

**TITLE:** **Mindfulness-Based Intervention and Transcranial Direct Current Stimulation to Reduce Heavy Drinking**

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## **BACKGROUND/SCIENTIFIC RATIONALE**

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Alcohol use is the third leading global contributor to the burden of disease (World Health Organization, 2009) and costs of excessive alcohol use in the United States exceeded \$220 billion in 2006 dollars (Bouchery, Harwood, Sacks, Simon, & Brewer, 2011). One-third of Americans meet lifetime criteria for alcohol use disorder (AUD) and 8.5% meet criteria for current AUD (Hasin, Stinson, Ogburn, & Grant, 2007). Of those with AUD who receive behavioral or pharmacological AUD treatment, most return to drinking within the first year following treatment (Witkiewitz & Marlatt, 2004; Witkiewitz & Masyn, 2008; Witkiewitz, 2008). As such, AUD has been characterized as a chronic relapsing disease (Leshner, 1997; McLellan, Lewis, O'Brien, & Kleber, 2000). Behavioral interventions for AUD are the most common form of treatment; however, increased understanding of the neurobiological dysfunction associated with addiction (Goldstein & Volkow, 2002; Koob & Volkow, 2010; Koob, 2006) has led to greater interest in treatment approaches that target specific neural systems (Goldstein & Volkow, 2002; Koob, 2006; Koob et al., 2014; Litten et al., 2015). The proposed study will evaluate the efficacy of combining two approaches designed to target behavioral and neurobiological dysfunction in addiction: mindfulness-based relapse prevention (MBRP) (Bowen et al., 2014; Witkiewitz, Bowen, Douglas, & Hsu, 2013; Witkiewitz & Bowen, 2010; Witkiewitz, Lustyk, & Bowen, 2013; Witkiewitz, Marlatt, & Walker, 2005; Witkiewitz, Warner, et al., 2014) and transcranial direct current stimulation (tDCS) (Feil & Zangen, 2010; Witkiewitz & Clark, 2015). The ultimate goal of this research is to develop a more efficacious intervention for reducing heavy drinking that has minimal side effects and great potential for large-scale dissemination.

Mindfulness-based relapse prevention (MBRP) for substance use disorders may be an ideal behavioral intervention for helping individuals cope with acute, cue-induced craving because it was designed to target experiences of craving and their role in the relapse process (Bowen et al., 2010; Brewer et al., 2011; Witkiewitz et al., 2005). Based on the results of numerous studies, MBRP is a feasible and efficacious behavioral treatment for substance use disorders (Bowen et al., 2009; Bowen et al., 2014; Witkiewitz et al., 2014). The recent use of tDCS over task relevant regions to alter behavior and improve learning holds incredible promise for use in cognitive behavioral intervention protocols. This proposed study will attempt to enhance learning of mindfulness practices that are taught in MBRP by providing tDCS during brief mindfulness training (BMT). The objective of this study is to establish the feasibility and obtain preliminary data on the effectiveness of using tDCS with MBRP to reduce heavy drinking.

Chronic alcohol use is strongly associated with poor behavioral and cognitive control (Bechara & Damasio, 2002; Bechara, Dolan, & Hindes, 2002; Goudriaan, Grekin, & Sher, 2007). Imaging studies, have found that AUD is associated with altered functioning in brain regions that support cognitive control such as dorsolateral prefrontal cortex (dlPFC), inferior frontal gyrus (IFG), and anterior cingulate cortex (ACC) (Claus, Feldstein Ewing, Filbey, & Hutchison, 2013; Pfefferbaum et al., 2001; Sullivan & Pfefferbaum, 2005) and degree of AUD severity predicts differential brain responses in these regions when performing cognitive control tasks. For example, in a functional magnetic resonance imaging (fMRI) study, Claus and colleagues (Claus et al., 2013) found severity of AUD was negatively associated with blood oxygen level dependent (BOLD) signal change in right IFG, pregenual ACC, and

inferior parietal lobe (IPL) during correct inhibition trials; and bilateral IFG and dorsal ACC during error trials of a Go/NoGo cognitive inhibition task. Using electroencephalography (EEG), numerous studies have found deficits in attention allocation, as evidenced by a decrement in P3 (e.g., P300) amplitudes during cognitive inhibition tasks among individuals with AUD and among individuals at risk for AUD, based on family history of AUD (Porjesz et al., 2005). Consistent with these findings, a combination fMRI-EEG study found that lower P3 amplitudes among subjects who were high-risk for AUD had significantly less activation in the bilateral IPL and reduced activation in the bilateral IFG as compared to subjects who were low-risk for AUD (Rangaswamy et al., 2004).

Numerous studies have provided support for the importance of craving (defined as the subjective desire to drink) in the relapse process and for the association between reactivity to alcohol cues, self-reported craving, and drinking outcomes (Claus, Ewing, Filbey, Sabbineni, & Hutchison, 2011; E. L. Garland, Franken, & Howard, 2012; Litt, Cooney, & Morse, 2000; Witkiewitz & Marlatt, 2004; Witkiewitz, 2013). Imaging work has consistently shown a diverse network of regions involved in cue reactivity such as ACC, ventral and dorsal striatum, orbitofrontal cortex (OFC), insula, and brainstem (Claus, Ewing, Filbey, Sabbineni, & Hutchison, 2011; Myrick et al., 2008; Schacht, Anton, & Myrick, 2013; Vollstädt-Klein et al., 2010). In a large sample (n=326) of individuals with AUD who completed a cue reactivity task and found that increased AUD severity was associated with greater engagement of ventral and dorsal striatum, ACC, amygdala, and precuneus during cue presentation (Claus, Ewing, et al., 2011). EEG studies have found increased P3 amplitudes in response to alcohol cues among individuals at risk for AUD (Bartholow, Lust, & Tragesser, 2010) and among AUD patients (Heinze, Wölfling, & Grüsser, 2007; Namkoong, Lee, Lee, & An, 2004), suggesting greater salience and motivational significance of alcohol cues (Bartholow, Henry, & Lust, 2007).

Reactivity to stress and negative affect is commonly considered one of the hallmark features of addiction (Koob, 2006; Sinha & Li, 2007). Our own work has found self-reported negative affect to be a primary predictor of alcohol relapse (Witkiewitz & Marlatt, 2004; Witkiewitz & Villarroya, 2009; Witkiewitz, 2011). Engagement of stress circuitry that includes the hypothalamic-pituitary-adrenal (HPA) axis and extended amygdala plays a key role in the development of stress and negative affect reactivity in AUD (Koob & Le Moal, 2008; Koob, 2006; Koob et al., 2014; Sinha et al., 2003). Resting EEG, including decreased alpha power (8-13 Hz) and increased theta (4-8 Hz) and beta power (13-30 Hz) has been associated with both stress response and addiction (Enoch et al., 2008; Hodgkinson et al., 2010).

Mindfulness can be defined as the awareness that arises through paying attention to the present moment in a purposeful and non-judgmental way. Mindfulness based interventions (MBIs) have been shown to be efficacious in reducing alcohol use (Chiesa & Serretti, 2013; Witkiewitz, Bowen, et al., 2014; Zgierska et al., 2009). Extant research suggests that MBIs might be effective in part by reducing craving (Bowen et al., 2009), decoupling the negative affect-craving association (Witkiewitz & Bowen, 2010), decoupling the craving-substance use association (Elwafi, Witkiewitz, Mallik, Iv, & Brewer, 2012), increasing the mindfulness-based processes of awareness, acceptance, and nonjudgment (Witkiewitz, Bowen, et al., 2013), and decreasing maladaptive responses to craving (Bowen, Witkiewitz, Dillworth, & Marlatt, 2007; Garland & Gaylord, 2010; Gifford et al., 2004).

Previous reviews of neuroimaging studies have posited several putative neural mechanisms of mindfulness (Brewer, Elwafi, & Davis, 2013; Chiesa, Brambilla, & Serretti, 2011; Chiesa, Brambilla, & Serretti, 2010; Chiesa, Serretti, & Christian, 2013; Hölzel et al., 2011; Witkiewitz, Lustyk, & Bowen, 2013). In healthy adults, 8 weeks of MBI was found to be associated with decreased functional connectivity between right insula and ventromedial prefrontal cortex (vmPFC) when mindfully attending to internal states (Farb et al., 2007), and increased right insula activation following sadness provocation (Farb et al., 2010). In a sample of smokers, decreased functional connectivity between the insula and the subgenual ACC was found when mindfully attending to smoking images compared to passively viewing the images, suggesting a decreased association between these reward regions (Westbrook et al., 2011). An EEG study examining P3 amplitudes during a Go/NoGo task found increased P3 amplitudes during inhibition among individuals with attention deficit hyperactivity disorder who received eight weeks of MBI, as compared to control; suggesting MBIs may increase inhibitory control (Schoenberg et al., 2014). In summary, MBIs may improve functional connectivity between the ACC

and dlPFC, as well as reduce the connectivity between the insula and vmPFC (Witkiewitz, Lustyk, & Bowen, 2013), which may contribute to increases in awareness and decreases in craving observed among AUD patients who receive MBIs (Witkiewitz, Bowen, et al., 2013).

