Title: Modulating Impulsivity in Suicidal Adolescents With Transcranial Direct Current Stimulation (tDCS)

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HUMAN RESEARCH PROTOCOL

Suicide is one of the leading causes of death in adolescence. To advance prevention and treatment efforts, there is a need for research in this area to move beyond identifying correlates or markers of suicidal risk to determining causal risk factors. The adoption of new experimental paradigms providing experimental control over candidate causal risk factors has been recommended as a means of meaningfully advancing the field. Impulsivity is a risk factor particularly relevant to adolescent suicidality. Although most studies linking impulsivity to suicidality examined impulsivity at the trait level, neuropsychological indices of this construct are state-sensitive, and thus may be more clinically meaningful insofar as they reflect proximal and modifiable risk rather than general risk for suicidal behavior.

One novel methodological paradigm that may hold promise in providing experimental control in the study of impulsivity is transcranial direct current stimulation (tDCS), a form of neurostimulation in which electrodes attached to the scalp deliver constant, low current stimulation to the brain. Although widely studied with adults, tDCS has rarely been applied in experiments with adolescents. Moreover, the mechanisms by which tDCS affects behavioral and cognitive impulsivity has not been adequately studied. One method to clarify the neural pathways underlying its effects is electroencephalography (EEG) and event-related potentials (ERPs).

As a necessary first step in assessing state-sensitive impulsivity as a causal risk factor for suicidality, this study will assess the short-term effect of tDCS on impulsivity. That is, the researchers will evaluate the potential for tDCS to the right inferior frontal gyrus (rIFG) and left orbitofrontal cortex (lOFC) to modulate behavioral and cognitive impulsivity, respectively, in adolescent suicide attempters. Adolescents in a psychiatric hospital program will be enrolled if they attempted suicide prior to their admission and who had made an impulsive attempt as measured on the C-SSRS (attempt initiated within a day of thinking of it). Participants will be randomized to receive either anodal tDCS to the rIFG, anodal tDCS to the lOFC. Randomization will occur through a computer program (like flipping a coin with participants having an equal chance of being in each group). This will occur after we determine if the participant is eligible for the study. There will be 20 participants in each group. Participants will not be told which group they are randomized into. Baseline impulsivity measures will be re-given after tDCS or sham stimulation to assess changes in impulsivity. Additionally, EEG/ERP data will be collected during the impulsivity tasks, and resting-state EEG data will be collected pre- and post-tDCS.

Participants Adolescents (N = 60) between the ages of 13 and 17 who have been admitted to an adolescent psychiatric hospital (inpatient or partial). Adolescents will be eligible to participate if they: (i) have attempted suicide prior to admission; (ii) had made an impulsive attempt as measured on the C-SSRS (attempt initiated within an hour of thinking of it); (iii) speak and read English fluently, (iv) have no significant cognitive disability based on a standard psychiatric exam, and (v) are not actively psychotic.

Exclusion criteria are: (i) a significant general medical or neurological condition; (ii) history of seizure, head injury, brain surgery or tumor; (iii) intracranial metallic implants or implanted electrical devices; (iv) substance abuse or dependence in the past six months.

Sample Availability. Hospital admission data suggests more than 60 adolescents would meet these study criteria over the two year recruitment period. We have found in other studies recruiting from this site to allow for adequate time for in-depth assessment batteries larger than that of the proposed study.

Consenting and Screening Evaluation. Parents and adolescent will be approached about participating in the study after review of their medical charts upon admission to the Bradley, Butler, or Hasbro. Study staff will obtain consent. All research staff will be trained in the steps necessary to obtain consent. All participants and their parents will be fully informed about the purpose and procedures of the study both verbally and through a written description contained in the assent/consent forms. All participants will be required to provide assent and their parents/guardians to sign an informed consent document in order to participate in the study.

Once consented, participants will be assessed for a suicide attempt prior to index psychiatric admission using the C-SSRS. Next participants will be screened for current psychosis and cognitive disability using the K-SADS-PL and the WASI, respectively, and complete the screening form. Those meeting all eligibility criteria will complete the PROMIS and Connors-3, which will be included as covariates in analyses. Eligible participants will also be asked about their current medication use, and the information they provide will be confirmed with a parent.

