

2001). Daily, spaced sessions can produce behavioral effects that persist for several weeks (Boggio et al., 2007; Reis et al., 2009; Stagg & Nitsche, 2011). Typically, tDCS is applied for 20 minutes (Berlim, Neto, & Turecki, 2009).

Boggio et al. (2008b) found that tDCS applied to the dorsolateral prefrontal cortex (DLPFC) reduced craving among individuals with alcohol dependence. However, after a thorough search of the literature, it does not appear that any replications of the Boggio et al. study have been published. The reasons for this are not known. The present study is a modification of the Boggio et al. study. Based on the results obtained by Boggio et al., it was hypothesized that tDCS over the DLPFC would reduce craving among alcohol users. The results of the present study will serve to expand the knowledge base pertaining to the efficacy of tDCS in reducing craving for alcohol.

Neurobiology of Craving

TDCS shows promise in the reduction of cravings. It has been studied in reducing cravings for smoking (Boggio et al., 2009b; Fregni et al., 2008a), foods (Fregni et al., 2008b; Goldman et al., 2011), marijuana (Boggio et al., 2010) and alcohol (Boggio et al., 2008b). The current study investigated the use of tDCS in reducing cravings among alcohol abusers. Neurobiologically, craving is related to the reward center in the medial forebrain bundle, which comprises the mesocorticolimbic dopamine pathway (Park, Sohn, Kim, Sohn, & Sparacio, 2007); the dorsolateral prefrontal cortex (DLPFC) is associated with craving through mesofrontolimbic connections (Boggio et al. 2008b). Neuroimaging studies demonstrate that the DLPFC is a major component of the neural substrate for alcohol craving (Boggio et al., 2008b). Research indicates that tDCS

stimulation of the DLPFC diminishes risk-taking behavior in normal adults (Fecteau et al., 2007a,b), modulates risk-taking in marijuana users (Boggio et al., 2010) and reduces alcohol cravings (Boggio et al., 2008b). In addition, repetitive transcranial magnetic stimulation (rTMS) applied to the DLPFC has been demonstrated to reduce alcohol cravings among alcohol dependent individuals (Mishra, Nizamie, Das, & Praharaj, 2009). These studies provide the rationale for targeting the DLPFC to reduce cravings in the present study.

Comparison to Existing Literature

As mentioned previously, the present study was a modification of the Boggio et al. (2008b) study. The main deviations from the aforementioned study and the rationale for these deviations were as follows:

1. Boggio et al. recruited research participants with a mean age of 41.3 who met the diagnostic criteria for alcohol dependence as defined by the DSM-IV-TR. In the present study, participants were recruited from a pool of undergraduate psychology students with a mean age of 23.8. Although the study was advertised as pertaining to problematic alcohol use, not all participants met the criteria for alcohol abuse. Some rarely consumed alcohol. The choice of recruiting from the undergraduate psychology research participant pool primarily was driven by necessity, as it was not possible to provide financial compensation for participation. However, it is possible that this recruitment method could produce results that are specifically applicable to college-age students, a population that is of interest to educators and policymakers. It also potentially could lead to the

development of interventions targeted to young adults who are in the process of developing problematic drinking behaviors but who do not yet meet the diagnostic criteria for alcohol abuse or dependence

2. Boggio et al. administered baseline assessments of craving, then increased craving using alcohol cues, reassessed craving, then administered sham or active tDCS, and finally, reassessed craving a third time. During the second protocol of the present study, alcohol cues were utilized in an attempt to increase craving, then craving was assessed, sham or active tDCS was applied, and finally, craving was reassessed a second time. The rationale for assessing craving only twice primarily was motivated by the limitations of recruiting from the undergraduate psychology research participant pool as the duration of each visit was about 4 hours, and the undergraduate participants were limited to 4 hours of research participation.
3. Although the Boggio et al. paper initially asserted that it utilized a double-blind design, the authors subsequently clarified that "participants and the evaluating investigators (except the investigators that applied the tDCS) were blinded to the treatment arm)" (p. 56). In the present study, participants were blinded to whether they were receiving active or sham stimulation. The investigator was aware of the stimulation condition with regard to both the application of stimulation and the evaluation of the results. Care was taken to behave identically during both active and sham stimulation sessions; however, the lack of a double-blind condition potentially could bias the study results and is acknowledged as a limitation. In addition, the lack of a double-blind design this should not be an issue with regard to the assessments that were not directly related to the measurement of craving as

mediated by tDCS (i.e., demographics and AUDIT). Therefore, any significant effects found within those data should be free of bias resulting from the lack of a double-blind design.

4. Boggio et al. applied anodal left/cathodal right stimulation, anodal right/cathodal left stimulation, and sham stimulation. The present study utilized only anodal left/cathodal right stimulation and sham stimulation. This was done for the purpose of simplifying the protocol as Boggio et al. found that "both strategies of DLPFC stimulation, that is, anodal left/cathodal right and anodal right/cathodal left stimulation, resulted in craving reduction" (p. 59).

Methods

Twenty-one participants were recruited via flyers posted around the University of New Mexico campus and via a web-based human subject pool management program developed for universities. The study design entailed each participant receiving both active and sham stimulation in separate visits spaced 3 to 7 days apart. During active stimulation, 2mA was applied for 20 minutes over the scalp using a NeuroConn DC Stimulator. The left DLPFC was identified using the 10-20 electrode placement system. Research demonstrates that the left DLPFC is located between the F3 and F5 electrodes, closer to F5 (Rusjan et al., 2010). Using this method, the anodal electrode was positioned over the left DLFPC at the approximate location of F5, and the cathodal electrode over the right DLFPC near F6. Sham stimulation entailed applying 2mA of stimulation for only the first 15 seconds of the session, so that the research participants felt the initial tingling sensation experienced during true active stimulation.

The research protocol was revised midway through the study. During the first protocol, participants completed the following instruments and tasks in this order:

1. Informed consent agreement.
2. Informed Consent Understanding Assessment. This consists of 9 true/false questions regarding the information contained in the consent form. If the participant answered any of the questions incorrectly, I reviewed the information to ensure that he/she understood.
3. Potential Applicant Screening Interview. This consists of 8 questions pertaining to various health conditions that could affect eligibility to participate:
    1) Have you ever had epilepsy, a stroke, or encephalitis?
    2) Have you ever had a concussion or head injury resulting in loss of consciousness?
    3) Have you ever been diagnosed with dementia or Alzheimer's disease?
    4) Have you ever been diagnosed with any other neurological disorder such as Parkinson's Disease, ALS, or Multiple Sclerosis?
    5) Have you ever been diagnosed with any mental illness?
    6) Have you ever been diagnosed with any form of heart disease?
    7) Are you currently on any form of medication or do you anticipate being on any form of medication at study time (date)?
    8) Are you pregnant or do you think you'll become pregnant by study time (date)?
4. Demographics form including information pertaining to age, sex, race/ethnicity, and education level.

5. Alcohol Use Disorders Identification Test (AUDIT; Babor, de la Feunte, Saunders, & Grant, 1989). This instrument was developed by the World Health Organization and is appropriate for use in a variety of cultural settings. It consists of 10 questions that have reliably identified high-risk drinkers: 3 questions about alcohol use, 4 questions about alcohol dependence, and 3 questions about problems resulting from drinking.
6. The Quick Mood Scale (QMS, Woodruffe-Peacock, Turnbull, Johnson, Elahi, & Preston, 1998). This is a 12-item assessment of current mood state designed specifically for use in clinical pharmacology studies.
7. The Alcohol Urge Questionnaire (AUQ, Bohn, Krahn, & Staehler, 1995). This consists of 8 questions assessing drinking urges, cravings, and reactivity to alcohol.
8. The Penn Alcohol Craving Scale (PACS; Flannery, Volpicelli, & Pettinati, 1999). This consists of 5 questions assessing the frequency, duration, and intensity of alcohol craving, as well as the ability to resist drinking.
9. An alcohol cue task (Pulido, Brown, Cummins, Paulus, & Tapert, 2010). The task uses 44 beverage pictures (22 alcohol and 22 non-alcohol) and 44 degraded stimuli, which were randomized with 15 fixation periods of 3 different durations (i.e., 2, 4, and 6 seconds to model the hemodynamic response) and programmed in E-Prime. The 8-minute task was run twice consecutively for a total of 16 minutes.
10. Either 20 minutes of tDCS stimulation at 2mA or 20 minutes of sham stimulation while chatting with the participant about school, work, etc.