PI Witkiewitz has conducted three randomized clinical trials (RCTs) evaluating mindfulness-based relapse prevention (MBRP) as a treatment for substance use disorder (Bowen et al., 2009, 2014; Witkiewitz, Warner, et al., 2014). MBRP is a manualized intervention combining cognitive behavioral skills with brief mindfulness training (BMT). Two RCTs have examined MBRP delivered as aftercare following inpatient or outpatient treatment as compared to (1) treatment as usual (TAU, which consisted of psychoeducation, relapse prevention, and 12-step groups) (Bowen et al., 2009); or (2) TAU and relapse prevention (RP) (Bowen et al., 2014). In both studies MBRP was associated with significantly fewer alcohol and drug use days (Cohen's  $d=0.28$ ) at 2-month (Bowen et al., 2009) and 12-month (Bowen et al., 2014) follow-ups. A third RCT examined MBRP as the primary intervention and found MBRP was significantly more effective in reducing alcohol and drug use days compared to RP (Cohen's  $d=0.36$ ) at a 15 week follow-up (Witkiewitz, Warner, et al., 2014).

Thus, data from three RCTs provide support for the efficacy of MBRP, as compared to alternative empirically supported treatments. Yet, the effect sizes are still small in magnitude and each of the former trials has been limited by considerable dropout and low engagement. MBRP treatment compliance rates range from 50-60% of participants attending the majority of sessions (Bowen et al., 2009, 2014; Witkiewitz, Warner, et al., 2014), as compared to compliance of 70% in RP (Bowen et al., 2014; Witkiewitz, Warner, et al., 2014). Clinically, we have observed participants struggle with the mindfulness practices, perhaps due to significant deficits in executive function (Aharonovich et al., 2006) and inhibitory control (Brewer, Worhunsky, Carroll, Rounsaville, & Potenza, 2008; Streeter et al., 2008). Those clients who are able to engage with MBRP experience fewer and less severe lapses, as well as report greater improvements in overall quality of life (Witkiewitz, Warner, et al., 2014).

Transcranial direct current stimulation (tDCS) is a safe and non-invasive brain stimulation technique that applies weak electrical current to stimulate brain regions (Clark et al., 2011; Coffman et al., 2012; Falcone, Coffman, Clark, & Parasuraman, 2012; Jacobson, Koslowsky, & Lavidor, 2012). Most tDCS studies compare active (1.0 to 2.0 milliamps (mA)) tDCS to a sham/control condition with either reduced current strength (i.e., 0.1 mA) or a ramp-up/ramp-down procedure that introduces a modest current for a brief amount of time. Active tDCS versus sham has been shown to enhance the effects of cognitive training in a number of domains, including memory, attention and other forms of cognition. One study found that tDCS produced a doubling of performance accuracy in a learning task (Falcone et al., 2012). There have been over 250 clinical trials using tDCS for a variety of disorders and diseases, with promising effects of tDCS in treating symptoms of schizophrenia (Brunoni et al., 2014), major depression (Shiozawa et al., 2014), Alzheimer's disease (Hansen, 2012), chronic pain (O'Connell, Wand, Marston, Spencer, & Desouza, 2014), and stroke (Bastani & Jaberzadeh, 2012). There are also preliminary data suggesting tDCS has an effect on addictive disorders (Feil & Zangen, 2010).

The neurobiological mechanisms of tDCS depend on a variety of factors, including current strength and duration; the number, polarity and specific placement of electrodes; the electrode composition and size; and individual differences in physiology. TDCS has been shown to alter neuronal activity, cerebral blood flow, synaptic transmission, oscillatory activity, functional connectivity, and neurotransmitter concentrations (Clark, Coffman, Trumbo, & Gasparovic, 2011; Hansen, 2012; Kim, Stephenson, Morris, & Jackson, 2014). **The placement we plan to use in the proposed research, which we have used successfully in our prior work, is up to 2.0 mA of anodal stimulation of the right IFG (i.e., BA F10) with a left upper arm cathode.**

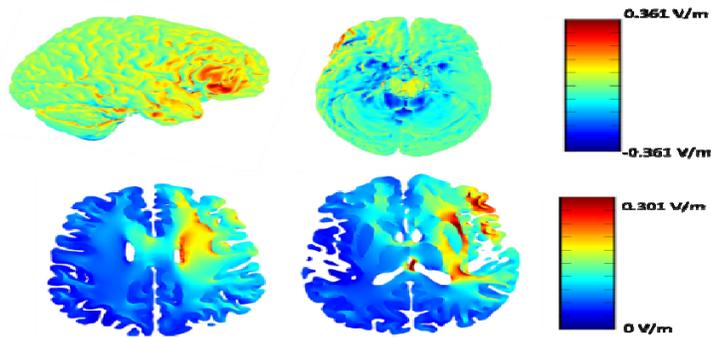


Figure 1. Modeled current distribution for IFG (anode) and contralateral arm (cathode) placement using FEM [Courtesy of Alexander David and Marom Bikson, CCNY]

Modeling of the electrical fields induced by the right IFG vs. left arm montage using finite element modeling (FEM (Datta, Bikson, & Fregni, 2010; Datta, Truong, Minhas, Parra, & Bikson, 2012), Figure 1), suggests that the largest effect is located underneath the anodal electrode, in the right IFG, including pars orbitalis, posteriorly into pars triangularis and to a lesser extent into the medial frontal regions. Increased excitability is also observed in the inferior aspect of the right temporal pole extending along the inferior temporal gyrus, the right OFC, and the right anterior insula. Subcortically, the strongest fields are located within white matter tracts surrounding the right striatum, portions of the right medial temporal lobe, and the inferior aspect of the cerebellum, including adjacent white matter regions connecting these structures. In addition to these regions, activity in other regions to which these areas are interconnected may also be altered. These may include a large portion of cortex, as well as higher-order areas that mediate cognitive and affective processes that may facilitate the ongoing acquisition and maintenance of mindfulness and produce benefits for treating AUD. Importantly, tDCS has been shown to impact the behavioral targets of the proposed study in healthy controls and patient samples, with active tDCS effects on inhibitory control (Levasseur-Moreau & Fecteau, 2012; Stramaccia et al., 2015), cue-reactivity and craving (Jansen et al., 2013; Nardone et al., 2012), and negative affective reactivity (Plewnia, Schroeder, Kunze, Faehling, & Wolkenstein, 2015; Pripfl & Lamm, 2015).

Most investigations of tDCS for addictive disorders have focused on intermediate phenotypes, including effects of tDCS on decision making and cue reactivity among individuals with stimulant use disorders (Conti, Moscon, Fregni, Nitsche, & Nakamura-Palacios, 2014; Conti & Nakamura-Palacios, 2013; Shahbabaie et al., 2014), smoking and nicotine use disorders (Boggio et al., 2009; Fecteau et al., 2014; Fregni et al., 2008), and marijuana use (Boggio et al., 2010). The growing literature of tDCS studies conducted with heavy drinkers and AUD patients have found significant effects of active tDCS on reductions in alcohol craving (Boggio et al., 2008; Den Uyl, Gladwin, & Wiers, 2015; Jansen et al., 2013; Nardone et al., 2012) and one small pilot RCT found significant effects of tDCS in preventing relapse and improving quality of life among patients with AUD (Klauss et al., 2014).

