Non-Invasive Brain Stimulation and Substance Use

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PROTOCOL SUMMARY 1

Title Non-Invasive Brain Stimulation and Substance Use

Purpose This pilot study will investigate the feasibility and effect of non-invasive transcranial alternating current stimulation (tACS) on distress tolerance and inhibitory control in individuals with substance use disorder.

Method Following screening, eligible participants will engage in two sessions. The primary outcomes, inhibitory control and distress tolerance, will be administered at each assessment session. During the first session, participants will complete both tasks while receiving the active sham tACS. During the second session, participants will complete both tasks and receive one of three tACS conditions based on a randomization procedure: (1) 10 Hz, (2) 40 Hz, or (3) active sham. Participants will also provide sociodemographic and mood information via self-report forms and interviews with research staff. Participants will be compensated at the end of the second session and debriefed at the end of all study data collection.

Population Participants will be patients with current substance use disorder, aged 18-55, and currently receiving outpatient substance use treatment. Participants will be recruited at the Garner location of the SouthLight Treatment Center located in Raleigh, NC.

Number of Sites This is a single site study Garner location of the SouthLight Treatment Center located in Raleigh, NC.

Study Duration We estimate 1 year to complete study enrollment and data collection.

Participation Duration Eligible participants will have a total of 4 contacts: (1) screening and the first session (approximately 1.5 hours), (2) a reminder call between the first and second session (approximately 5 minutes), (3) the second session (approximately 1.5 hours), and the debriefing at the completion of all data collection (approximately 15 minutes). We estimate that total participation to be approximately 3 hours and 20 minutes.

Description Transcranial alternating current stimulation (tACS) may be a particularly promising approach as it is a safe and non-invasive method of electric stimulation that has the potential to effectively modulate neural network and circuit dynamics, closely aligning with a network-based conceptualization of affective and cognitive processes, such as distress tolerance and inhibitory control. Furthermore, tACS allows for targeted stimulation with the potential to modulate specific frequencies of endogenous cortical oscillations at the administered frequency of stimulation (Hermann et al., 2013). More specifically, this more targeted approach allows for direct enhancement of selective cognitive functions. We will be using an active sham, 10 Hz tACS, and 40 Hz tACS. Utilizing an active sham stimulation condition will allow for higher confidence that changes in task performance, associated arousal, and affective symptoms are due to experimental manipulation rather than the placebo effect.

Schematic of Study Design

Table 1. Participants will be randomized into one of three of the following groups:

Group 1	Active Sham
Group 2	10 Hz tACS
Group 3	40 Hz tACS

Research Staff

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STUDY DESIGN 2

The design of this pilot study is a randomized, sham-controlled, single-site study, which will be used to ideally demonstrate the feasibility administering tACS and to investigate the effects of tACS on distress tolerance and inhibitory control (Primary Outcomes) among treatment-seeking individuals with substance use disorder. Participants will be assigned to a block based on their age: (1) 18-25 years old, (2) 25-35 years old, (3) 35-45 years old, and (4) 45-55 years old. Within each block, participants will be randomized to one of three groups: (1) tACS at 10 Hz, (2) tACS at 40 Hz, or (3) active sham stimulation. This randomization will be done by an individual that is not part of the research staff. We hypothesize that individuals who receive 10 Hz tACS will demonstrate a significantly greater increase in distress tolerance compared to individuals who receive the active sham condition and the 40 Hz tACS condition.

Research staff will recruit individuals at the Garner location of the SouthLight Treatment Center in Raleigh, NC by making weekly announcements at the end of the substance abuse intensive outpatient program (SAIOP) groups. Eligible participants will be screened using the Word Reading Subtest of the Wide Range Achievement Test (WRAT), Fagerstrom Test for Nicotine Dependence, and the Alcohol Use Disorder, Substance Use Disorder, and Psychotic Disorder Modules of the Mini International Neuropsychiatric Interview (MINI) 7.0, which will both be administered in an interview format. Eligibility based on the study's inclusion and exclusion will be recorded on the Screening Form. Potential participants who do not meet criteria for the study will be informed of this decision and thanked for their time. Eligible patients who are willing to participate, provide informed consent, and sign the HIPAA Authorization Form and the UNC Release of Information Form will continue to the procedure of the first session.

Participants will receive compensation upon the completion of their second session. If the individual withdraws from the study before completing the second session, they will not be compensated. This information will be clearly delineated verbally during the informed consent procedure and in written form in the consent form. Participants will be compensated with $30 in cash upon completion of their second session.