After completing these assessments, participants will be randomly assigned to receive either anodal tDCS to rIFG, anodal tDCS to lOFC, or sham stimulation. tDCS at a constant current of 1.5 mA and sham stimulation will be applied for one 20-minute session. In the sham condition, the current will be ramped up to 1.5mA for 30 seconds and then ramped back down to 0. As this commonly used sham procedure produces a brief tingling sensation, participants are kept unaware of their experimental condition. Prior to and tDCS, participants will complete the SST and TCIP, while EEG is recorded to extract ERPs in a single-blind procedure. The participants and PI Liu will be blind to experimental condition, but Co-I Carpenter will not be blinded. Resting-state EEG, for 5 minutes, will be recorded before pre-stimulation tasks and after post-stimulation tasks. These tasks were specifically chosen because they can be administered well within an hour, the approximate duration of effect from a single-session of tDCS. The side effects questionnaire will be administered following the tDCS session. Ordering of tasks will be counterbalanced. These assessments will take about 3.5 hours total and they will be audio recorded for supervision and training purposes with participants' permission. They will take place in an interview room in the hospital, outside of any clinical care. Adolescent participants and parents will be paid $100 and $25, respectively, upon completion of the study.

Assessment Measures.

i. Self-report measures

Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999): The WASI uses vocabulary, similarities, block design, and matrix reasoning subtests similar to those of the WAIS to provide an estimate of full scale IQ in approximately 30 minutes.

Depressive symptoms will be assessed using the pediatric version of the PROMIS depression scale. Higher scores reflect greater symptom severity.

The *Conners-3 Self-Report (Conners-3 SR; Kollins, Epstein, & Conners, 2004)*: Current ADHD symptoms will be assessed with the Connors-3, with higher scores reflecting greater severity. ADHD will be a covariate in all analyses, as impulsivity is a hallmark of this disorder.

Suicidal ideation will be measured using the Passive and Active Suicidal Ideation Scale (PASIS). Higher scores reflect greater severity of ideation.

Suicide Intent Scale (SIS): The SIS is an interviewer rating scale that assesses the degree of suicidal intent of a suicide attempt. Higher scores reflect greater suicidal intent.

Screening questionnaire: The screening questionnaire was adapted from those used in other tDCS studies conducted by Co-I Carpenter. This questionnaire is meant to check for potential head trauma and metallic implants.

Side effects questionnaire: The side effects questionnaire was adapted from those used in other tDCS studies conducted by Co-I Carpenter This questionnaire is meant to check for any adverse events from the tDCS stimulation.

Lastly, participants will be asked to report their current medication use, and the information they provide will be confirmed with a parent.

ii. ***Semi-structured interview assessments***

Schedule for Affective Disorders and Schizophrenia for School Aged Children - Present and Lifetime Versions (K-SADS-PL; Kaufman et al., 1997): The K-SADS-PL is a semi-structured diagnostic interview which provides a reliable and valid assessment of DSM-IV psychopathology in children and adolescents. Probes and objective criteria are provided to rate individual symptoms. Inter-rater agreement is high (range: 93% to 100%). Test-retest reliability and kappa coefficients are in the excellent range for present and lifetime diagnoses. Modules selected on the basis of relevance to suicide risk will be administered. These include depressive disorders, mania, psychosis, anxiety disorders, eating disorders, conduct disorder, alcohol and substance abuse, and post-traumatic stress disorder.

Columbia-Suicide Severity Rating Scale (C-SSRS; Posner et al., 2011): The C-SSRS is an interviewer-rating scale, will be used to assess the occurrence of suicide attempts, and to differentiate suicide attempts from interrupted attempts and aborted attempts. To differentiate suicide attempts from nonsuicidal suicidal self-injury, the

former will be defined as any "self-destructive behavior with at least implied intent to die."

iii. ***Computerized neurological tasks – DDT (TCIP), SST***

Two Choice Impulsivity Paradigm (TCIP; Dougherty et al., 2003): The TCIP will be used as a delay discounting task (DDT) to assess impulsive choice, which requires participants to choose between immediate but small rewards and delayed but larger rewards over 50 trials. Delay discounting (or impulsive choice), is the tendency to undervalue an anticipated future reward as the time delay to obtaining the reward increases. A higher discounting rate (i.e., preference for smaller immediate rewards over larger delayed rewards) is viewed as reflecting greater cognitive impulsivity.