AUD has been characterized as a chronic relapsing condition (McLellan et al., 2000) with hallmark features that include loss of inhibitory control, heightened salience of alcohol cues and experiences of craving, and persistent negative affect. Each of these hallmark features has been successfully targeted independently with two novel interventions: mindfulness-based intervention and tDCS. Mindfulness-based interventions have enduring effects, but treatment engagement remains a barrier to success. Given effects of tDCS on improvements in state mindfulness and executive functioning in our prior studies (described below), **we hypothesize that tDCS could significantly increase engagement with mindfulness training.** Both tDCS and mindfulness have independently shown benefits for treating AUD. The combination of tDCS and mindfulness may provide synergistic benefits to reducing symptoms of AUD greater than each can provide alone. The proposed study will provide a sufficiently powered, sham-controlled double blind investigation of the efficacy of MBRP in combination with active tDCS as an intervention for AUD. The design will also allow us to examine changes in inhibitory

control, cue reactivity and craving, negative affect reactivity, and cognitive behavioral skills training acquisition as mechanisms of behavior change following the intervention.

Many individuals with AUD never receive treatment (Substance Abuse and Mental Health Services Administration, 2014). For those who seek care, relatively few efficacious treatments are available (Jonas et al., 2014; National Institute for Health and Care Excellence, 2011; Zindel & Kranzler, 2014). The low rates of utilization of treatments for AUDs and the modest efficacy of existing interventions underscore the need to develop and test new treatments that are more efficacious and attractive to patients. **Mindfulness-based interventions and tDCS are already being developed and marketed for at-home use** (Conti et al., 2014; Fecteau et al., 2014), **while both interventions (MBRP and tDCS) are relatively low cost with minimal side effects and have great potential for dissemination.** The application of tDCS can be directed to specific regions of interest allowing for induction of long-term neural plasticity that is regionally specific, a significant advantage over pharmacological treatments that bind to receptors without regional specificity. It may ultimately be possible to personalize tDCS application to specific neural dysfunction, which has important implications for personalized medicine approaches to addiction treatment (Litten et al., 2015).

## OBJECTIVES/AIMS

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The goal of this study is to examine the efficacy of a MBRP and tDCS intervention in reducing drinking and impacting mechanisms of behavior change among individuals who are interested in reducing their alcohol drinking. The aims of the proposed research are:

**Primary Aim: To examine the efficacy of a mindfulness-based intervention, in combination with active tDCS (up to 2.0 milliamp (mA)) versus sham (0.0 mA) tDCS of the right inferior frontal gyrus (rIFG), in reducing drinks per drinking day.**

Individuals who are interested in reducing their drinking will be recruited from the community and clinician referrals. All participants will receive group MBRP for 8 sessions with each session lasting 2 hours, for up to 8 weeks, and will also be randomized to receive active up to 2.0 mA tDCS or sham 0.0 mA tDCS. Participants will complete weekly self-report measures during treatment and self-report, behavioral, and EEG assessments at baseline, end of treatment, and two months following treatment.

Hypothesis 1. Active tDCS, as compared to sham tDCS, will be associated with significant reductions in drinks per drinking day after treatment and 2 months following treatment.

**Secondary Aim: To examine mechanisms of drinking behavior changes following treatment.**

Hypothesis 2. Effect of active tDCS on drinks per drinking day at the 2-month follow-up will be mediated by greater mindfulness, greater inhibitory control and reductions in cue-reactivity, craving, and negative affect during treatment and at the post-treatment assessment. The effect of the “dose” of treatment, including session attendance and amount of mindfulness practice, on drinks per drinking day at 2-months will be mediated by greater mindfulness and inhibitory control and reductions in cue-reactivity, craving, and negative affect.

Hypothesis 3. Based on prior EEG studies of alcohol use disorder and mindfulness, we hypothesize significantly increased amplitude of the P3 (e.g., P300) component of the event-related brain potential (ERP) during cognitive inhibition and reduced P3 amplitude in response to alcohol cues in the active tDCS group at post-treatment, as compared to sham tDCS. Changes in ERPs among those who receive active tDCS with MBRP will be significantly associated with reductions in drinks per drinking day following treatment.

## STUDY DESIGN

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### I. *Target Population and Inclusion/Exclusion Criteria*

Participants for the proposed research include up to 350 individuals ages 18 and over who will be recruited from the Albuquerque Metropolitan Area using the following inclusion criteria:

- 1) interested in reducing alcohol drinking and consumed alcohol in past 30 days
- 2) right-handed
- 3) able to communicate in English

The inclusion criteria are based on our long-term goal of developing an intervention with broad appeal for most individuals who are interested in reducing drinking. The right-handed inclusion is based on the fact that the majority of people are right-handed and the effects of tDCS may be influenced by handedness (a proxy for hemispheric dominance; Schade et al., 2012). Ultimately we plan to develop separate tDCS montages that are specific to right and left hemisphere dominance, but for the purposes of this initial study we opted for increasing internal validity by excluding left-handed individuals.

The following exclusion criteria will be used for all participants

- (1) lifetime diagnosis of schizophrenia or bipolar disorder or current SUD other than nicotine or marijuana assessed via the phone screening questionnaire
- (2) cardiac pacemaker
- (3) implantable defibrillator
- (4) metal objects in upper body that might interfere with tDCS, or that tDCS may interfere with their function, including metal plates, screws and prosthetics in head, certain older tattoos and permanent makeup using metal containing inks, aneurysm clips, neural stimulators of any kind, ear implants or hearing aids, insulin pumps, drug infusion devices and dental appliances
- (5) for females, pregnant or attempting to get pregnant
- (6) history of seizures or seizure disorder
- (7) allergic to latex, rubber, conductive medium like saline or electrode gel
- (8) if assigned to active tDCS and unable to tolerate 1.5 mA of tDCS during a baseline stimulation session
- (9) history of severe alcohol withdrawal including tremors, seizures, or delirium tremens
- (10) currently or previously prescribed anti-seizure medications or medications for alcohol withdrawal
- (11) score of 8 or greater on the Clinical Institute Withdrawal of Alcohol Assessment Scale – Revised at any tDCS sessions
- (12) unable to attend treatment groups at scheduled time and unwilling to wait for group treatment at a time that works for the participant
- (13) Arrested, charged, or convicted of a violent crime (e.g., aggravated assault) in the past 2 years or any history of assault with a deadly weapon, as indicated by the caselookup.nmcourts.cov database.

The exclusion of lifetime schizophrenia or bipolar disorder diagnoses was largely based on concerns of individuals with these disorders possibly needing a higher level of care than what we can provide as part of this study, particularly if symptoms were to be exacerbated by participation in the study. In addition, there is some anecdotal evidence that mindfulness practice may, in very rare cases, be associated with psychotic and manic episodes. To our knowledge this concern has not been verified in the empirical literature, but given the experimental and preliminary nature of the proposed study we have opted to exclude these individuals. The exclusion of individuals with comorbid drug use disorder, other than nicotine and marijuana, was desired because of the early stages of this research and the limitations of intervention content, measurement tools and cue presentation if individuals are more triggered or impacted by other drugs of abuse. Other drug use disorder could reduce applicability of an alcohol focused treatment and potentially reduce the impact of alcohol cues in the cue reactivity task. The remaining exclusion criteria, (2 to 10), were selected for safety concerns in the use of tDCS and/or EEG. The exclusion of individuals who have been arrested, charged, or convicted of a violent crime in the past 2 years or crime involving a firearm or other deadly weapon at any time is to protect the research staff and other participants from the potential of violence by a participant in the group.

## II. *Participant Enrollment*

Up to 350 individuals who want to reduce their drinking will be recruited for the study.

## III. *Recruitment and Screening Procedures*

Flyers posted in the Albuquerque metropolitan area, postings on online advertising sources (e.g. Craigslist), social media (e.g., Facebook), newspaper and radio advertisements, and flyers posted at treatment agencies and primary care provider offices will be the primary methods of recruitment. We will also recruit participants through referrals from studies of non-treatment seeking heavy drinkers currently being conducted at the Mind Research Network (MRN) and at CASAA (IRB through the HRRC). Study staff on the MRN and CASAA studies will be given recruitment information (e.g., the approved study flyer) to provide the information about our study for treatment seekers who are excluded from their studies of non-treatment seekers. Similar strategies have been used to successfully recruit larger sample sizes in previous studies. Participants will undergo an initial telephone screening to ascertain interest in the research study, interest in reducing drinking, and self-reported right handedness, as well as absence of the exclusion criteria. If they meet the basic requirements of the study, we will then check the public databases (nmcourts.gov) for information about arrests, charges, or convictions of violent crimes. If they are not listed in the nmcourts.gov for violent crimes in the past 2 years or any history of assault with a deadly weapon, then they will be scheduled for an eligibility assessment session, during which time the baseline stimulation session will be conducted, a medical history form and handedness questionnaire will be administered, and informed consent will be obtained. A second check of nmcourts.gov will then occur to confirm that the individual was not arrested, charged, or convicted between the screening session and the baseline assessment. In addition, participants will complete a pregnancy test (for women who could be pregnant) and will be breathalyzed to ensure a BrAC of 0.0. In terms of minority inclusion, individuals of all racial/ethnic backgrounds will be eligible. The racial/ethnic breakdown is expected to reflect the demographics of the Albuquerque area (i.e., predominantly Caucasian/non-Hispanic or Hispanic). Furthermore, we will provide flyers to grassroots minority organizations in the Albuquerque metropolitan area to increase the awareness of our research among minority groups. In addition, we will work on reducing the logistical and psychological barriers to participation among minority groups by providing transportation (bus vouchers), and addressing issues such as fear or distrust of research and the lack of familiarity with research procedures like randomization. In terms of gender composition, we expect that the final sample will be 40% female.