11. Repeated the QMS, AUQ, and PACS.

Analyses of the data obtained from the first 10 participants returned null results on all pre- to-post measures. A power analysis determined that if any true effect were occurring as a result of active stimulation, a sample size of more than 100 participants would be necessary in order to detect it. However, many of the participants reported that the alcohol cue task induced feelings of alcohol craving. It therefore seemed plausible that the alcohol cue task could be used as a method of "creating cravers." An amended protocol therefore was submitted to the Institutional Review Board. The revised second protocol entailed administering the alcohol cue task prior to administering the QMS, AUQ, and PACS, and then re-administering these measures following active or sham stimulation. In addition, it was determined that all participants should engage in the same task during active/sham stimulation in order to reduce potential variance resulting from differences in "chat" content. Thus, participants in the second protocol received either 20 minutes of tDCS stimulation at 2mA or 20 minutes of sham stimulation while viewing a neutral slideshow portraying images of landscapes.

Data Analysis

All statistical analyses were performed using SPSS version 19.0 (IBM Corp., 2010) and G*Power 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007). All analyses were performed within the total sample, the first protocol, and the second protocol.

Demographics.

Frequency analyses were used to determine the total number of participants, number of participants who received active or sham stimulation, number of participants

who failed to return for the second visit, and how many of the participants' failures to return for the second session resulted in missing active stimulation data or missing sham stimulation data. Frequency analyses also were used to determine the number of participants by sex, race, and education level. Measures of central tendency were calculated to report the mean, median, and modal ages of the participants. Chi-square analyses were used to determine whether participants in the first and second protocols exhibited significant differences in sex, race, or education level. Independent samples t-tests were used to determine whether participants in the first and second protocols exhibited significant differences with regard to age.

Alcohol Use Disorders Identification Test (AUDIT).

Total scores were calculated. Possible scores on the AUDIT range from 0 to 40. A total score of 8 or more is a recommended indicator of alcohol-related problems. The instrument contains subscales for consumption at a hazardous level (a score greater than zero on items 2 or 3), the presence or incipience of alcohol dependence (a score greater than zero on items 4-6), and the experience of alcohol-related harm (a score greater than zero on items 7-10). Measures of central tendency were computed to determine the mean, median, and modal scores. Frequency analyses determined the number of participants who exhibited alcohol-related problems, hazardous alcohol use, the presence or incipience of alcohol dependence, and the experience of alcohol-related harm. Frequency analyses also were used to determine the number of participants who provided various responses to the 10 questions included within the AUDIT. Paired-samples t-tests were used to determine whether participants in the first and second protocols exhibited

significant differences with regard to total AUDIT scores. Chi-square analyses were used to determine whether participants in the first and second protocols exhibited significant differences with regard to hazardous alcohol use, the presence or incipience of alcohol dependence, and the experience of alcohol-related harm.

Penn Alcohol Craving Scale (PACS).

Total scores were calculated. Possible scores on the PACS range from 0 to 30. Measures of central tendency were calculated to report the mean, median, and modal scores at pre- and post-stimulation for both active and sham stimulation. Pre- to post-stimulation difference scores were computed for active and sham stimulation. Paired samples t-tests were utilized to determine whether there were any significant differences among the difference scores for active versus sham stimulation. A one-way ANOVA was used to determine whether participants in the first and second protocols exhibited significant differences with regard to baseline scores, follow-up scores, and difference scores for both active and sham stimulation.

Alcohol Use Questionnaire (AUQ).

Total scores were calculated. Scores on the AUQ range from 8 to 56. Subtracting 8 from each score created a scale of 0 to 48. As with the PACS, measures of central tendency were calculated to report the mean, median, and modal scores at pre- and post-stimulation for both active and sham stimulation. Pre- to post-stimulation difference scores were calculated for active and sham stimulation. Paired samples t-tests were utilized to determine whether there were any significant differences among the difference scores for active versus sham stimulation. A one-way ANOVA was used to determine whether participants in the first and second protocols exhibited significant differences

with regard to baseline scores, follow-up scores, and difference scores for both active and sham stimulation.

Within the second protocol, a power analysis completed in G*Power 3.1 was utilized to determine the number of participants necessary to detect a significant effect. Pre- to post-stimulation difference scores on the AUQ were plotted against AUDIT scores and baseline (first visit) PACS scores within the first and second protocols for both active and sham treatment in order to identify potential cutoff scores for treatment efficacy. Pre- to post-difference scores on the AUQ were correlated with AUDIT and baseline PACS scores. Finally, hierarchical regression analyses were performed in order to determine whether linear relationships might exist between changes in AUQ scores and AUDIT/baseline PACS scores.

Quick Mood Scale (QMS).

Per the scoring information provided by the authors of the QMS, the 12 scales were combined into 6 subscales by taking the "positive" of each dimension (e.g., relaxed), scoring the response between 0 and 4, then subtracting the "negative" response (e.g., anxious), also scored between 0 and 4, then adding 4 to give a positive result between 0 and 8. This yielded 6 QMS scores per participant at baseline and 6 QMS scores per participant post-treatment for both the active and sham conditions. As with the PACS and AUQ, measures of central tendency were calculated to report the mean, median, and modal scores at pre- and post-stimulation for both active and sham stimulation for each of the 6 subscales. Pre- to post-stimulation difference scores were computed for each of the 6 subscales for both active and sham stimulation. Paired samples t-tests were utilized to determine whether there were any significant differences

among the difference scores for each of the 6 subscales for active versus sham stimulation. A one-way ANOVA was used to determine whether participants in the first and second protocols exhibited significant differences with regard to any baseline subscale scores, any follow-up subscale scores, and any difference scores.

Results

Demographics

Total sample.

The sample is comprised of 21 participants. Ten participants received the first protocol, and 11 received the second. Of these, 3 failed to return for the second visit, resulting in missing active stimulation data for 1 participant and missing sham data for 2 participants. Of the 18 participants who received both active and sham stimulation, 10 received active stimulation during the first visit and 8 received active stimulation during the second visit. Thirteen of the participants were male and 8 were female. Thirteen participants identified as White/Caucasian, 6 as Hispanic/Latino/Latina, 2 as Asian American/Pacific Islander, 1 as Native American/American Indian, 1 as Chicano/Chicana, and 1 as Other (an Asian international student). Sixteen participants had completed some college, 2 had obtained an Associate's degree, 1 had completed some graduate school, 1 had obtained a Master's degree, and 1 had obtained a Ph.D. Participants ranged in age from 18 to 56, with a mean age of 23.90 (SD = 8.93) and median and modal ages of 21.

Chi-square tests found no significant differences between the participants in the first and second protocols based on gender, $X^2(1, N = 21) = .53$, $p = .66$; race $X^2(1, N =$

21) = .4.96, p = .29; or education level X^2(1, N = 21) = .53, p = .29. Independent samples t-tests found no significant differences between the participants in the first and second protocols based on age t(19) = -.38, p = .70.

First protocol.

The first protocol is comprised of 10 participants. Of these, 2 participants failed to return for the second visit, resulting in missing active stimulation data for 1 participant and missing sham data for 1 participant. Of the 8 participants who received both active and sham stimulation, 5 received active stimulation during the first visit and 3 received active stimulation during the second visit. Seven participants were male and 3 were female. Four participants identified as White/Caucasian, 4 as Hispanic/Latino/Latina, 1 as Asian American/Pacific Islander, 1 as Chicano/Chicana, and 1 as Native American/American Indian. Eight participants had completed some college and 2 had obtained an Associate's degree. Participants ranged in age from 18 to 39, with a mean age of 23.1 (SD = 6.82) and median and modal ages of 21.

Second protocol.