STUDY ENROLLMENT AND WITHDRAWAL 3

Participant Inclusion Criteria 3.1

In order to be eligible to participate in this study, a participant must meet all of the following criteria:

- Ages 18-55
- Current DSM-V Substance Use Disorder, diagnosed by the Mini International Neuropsychiatric Interview (MINI) 7.0
- Current smoker, as assessed by the Fagerstrom Test for Nicotine Dependence (FTND)
- Abstinent from all substances (except nicotine) for at least the past 2 weeks
- Verbal & written informed consent (signed & dated)

Participant Exclusion Criteria 3.2

A potential participant who meets any of the following criteria will be excluded from participation in this study:

- < 6 months since an electroconvulsive therapy (ECT) session
- Current DSM-V Psychotic Disorder, diagnosed by the Mini International Neuropsychiatric Interview (MINI) 7.0
- Inability to read at a minimum of a 5th grade reading level, as assessed by the Wide Range Achievement Test (WRAT) Word Reading Subtest
- Non-English speaker
- Pregnancy and/or nursing
- Prior brain surgery
- Ongoing or history of traumatic brain injury (TBI), reoccurring seizures, stroke, or brain tumors
- Medical or neurological illness (e.g., cardiac disease, AIDS, liver or renal impairment), or treatment for such an illness that could interfere with study participation
- Any brain devices or implants (e.g., cochlear implants, aneurysm clips)
- Current use of antiepileptic drugs
- Current use of benzodiazepines

Reporting of Pregnancy 3.3

Female participants who are enrolled in the study with undergo safety screening. At the first assessment during the screening procedure, female participants will be asked to take a pregnancy test by providing a urine sample. Although the theoretical risk to the mother or fetus is exceedingly small, no safety data for pregnancy is known to exist for transcranial direct current stimulation (tDCS) or transcranial alternating current stimulation (tACS) studies. Thus, if at any time a female participant is found to be pregnant (by verbal confirmation or a positive pregnancy test). she will be excluded from the study.

Reasons for Withdrawal 3.4

We will not withdraw participants from the study unless they fulfill one of the following criteria:

- Voluntarily refuse continued participation in the study
- Demonstrate an inability to comply with study procedures where collected data is found to be unreliable, misconstrued, or fabricated
- Reveal information that they did not reveal during the screening procedure that prevents them from participating (e.g., personal or family history of a neurological condition, current use of an antiepileptic drug, pregnancy).
- Experience serious adverse side effects (e.g., seizure)
- Fail to attend the second session
- Are asked to leave SouthLight by SouthLight staff before their expected treatment completion date due to disruptive behavior or poor attendance to their treatment program. In these cases, participants may no longer be eligible for participation in the study, even if they have already been screened and consented.

Referral Procedure 3.5

In the event that participants are found to be in need of medical attention or psychological counseling, senior research staff will determine necessary routes of treatment and care and refer participants to appropriate medical and psychological services. In addition, research staff will inform SouthLight health care professionals (e.g., medical doctors, nurses, psychologists, counselors) in the case that immediate medical attention or psychological counseling is deemed necessary.

Termination of Study 3.6

This study may be prematurely terminated if, in the opinion of the investigator, there is sufficient reasonable cause. Circumstances that may warrant termination include, but are not limited to:

- Experience of a recruitment rate of < 20% of approached patients at SouthLight (who would otherwise qualify for our study); we will cease recruitment due to limitations surrounding generalizability.
- An event during which a participant experiences a seizure during an assessment, a temporary hold will be placed over the study and further investigation will be pursued. Based on investigational findings, the study may be stopped prematurely or may be continued with further safety measures in place. If more than one participant experiences a seizure during his/her assessment, the study will be stopped prematurely. These individuals will be referred for further medical attention.

The IRB will be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

STUDY SCHEDULE 4

Recruitment 4.1

Research staff will recruit individuals at the Garner location of the SouthLight Treatment Center in Raleigh, NC by making weekly announcements at the end of the substance abuse intensive outpatient program (SAIOP) groups. Research staff will introduce themselves as members of the UNC research team and provide brief information about the research that they are conducting in order to learn more about addiction. This brief information will include an overview of the study procedures including two research sessions and the potential to review non-invasive, safe brain stimulation while playing computer games, in addition to answering interview questions and filling out self-report questionnaires. Any interested individuals will be asked to stay after their group to discuss the date of the next screening session.