## IV. *Informed Consent Process*

Following phone screen, eligible participants will be invited to the Psychology Clinical Neuroscience Center (PCNC) for the baseline session, which includes being breathalyzed to ensure a breath alcohol concentration (BAC) of 0.0 and the informed consent process. At the first appointment, prior to any testing, consent forms approved by the UNM IRB will be administered by an approved research team member in a confidential office. Research staff will review the consent form, page by page, with each participant and solicit answers to critical questions (such as, "What are the limitations of confidentiality?" and "What are the risks associated with this study?") at the end of each section to ensure that the participant has understood these issues. The consent process will be documented in the participant's file on a dated consent documentation note form. Consent forms will be at the 6th grade reading level. Signed consent forms will be stored separately from participant data in a secure location in the PI's locked office. Participants will be given copies of signed consent forms at this appointment.

We are requesting a waiver of HIPAA Authorization for the disclosure of PHI for the study's use of an eligibility screening form administered over the phone. Since the form is administered without the physical presence of the potential participant, we would be unable to obtain their written authorization to disclose the information asked for on the form. All PHI, aside from the first and last name of the

participant, will be destroyed for participants who are screened out of the study at the time when it is determined that they are not eligible to participate. The first and last names of participants who screen out will be kept to prevent attempts at re-screening into the study. First and last names of those who screen out will be deleted at the end of data collection. All other elements of the research study, aside from any described on other waiver requests, will proceed only if normal HIPAA authorization procedures have been conducted.

For economic and time efficiency reasons, the research could not practicably be conducted without the phone screen. We collect important information during the phone screen that allows us to determine eligibility for research protocols. For participant convenience, it is more practical to gather this information over the phone rather than by scheduling appointments for such brief procedures. This also improves job efficiency for research staff, as they can dedicate their appointment slots to individuals who meet preliminary study inclusion criteria.

We need to control for several variables in the study, and we could not fully evaluate our proposed hypotheses without access to information allowing us to determine specific characteristics. A majority of the information on the phone screening form also determines whether the participant can safely take part in the research and is used to protect individuals (i.e. individuals who may have heart disease or be pregnant). There is no reason to schedule research appointments with individuals who are ineligible for the intervention.

Individuals who are not eligible for the research will be offered a list of community resources for additional alcohol and mental health treatment. The same list will be offered to individuals who are eligible to participate in the research and who want or need additional resources.

## V. *Data Collection Procedures*

**Procedures.** Following phone screen, eligible participants will be invited to the Psychology Clinical Neuroscience Center (PCNC) for the baseline session, which includes being breathalyzed to ensure a breath alcohol concentration (BAC) of 0.0, pregnancy testing for fertile female participants, providing informed consent, completing a battery of self-report and behavioral measures, baseline EEG, and baseline stimulation session. Participants who have a BAC > 0.0 will be rescheduled, given snacks and water until their BAC is reduced to < 0.04 in accordance with NIAAA guidelines, and will be provided a taxi voucher. Participants will take part in the intervention for 8 two and a half hour sessions up to 8 weeks. At each 150-minute session, participants will undergo 30 minutes of initial assessment and verification of session eligibility (e.g., breathalyzer, withdrawal assessment, pregnancy tests, and self-report), 30 minutes of tDCS during a guided meditation practice followed by 90 minutes of MBRP session content. The overarching goal of the meditation is to help participants obtain greater mental clarity through training attention and awareness, decreasing emotional reactivity, and improving general well-being. All study participants will be assigned to the MBRP condition. All tDCS sessions will be double blinded with active and sham tDCS participants within all groups. Pilot testing of this protocol has demonstrated feasibility of combining active and sham tDCS within a single group, while maintaining the blind.

**Measures.** Table 1 provides the assessment schedule for the proposed study. Consistent with the Secondary Aim to understand the mechanisms of behavior change at multiple levels of analysis, we have included self-report and behavioral assessments of inhibitory control (NIH Cognition Toolbox, UPPS Impulsive Behavior Scale, Stop Signal Task), cue reactivity and craving (Penn Alcohol Craving Scale, Cue Reactivity), and negative affect (NIH Emotions Toolbox, Negative Affect Reactivity). We have also included a blinding questionnaire to assess the degree to which individuals were blinded to the active versus sham tDCS randomization condition. Breathalyzer tests will be conducted prior to all interviews. Participants who have a BAC > 0.0 will be rescheduled, given snacks and water until their BAC is reduced to < 0.04 in accordance with NIAAA guidelines, and will be provided a taxi voucher.

During each assessment period (i.e. baseline, end-of-treatment, and 2-month post-treatment follow-ups), self-report measures, and the EEG sessions will occur within one week of the self-report assessment on separate days or on a single day with a break between assessments. All assessments (behavioral, EEG) and treatment sessions will take place in the PCNC. The PCNC has three private assessment rooms to conduct behavioral assessments, as well as an EEG preparation room and shielded acquisition room.

Measure	Description/Purpose	Follow-up		
		Baseline	Post	2-Mo
Locator Form	Contact information for scheduling appointments	X	X	
Edinburgh Handedness scale	Right handedness (inclusion criteria)	X		
Electroencephalography (EEG)	Electrical activity of the brain	X	X	
Demographic form	Age, gender, education, ethnicity	X		
	Marital & employment status, income	X	X	X
Drinking History Questionnaire	Drinking history: onset, prior/current treatment	X	X	X
Form 90	Alcohol & illicit drug use, treatment seeking & AA	X	X	X
Structured Clinical Interview for DSM-IV modified for DSM-5 to include craving item	AUD diagnosis/comorbid SUD diagnoses	X	X	X
Short Inventory of Problems	Brief measure of alcohol-related problems	X	X	X
Penn Alcohol Craving Scale (PACS)	Self-reported craving for alcohol	X	X	X
Impaired Control Scale	Self-reported craving, difficulty controlling craving	X	X	X
International Affective Pictures Series (IAPS)	Behavioral measure cue/negative affect reactivity	X	X	X
UPPS Impulsive Behavior Scale	Urgency, lack of planning, perseveration	X	X	X
Stop Signal Task	Behavioral measure of cognitive control	X	X	X
Mindfulness daily practice tracking sheet	Current mindfulness practices	X	X	X
Breath Counting Tool	Behavioral measure of mindfulness	X	X	X
Toronto Mindfulness Scale	"State" mindfulness	X	X	X
NIH Emotions Toolbox	Social relationships, negative affect, and stress	X	X	X
NIH Cognition Toolbox	Executive function (shifting/attention), memory	X	X	X
Avoidance and Inflexibility Scale	Behavioral avoidance	X	X	X
Regulatory Flexibility Scale	Coping flexibility	X	X	X
Monetary Choice Questionnaire	Delay discounting	X	X	X
Treatment History Form	Assess ongoing treatment and prior/ongoing experience with meditation	X	X	X
Treatment Goals Form	Assess current treatment goal (e.g., controlled drinking, abstinence)	X	X	X
Applied Mindfulness Process Scale	Assess mindfulness skills learned during intervention		X	X
Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised	Measure of current alcohol withdrawal symptoms	X		
Blinding Questionnaire	One question assessing knowledge of condition		X	

**Primary Drinking Outcome.** The *Form 90* (Miller, 1996) is a semi-structured interview that gathers daily calendar-based alcohol and illicit drug use data. A 2-month assessment window will be used at each of the time-points. The *Form 90* will be used to derive estimates of the primary outcome: drinks per drinking day. The *Form 90* has demonstrated reliability in the collection of alcohol and drug use data (Maisto, Conigliaro, Gordon, McGinnis, & Justice, 2008; Sobell, Brown, Leo, & Sobell, 1996).