The second protocol is comprised of 11 participants. Of these, 1 participant failed to return for the second visit, resulting in missing active data for that participant. Of the 10 participants who received both active and sham stimulation, 5 received active stimulation during the first visit and 5 received active stimulation during the second visit. Five participants received active stimulation during the first session and 6 received active stimulation during the second session. Six participants were male and 5 were female. Nine participants identified as White/Caucasian, 2 as Hispanic/Latino/Latina, 1 as Asian American/Pacific Islander, and 1 as Other (an Asian international student). Eight

participants had completed some college, 1 had completed some graduate school, 1 had obtained a Master's degree, and 1 had obtained a Ph.D. Participants ranged in age from 18 to 56, with a mean age of 24.64 (SD = 10.79), median age of 22, and multiple modal ages (18, 19, and 24).

Alcohol Use Disorders Identification Test (AUDIT)

According to the AUDIT scoring guidelines, AUDIT scores in the range of 0-7 represent the no alcohol problems, scores in the range of 8-15 represent moderate alcohol problems, and scores of 16 and above represent high level alcohol problems. In addition, points scored above 0 on questions 1 or 2 indicate hazardous alcohol consumption; points scored above 0 on questions 4, 5, or 6 indicate the presence or incipience of alcohol dependence; and points scored above 0 on questions 9 or 10 indicate the presence of alcohol-related harm. Thus some participants fell into the categories of hazardous alcohol consumption, the presence or incipience of alcohol dependence, and/or the presence of alcohol-related harm despite the fact that their total AUDIT scores indicated no alcohol problems (total AUDIT score < 8).

Total sample.

Scores on the AUDIT can range from 0 (no alcohol problems) to 40 (severe alcohol problems. AUDIT scores in the range of 8-15 represent moderate alcohol problems, and scores of 16 and above represent high level alcohol problems. Within the total sample, cores on the AUDIT ranged from 0 to 27, with a mean score of 9.95 (SD = 7.82) and median and modal scores of 8. The types of alcohol problems experienced by participants per their AUDIT scores are depicted in Table 1.

Table 1

Number of Participants per Type of Alcohol Problem, Total Sample (N = 21)

Type of Alcohol Problem	Number of Participants per Type of Problem
No alcohol problems	10
Moderate alcohol problems	5
High level alcohol problems	6
Hazardous alcohol consumption	16
Presence or incipience of alcohol dependence	12
Presence of alcohol-related harm	15

In response to question #1, "How often do you have a drink containing alcohol," 2 participants reported that they never drank alcohol, 1 reported drinking monthly or less, 4 reported drinking 2 to 4 times a month, 10 reported drinking 2 to 3 times a week, and 4 reported drinking 4 or more times a week. In response to question #2, "How many drinks containing alcohol do you have on a typical day when you are drinking," 7 participants indicated 1 or 2, 11 participants indicated 3 or 4, 2 participants indicated 5 or 6, and 1 participant indicated 7 to 9. Responses to other AUDIT questions within the total sample can be found in Tables 2 and 3.

Table 2

Number of Participants per AUDIT Response for Questions 3 through 8, Total Sample (N = 21)

AUDIT Question		Number of Participants per Response				
		Never	Less than monthly	Monthly	Weekly	Daily or almost daily
3.	How often do you have six or more drinks on one occasion?	7	7	4	3	0
4.	How often during the last year have you found that you were not able to stop drinking once you had started?	13	6	1	1	0
5.	How often during the last year have you failed to do what was normally expected of you because of drinking?	10	7	3	0	1
6.	How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	17	1	1	2	0
7.	How often during the last year have you had a feeling of guilt or remorse after drinking?	10	8	1	1	1
8.	How often during the last year have you been unable to remember what happened the night before because of your drinking?	8	9	3	1	0

Table 3

Number of Participants per AUDIT Response for Questions 9 and 10, Total Sample (N = 21)

AUDIT Question		Number of Participants per Response		
		No	Yes, but not in the last year	Yes, during the last year
9.	Have you or someone else been injured because of your drinking?	16	0	5
10.	Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	17	0	4

Independent samples t-tests revealed no significant differences between participants in the first or second protocols with regard to AUDIT scores, $t(16.27) = -.25$, $p = .80$. Chi-square analyses revealed no significant differences between groups with regard to the presence of alcohol problems, $X^2(1, 21) = .44$, $p = .67$; the presence or incipience of alcohol dependence, $X^2(1, 21) = .40$, $p = .67$; or the presence of alcohol-related harm, $X^2(1, 21) = 3.27$, $p = .15$. The groups were significantly different with regard to the hazardous alcohol consumption, $X^2(1, 21) = 5.97$, $p = .04$. The groups were quite different in this regard, as all 10 participants in the first protocol produced AUDIT scores indicative of hazardous alcohol consumption, whereas only 6 of the 11 participants in the second protocol produced AUDIT scores indicative of hazardous alcohol consumption.

First protocol.

Scores on the AUDIT within the first protocol ranged from 4 to 20, with a mean score of 9.50 (SD = 5.60), a median score of 8, and modal scores of 5 and 8. The types of alcohol problems experienced by participants within the first protocol per their AUDIT scores are depicted in Table 4.

Table 4

Number of Participants per Type of Alcohol Problem, First Protocol (n = 10)

Type of Alcohol Problem	Number of Participants per Type of Problem
No alcohol problems	4
Moderate alcohol problems	4
High level alcohol problems	2
Hazardous alcohol consumption	10
Presence or incipience of alcohol dependence	5
Presence of alcohol-related harm	9

In response to question #1, "How often do you have a drink containing alcohol," no participants within the first protocol reported that they never drank alcohol, 1 reported drinking monthly or less, 2 reported drinking 2 to 4 times a month, 6 reported drinking 2 to 3 times a week, and 1 reported drinking 4 or more times a week. In response to question #2, "How many drinks containing alcohol do you have on a typical day when you are drinking," 1 participant indicated 1 or 2, 8 participants indicated 3 or 4, 1 participant indicated 5 or 6, and no participants indicated 7 to 9. Responses to other AUDIT questions for participants within the first protocol can be found in Tables 5 and 6.

Table 5

Number of Participants per AUDIT Response for Questions 3 through 8, First Protocol (n = 10)

AUDIT Question	Number of Participants per Response				
	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
3. How often do you have six or more drinks on one occasion?	1	6	2	1	0
4. How often during the last year have you found that you were not able to stop drinking once you had started?	7	2	1	0	0
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	5	4	1	0	0
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	9	0	1	0	0
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	2	7	1	0	0
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	3	6	1	0	0

Table 6

Number of Participants per AUDIT Response for Questions 9 and 10, First Protocol (n = 10)

AUDIT Question	Number of Participants per Response		
	No	Yes, but not in the last year	Yes, during the last year
9. Have you or someone else been injured because of your drinking?	8	0	2
10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	8	0	2

Second protocol.

Scores on the AUDIT within the second protocol ranged from 0 to 27, with a mean score of 10.36 (SD = 9.68), a median score of 7, and a modal score of 3. The types of alcohol problems experienced by participants within the second protocol per their AUDIT scores are depicted in Table 7.

Table 7

Number of Participants per Type of Alcohol Problem, Second Protocol (n = 11)

Type of Alcohol Problem	Number of Participants per Type of Problem
No alcohol problems	5
Moderate alcohol problems	1
High level alcohol problems	4
Hazardous alcohol consumption	6
Presence or incipience of alcohol dependence	7
Presence of alcohol-related harm	6

In response to question #1, "How often do you have a drink containing alcohol," 2 participants within the second protocol reported that they never drank alcohol, no participants reported drinking monthly or less, 2 reported drinking 2 to 4 times a month, 4 reported drinking 2 to 3 times a week, and 3 reported drinking 4 or more times a week. In response to the question #2, "How many drinks containing alcohol do you have on a

typical day when you are drinking," 6 participants indicated 1 or 2, 3 participants indicated 3 or 4, 1 participant indicated 5 or 6, and 1 participant indicated 7 to 9. Responses to other AUDIT questions for participants within the second protocol can be found in Tables 8 and 9.

Table 8

Number of Participants per AUDIT Response for Questions 3 through 8, Second Protocol (n = 11)

AUDIT Question	Number of Participants per Response				
	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
3. How often do you have six or more drinks on one occasion?	6	1	2	2	0
4. How often during the last year have you found that you were not able to stop drinking once you had started?	6	4	0	1	0
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	5	3	2	0	1
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	8	1	0	1	1
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	8	1	0	1	1
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	8	1	0	1	1

Table 9

Number of Participants per AUDIT Response for Questions 9 and 10, Second Protocol (n = 11)

AUDIT Question		Number of Participants per Response		
		No	Yes, but not in the last year	Yes, during the last year
9.	Have you or someone else been injured because of your drinking?	8	0	3
10.	Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	9	0	2

Penn Alcohol Craving Scale (PACS)

Total sample.