Screening 4.2

Research staff will meet with interested individuals one-by-one in a private room where they will be screened to determine eligibility based on the study inclusion and exclusion criteria. Potential participants will be screened using the Word Reading Subtest of the Wide Range Achievement Test (WRAT) and the Alcohol Use Disorder and Substance Use Disorder Modules of the Mini International Neuropsychiatric Interview (MINI) 7.0, which will both be administered in an interview format. During the screening procedure, research staff will also ask potential participants about their age, most recent substance use, pregnancy/nursing status (females only), current medical conditions and medical history, current medications, and most recent electroconvulsive therapy (ECT) session. Eligibility based on the study's inclusion and exclusion will be recorded on the Screening Form. Potential participants who do not meet criteria for the study will be informed of this decision and thanked for their time. Eligible patients who are willing to participate, provide informed consent, and sign the HIPAA Authorization Form and the UNC Release of Information Form will continue to the procedure of the first session. Administration of the screening procedure should take no longer than 45 minutes.

Stimulation Sessions 4.3

First Session Participants will be escorted to a private room. Female participants will undergo a pregnancy test that must be negative in order for further participation in the study. Female participants will be asked escorted to the bathroom and asked to provide a urine sample. Upon collection, the research staff will run the pregnancy test and inform the participant of the results in a private room. Female participants that have a positive pregnancy test will be provided a written referral to a SouthLight on-site physician that is a member of the participant's treatment team in order to obtain information on follow-up services, as well as a list of OBGYN referrals that will be prepared with SouthLight staff before initiation of study recruitment and enrollment procedures. Female participants that have a positive pregnancy test will also be informed of their withdrawal from study participation and thanked for their time and efforts. Participants who remain eligible for the study will complete a battery of self-report and interview measures with research staff, including the Contact Form, Demographics Form, Use of Medications Form, Beck Anxiety Inventory (BAI), Beck Depression Inventory-II (BDI-II), Psychiatric Research

Interview for Substance and Mental Disorders (PRISM) Timeline, Timeline Followback (TLFB), and the Timeline Followback (TLFB) Supplementary Form. After the participant completes these measures, the research staff will have the participant sit in front of the computer and fill out the pre-tasks Positive and Negative Affect Schedule (PANAS) and Brief Substance Craving Scale (BSCS). Next, the research staff will attach the physiological recording equipment and begin recording. Then, the research staff will prepare the stimulator and the participant, including measuring the participant's head for proper coordinate determination and applying the stimulation electrodes. Then the research staff will initiate the active sham stimulation. The participant will then engage in the Go/No-Go task, rate his/her level of distress on the Subjective Units of Distress Scale (SUDS.), and complete the distress tolerance (DT) task, the Computerized Paced Auditory Serial Addition Task (PASAT-C). After the participant completes the DT task, the research staff will stop the stimulation and remove the physiological recording equipment, and the participant will complete the post-tasks PANAS, BSCS, PASAT-C Questionnaire, and the Post-Stimulation Questionnaire. Twenty minutes after the completion of the DT task, the research staff will assess the participant's level of distress by asking the participant to rate how distress s/he is feeling again using the SUDS. If the participant provides a SUDS rating 2 or more points higher than their pre DT task SUDS rating, the research staff will guide the participant through a planned relaxation exercise using a pre-recorded audio file until their SUDS has returned to baseline. After, the participant will be given a reminder card with the date, time, and location of the second session. After the completion of the first session, participants will be randomized by a non-research team member to one of the three stimulation conditions using a stratified randomization procedure.

Second Session Upon their arrival, participants will be escorted to a private room. The participant will complete a battery of self-report and interview measures with research staff, including updates on the Demographics Form, Use of Medications Form, TLFB, and the Contact Form. The research staff will have the participant sit in front of the computer and fill out the pre-tasks PANAS and BSCS. Next, the research staff will attach the physiological recording equipment and begin recording. Then, the research staff will prepare the stimulator and the participant, including measuring the participant's head for proper coordinate determination and applying the stimulation electrodes. Then the research staff will initiate the stimulation, based on the participant's randomization condition. The participant will then engage in the Go/No-Go task. After the participant completes the Go/No-Go task, the participant will rate his/her level of distress on the SUDS, and then completed the DT task. After the participant completes the DT-task, the research staff will stop the stimulation and remove the physiological recording and tACS equipment, and the participant will complete the post-tasks PANAS, BSCS, PASAT Questionnaire, and the Post-Stimulation Questionnaire. Twenty minutes after the completion of the PASAT, the research staff will assess the participant's level of distress by asking the participant to rate how distress s/he is feeling again using the SUDS. If the participant provides a SUDS rating 2 or more points higher than their first SUDS rating, the research staff will guide the participant through a planned relaxation exercise using a pre-recorded audio file. Participants will be compensated and thanked for their time and efforts.