**Weekly During Treatment Measures.** An abbreviated assessment battery will be administered weekly during treatment to assess state mindfulness (Toronto Mindfulness Scale (Lau et al., 2006)), mindfulness practice in the prior week, craving (PACS; Flannery Volpicelli, & Pettinati, 1999), negative urgency and lack of planning items from the UPPS (Littlefield et al., 2015; Whiteside & Lynam, 2001), and negative affect (Short Forms of Anger, Sadness, Stress from NIH Emotions Toolbox; Salsman et al., 2013).

**Behavioral Tasks.** All behavioral tasks will be completed via computer during EEG to provide a measure of electrical brain activity during rest and completion of the tasks. To examine inhibitory control, we will use a *Stop Signal Task* (Logan, Van Zandt, Verbruggen, & Wagenmakers, 2014) in which participants make left-right judgments of the directionality of an arrow presented on the screen. For each trial, a circle will appear for 500 ms, followed by a left or right-pointing arrow for up to 1 second, and between 500 ms and 2500 ms jittered inter-trial interval to reduce anticipatory responses. Approximately 25% of trials will be "stop trials" with a tone played to signal participants to inhibit the

current response. This timing of the tone is dynamically adjusted to ensure successful inhibition on approximately 50% of trials. There will be 240 trials across six blocks (~10 minutes) (Wessel & Aron, 2015). To measure cue-elicited responses to alcohol, we will use a visual cue presentation task. Following the designs of (Bartholow, Lust, & Tragesser, 2010; Myrick et al., 2008; Vollstädt-Klein et al., 2010), participants will view pictures of alcohol containing beverages and neutral pictures from the *International Affective Pictures Series (IAPS)* (Lang, Bradley, & Cuthbert, 1999) and from the web. Alcohol and neutral pictures will be matched for color and complexity as well as other potentially important confounds (e.g., presence of people). We will examine responses to approximately 100 trials each of alcohol pictures and control pictures in a mixed event design (~15 minutes), in order to reduce predictability of the picture type. To assess negative affect reactivity, participants will complete an anticipatory reactivity task in which arbitrary cues (circle or square) predict either neutral or aversive pictures from the *IAPS* (Lang et al., 1999). Participants will be instructed to press a button as fast as possible when the white square appears. If a response threshold is met, participants will see the neutral pictures or be able to avoid viewing the negative pictures. Importantly, the response threshold is dynamically determined throughout the task to ensure success/failure on approximately 66% of neutral/negative trials. Analyses will focus on the anticipatory period between the cue and picture. We are interested in examining differences between anticipation and experience of negative compared to neutral pictures. We will use 150 trials per cue condition to ensure an adequate signal to noise ratio (Brown, Goodman, & Inzlicht, 2013) (~20 minutes). Finally, we will include a novel *breath-counting task* that has been validated as a behavioral measure of mindfulness (Levinson, Stoll, Kindy, Merry, & Davidson, 2014). Participants will be instructed to count breaths from 1 to 9, pressing one button for breaths 1-8 and pressing another button on the 9<sup>th</sup> breath. The counting will be interrupted at random by three question probes assessing awareness and current breath count. There will be 12 question probes every 60-120 seconds (~18 minutes).

## **Procedures & Interventions**

**Screening (30 minutes).** Initial eligibility will be determined via telephone with a Screening Questionnaire. Individuals who do not meet criteria for the study will be referred to community drinking reduction programs. The phone screening form will be destroyed for those who are not eligible. First and last names of those who are excluded will be maintained to prevent re-screening. De-identified demographic information and reasons for ineligibility for those who are ineligible will be recorded in a separate document without identifiers for reporting purposes. Eligible individuals will be scheduled for a baseline assessment session. Phone screening forms and contact information for participants who are screened in will be maintained in a password protected file. The phone screening form will be de-identified and only linked to the participant with the participant ID.

**Baseline (up to 5 hours).** Informed consent will be obtained, and participants will complete the Handedness Questionnaire and pregnancy test (fertile female participants only). Participants will complete assessments listed in Table 1. Participants will also complete a baseline tDCS stimulation session lasting less than 10 minutes. This baseline session will be to familiarize the participants to tDCS outside of the group setting, to explain the stimulation protocol, and to answer any questions that participants might have about the tDCS procedure. Participants in the active condition who have difficulty tolerating the 2.0 mA current during the baseline stimulation session will be tested at 1.5 mA. If 1.5 mA is tolerated then participants will be enrolled in the trial at 1.5 mA. If 1.5 mA is not tolerated during the baseline stimulation session then participants will be deemed ineligible. Participants who fail study eligibility requirements at this point will be compensated for their time and referred to community alcohol treatment programs.

**MBRP + tDCS Sessions (2 hour treatment groups + 30 minutes for initial assessments, breathalyzer, pregnancy tests, and withdrawal assessments).** Following the baseline session, participants will begin a series of weekly or twice weekly group MBRP + tDCS intervention sessions for up to eight weeks at the PCNC. To maximize the availability of groups and to accommodate various therapist schedules we will run groups either twice per week for four weeks or once per week for eight weeks. All participants will receive up to 8 two hour sessions of MBRP + tDCS, regardless of the group schedule.

At the beginning of each session the subject will be asked to complete a baseline mood assessment, all participants will be breathalyzed, and fertile female participants will be asked to complete a pregnancy test. Women who are pregnant will not be allowed to complete the study and will be told in private of their pregnancy status. Participants who have a BAC > 0.0 will be rescheduled, given snacks and water until their BAC is reduced to < 0.04 in accordance with NIAAA guidelines, and will be provided a taxi voucher. We will also assess all participants for potential alcohol withdrawal at the time of each tDCS session. If participants show significant signs of withdrawal and/or have a score of 8 or greater on the Clinical Institute Withdrawal of Alcohol Assessment Scale (CIWA), then the research assistant will recommend the subject go to the UNM Hospital for further assessment. Our previous studies with more severely dependent individuals occasionally encountered patients with severe withdrawal, and this protocol was used successfully without any adverse consequences. Subjects with CIWA scores of 8 or greater at any session will be excluded from the research study. These aspects of the study will take approximately 30 minutes to complete.

Subjects will then receive 30 minutes of either active or sham tDCS stimulation, depending on their group assignment. A sensation questionnaire will be administered after 5 minutes of tDCS, 15 minutes, and 25 minutes of tDCS. At the end of tDCS stimulation participants will be asked a few questions regarding their mood and mental state to make sure that they have no lingering effects of the stimulation. After tDCS stimulation the remaining time will be used for MBRP session content (described below).

**Post-Treatment Assessment (up to 5 hours).** After completing the MBRP + tDCS sessions (i.e., up to two weeks after final tDCS/mindfulness session), participants will complete the assessments listed in Table 1 at the PCNC.

**Follow-Up Assessment (up to 2 hours).** At 2 months following completion of MBRP+tDCS, participants will complete the assessments listed in Table 1, with the exception of EEG, at the PCNC.

## **Interventions:**

### **Transcranial Direct Current Stimulation (tDCS)**

Previous reports suggest heavy drinking is related to dysfunction in brain regions related to attention and inhibitory control (Ahmadi et al., 2013) and that activation of the inferior frontal gyrus results in improved learning (Clark et al., 2010), tDCS will be applied over right inferior frontal gyrus (rIFG) implicated in inhibitory control and avoidant behavior (e.g., Aron, 2007). According to standard tDCS procedures, saline or gel soaked electrodes will be placed on the scalp, and will be held in place with an armband. Similar to the methods we have previously used, the anode will be placed on the scalp over the rIFG and the cathode will be placed on the contralateral shoulder. The electrodes will deliver a very weak electrical current that may briefly result in an itching or tingling sensation. TDCS will begin 5 minutes before the beginning of meditation, during which participants will rate physical sensations associated with application of tDCS; if participants rate sensations as anything higher than persistent itching, the session will be terminated. Participants in the Active tDCS condition will receive 2.0 mA for 30 minutes of stimulation during the training session. Participants in the Sham tDCS condition will receive a 30 second ramp-up of current to up to 2.0 mA to provide an initial sensation and then the system will ramp-down to 0.0mA for the remaining 30 minutes. Upon completion of the last MBRP + tDCS session, participants will be queried whether they think they received real tDCS or sham.

tDCS equipment consists of either an Soterix Medical 1 x 1 Transcranial Direct Current Model mini-Clinical Trial Stimulator (Model 1601) or an Activa Dose II Iontophoresis Delivery Unit generator with a nine-volt battery, electrode wires and rubber electrodes, easy pad sponge electrode covers (for Soterix Medical) or rubber covers (Active Dose II), and latex-free, self-adherent bandages, coban (head wrap for Active Dose II) or elastic fasteners (Soterix Medical), in order to ensure safe and comfortable conduction of current to the subject. The procedure ensures that no metallic equipment will make contact with participants while tDCS is active. The Soterix Medical 1 x 1 and Active Dose II are not FDA approved for intended use, however the device poses non-significant risk (NSR) and we have used the

Active Dose II device safely on over 1000 participants in our prior research studies. The Soterix Medical 1 x 1 tDCS Model 1601 has also been used in several research studies. We will closely monitor the Soterix Medical Model 1601 device and if we experience any adverse events then we will discontinue use and notify the IRB immediately.