Scores on the PACS can range from 0 (no craving) to 30 (extreme craving). At baseline prior to active stimulation, scores on the PACS ranged from 1 to 17, with a mean score of 8.11 (SD = 4.40), a median score of 6.5, and modal scores of 4 and 5. Following active stimulation, scores again ranged from 1 to 17, with a mean score of 7.95 (SD = 4.43), a median score of 6, and a modal score of 4. A computation of difference scores (PACS follow-up score minus PACS baseline score) produced difference scores ranging from -1 to 2, with a mean of 0 (SD = .77) and median and modal scores of 0.

At baseline prior to sham stimulation, scores on the PACS ranged from 0 to 20, with a mean score of 8.10 (SD = 5.58), a median score of 5.5, and multiple modal scores (3, 4, and 5). Following sham stimulation, scores ranged from 0 to 17, with a mean score of 7.7 (SD = 5.27), and median and modal scores of 6. A computation of difference

scores produced difference scores ranging from -4 to 2, with a mean of -.40 (SD = 1.76) and median and modal scores of 0.

A paired samples t-test comparing PACS difference scores revealed no significant difference between active and sham stimulation difference scores, $t(16) = -.98$, $p = .27$. A one-way ANOVA found no significant differences between the two protocols for baseline active PACS scores, $F(1,16) = .12$, $p = .75$; follow-up active PACS scores, $F(1, 17) = .06$, p = .81; active difference scores, $F(1, 16) = .37$, $p = .55$; baseline sham scores, $F(1, 18) = .00$, $p = .99$; follow-up sham scores, $F(1, 18) = .003$, $p = .95$; or sham difference scores, $F(1, 18) = .02$, $p = .88$.

First protocol.

At baseline prior to active stimulation, scores on the PACS ranged from 4 to 13, with a mean score of 8.5 (SD = 3.42), a median score of 8.5, and no modal score. Following active stimulation, scores ranged from 5 to 14, with a mean score of 8.22 (SD = 3.15), a median score of 7, and a multiple modal scores (5, 6, and 10). A computation of difference scores (PACS follow-up score minus PACS baseline score) produced difference scores ranging from -1 to 2, with a mean of .12 (SD = .99) and median and modal scores of 0.

At baseline prior to sham stimulation, scores on the PACS ranged from 3 to 17, with a mean score of 8.11 (SD = 5.65), a median score of 6, and a modal score of 11. Following sham stimulation, scores ranged from 0 to 17, with a mean score of 7.78 (SD = 5.07), a median score of 6, and modal scores of 5 and 6. A computation of difference scores produced difference scores ranging from -4 to 2, with a mean of -.33 (SD = 2.24) and median and modal scores of 0.

A paired samples t-test comparing PACS difference scores revealed no significant difference between active and sham stimulation difference scores, $t(6) = -.60$, $p = .57$.

Second protocol.

At baseline prior to active stimulation, scores on the PACS ranged from 1 to 17, with a mean score of 7.8 (SD = 5.22), a median score of 5.5, and modal scores of 4 and 5. Following active stimulation, scores again ranged from 1 to 17, with a mean score of 7.7 (SD = 5.50), a median score of 5, and a modal score of 4. A computation of difference scores (PACS follow-up score minus PACS baseline score) produced difference scores ranging from -1 to 1, with a mean of -.1 (SD = .57) and median and modal scores of 0.

At baseline prior to sham stimulation, scores on the PACS ranged from 0 to 20, with a mean score of 8.09 (SD = 6.45), a median score of 5, modal scores of 3 and 4. Following sham stimulation, scores ranged from 0 to 17, with a mean score of 7.64 (SD = 5.70), a median score of 6, and modal scores of 3 and 4. A computation of difference scores produced difference scores ranging from -4 to 1, with a mean of -.45 (SD = 1.37) and median and modal scores of 0.

A paired samples t-test comparing PACS difference scores revealed no significant difference between active and sham stimulation difference scores, $t(9) = .74$, $p = .48$.

Alcohol Urge Questionnaire (AUQ)

Total sample.

Scores on the AUQ can range from 0 (no craving) to 48 (extreme craving). At baseline prior to active stimulation, scores on the AUQ ranged from 0 to 36, with a mean score of 10.32 (SD = 10.07), and median and modal scores of 6. Following active

stimulation, scores ranged from 0 to 42, with a mean score of 7.63 (SD = 9.72), a median score of 6, and modal scores of 1 and 6. A computation of difference scores (AUQ follow-up score minus AUQ baseline score) produced difference scores ranging from -24 to 9, with a mean of -2.68 (SD = 7.23), a median score of -1, and modal scores of -6 and 0.

At baseline prior to sham stimulation, scores on the AUQ ranged from 0 to 23, with a mean score of 6.8 (SD = 7.51), a median score of 4.5, and a modal score of 0. Following sham stimulation, scores again ranged from 0 to 23, with a mean score of 6.25 (SD = 6.49), and median and modal scores of 0. A computation of difference scores produced difference scores ranging from -11 to 14, with a mean of -.25 (SD = 6.09) and median and modal scores of 0.

A paired-samples t-test revealed no significant differences between active and sham stimulation difference scores, $t(17) = -1.14$, $p = .27$. A one-way ANOVA revealed no significant differences between the two protocols for baseline active AUQ scores, $F(1, 17) = .90$, $p = .36$; follow-up active AUQ scores, $F(1, 17) = .38$, $p = .54$; baseline sham AUQ scores, $F(1, 18) = .61$, $p = .44$, follow-up sham AUQ scores, $F(1, 18) = .08$, $p = .78$; or sham difference scores, $F(1, 18) = .81$, $p = .38$. There was a significant difference between the two protocols for active AUQ difference scores, $F(1, 17) = 6.02$, $p = .02$. Active stimulation difference scores for the first protocol produced a mean difference of 1.11 (an increase in craving), whereas active stimulation difference scores for the second protocol produced a mean difference of -6.1 (a decrease in craving).

A correlation of AUQ pre- to post-stimulation scores and AUDIT scores was nonsignificant for active stimulation, $r(17) = -.39$, $p = .10$. AUQ difference scores for

sham stimulation showed a significant negative correlation with AUDIT scores, $r(18) = -.53$, $p = .02$. A correlation of AUQ active stimulation difference scores and baseline (first visit) PACS scores were nonsignificant for active stimulation, $r(17) = -.37$, $p = .12$. A correlation of AUQ sham stimulation difference scores and baseline PACS scores showed a significant negative correlation, $r(18) = -.48$, $p = .03$. Within the total sample, participants with lower AUDIT and baseline PACS scores were significantly less likely to show a response to sham stimulation, but were neither more or less likely to show a response to active stimulation.

First protocol.

At baseline prior to active stimulation, scores on the AUQ ranged from 0 to 18, with a mean score of 8 (SD = 11.15), a median score of 5, and a modal score of 1. Following active stimulation, scores ranged from 0 to 42, with a mean of 9.11 (SD = 12.80), a median score of 6, and no modal score. A computation of difference scores (AUQ follow-up minus AUQ baseline) produced difference scores ranging from -6 to 9, with a mean of 1.11 (SD = 4.86), a median of 1, and no modal score.

At baseline prior to sham stimulation, scores on the AUQ again ranged from 0 to 18, with a mean of 5.33 (SD = 5.54), a median score of 5, and modal scores of 0 and 6. Following sham stimulation, scores on the AUQ ranged from 0 to 13, with a mean score of 5.78 (SD = 4.21), and median and modal scores of 7. A computation of difference scores produced difference scores ranging from -11 to 14, with a mean of 1.11 (SD = 7.01), and median and modal scores of 0.

A paired-samples t-test revealed no significant difference in difference scores between active and sham stimulation, $t(7) = .28$, $p = .79$.