Stop-Signal Task (SST; Hamilton et al., 2015): The SST will be used to assess behavioral impulsivity. The SST requires participants to respond to a target stimulus as quickly and accurately as possible by pressing a button, but also to withhold their response when they hear an auditory signal. Thus, this task involves a competition between activating and inhibiting processes.

iv. ***tDCS and EEG.*** tDCS will be applied and EEG recordings made using a starstim/enobio device, with stimulation and recording electrodes located inside the cap. This device provides the user with up to 8 stimulating electrodes that can be programmed through software to be either anodal or cathodal in polarity and up to 32 recording electrodes. When not being used for stimulation, the 8 stimulating electrodes can also be used for recording, allowing for a total of 40 electrodes to be used for recording EEG pre- and post-stimulation. As in past studies, electrodes will be placed according to standard 10-10 coordinates corresponding to the rIFG (anode over F8 and cathode over FP1), which has been associated with behavioral impulsivity, and the lOFC (anode over FP1 and cathode over FP2), which has been linked with cognitive impulsivity.

Data analysis

Aim	Hypothesis	Dependent	Independent†	Analysis	MDE‡
1	H1	SST	tDCS/rIFG, time, tDCS/rIFG×time	GLM (repeated-measures ANOVA)	d=0.35
2	H2	SST	As above, plus reduced theta power (EEG), increased P3 (ERP)	As above with effects for EEG and ERP added; change in tDCS parameter estimate informs mediation	r=0.35
EA	EH1	DDT	tDCS/lOFC, time, tDCS/lOFC×time	GLM (repeated-measures ANOVA)	d=0.35
	EH2	DDT	As above, plus reduced VLFO (EEG), reduced SCPs (ERP)	As above with effects for EEG and ERP added; change in tDCS	r=0.35

		parameter estimate informs mediation

† All analyses will include PROMIS (depressive symptoms) and Connor-3 (ADHD symptoms) as covariates
‡ MDE minimal detectable effect, expressed as standardized mean difference (Cohen's d) for aim 1 and minimal detectable correlation for aim 2 (n=60), assuming type-I error level 5% and type-II error level 20%. Repeated-measures ANOVA assumes correlation of 0.9 of repeated measures.

Protection of Human Subjects

Source of Research Material

Adolescents will complete interviews, self-report measures, computer tasks, EEG testing, and tDCS. The data will be obtained for research purposes.

Recruitment and Consent

Parents and adolescents will be contacted about participating in the study after their medical records have been reviewed upon admission to Bradley, Butler or Hasbro. Medical charts will be reviewed by trained members of the research team familiar with the study criteria. These study staff will coordinate with treatment providers to arrange times to meet with potentially eligible patients and their parents in person. The staff will present and explain the study to the adolescent patient and his or her parent at Bradley, answer any questions they may have, and, if appropriate, present and explain the consent forms. All patients and parents will be fully informed of the purposes and procedures of the study. PI Liu will train the research staff in the steps necessary to obtain consent. All participants and parents will be fully informed about the purpose and procedures of the study both verbally and through a written description contained in the assent/consent forms. PI Liu and other study staff will be responsible for soliciting and obtaining informed consent/assent after any questions have been addressed. All participants will be required to provide assent and their parents or guardians to sign an informed consent document in order to participate in the study. Patients will be provided with a copy of the consent document, and the original will be placed in the PHI filing cabinet.

Potential Risk

This study does not pose greater than minimal risk. Risks associated with participating in this study include some emotional discomfort that may be elicited by discussing sensitive matters such as suicidal thoughts and instances in which the child has tried to harm him- or herself. The child may refuse to answer any questions that lead to too much discomfort. If he or she expresses suicidal thoughts, we will notify the child's doctors so that they can take appropriate precautions. During the interviews and assessments, and when the child is completing the computer tasks he or she may become bored or tired. We will offer breaks frequently, and the child will be told that he or she can quit at any time if he or she gets tired.