We will use both tDCS devices in this study for two reasons. First, we will have 10 of the Soterix Medical units and 8 of the Activa Dose II units. We will run groups of 8-12 and may need to supplement the Soterix Medical units with an Activa Dose II unit if all 12 participants attend a group. Second, if we have any equipment problems with the Soterix Medical units then we will be able to continue running the two year study with the Activa Dose II units. Third, we have not used the Soterix Medical units in prior trials and if we do experience adverse events with the Soterix Medical units then we will continue treatment with the Activa Dose II units.

### **Mindfulness Based Relapse Prevention**

MBRP therapists will have at least a Master's degree in psychology or related field or have a Bachelor's degree in Psychology and be enrolled in an American Psychological Association-approved Clinical Psychology doctoral degree program, and experience with group treatment of AUD. Therapists will be trained and supervised by Dr. Witkiewitz, a licensed clinical psychologist with experience in MBRP therapist training and supervision. All MBRP sessions will be audio-recorded for supervision purposes and will be coded for adherence and competence using the MBRP-Adherence and Competence Scale. All treatment sessions will be 2 hours, with the first 30 minutes consisting of tDCS and guided meditation practice. After tDCS, sessions will include discussions of mindfulness as a means of coping with craving, cognitions, and emotions, role play exercises, and mindfulness practice. Participants will be given audio format files (e.g., mp3 players or CDs) developed specifically for MBRP for mindfulness practice outside of sessions.

### *VI. Study Timelines*

Screening and informed consent will take approximately 30 minutes. We anticipate that baseline and post-treatment behavioral testing sessions will require up to 5 hours each (approximately 10 hours total). The 2-month follow-up assessment will not include EEG and is expected to take 2 hours. The MBRP + tDCS interventions will require 2 hours and 30 minutes per session, including 30 minutes for initial questionnaires and withdrawal assessments, 15 minutes for tDCS setup, sensation checks, and cleanup at the end, 30 minutes for the tDCS, and 75 minutes for the MBRP intervention content. Thus, total participation time for MBRP + tDCS will be 16 hours over up to 8-weeks. Total participation time, after screening and consent, will be up to 32 hours.

### *VII. Study Location(s)*

Assessments and intervention sessions will take place in the Psychology Clinical Neuroscience Center in Logan Hall, Department of Psychology, University of New Mexico. Data analysis will be done at Logan Hall, Department of Psychology, University of New Mexico in offices maintained by PI Witkiewitz.

### *VIII. Participant Compensation*

We propose an incentive structure to maximize compliance that is consistent with other successful tDCS studies conducted by the investigative team. Participants will be paid up to \$20/hour for their participation during assessments: baseline (up to \$100), session questionnaires during 8-sessions of treatment (\$80), post-treatment (up to \$100), and 2-month post-treatment (up to \$40), plus an additional \$10 bonus for completing the post-treatment assessment, a \$20 bonus for completing the 2-month follow-up assessment, and a \$50 bonus for completing all assessment sessions, making the maximum compensation \$400. To increase retention, participants will be asked to provide addresses,

phone numbers, and email addresses, as well as the names and phone numbers for friends and family members who “*will always know where you are.*” We have used these methods in our prior studies and achieved 87.5% or greater follow-up rates.

## IX. *Study Resources*

The Psychology Department is located in Logan Hall on the south edge of The University of New Mexico’s main campus. This 55,334 square foot, three story building is comprised of faculty, staff and graduate student office space, four classrooms, a library, a conference room, an undergraduate student computer lab, a graduate student computer lab, and human research and/or animal research facility lab space.

In May 2010 the Psychology Department was awarded a grant from NIH for almost \$5,000,000 as part of the Recovery Act Limited Competition: Core Facility Renovation, Repair, and Improvement. The funds were used to renovate the Psychology Department’s neuroscience research space into a state-of-the-art Psychology Clinical Neuroscience Center (PCNC). The PCNC, directed by Co-I Clark, is a Category-I center in the Department of Psychology at UNM. This 10,000 square foot, \$5.5 million renovation includes 5 research pods containing offices for over 20 personnel, 4 imaging laboratories, 3 meeting rooms, and a data processing laboratory and classroom for up to 20 students with computer systems for each. Administrative resources include offices for the PCNC Director and for a Program Coordinator, as well as offices for a Computer Programmer and IT Manager.

### **Space**

Laboratory The PCNC has separate pediatric and adult electroencephalography (EEG) core laboratories (described in detail below), a neurostimulation core laboratory, a large computer core laboratory and a dedicated imaging computer room for data acquisition and analysis for EEG, along with imaging and stimulation laboratories of individual faculty.

Clinical Within the PCNC, three private assessment rooms (all equipped with closed doors and sound screens) are available to research staff.

Office Dr. Witkewitz has a private faculty office, as well as four individual Research Assistant offices and access to a conference room.

Meeting Space The PCNC offers multiple group meeting locations to facilitate research. Rooms will accommodate groups from 10 to 40 participants. The rooms are available for investigator and team meetings, research seminars and other research gatherings. Smaller private rooms are available for small group meetings and one-on-one participant and stakeholder interactions.

### **Personnel Resources**

All study staff will be trained in recognizing signs and symptoms of intoxication as well as withdrawal symptoms. The UNM Psychology Department is located less than 1 mile away from several hospitals, including the UNM Hospital Emergency Department. The PI is a licensed clinical psychologist with extensive experience in the prevention and treatment of substance use disorder. The PI will train and supervise research staff and the study therapists to utilize data provided at each assessment point as well as clinical judgment to monitor and evaluate the condition of participants.

## **EXPECTED RISKS/BENEFITS**

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### I. *Potential Risks*

There are only minor risks associated with participation in this study. Potential risks of completing self-report and behavioral assessments include: 1) some discomfort associated with the nature of interview questions; and 2) breach of confidentiality. Potential risks of tDCS include: 1) skin damage (rare) or skin irritation; 2) neural tissue damage (rare); 3) pain (rare); 4) alterations in mood or affect (rare); and 5)

electrical shock (rare). As enumerated below, we will take every possible step to reduce risk and discomfort to research participants.

## **Protections Against Risk**

**General Protections.** All study staff will be trained in recognizing signs and symptoms of intoxication as well as withdrawal symptoms. The UNM Psychology Department is located less than 1 mile away from several hospitals, including the UNM Hospital Emergency Department. The PI is a licensed clinical psychologist with extensive experience in the prevention and treatment of substance use disorder. The PI will train and supervise research staff and the study therapists to utilize data provided at each assessment point as well as clinical judgment to monitor and evaluate the condition of participants.

**Assessment Protections.** While the nature of the research dictates that data cannot be collected anonymously, additional safeguards will be put in place to protect against breach of confidentiality. Each participant will be assigned a unique ID code at screening. After phone screening, the phone screening form will be destroyed for those who are not eligible. First and last names of those who are screened out will be maintained in order to identify individuals who attempt to re-screen. De-identified demographic information and reasons for ineligibility for those who are ineligible will be recorded in a separate document without identifiers for reporting purposes. Eligible individuals will be scheduled for a baseline assessment session and their phone screening form will be de-identified and only linked to the participant with the participant ID. Contact information for participants who are screened in will be maintained in a password protected file. All assessments for a given participant will be coded with his/her ID code. Questionnaire data will be collected using Mind Research Network COINS system, hosted on a secure Mind Research Network server supporting 128-bit encryption and protected electronically using the most up-to-date security software available. Other data will be retained at the UNM Psychology Clinical Neuroscience Center (PCNC) in locked file cabinets and on password protected electronic files on computers with restricted access. A single master list linking participant names and ID codes will be stored onsite in a separate locked file cabinet, and will only be available to research staff. Further, a Certificate of Confidentiality, which provides additional protection against obligatory release of confidential information, will be obtained from the Department of Health and Human Services prior to participant recruitment.