Pre- to post-treatment difference scores on the AUQ were plotted against AUDIT scores for both active and sham stimulation. The results are depicted in Figure 1.

a) b)

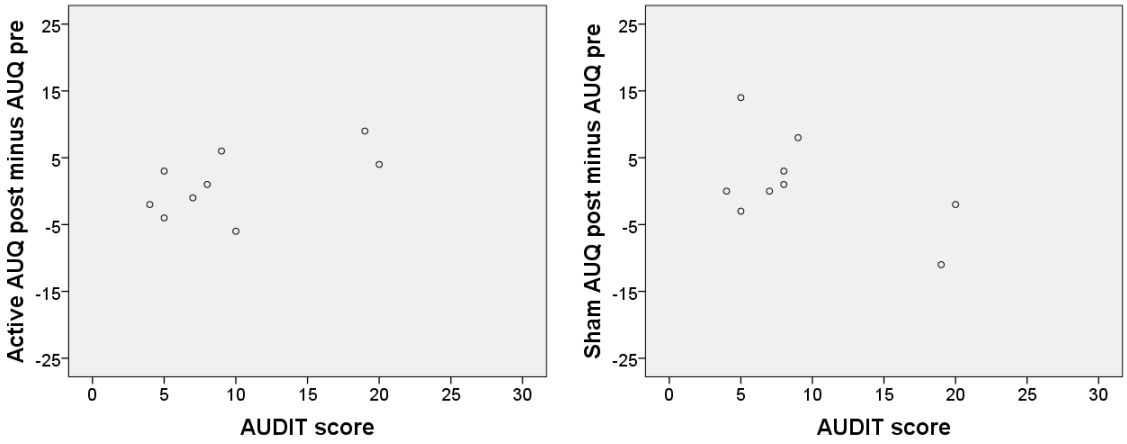


Figure 1. First protocol. Difference of AUQ scores (post tDCS minus pre tDCS) vs. AUDIT for a) active tDCS (n = 9) and b) sham tDCS (n = 9).

As with the AUDIT, pre- to post-treatment difference scores on the AUQ were plotted against baseline (first visit) PACS scores for both active and sham stimulation in order to determine cutoff scores for treatment efficacy. The results are depicted in Figure 2.

a) b)

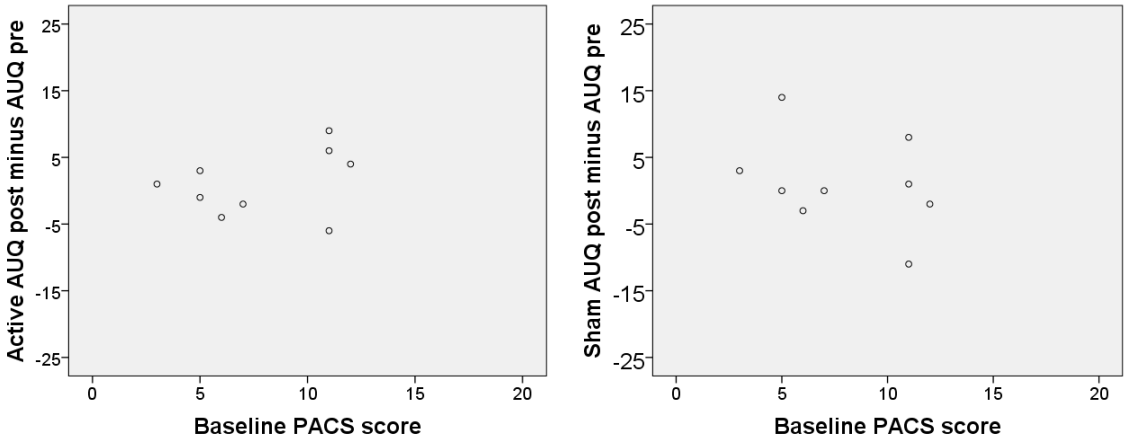


Figure 2. First protocol: Difference of AUQ scores (post tDCS minus pre tDCS) vs. baseline PACS for a) active tDCS (n = 9) and b) sham tDCS (n = 9).

A correlation of AUQ pre- to post-stimulation difference scores and AUDIT scores were nonsignificant for both active and sham stimulation, $r(7) = .59$, $p = .09$ and $r(7) = -.55$, $p = .12$. Similarly, correlations of AUQ difference scores and baseline (first visit) PACS scores were nonsignificant for both active and sham stimulation, $r(7) = .33$, $p = .39$ (active) and $r(7) = -.34$, $p = .37$ (sham). Within the first protocol, participants with lower AUDIT and baseline PACS scores were no more or less likely to show a response to active or sham stimulation.

Second protocol.

At baseline prior to active stimulation, scores on the AUQ ranged from 0 to 27, with a mean score of 12.4 (SD = 9.07), a median score of 9.5, and a modal score of 6. Following active stimulation, scores on the AUQ ranged from 0 to 17, with a mean score of 6.3 (SD = 6.29), a median score of 4.5, and modal scores of 1 and 6. Following active stimulation, scores ranged from 0 to 17, with a mean score of 6.3 (SD = 6.29), a median score of 4.5, and modal scores of 1 and 6. A computation of difference scores produced

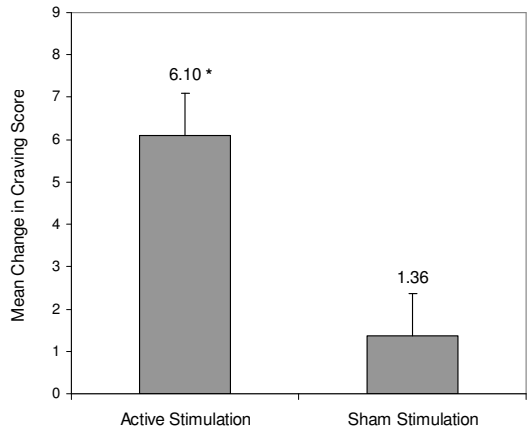
difference scores ranging from -24 to 0, with a mean of -6.1 (SD = 7.50), a median of -4.5, and a mode of 0.

At baseline prior to sham stimulation, scores on the AUQ ranged from 0 to 23, with a mean score of 8 (SD = 8.89), a median score of 3, and modal scores of 0 and 3. Following sham stimulation, scores on the AUQ again ranged from 0 to 23, with a mean score of 6.64, a median score of 4, and a modal score of 0. A computation of difference scores produced difference scores ranging from -11 to 6, with a mean of -1.36 (SD = 5.32), a median of 0, and multiple modal scores (-3, 0, and 1).

A paired-samples t-test of difference scores between active and sham stimulation revealed a result that approached significance, $t(9) = -2.14$, $p = .06$. Given that the result approached significance, a power analysis was performed using G*Power 3.1. The effect size of this result produced a Cohen's *d* statistic of .68, a medium to large effect size. Achieved power was .52. G*Power determined that in order to achieve power of .95, a sample size of 26 would be necessary. Achieving a more reasonable power of .80 would require a sample size of 15. The current sample size within the second protocol is 10 for active stimulation and 11 for sham stimulation.

Due to the near-significant result for difference scores between active and sham stimulation, paired-samples t-tests were computed to compare pre- to post-stimulation response to active and sham stimulation. The result for active stimulation was significant, $t(9) = 2.57$, $p = .03$, again with a medium to large effect size ($d = .73$). The result for sham stimulation was nonsignificant, $t(10) = .85$, $p = .42$. As mentioned previously, active stimulation produced a mean reduction in craving scores of -6.10 (SD = 7.50),

whereas sham stimulation produced a mean reduction in craving scores of -1.36 (SD = 5.32). These results are depicted in Figure 3.



*p < .05.

Figure 3. Second protocol: Difference of AUQ scores for active tDCS (n = 10) and sham tDCS (n = 11).