Debriefing At the completion of all study data collection, participants will be contacted via telephone in order to complete the debriefing procedure. Participants will have the opportunity to

ask questions and voice concerns, as well as withdraw their data, if they choose. After the debriefing procedure, participants will not be re-contacted.

STUDY PROCEDURES & EVALUATIONS 5

Clinical Evaluations 5.1

Several clinical evaluations will be used throughout this study. These assessments are listed below.

Beck Anxiety Inventory (BAI; Beck et al., 1988) – The BAI is a 21-item self-report questionnaire that assesses the severity of anxiety. It has demonstrated high internal consistency (α=.92), strong convergent validity with other clinical measures of anxiety (r=.25-.51). The questionnaire will be administered at the first session and is estimated to take about 5 minutes to complete.

Beck Depression Inventory - II (BDI-II; Beck et al., 1996) – The BDI-II is a 21-item self-report questionnaire that assesses symptoms of depression currently and in within the past 7 days. It has demonstrated strong convergent validity with other measures of depression (r=.71) compared to measures of anxiety (r=.47). It has also demonstrated no association with demographic variables including gender, ethnicity, and age. The questionnaire will be administered at the first session and is estimated to take about 5 minutes to complete.

Brief Substance Craving Scale (BSCS; Somoza et al., 1995) - The BSCS is a 16-item self-report questionnaire that assess craving for substances during the past 24 hours. For the purposes of this study, the first item ("The intensity of my craving, that is, how much I desired this substance in the past 24 hours was...") will be administered before and after completion of the PASAT. This item is assessed is a 5-point Likert scale (0=none at all, 1=slight, 2=moderate, 3=considerable, 4=extreme). This item is estimated to take less than 1 minute to complete.

Demographics Form – This form will include basic demographic questions including age, sex, date of first day of last menstrual cycle (for females only), ethnicity/race, education level, employment status, occupation, and income. The questionnaire is estimated to take about 5 minutes to complete.

Fagerstrom Test for Nicotine Dependence (FTND; Heatherton et al., 1991) - The FTND is a 6-item self-report questionnaire that assesses the severity of nicotine dependence. The questionnaire will be administered during the screening procedure and is estimated to take 2-3 minutes to complete.

Go/No-Go Task (as used in Bell et al., 2014) – This version of the Go/No-Go consists of a series of neutral scenes from the International Affective Picture System (IAPS) (Lang et al., 1999). Participants view a serial stream of pictures and are instructed to continuously press a button on the computer keyboard, but inhibit responses when pictures are presented consecutively. Accuracy (% correct non-occurrences/omissions) and mean response time will be recorded. This task will be used to assess inhibitory control. The task will take approximately 12 minutes to complete.

MINI International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) - The MINI is a short, structured diagnostic interview. It will be administered during the screening

procedure in order to assess for a current substance use disorder (Modules I and J) and psychotic disorder (Module K). The interview will take approximately 20 minutes to complete.

Computerized Paced Auditory Serial Addition Task (PASAT-C; Lejuez et al., 2003) – The computerized PASAT is a psychological distress-inducing task. Numbers are presented sequentially on a computer screen and participants are asked to add the currently presented number to the previously presented number before the next number is presented. Participants select the answer using a computer mouse on a number pad displayed on the computer screen below the presented numbers. Presented numbers range from 0 to 20 with no sums greater than 20 in order to limit the role of mathematical skill. During the easy/titration phase (5 minutes), an algorithm will automatically titrate the speed of the number presentations in order to account for some individual differences in cognitive capacity, but not to secure equal performance among individuals. During the hard phase (5 minutes), the individually titrated task speed will be maintained throughout. During the distress tolerance (DT) phase (up to 15 minutes), the individually titrated task speed will be maintained throughout, but individuals will be told that they have the option to quit the task at any point. Incorrect or delayed responses are met with an aversive explosion sound. Participants will be told that their score, presented in the corner of the computer screen will increase by 1 point with each correct answer. In addition, participants will be told that compensation for the task will be determined by their performance on the task. Accuracy (% correct and % omitted), mean inter-stimulus interval (ISI = ISImean - ISIbaseline), and latency to task termination (i.e., quit time) will be recorded. Participants will engage in this task at both sessions, always after the Go/No-Go task. The task will take between 10 and 25 minutes, depending on if and when a participant decides to quit the task during the distress tolerance phase.