**EEG Protections.** EEG is considered a safe and noninvasive procedure. There is some risk of seizure during EEG among individuals with seizure disorders, so we will be excluding any participants with a history of seizures or seizure disorder. Participants will be monitored throughout the procedure. If there is any discomfort, the procedure will be discontinued. The PCNC has facilities available to wash off the EEG gel.

**tDCS Protections.** Normal patient handling procedures are followed to eliminate risks. The participants will be able to communicate with the investigators at all times. The participant's emotional state, mood, and physical sensation will also be monitored with a questionnaire administered before, during, and after the tDCS procedure. The following potential risks that could be associated with transcranial direct current stimulation have been identified and we address them below. We have conducted over 1200 tDCS sessions using the Activa Dose device in our lab and experienced only one adverse event, which was a minor skin burn resulting from an exposed wire. Since the adverse event we have shrink-wrapped all of our wires (see Figure 2a and 2b below) and have experienced no other events. The Soterix 1x1 Mini-CT units were designed for clinical trials and have been tested in numerous treatment studies and clinical trials (<http://soterixmedical.com/>). All devices were designed by bioengineers using medical grade materials.

Figure 2a. Electrode setup for tDCS.

Figure 2b. Shrink-wrapped wires and banana plugs.



Pain. A very strong, focal current density can result in pain. We will be using large electrodes and weak electrical current. With protocols similar to ours, most participants report only mild, transient tingling at the stimulation site resulting from tDCS. Any participant report of pain resulting from tDCS will result in immediate termination of stimulation.

Alterations in mood or affect. There is evidence that tDCS can result in changes in mood. While no studies have reported negative mood resulting from DC stimulation, several studies have reported improved mood after tDCS. It should be noted that in these studies stimulation was applied for significantly longer durations. Studies designed to investigate the safety aspects of tDCS have reported no significant changes in mood as measured with the visual analogue mood scale and no significant changes in measures of fatigue when comparing stimulation to sham. Participants will receive 90 minutes of group mindfulness treatment after stimulation is discontinued and the group clinician will monitor the mental state of all participants throughout the group treatment.

Neural tissue damage. At very high current densities and long durations of stimulation there is a possibility that DC stimulation can result in neuronal tissue damage due to neuronal hyperactivity or brain tissue heating. In our study, we propose to use electrodes with at least 3.3 X 3.3 cm<sup>2</sup> sponge/skin contact to induce 2 mA stimulation resulting in a maximum current density of 0.19mA/ cm<sup>2</sup> at the scalp surface. Most likely, 90% of this current will be shunted through the cerebrospinal fluid and the skin. Current distribution models of DC stimulation suggest that 2mA current at the scalp surface will result in a maximum current density of 0.00986 mA/ cm<sup>2</sup> in the brain. While this current density is enough to elicit a transient modulation in cortical excitability, it does not elicit tetanic and/or suprathreshold excitation necessary to cause neuronal damage. Brain tissue heating is also insignificant for this level of stimulation. Moreover, the duration of stimulation specified in our design (~30 minutes) is well within the bounds of normal procedures. Protocols similar to ours do not reveal changes in structural magnetic resonance images or pathological EEG signals resulting from tDCS. For these reasons, we believe that our stimulation protocol is within safe parameters and that the possibility of neuronal tissue damage is extremely unlikely.

To minimize any possible tissue damage, participants will fill out a tDCS sensation questionnaire form throughout the tDCS procedure. This questionnaire allows us to monitor what the participants are physically feeling (including sensations of “itching,” “heat/burning,” and “tingling”) at the electrode sites. This will be given at the following time points: approximately 1 minute after start of tDCS, approximately 5 minutes after start of tDCS, and approximately 20 minutes after start of tDCS. If at any time the participant reports a sensation level of 7 or above, based on a 10 point scale, we will immediately discontinue the stimulation. In addition, participants are instructed to tell us at any time if the sensations are uncomfortable or if they would like the tDCS to be discontinued for any reason.

Skin damage or irritation. There is a slight risk of skin damage or irritation resulting from tDCS stimulation. With the exception of one study that reported transient redness at the stimulating electrode site in two men who had recently shaved their heads, we have encountered no reports of skin damage or irritation in any of the tDCS literature. Stimulation parameters similar to the ones proposed in the application have not resulted in skin damage in our previous studies. We will be using at least 3.3 X 3.3 cm<sup>2</sup> saline water or gel-soaked electrodes for our study which minimizes the possibility of chemical reactions at the electrode-skin interface and resultant skin damage. The scalps of each participant will

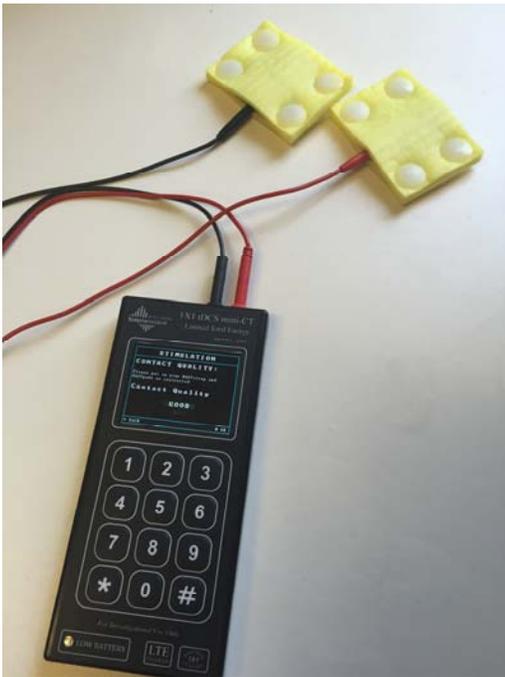
be visually inspected immediately before stimulation. Any identified irritation or evidence of recent shaving of the head will postpone that participant's participation in the study. Participants will be encouraged at the beginning of the tDCS procedure to report any pain or discomfort that they may encounter throughout the procedure. Any such reports, or evidence of redness or irritation of the scalp, will result in the immediate termination of stimulation. We have found in our recent work that saline water soaked electrodes have acceptable sensation ratings for most individuals, but for some individuals (particularly those with more sensitive skin) gel electrode solution reduces irritation. Thus, we include the option of either saline-soaked or gel soaked electrodes, which can further reduce skin irritation for some participants.

Electrical shock. As with any contact between persons and electrical apparatuses, there is a slight possibility of electrical shock. At UNM we have had no incidents of significant electrical shock resulting from DC stimulation, and we do not anticipate this event occurring in our experiment. One of the advantages of using the ActivaDose II stimulator (Figure 3) to induce DC current is that the current is obtained from a 9-volt battery and can be limited to a safe level. The Soterix medical stimulation (Figure 4) is powered by a lithium ion battery and the stimulation is capped at 2.5 mA from the device. Our testing of the Soterix device using a multimeter has indicated that when the Soterix unit is set at a certain mA that it never exceeds that voltage. Using either unit ensures that electrical shocks resulting from current surges will not occur. Further, we will ensure that participants are not in contact with any potential conductors other than those specified in the experimental design (e.g. the tDCS stimulator). This measure greatly reduces the likelihood that electrical shock will result from short circuiting or inadequate insulation.

Figure 3. ActivaDose II stimulator and electrode set-up with blinding box apparatus.



Figure 4. Soterix Medical 1x1 mini-CT tDCS stimulator with electrode set-up.



## II. *Benefits*

These studies are expected to add to the knowledge base on potential interventions for alcohol use. In addition, the mindfulness and tDCS application is expected to significantly decrease drinking for participants in the active condition and is also likely to reduce drinking in the mindfulness + sham condition. Given only a slight risk to participants and the greater possibility of long-term benefits to the knowledge base and to treatment interventions for AUD, the risks/benefits ratio seems reasonable. From a larger perspective, the findings of this investigation will increase the body of knowledge about the efficacy of a novel intervention for at-risk drinking and more broadly, will advance a biobehavioral conceptualization of treatment for AUD. The current research will address several gaps in the treatment literature with regard to the potential effects of mindfulness-based approaches for AUD. Although research has supported mindfulness-based relapse prevention (MBRP) as an effective intervention, our preliminary data suggests that its efficacy may be augmented by the addition of transcranial direct current stimulation to enhance engagement with treatment, increase rates of abstinence, and potentially further reduce heavy drinking. Further, the proposed study will assess behavioral mechanisms of change. Considering these clinically relevant and innovative study goals as well as the potential individual and societal benefits, the knowledge that may be gained in the current study will outweigh the risks for individual participants.