Pre- to post-treatment difference scores on the AUQ were plotted against AUDIT scores for both active and sham stimulation in order to determine cutoff scores for treatment efficacy. The results are depicted in Figure 4.

a) b)

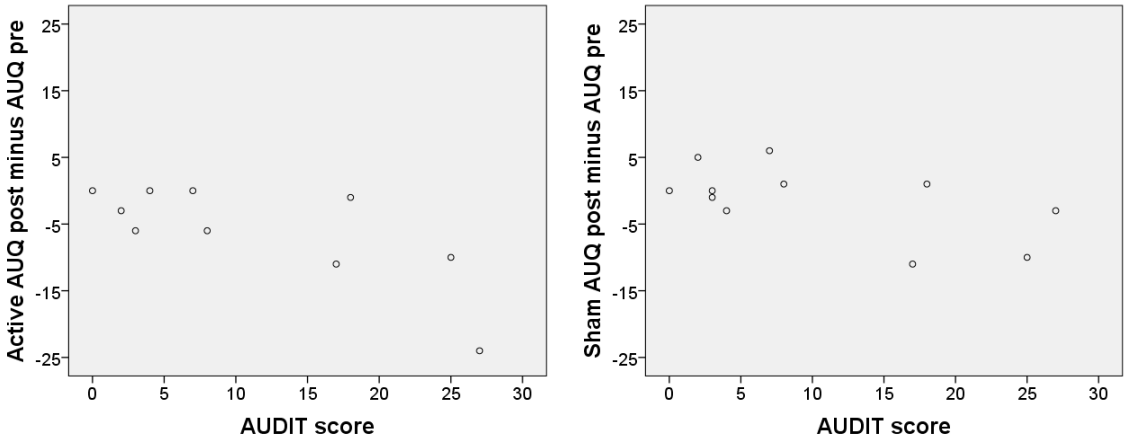


Figure 4. Second protocol: Difference of AUQ scores (post tDCS minus pre tDCS) vs. baseline PACS for a) active tDCS (n = 10) and b) sham tDCS (n = 11).

As with the AUDIT, pre- to post-treatment difference scores on the AUQ were plotted against baseline (first visit) PACS scores for both active and sham stimulation in order to determine cutoff scores for treatment efficacy. The results are depicted in Figure 5.

a) b)

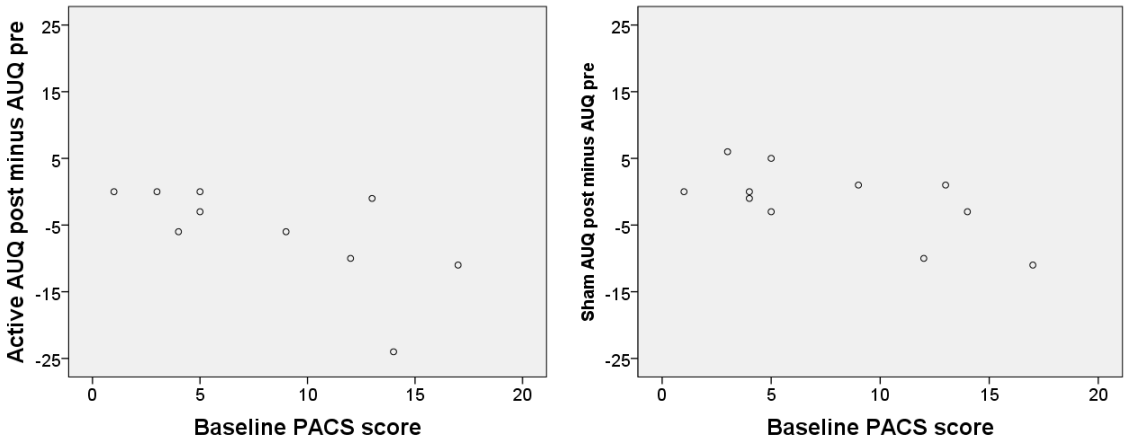


Figure 5: Second protocol: Difference of AUQ scores (post tDCS minus pre tDCS) vs. baseline PACS for a) active tDCS (n = 10) and b) sham tDCS (n = 11).

A correlation of AUQ pre- to post-stimulation scores and AUDIT scores was significant for active stimulation, $r(8) = -.75$, $p = .01$. AUQ difference scores for sham stimulation showed a near-significant negative correlation with AUDIT scores, $r(9) = -.58$, $p = .06$. Correlations of AUQ active stimulation difference scores and baseline (first visit) PACS scores were significant for both active and sham stimulation, $r(8) = -.66$, $p = .04$ (active) and $r(9) = -.65$, $p = .03$ (sham). Within the second protocol, participants with lower AUDIT and baseline PACS scores were significantly less likely to show a response to both active and sham stimulation.

Multiple regression analyses were conducted to test whether AUDIT or baseline PACS scores significantly predicted participants' response to active tDCS or sham stimulation. In the first regression analysis, the predictor variable AUDIT score was entered in step 1 and baseline PACS score was entered in step 2. The dependent variable was change in AUQ scores following active tDCS stimulation. The results of the regression indicated that AUDIT scores explained 55.8% of the variance in response to active tDCS stimulation, $R^2 = .56$, $F(1, 8) = 10.01$, $p = .01$. Adding baseline PACS scores to the model accounted for only a 0.1% increase in the predicted variance of change in AUQ scores, which was a nonsignificant result, $R^2 = .56$, $F(1, 7) = .02$, $p = .88$. Additional details can be found in Table 10.

Table 10

Summary of Hierarchical Regression Analysis for Variables Predicting Active Stimulation tDCS Response (n = 10)

	Model 1			Model 2		
Variable	B	SE B	β	B	SE B	β
AUDIT score	-.57	.18	-.75*	-.52	.37	-.68
Baseline PACS score				-.10	.68	-.07
R^2		.56		.	.56	
F for change in R^2		10.09*			.02	

*p < .05.

In the second regression analysis, baseline PACS score was entered in step 1 and AUDIT score was entered in step 2. The results of the regression indicated that baseline PACS scores explained 43.7% of the variance in response to active tDCS stimulation, $R^2 = .44$, $F(1, 8) = 6.20$, $p = .04$). Adding AUDIT scores to the model accounted for a 12.3% increase in the predicted variance of change in AUQ scores, which was a nonsignificant result, $R^2 = .56$, $F(1, 7) = .1.94$, $p = .21$. Additional details can be found in Table 11.

Table 11

Summary of Hierarchical Regression Analysis for Variables Predicting Active Stimulation tDCS Response (n = 10)

	Model 1			Model 2		
Variable	B	SE B	β	B	SE B	β
AUDIT score	-0.91	0.37	-.66*	-.10	.68	-.08
Baseline PACS score				-.52	.37	-.68
R^2		.44		.	.56	
F for change in R^2		6.20*			1.94	

*p < .05.

In the third regression analysis, the predictor variable AUDIT score was entered in step 1 and baseline PACS score was entered in step 2. The dependent variable was change in AUQ scores following sham tDCS stimulation. The results of the regression indicated that AUDIT scores explained 33.9% of the variance in response to sham tDCS stimulation, $R^2 = .34$, $F(1, 9) = 4.62$, $p = .06$. Adding baseline PACS scores to the model accounted for an 8.7% increase in the predicted variance of change in AUQ scores, $R^2 = .43$, $F(1, 8) = 1.22$, $p = .30$. These results were nonsignificant, although the amount of variance pre- to post-sham AUQ scores accounted for by the AUDIT approached significance at $p = .06$. Additional details can be found in Table 12.

Table 12

Summary of Hierarchical Regression Analysis for Variables Predicting Sham Stimulation tDCS Response (n = 11)

	Model 1			Model 2		
Variable	B	SE B	β	B	SE B	β
AUDIT score	-.32	0.15	-.58*	-.04	.30	-.07
Baseline PACS score				-.59	.54	-.59
R^2		.34		.	.43	
F for change in R^2		4.62*			1.22	

*p < .05.

In the fourth regression analysis, the predictor variable baseline PACS score was entered in step 1 and AUDIT score was entered in step 2. The results of the regression indicated that baseline PACS scores explained 42.5% of the variance in response to sham tDCS stimulation, $R^2 = .42$, $F(1, 9) = 6.66$, $p = .03$. Adding AUDIT scores to the model accounted for only a 0.1% increase in the predicted variance of change in AUQ scores, which was a nonsignificant result, $R^2 = .43$, $F(1, 8) = .02$, $p = .90$. Additional details can be found in Table 13.

Table 13

Summary of Hierarchical Regression Analysis for Variables Predicting Sham Stimulation tDCS Response (n = 11)

	Model 1			Model 2		
Variable	B	SE B	β	B	SE B	β
AUDIT score	-.65	.25	-.65*	-.59	.54	-.59
Baseline PACS score				-.04	.30	-.07
R^2		.42		.	.43	
F for change in R^2		6.66*			.02	

*p < .05.

Quick Mood Scale (QMS)

Total sample.