PASAT Questionnaire – This will be administered following administration of the DT task. The questionnaire is composed of 4 questions asking about the participant's experience playing the computer game. The questionnaire is estimated to take about 2-3 minutes to complete.

Positive and Negative Affect Scale (PANAS; Crawford & Henry, 2004) – This is a 20-item self-report measure that assesses changes in positive (PA) and negative (NA) affect. PA assesses the extent to which an individual feels enthusiastic, alert, and active. NA assesses the extent to which an individual feels subjective distress and additional components of negative mood such as anger, contempt, disgust, and guilt. Individuals are asked to rate to what extent a they have felt a feeling/emotion (represented by single words, e.g., hostile, guilty, interested) over a specified time interval (e.g., at the present moment, today, past few days, week, past few weeks, year, in general). In this study, participants will be asked to rate based on how they feel at the present moment. The PANAS has demonstrated good internal consistency for both the PA (α=.89) and NA (α=.85) scales (Watson et al., 1988). This will be administered before and after each time a participant completes the PASAT. The questionnaire is estimated to take about 2-3 minutes to complete.

Psychiatric Research Interview for Substance and Mental Disorders (PRISM) Timeline (Hasin et al., 1996; 1998; 2001; 2006) - This is a structured clinical interview that assesses a wide range

of psychiatric disorders. For the purposes of our study, we will be using the Substance Screening Subscale timeline to assess previous periods of chronic intoxication and binge use of various substances. This is estimated to take about 5-20 minutes, depending on the participant's substance use history.

Subjective Units of Distress Scale (SUDS; Wolpe, 1969) - The SUDS is a scale to measure an individual's self-reported distress from 0 to 100, with higher ratings indicating higher levels of distress. It will be used administered to assess participants' residual level of distress at the completion of the testing session. It is estimated to take less than 1 minute to complete.

Timeline Followback (TLFB; Sobell et al., 1979) – The TLFB is a clinician administered measure of substance use. It has demonstrated high test-retest reliability (ICC=.70-.94, $p<.001$), convergent and discriminant validity with other measures, agreement with collateral informants' reports of patients' substance use, and agreement with the results form patients' urine analysis (Fals-Sterwart et al., 2000). The measure is estimated to take about 10 minutes to complete.

Timeline Followback (TLFB) Supplementary Form – This form provides a summary of an individual's most recent substance use, as well as the amount, duration, and frequency. This form is estimated to take about 5-10 minutes to complete.

Use of Medications Form - This form asks individuals about their current use of mood- and non-mood-related medications. This will be administered in an interview format and will be administered at both sessions. It is estimated to take approximately 3-5 minutes to complete.

Wide Range Achievement Test Revised (WRAT-R) Word Reading Subtest (Jastak & Wilkinson, 1984) – This assesses an individual's ability to read and comprehend words. In particular for this study, this will be used during the screening procedure to assess an individual's reading level prior to providing consent in order to determine if an individual can read at a fifth grade level. This is necessary for an individual to be able to comprehend and participate in the written proportions of the study. The assessment is estimated to take about 10 minutes to complete.

Equipment & Forms 5.2

BIOPAC Data Acquisition System (BIOPAC Systems, Inc., Goleta, CA) – Autonomic arousal will be measured throughout both assessments from measures of galvanic skin response (GSR), heart rate (HR), and pulse using two wireless devices of the BIOPAC MP150 system (BIOPAC, 2011). GSR will be recorded using the GSR wireless module, which will be wrapped comfortably around the participant's wrist and Ag/AgCl electrodes attached to the first and third fingers of the participant's non-dominant hand. HR and pulse will be recorded using the ECG wireless module, which will be wrapped around the participant's waist and secured to the chest using an adhesive, and recorded from electrodes attached to the participant's upper chest and lower rib. GSR and HR will be recorded throughout the entire duration of both tasks (Go/No-Go and PASAT) at both sessions.

Contact Form – This form including the participant's best phone numbers, addresses, and alternate contacts, will be used to improve study retention by maintaining contact with

participants throughout the duration of the study. It will be administered in an interview format and is estimated to take about 10 minutes.