## III. *Privacy of Participants*

All consent procedures and experimental procedures will be conducted in offices maintained by the study investigators with appropriate privacy procedures (e.g. locked doors, opaque window coverings, and soundproof offices) in place. All PHI will be password protected and stored on a secure database accessible only by approved study personnel who are CITI certified in HIPAA confidentiality. While the nature of the research dictates that data cannot be collected anonymously, additional safeguards will be put in place to protect against breach of confidentiality. Each participant will be assigned a unique ID code at screening. All assessments for a given participant will be coded with his/her ID code. Questionnaire data will be collected using the Mind Research Network COINS system, hosted on a secure Mind Research Network server supporting 128-bit encryption and protected both physically (located in a locked room) as well as electronically using the most up-to-date security software available. Other data will be retained at the UNM Psychology Clinical Neuroscience Center (PCNC) in locked file cabinets and on password protected electronic files on computers with restricted access. A

single master list linking participant names and ID codes will be stored onsite in a separate locked file cabinet, and will only be available to research staff. Further, a Certificate of Confidentiality, which provides additional protection against obligatory release of confidential information, will be obtained from the Department of Health and Human Services prior to participant recruitment.

#### IV. *Unanticipated Problems/Adverse Events*

We would terminate the study if we found there were significant unanticipated adverse consequences for participation. For example, we would terminate the study if we found statistically significant preliminary results indicating that participants receiving the active tDCS were drinking at a higher rate than those in the sham condition. Analyses to compare sham versus active tDCS treatment efficacy will be conducted in February 2018, after a sufficient number of subjects have been treated, and at the time of submitting our annual progress report to NIH, which will occur in June 2018. We would also terminate the study if we became aware of any publications with such findings in other studies. Any unanticipated problems or adverse events will be reported to the IRB promptly and within 7 days of occurring.

#### V. *Participant Complaints*

If a participant wishes to issue a complaint, they may notify any research team member or Dr. Katie Witkiewitz at (505) 925-2334, Monday through Friday, 9am - 5 pm. Alternatively, they can write to her at the PCNC, MSC 03-2220, Logan Hall, Albuquerque, NM 87131 or via email at [katiew@unm.edu](mailto:katiew@unm.edu). They may also contact the UNM Office of the IRB, (505) 277-2644, [irbmaincampus@unm.edu](mailto:irbmaincampus@unm.edu). Website: <http://irb.unm.edu/>  
All of this information is given to them upon their admittance to the study in their consent form.

### STUDY DATA

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#### I. *Data Management Procedures and Confidentiality*

Online surveys and data collection forms have been used in our previous studies, and will be re-tested prior to utilization. Data are monitored on a daily basis during the baseline period to track response rates, evaluate success of the randomization procedure for producing equivalent groups, and assess data quality. Data are monitored on a weekly basis during each follow-up assessment period. Data cleaning is minimal because COINS has safeguards in place to minimize data entry errors. All data will be inspected continuously throughout the trial by a RA who is familiar with potential problems with data acquisition. All data will be double-checked by two independent persons. Scoring syntax that was developed for our prior studies will be used to produce summary variables, and standard procedures will be utilized for dealing with missing data.

We have taken a number of measures to ensure the confidentiality and integrity of the data and the safety of the participants. As described in the protections for human subjects sections above, all data from the proposed study will be identified by a numerical ID code only, which will be assigned during the phone screening. After phone screening, the phone screening form will be destroyed for those who are not eligible, although first and last names will be recoded to prevent re-screens and the demographic information and reasons for ineligibility for those who are ineligible will be recorded in a separate document without identifiers for reporting purposes. For eligible individuals the phone screening form will be de-identified and only linked to the participant with the participant ID code. The information linking the numerical participant ID code to identifying information will be maintained separately in a locked filing cabinet and kept separate and secure from the de-identified. All identifying information will be stored in a separate encrypted and password protected file and will not be linked with the screening or assessment data. At the conclusion of the study, the list linking the ID code to identifying information will be destroyed. Further, a Certificate of Confidentiality, which provides additional protection against obligatory release of confidential information, will be obtained from the Department of Health and Human Services.

## II. *Data Analysis/Statistical Considerations*

**Power analysis and sample size considerations.** We conducted power analyses using effect sizes from a pilot study ( $d=0.64$  and  $d=0.43$  on drinks per drinking day at post- and 2-month follow-up). With desired power  $>0.80$ , a two-tailed  $\alpha < 0.05$ , and three time-points, we will need 70 participants to detect a medium effect of active tDCS + MBRP vs. sham tDCS + MBRP on drinks per drinking day at follow-up. For mediation analyses we will need 74 participants to detect a medium effect. Attrition of 15% is anticipated based on our pilot tDCS study and thus we propose to recruit  $n=86$  participants to allow for some attrition. We anticipate screening up to 350 participants in order to recruit a sample of 86 participants.

**Data Analyses and Missing Data.** The primary study aim is to test the overall efficacy of the active tDCS + MBRP intervention compared to a sham tDCS + MBRP group. We will use maximum likelihood estimation for all analyses, which provides the variance-covariance matrix for all available data and is the preferred method for estimation when some data are missing. Variables associated with missing data and those used in randomization (gender, age, treatment history) will be covaried in all analyses.

**Aim #1: Efficacy Analyses.** All assessment data will be analyzed for outliers and missing cases to detect any bias that might result from differential attrition. The efficacy of active tDCS + MBRP versus sham tDCS + MBRP will be examined using a generalized linear mixed model with drinks per drinking day at the end of treatment and follow-up as the primary outcomes. We hypothesize active tDCS will be associated with significantly larger reductions in drinks per drinking day following treatment, as compared to sham tDCS. Interim analyses to compare sham versus active tDCS treatment efficacy will be conducted in February 2017, after a sufficient number of subjects have been treated, and at the time of submitting our annual progress report to NIH, which will occur in June 2017.

**Secondary Aim: Mediation Analyses.** Mediation models will be estimated for weekly and post-treatment assessments of mindfulness, inhibitory control, cue reactivity and craving, and negative affect using the product of coefficients method<sup>19,132</sup>. We will look at self-report and behavioral assessments of each proposed mediator in separate analyses and we will also examine whether latent variables of each construct provide an adequate fit and can be used in the analyses. The mediated effect will be obtained by multiplying coefficients for the regression of the mediators (either separate measures or latent constructs) on treatment condition and for the regression of drinks per drinking day at the 2-month follow-up on the mediators. We will use bootstrapping to obtain 95% confidence intervals of the mediated effect. We hypothesize the effects of active tDCS on drinks per drinking day will be mediated by greater mindfulness, greater inhibitory control and reductions in cue reactivity, craving, and negative affect in the active tDCS group, as compared to sham tDCS.

**EEG Analysis.** EEG analyses will focus on the association between EEG biomarkers (e.g., resting state alpha, theta, beta, and gamma activity, P3 amplitude during tasks) and drinking outcomes, as well as changes in behavioral task performance. Data will be analyzed using MATLAB-based signal processing toolboxes (e.g., EEGLAB, ERPLAB, EEGIFT). We hypothesize significantly increased P3 amplitudes during cognitive inhibition and reduced P3 amplitude in response to alcohol cues in the active tDCS group at post-treatment, as compared to sham tDCS.

## III. *Participant Withdrawal*

If a participant wishes to withdraw from the study all of their information held at the Psychology Clinical Neuroscience Center will be destroyed. They have the right to withdraw their consent or stop participating at any time. They can refuse to answer any question(s) or refuse to participate in any procedure for any reason. Refusing to participate in this study will not result in any penalty or loss of benefits to which they are otherwise entitled.

If they wish to stop participating at any time, they can notify a study team member or Dr. Katie Witkiewitz at (505) 925-2334, Monday through Friday, 9am - 5 pm. Alternatively, they can write to her at the PCNC, MSC 03-2220, Logan Hall, Albuquerque, NM 87131. All of this information is given to them upon their admittance to the study in their consent form. On the other hand, if the experimenters

decide that a participant is not eligible to continue with the study, their participation may be terminated without their consent.

## PRIOR APPROVALS/REVIEWED AT OTHER IRBS

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No prior approvals.

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