Scores on each of the 6 subscales of the QMS can range from 0 to 8. During active stimulation, mean baseline scores on the QMS were as follows: wide awake/drowsy = 5.16 (SD = 1.92), relaxed/anxious = 5.63 (SD = 1.26), cheerful/depressed = 6.11 (SD = 1.20), friendly/aggressive = 6.68 (SD = 1.00), clear-headed/confused = 6.00 (SD = 1.20), and well-coordinated/clumsy = 6.16 (SD = 1.54). Post-stimulation, mean scores on the QMS were wide awake/drowsy = 3.58 (SD = 2.06),

relaxed/anxious = 6.53 (SD = 1.07), cheerful/depressed = 6.26 (SD = .93), friendly/aggressive = 6.53 (SD = .77), clear-headed/confused = 5.89 (SD = 1.45), and well-coordinated/clumsy = 5.89 (SD = 1.05).

During sham stimulation, mean baseline scores on the QMS were as follows: wide awake/drowsy = 5.00 (SD = 1.76), relaxed/anxious = 5.62 (SD = 1.16), cheerful/depressed = 6.24 (SD = .94), friendly/aggressive = 6.62 (SD = .97), clear-headed/confused = 6.29 (SD = 1.10), and well-coordinated/clumsy = 6.00 (SD = 1.34). Post-sham stimulation, mean scores on the QMS were wide awake/drowsy = 3.81 (SD = 1.81), relaxed/anxious = 6.29 (SD = 1.27), cheerful/depressed = 6.10 (SD = .94), friendly/aggressive = 6.24 (SD = 1.09), clear-headed/confused = 5.86 (SD = 1.20), and well-coordinated/clumsy = 5.48 (SD = 1.50).

A one-way ANOVA found no significant differences between the two protocols for any baseline or follow-up QMS score, including difference scores, with p values ranging from .18 to .98. Paired sample t-tests of difference scores from baseline to post-stimulation revealed no significant differences, with *p* values ranging from .26 to 1.0.

First protocol.

During active stimulation, mean baseline scores on the QMS were as follows: wide awake/drowsy = 5.67 (SD = 1.32), relaxed/anxious = 5.22 (SD = .97), cheerful/depressed = 6.11 (SD = 1.05), friendly/aggressive = 6.89 (SD = .78), clear-headed/confused = 6.33 (SD = .87), and well-coordinated/clumsy = 6.44 (SD = 1.74). Post-stimulation, mean scores on the QMS were wide awake/drowsy = 3.67 (SD = 2.19), relaxed/anxious = 6.33 (SD = 1.22), cheerful/depressed = 6.11 (SD = 1.05),

friendly/aggressive = 6.44 (SD = .88), clear-headed/confused = 5.89 (SD = 1.45), and well-coordinated/clumsy = 5.89 (SD = 1.05).

During sham stimulation, mean baseline scores on the QMS were as follows: wide awake/drowsy = 4.60 (SD = 1.58), relaxed/anxious = 5.30 (SD = 1.16), cheerful/depressed = 6.10 (SD = .88), friendly/aggressive = 6.60 (SD = .97), clear-headed/confused = 6.10 (SD = .74), and well-coordinated/clumsy = 5.90 (SD = 1.73). Post-sham stimulation, mean scores on the QMS were wide awake/drowsy = 3.5 (SD = 2.07), relaxed/anxious = 6.20 (SD = 1.40), cheerful/depressed = 6.00 (SD = 1.05), friendly/aggressive = 6.30 (SD = .89), clear-headed/confused = 5.50 (SD = 1.18), and well-coordinated/clumsy = 5.50 (SD = 1.58).

Paired sample t-tests of difference scores from baseline to post-stimulation revealed no significant differences, with *p* values ranging from .13 to .88.

Second protocol.

During active stimulation, mean baseline scores on the QMS were as follows: wide awake/drowsy = 4.70 (SD = 2.31), relaxed/anxious = 6.00 (SD = 1.41), cheerful/depressed = 6.10 (SD = .99), friendly/aggressive = 6.50 (SD = 1.18), clear-headed/confused = 5.70 (SD = 1.42), and well-coordinated/clumsy = 5.90 (SD = 1.37). Post-stimulation, mean scores on the QMS were wide awake/drowsy = 3.50 (SD = 1.96), relaxed/anxious = 6.70 (SD = .95), cheerful/depressed = 6.40 (SD = .84), friendly/aggressive = 6.60 (SD = .70), clear-headed/confused = 5.50 (SD = 1.90), and well-coordinated/clumsy = 6.20 (SD = 1.23).

During sham stimulation, mean baseline scores on the QMS were as follows: wide awake/drowsy = 5.36 (SD = 1.91), relaxed/anxious = 5.91 (SD = 1.14),

cheerful/depressed = 6.36 (SD = 1.03), friendly/aggressive = 6.64 (SD = 1.03), clear-headed/confused = 6.45 (SD = 1.37), and well-coordinated/clumsy = 6.09 (SD = 1.04). Post-sham stimulation, mean scores on the QMS were wide awake/drowsy = 4.09 (SD = .1.58), relaxed/anxious = 6.36 (SD = 1.21), cheerful/depressed = 6.18 (SD = 1.05), friendly/aggressive = 6.18 (SD = 1.33), clear-headed/confused = 6.18 (SD = 1.17), and well-coordinated/clumsy = 5.45 (SD = 1.51).

Paired sample t-tests of difference scores from baseline to post-stimulation revealed no significant differences, with *p* values ranging from .17 to .85.

Discussion

As described in the previous section, the first protocol produced null results on all measures. The second protocol produced significant or near-significant findings with regard to comparisons of group means for pre- to post-stimulation difference scores on the AUQ, active versus sham pre- to post-stimulation scores, correlations of AUQ with AUDIT and baseline PACS scores, and regression analyses predicting treatment response from AUDIT and baseline PACS scores. These results are discussed in detail in the following pages.

The results of the AUDIT revealed a sample that contained a substantial number of participants with problematic drinking. Several participants indicated that they consumed 5 or more drinks containing alcohol on a typical drinking day, and that they did so on a weekly basis. Several participants reported drinking first thing in the morning, failing to fulfill obligations due to drinking, feeling guilt or remorse after drinking, experiencing blackouts, and sustaining alcohol-related injuries. According to their

AUDIT scores, more than half of participants had problems with drinking and more than a quarter had high-level alcohol problems. About three quarters of participants showed signs of hazardous alcohol consumption and/or alcohol-related harm. About half of participants exhibited the presence or incipience of alcohol dependence. It is possible that the relatively high prevalence of problematic drinking was the result of participant self-selection bias, as the recruitment flyers mentioned alcohol craving and posed the question, “Concerned about your alcohol use?” However, the sample ultimately was heterogeneous, with AUDIT scores ranging from 0 to 27. Thus the recruitment strategy was appropriate for the purpose of correlating AUDIT scores with tDCS response as measured by changes in AUQ scores.

The results pertaining to the AUQ are interesting. Although the first protocol returned null results regarding changes in craving from baseline to post-treatment for active versus sham stimulation as measured by difference scores (post-stimulation scores minus pre-stimulation scores), the results of the second protocol approached significance. This highlights the importance of inducing pre-treatment craving for alcohol studies. In addition, a comparison of pre- to post-stimulation AUQ scores for active and sham stimulation within the second protocol produced a statistically significant finding for active stimulation, but not for sham stimulation. This provides evidence that the reduction in craving within the second protocol was not the result of an expectancy or placebo effect. The second protocol included 10 participants for active stimulation and 11 participants for sham stimulation; a power analysis indicated that a sample size of 26 would be required in order to achieve a power equaling .95 and a sample size of 15 would be required in order to achieve a power equaling .80. Thus it is possible that a larger

sample size could have resulted in the detection of a significant effect with regard to difference scores. As noted by Brunoni et al. (2012), “Type II (false-negative) errors occur in small studies and are related to underpowered trials…. most phase II tDCS trials recruit small samples and are prone to this error” (p. 187).