Debriefing Information Sheet – Participants will be provided with appropriate and correct information about their study participation and of particular note, of the minor deception involved in the study. Participants will also be given a chance to ask any questions about the study. Participants and experimenters will sign and date the information sheet to document the completion of the debriefing procedure.

Drop Out Questionnaire – This questionnaire will document the reason for a participant's (self-initiated) withdrawal from the study. This questionnaire is estimated to take 2-3 minutes to complete.

Planned Relaxation Exercise – Participants will be led through a planned relaxation exercise if they report residual distress as indicated on the SUDS, using a pre-recorded audio file. The audio for the exercise is approximately 3 minutes long.

Post-Stimulation Questionnaire - This questionnaire will be administered after the stimulation procedures at both sessions in order to assess (1) safety of the tACS, (2) participant experiences with the tACS, and (3) physical and psychological symptoms that participants may believe are associated with tACS. This data will be used to assess whether participants were successfully blinded during the course of the study. This questionnaire is estimated to take about 5 minutes to complete.

Pregmate One Step Urine Human Chorionic Gonadotropin (hCG) Pregnancy Test – Female participants will provide a urine sample for a pregnancy test at the beginning of the first session to confirm that they are not pregnant before undergoing the stimulation procedures. The urine pregnancy test will provide results after 5 minutes.

Screening Form – This form will be used to record a participant's eligibility status according to the study's inclusion and exclusion criteria.

Transcranial Current Stimulator (Pulvinar Neuro LLC, 2016) - We will be using a transcranial current stimulator developed, XCSITE 100, by Pulvinar Neuro LLC for investigational research purposes. The device is not implanted and has not been designed for or being used to support or sustain human life. This device does not have a potential for serious risk to the health, safety, or welfare of the participant. There has never been an instance of serious side-effect reported due to use of transcranial brain stimulation. This device has been used in previous studies by the Frohlich Lab and which have always been classified as "non-significant risk" by the UNC IRB. This device is functionally equivalent to the CE-certified Neuroconn Plus stimulator. The use of this device in this study has previously received a NSR designation on initial review by the full UNC IRB. Both devices are electrically equivalent and provide the same stimulation. In addition, the stimulator has built in safety features. The device is equipped with 5 different stages of safety protection, all of which protect the stimulant from high currents. (See Additional Device Information for more details.)

Additional Device Information

The device consists of the following main components/subsystems:

1. Tablet with user interface application (App)
2. Microprocessor
3. Function generator chip
4. Voltage controlled current source
5. Safety circuitry

First, the stimulation parameters are specified by the user through the app. The parameters are:

1. Number of channels
2. Alternating (AC) or Direct Current (DC)
3. Verum or Active Sham Stimulation
4. Amplitude in miliamperes
    a. 2 mA peak-to-eak sine wave stimulation
5. Stimulation frequency (ignored for direct current) in Hertz
    a. 10 or 40 Hz
6. Stimulation duration in seconds
7. Ramp Up duration in seconds
8. Ramp Down duration in seconds
9. Active Sham duration (ignored for verum stimulation) in seconds

Next, the parameters are sent via Bluetooth™ to the microprocessor. The microprocessor interprets these parameters if the parameters fall within the acceptable ranges the microprocessor returns them to the app for verification and programs the function generator chip accordingly. Once started by pressing the physical button on the device, the function generator then creates the programmed waveform, which is ultimately a voltage signal. The voltage signal is applied to a voltage controlled current source, which generates the specified amount of current through an arbitrary load resistance.

Operation

A. The desired current value is scaled to a register value and stored in the function generator.
B. The value in the register determines the percent of full scale output current, generated by the function generator.
C. The generated current waveform from the function generator is driven through a specified resistance. The resulting voltage drop is amplified by an instrumentation amplifier.
D. The voltage waveform from the output of the instrumentation amplifier is applied to a voltage controlled current source.

Current Sensor Circuit - A 33.2 Ω sense resistor is placed in series with the stimulation electrodes on the high side. Since high-side current sensing is used, any short circuit of the

electrode terminals to ground will be detected. The stimulation current flows through this resistor and generates a voltage. The voltage across this resistor is sensed and amplified by the AD628 difference amplifier. The gain of the difference amplifier is set to 9.9039. The current sensor voltage is then shifted before it is read by the microprocessor and the hardware overcurrent safety feature.