Additionally, there is minimal risk in participating in EEG testing or tDCS, as both of these procedures have been demonstrated to be safe for adolescents. tDCS has also been shown to be safe in adults. It has been studied less among children, but studies that have been done so far demonstrate it to be safe for this age group (Andrade et al., 2014; Kessler et al., 2013; Krishnan

et al., 2015; Moliadze et al., 2015). In particular, stimulations at 1.5mA (which will be used in the current study) have been found to be safe and well tolerated in pediatric samples (Kessler et al., 2013). In a recent safety study of tDCS conducted by Poreisz and colleagues (2007) the most common effects were mild tingling sensations (75%), light itching sensation (30%), moderate fatigue (35%), and transient mild headache (11.8%); and most of these effects did not differ from those of placebo stimulation. For the current study, the participant will be asked to report any discomfort immediately. If the participant reports discomfort, the stimulation can be turned off immediately. Participants' parents will be encouraged to bring acetaminophen or ibuprofen in the case of a headache. These medications have promptly resolved discomfort in all prior cases of headaches or neck ache induced by tDCS. EEG is a safe and painless technique that is routinely used in clinical medicine. Lastly, all equipment has been tested by biomedical engineers at Neuroelectrics, who have certified their safety.

Protection against Risk

All study procedures will be explained to the participants with an emphasis on the voluntary nature of the study. Furthermore, staff members will be trained to respect participants' wishes regarding their participation in the study or certain aspects of the study's procedure (see Appendix).

Potential risk from breach of confidentiality will be minimized by strictly adhering to the guidelines for research outlined by the Lifespan IRB, Rhode Island state law, the Federal Health Insurance Portability and Accountability Act of 1996 and its regulations ("HIPAA"), and the DHHS Federal Policy for the Protection of Human Subjects (45 CFR Part 46 Subpart D). This will include identifying participant research data by numeric ID only and maintaining any records containing potentially identifying information separate from any research data. Research data, as mentioned, will be accessible only to research staff and, and all electronic data will be password protected. Participant confidentiality will be breeched only to protect the safety and welfare of research participants and only in accordance with state and federal law. All records will be kept in a locked file and will be available only to research personnel who are knowledgeable of human subjects protection guidelines. A password will be necessary to access the computer data file. No names, only identification codes, will be used in presenting data in lectures, seminars, and papers. No names will be released without written consent of the parents or young adults who provided consent. Patients will be given full access to their data and professional interpretation if requested after completion of the study.

Participant confidentiality will be breached only to protect the safety and welfare of research participants and only in accordance with state and federal law. It is possible that situations will arise in which children or parents provide the study staff with information that they are legally and ethically obligated to disclose (e.g., suicidal or homicidal intent, IV drug use, sexual abuse). All participants are informed in advance through the process of informed consent of the legal and ethical obligations of study staff should these issues arise. Whenever possible, study staff will handle these situations therapeutically. For example, if time limits and safety concerns allow, parents will be informed in advance and provided the opportunity to participate in the mandated report process. Research staff will contact PI Liu who will be responsible for

any on-site clinical decision-making. We have used these procedures in our other studies and they have been approved by our IRB**.**

Research data (written records and tapes of interviews) will be kept in a locked file and electronic data will be password protected. All of these study related materials will only be accessible to research staff. To minimize the risk of distress stemming from assessment procedures, the interviewers will be trained on how to monitor participant response to answering questions about sensitive/stressful topics. Interviews will be scheduled at times most convenient for the families, and they will be compensated for time, travel, and any inconvenience entailed by completing the interview.

All patients will be monitored with regard to suicidality and a safety plan will be implemented as needed. The safety plan will include: 1) the adolescent telling a designated adult if suicidal; 2) developing a coping plan; and 3) parents' commitment to providing a safe environment. The participant's psychiatrist or treatment provider will also be contacted with permission of the participant.

A safety plan will also be implemented as needed with regard to tDCS. Participants will be monitored closely during the study period and any side effects will be documented. All adverse events will be recorded and scored for severity and for relationship to the study as described, and all serious and unexpected adverse events will be reported to the IRB within 72 hours. Dr. Felipe Fregni, Dr. Jorge Morales-Quezada, Dr. Noah Philip, Dr. Daniel Press, and Dr. Sarah Garnaat, and Dr. Brian Kavanaugh have agreed to be available to review and address any safety concerns and to review all study safety and efficacy data in a signed report twice a year. Their contact information is listed below:

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Although the physiological effects of tDCS at the intended dose wears off within an hour, we will follow-up with the parents, at the end of the study after the minor has received this stimulation to ensure the safety of the minor and ask that they monitor the minor.

Potential Benefits of the Proposed Research

There are no direct benefits from participating in the study. However, the information obtained from this study will further our understanding of impulsivity in suicidal adolescents and elucidate potential methods for modulating impulsivity among these adolescents. The potential benefits also include a more thorough understanding of impulsivity in suicidal adolescents will help inform future research and treatment of this population.

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