Plots of AUDIT scores and baseline (first visit) PACS scores versus craving difference scores from pre- to post-stimulation as assessed by the AUQ also are interesting. It would appear that PACS scores above 10 and AUDIT scores above 15 are viable thresholds for treatment efficacy. Participants below these cutoffs tended to show little effect for active stimulation within both protocols. Within the first protocol, participants who scored above these cutoffs varied widely in response to active stimulation; some showed increased craving and others showed decreased craving. Within the second protocol, participants who scored above these cutoffs consistently showed decreased craving or zero change in craving. This supports the “near significant” finding within the second protocol for craving difference scores. It is possible that the use of these cutoffs as inclusion criteria could result in significant changes in craving difference scores even without increasing the current sample size of 10 (active stimulation) and 11 (sham stimulation) to the sample size of 15 necessary in order to achieve a power of .80.

The results of the correlation analyses further serves to illustrate the potential utility of establishing cutoff scores on the AUDIT and PACS as inclusion criteria. Within the total sample, participants with lower AUDIT and baseline PACS scores were significantly less likely to show a response to sham stimulation, but were neither more nor less likely to show a response to active stimulation. The strength of the relationship

between AUDIT scores and sham stimulation response was strong at 53.3%. A similarly strong relationship was found between baseline PACS scores and sham stimulation response at 48.4%. These significant correlations disappeared when examining only those participants in the first protocol; thus, the results found within the total sample likely were driven by the participants within the second protocol. Within the second protocol, participants with higher AUDIT and baseline PACS scores were significantly (or very nearly significantly) more likely to show a response to both active and sham stimulation. The strengths of these relationships were strong, ranging from 58.2% to 74.7%. The strongest of these negative relationships was seen with regard to AUDIT scores and active stimulation.

The results of the regression analyses shed additional light on the relationship between AUDIT and baseline PACS scores and treatment response. A significant linear relationship existed between response to active stimulation and both AUDIT and baseline PACS scores, though AUDIT was a better predictor than baseline PACS scores. The use of both assessments in predicting response to active stimulation is unwarranted as adding PACS to the regression model added virtually no additional predictive utility. With regard to response to sham stimulation, however, AUDIT scores were not a significant predictor of treatment response (although the result approached significance). In the case of sham stimulation, PACS was a significant predictor of treatment response. Thus, in studies using both active and sham stimulation, the use of both instruments is recommended. The reason that AUDIT was a better predictor of response to active stimulation and PACS was a better predictor of response to sham stimulation is not known. It is possible that this effect is due to the fact that the two instruments measure

different constructs. AUDIT was developed to screen for excessive drinking, hazardous (risky) drinking, and alcohol dependence. In contrast, PACS was developed to assess the frequency, intensity, and duration of alcohol cravings as well as the ability to resist drinking. It is possible that subjective recollections of recent craving predict reductions in current craving (as measured by the AUQ) in response to sham stimulation, whereas the presence or history of excessive drinking and alcohol-related negative consequences predict response to active stimulation.

Finally, the null findings for the QMS are promising. The lack of change in mood from pre- to post-stimulation indicates that potential changes in craving were not the result of changes in mood induced by the stimulation. Because the QMS was designed specifically for use in clinical pharmacology studies, this is appears to be a valuable instrument to control for changes in mood in future tDCS study replications.

Limitations and Recommendations for Future Research

The results of analyses pertaining to the demographic questions are unsurprising given that the study sample was recruited from the psychology undergraduate research subject pool. However, it is worth noting that the study sample is not representative of the racial/ethnic makeup of UNM students (UNM OIR, 2012). Students identifying as White/Caucasian are overrepresented in the sample, while other minorities (most notably Hispanic students) are underrepresented. Future research may benefit from endeavoring to recruit a study sample that is more representative of the population to which the results are to be generalized.

In retrospect, the PACS was not a viable choice for measuring within-session pre- to post-differences in craving because it asks respondents to report their experiences with alcohol craving during the past week. If the PACS had shown significant differences from baseline to post-stimulation, the result would represent changes in retrospective recall of alcohol craving rather than reductions in present craving. No such change in retrospective recall was observed. In future studies involving repeated sessions of tDCS designed to be a treatment for alcohol use disorders, the PACS would be an appropriate instrument for use as a one-time assessment of alcohol craving severity during the week prior to the study. This would be a useful addition to the assessment of problematic alcohol use and alcohol-related consequences measured by the AUDIT. Participants in the current study completed both visits spaced 3 to 7 days apart. Future replications with designs that entail daily participant visits over 1-2 weeks could benefit from using the PACS as a pre- to post-treatment measure.

Although the results of an analysis comparing pre- to post-stimulation difference scores for active and sham stimulation approached significance, it remains a null finding. However, it seems unlikely that the tDCS was ineffective given that a comparison of pre- to post-stimulation scores on the AUQ produced a significant finding for active stimulation, but not for sham stimulation. It is possible that investigator inexperience played a role in the result of null findings with regard to difference scores. Brief assessment instruments intentionally were chosen so as to reduce the paperwork burden for participants. While completing follow-up assessments at a second visit, one participant mentioned that he remembered his baseline responses and even his responses from his previous visit a few days prior, and that it was difficult for him to avoid simply

replicating his responses. This may have been the case with many participants. As noted by Sayette et al. (2000), "…high levels of association across items on a craving scale may be due in part to a response bias to present consistent responses…" (p. S197-S198). It is possible that the use of an assessment with a greater number of test items would increase sensitivity. Future study replications would benefit from utilizing a lengthier craving assessment with high internal consistency and administering different items from the instrument at each visit. Another viable option would be to utilize two or more instruments with high concurrent validity. This would eliminate the potential bias to present consistent responses across identical pre- and post-treatment items.

Baseline scores on the AUQ tended to be quite low. According to this assessment instrument, many participants reported little to no craving at baseline. This resulted in a "floor effect," as it is not possible to reduce craving among participants who are not experiencing craving. The revised second protocol entailing the administration of the alcohol cue task prior to assessing baseline craving levels seemed to ameliorate this to some extent. Future research may benefit from targeting recruitment specifically to participants who experience frequent feelings of craving. While the current study utilized recruitment flyers specifically targeting students who were concerned about their drinking habits, some participants were motivated to enroll in the study for other reasons, such as convenient time slots. They were not completely forthcoming about their lack of drinking concerns upon enrolling in the study. Future study replications likely would benefit from the use of minimum scores on the AUDIT and PACS as described previously.

Finally, although craving scores as measured by the AUQ were increased in the second protocol by the presentation of alcohol cues, the use of a more realistic study environment may be beneficial to future research. The current study was conducted in a sterile lab environment that was not representative of the environments in which participants typically would consume alcohol. Conducting the study in a replica of a bar or even a home living room may increase the validity of the results.

Conclusion

Craving is implicated in the development and maintenance of alcohol abuse and dependence, with many researchers asserting that the reduction or elimination of craving is a worthwhile target in the treatment of addiction. There is a clear need for a practical, low-cost intervention for craving in the field of substance abuse treatment. Noninvasive brain stimulation techniques such as tDCS show promise for this application. Boggio et al. (2008b) found that tDCS delivered to the dorsolateral prefrontal cortex significantly decreased alcohol craving compared to sham stimulation among individuals with alcohol dependence. The present effort is the first to follow up on this initial report. Within the second protocol of the current study, a comparison of pre- to post-stimulation difference scores for active versus sham stimulation produced a reduction in craving that approached significance. A comparison of pre- to post-stimulation scores for active stimulation produced a significant reduction in craving, whereas a comparison of pre- to post-stimulation scores for sham stimulation was nonsignificant. The second protocol of the current study entailed the use of visual cues to induce craving for alcohol. This technique was not employed within the first protocol, which yielded poor results. The use

of a realistic drinking environment that induces craving may serve to enhance this effect. In addition, a power analysis determined that a larger sample size within the second protocol potentially could have resulted in statistically significant findings.

A significant linear relationship existed between response to active stimulation and both AUDIT and baseline PACS scores within the second protocol. Increased frequency and intensity of alcohol cravings and increased severity of alcohol abuse were significant predictors of reduction in craving following active stimulation, implying that the inclusion of participants with more severe alcohol use disorders would produce statistically significant results.

Taken together, these findings support the hypothesis that tDCS is a viable option for reducing cravings among individuals with alcohol use disorders. Future research utilizing larger sample sizes and targeting participants who meet the diagnostic criteria for alcohol abuse or dependence is recommended to lend additional evidence to this hypothesis.

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