Voltage Sensor Circuit - The differential voltage across the electrodes is measured so that the impedance can be calculated. The voltage is measured by buffering the positive electrode and negative electrode each with a unity gain op-amp circuit. The voltage sensor output is then shifted before it is read by the microprocessor using the same level shifting circuit described in the current sensor section.

Safety Precautions

The device is equipped with 5 different stages of safety protection, all of which protect the stimulant from high currents. The stages are as follows:

1. Software parameter validation. All stimulation parameters are checked to be within the allowable ranges for those parameters. If values outside of this range are entered the app will not allow stimulation to start.
2. Automatic software current cutoff. The output of the current sensor described above is read by a microprocessor, which compares the reading to a value of +/- 2.3 mA peak. If the current exceeds these limits, stimulation is stopped, a relay in series with the electrode is opened, and the power supply used for stimulation is turned off. The user is then given the option to investigate the issue, and cancel or resume the test. Since high-side current sensing is used (described above), any short circuit of the electrode terminals to ground will be detected.
3. Automatic hardware current cutoff. The output of the current sensor is fed into a pair of comparators which detect if the current exceeds +/- 4.5 mA. If so, the fault is latched such that the relay in series with the electrodes is opened. Additionally, the microprocessor is notified of this instance through an interrupt. Upon this interrupt, the microprocessor immediately stops stimulation and the power supply used for stimulation is turned off.

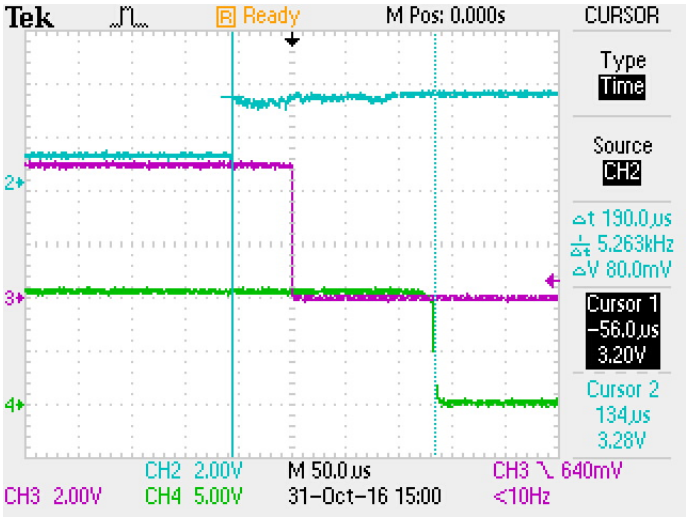

Figure 1: Example hardware cutoff function. At – 54 µs, the current sensor is raised artificially (blue). With a latency of 54 µs, the high voltage rails are turned off (purple). The stimulation output (green) is zeroed 190 µs after the high current was detected.

4. Permanent hardware current cutoff. A 5 mA fast-acting fuse is in series with the electrode connector. If the above over-current detection methods fail, the fuse will blow, and the participant will no longer be electrically connected to the current generator.
5. Power supply fuse. Finally, if for any other reason the entire device draws too much current, the main power supply fuse is blown. This fuse is rated for 400 mA which is approximately 200% of nominal operating current.

Risk Monitoring 5.3

Risk of discomfort or injury caused by tACS administration is rare. tACS has been successfully utilized without any reports of serious side effects, deeming tACS an extremely safe and non-invasive approach to modulate neural oscillations. tACS passes weak electric current through the scalp, which is routinely done using other methodologies such as electroencephalography (EEG). It is important to note that tACS does not use the same procedures/methods as electroconvulsive therapy, that applies many orders of magnitude higher of stimulation current. tACS uses a weak electric current, such as it does not produce super-threshold activation of neurons (Frohlich & McCormick, 2010).

There is a rare, theoretical likelihood that neural stimulation can lead to epileptic discharges. Previous studies using tDCS in patients with depression and schizophrenia have reported no seizures (Berlim et al., 2013; Brunelin et al., 2012). In order to minimize this occurrence, we will exclude individuals with personal and family history of neurological conditions and individuals who are currently taking benzodiazepines from the study during the screening procedure. For the same reason, we will also exclude individuals that have not been abstinent for more than 2 weeks from the study during the screening procedure.

In previous tACS research, some individuals have reported transient tingling underneath the electrodes on the scalp, including itching, headache, burning sensations, and minor discomfort. However, a recent meta-review has failed to find any significant differences in occurrence rates of these symptoms between tDCS and a sham control condition (Brunoni et al., 2011). In addition, rTMS has also proven to be well tolerated by individuals with substance use disorders (Gorelick et al., 2014). More specifically, in studies utilizing rTMS on individuals with substance use disorders, active and shame rTMS groups had comparable drop-out rates and no reports of serious or unexpected adverse events.

Safety Monitoring 5.4

After each stimulation session (active sham and tACS), the Stimulation Adverse Effects Questionnaire will be administered. This will be used to document any side effects experienced during stimulation. In addition, throughout the stimulation sessions, the researcher will check with the participant to make certain that no discomfort or injury is felt or has occurred. In the case that a participant reports unmanageable discomfort or pain, the stimulation session will be terminated immediately.

DATA ANALYSIS 6

Sample Size Considerations 6.1

Due to the fact that this is a pilot study, and the first study (to our knowledge) to administer tACS in a sample of substance users, we utilized effect size estimates from tACS studies with mainly healthy controls. Using G*Power 3.1, we conducted a power analysis with a conservative effect size of 0.3 and a desired power of 0.80, which calculated a total sample size needed of 39 participants. The results of this pilot study will provide effect size estimates to conduct a power analysis in future studies specifically with a sample of substance users. We plan to report effect sizes between 0.3 and 0.5 (Chi et al, 2010; Kar & Kerkelberg, 2014)

Data Management 6.2

Interview and hardcopy questionnaires that cannot be computerized will be entered into Excel (password protected) and SPSS databases on a secure UNC server, only accessible to the research staff. Data will be coded with study ID numbers that can only be matched to a participant's name via a database stored in a separate, secure location on the server, only accessible to the researcher staff using a password. Data entry of these questionnaires will utilize a double-entry approach, such that data will be entered twice by two separate researchers. A third researcher will clean the data using SPSS Data Entry Builder to identify and correct discrepancies between the primary and secondary entries. The project coordinator will be responsible for ensuring data quality and control, and data management oversight.

Confidentiality 6.3

All of the information obtained from participants will be entirely for research purposes and de-identified using study IDs. Data will be kept in locked confidential filing cabinets in a secure office space at UNC, only accessible to the research staff. The consent forms and the Contact Forms will be kept separately from the data in a locked filing cabinet, also only accessible to the principal investigator and the study coordinator. All computerized data collection methods will use a secure, encrypted web survey, using the Qualtrics online survey platform. Only study IDs will be used in the collection of this data. This data will be stored on a secure network at UNC, only accessible to research staff. All data will be stored in password protected files on password protected computers located in a secure office space at UNC. Only research staff will have access to these files, computers, and office space. Data will only be transmitted via HIPAA compliant storage devices or encrypted email services

Final Analysis Plan 6.4

Aim 1 To investigate the real-time effect of transcranial alternating currently stimulation (tACS) on inhibitory control and distress tolerance.

Descriptive statistics (e.g., mean, standard deviation, variance, range) will be generated for all continuous study variables. Continuous study variables will also be examined for normality and homogeneity of variances using visual inspection methods (e.g., histograms, box plots, residuals, Normal Q-Q plots) and quantitative methods (Shapiro-Wilk test). If these assumptions

are violated, the continuous study variables will be transformed, as necessary (e.g., log transformation). We will use hierarchical linear regression to test whether there is a statistically significant effect of condition (tACS at 10 Hz, tACS at 40 Hz, or active sham stimulation) on session 2 DT and IC (controlling for session 1).

The latency to quit on the PASAT during the distress tolerance phase and d-prime on the Go/No Go primary outcomes of this pilot study.

Aim 2 To demonstrate the feasibility of administering transcranial alternating currently stimulation (tACS) among a sample of adults with SUD recruited from a substance use outpatient treatment center. Descriptive statistics and frequencies will be generated for all study variables related to assessing the feasibility of administering tACS (e.g., drop-outs, occurrence of unexpected and/or adverse events and side effects).

Given that this is a pilot study, we hope to use the results of this study to act as a foundation for a larger, future study with the aim of examining the effect of tACS on substance use treatment outcomes and engagement among treatment-seeking adults with SUD, with a focus on distress tolerance and inhibitory control as mechanisms of change. This larger, future study will be in line with our long-term goal of developing and implementing a novel non-invasive brain stimulation paradigm, using tACS, for the treatment of substance use disorders.