Cover Sheet

Protocol Name: Treating Self Injurious Behavior: A Novel Brain Stimulation Approach

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Treating Self Injurious Behavior: A Novel Brain Stimulation Approach

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Contact Principal Investigator:
Jeffrey Miller, MD
Email: jm2233@columbia.edu
Telephone: 646-774-7613

Co-Investigator(s):
Barbara Stanley, PHD
Daniel Javitt, MD, PHD
Ashley Yttredahl

Research Chief:
J John Mann, MD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation without modifications

Department & Unaffiliated Personnel

Department

What Department does the PI belong to?
MIND/Psychiatry
Within the department, what Center or group are you affiliated with, if any?
N/A

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York

State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.

Richard Carson, Ph.D., Yale University, Co-Investigator
Marc Potenza, MD, PhD - Yale University, Co-Investigator/ Study Physician
Jiansong Xu, MD, PhD – Yale University, Co-Investigator

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Internet-based Data Collection or Transmission
✓ MRI
✓ Use of Investigational Drug or Device

Population

Indicate which of the following populations will be included in this research

✓ Adults
✓ Adults over 50
✓ Employees or Students

Research Support/Funding

Will an existing internal account be used to support the project?
No
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract is currently funded
Source of Funding
Foundation
Sponsor
Citronberg Fellowship

Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
No

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

Lay Summary of Proposed Research

The purpose of this study is to explore the tolerability and effectiveness of transcranial direct current stimulation (tDCS) as a potential treatment for non-suicidal self-injury (NSSI). NSSI is the deliberate attempt to harm oneself, most often through cutting or burning, without suicidal intent. NSSI is a maladaptive emotion-regulation strategy often triggered by negative emotions, especially those involving feelings of rejection. tDCS is a low-cost, portable, well-tolerated, non-invasive form of brain stimulation that delivers a low current to a specific area of the brain via electrodes. Several studies have demonstrated its effectiveness in treating an array of conditions, depending on electrode placement, including depression and chronic pain. tDCS may also facilitate adaptive emotion regulation; researchers have also successfully used tDCS to reduce negative emotions and aggressive responses to social rejection. We therefore seek to explore tDCS as a potential treatment for NSSI. This pilot feasibility study seeks 1) to examine how tDCS is tolerated in a sample of individuals who engage in frequent NSSI; 2) to gather pilot data regarding changes in neural responses to social rejection after a series of tDCS sessions in this clinical population of individuals who engage in NSSI; 3) to gather pilot data on the effects of tDCS on NSSI behaviors and urges. A sample of up to 10 volunteers will pilot the social feedback task during fMRI to assess its feasibility before beginning fMRI procedures in our patient sample. This task will involve participants playing a virtual ball-tossing game with two cartoon characters over the computer. We seek to recruit a sample of 22 individuals who engage in frequent NSSI to complete all study procedures, including neuroimaging. Individuals will be randomized to receive active- or sham-tDCS for two twenty-minute applications on each of six alternating days over approximately two weeks. tDCS delivery using a remotely-supervised treatment protocol will minimize the burden of study visits and allow patients to continue participating in research from the comfort of their homes when in-person procedures are not possible. During tDCS, participants will listen to an audio file with different sounds and a voice instructing them to switch their attention between the different sounds. The fMRI task will be performed at baseline and again after the completion of 12 sessions of tDCS. Subjects' NSSI and urges to engage in NSSI will be recorded for three weeks in real-time, using an iPod- based system that reminds subjects to stop at certain times during the day to record their

thoughts, feelings, and behaviors. This will allow measurement of NSSI urges and behaviors for one week before, one week during, and one week after the tDCS intervention. The long-term goal of this study is to identify a novel form of treatment for NSSI and to better understand NSSI pathophysiology.

A sample of 24 patients who engage in NSSI will also be recruited to evaluate the feasibility of at-home self-administration of tDCS. tDCS delivery using a remotely-supervised treatment protocol will minimize the burden of study visits and allow patients to continue participating in research from the comfort of their homes when in-person procedures are not possible. These participants will undergo similar study procedures as described above for patients with NSSI, except for the MRI scan, in order to explore aims 1 and 3 above in a remote setting. Those in the remote arm of the study will complete an additional week of tDCS sessions, totaling 12 sessions over 6 days. We will continue to offer three months of treatment visits with a study psychiatrist at no-cost at the conclusion of study procedures, which will be provided via telemedicine.

Background, Significance and Rationale

Background, Significance and Rationale

Non-suicidal self-injury (NSSI), “the deliberate, self-inflicted destruction of body tissue without suicidal intent” ((Nock & Favazza, 2009), http://www.itriples.org/isss-aboutself-i.html), is a serious psychiatric problem (Briere & Gil, 1998; E. D. Klonsky, 2011) that is observed across a broad array of psychiatric and developmental conditions, including major depression, borderline personality disorder, intellectual disabilities, autism, Prader-Willi Syndrome, and Lesch-Nyhan Syndrome (Symons et al., 2001). NSSI is one of the most predictive risk factors for suicide attempts (Andover & Gibb, 2010; Favaro et al., 2008; E. David Klonsky, May, & Glenn, 2013; Lloyd-Richardson, Perrine, Dierker, & Kelley, 2007; Nock, Joiner, Gordon, Lloyd-Richardson, & Prinstein, 2006), and has a high prevalence, with estimates suggesting that about 21% of adult psychiatric inpatients (Briere & Gil, 1998) and 30-40% of adolescent inpatients have a history of NSSI (Darche, 1990). As the pathophysiology of NSSI is not well understood, clinicians have limited ability to predict which treatments will be most effective for specific individuals suffering from NSSI, making cases frequently persistent and treatment-refractory (Perry et al., 2009). Novel studies based on possible underlying mechanisms for NSSI are greatly needed to reduce the morbidity and mortality associated with this behavioral phenomenon.

NSSI is a maladaptive emotion regulation strategy. People who engage in NSSI are more likely to have high sensitivity to social rejection and perceived social rejection can trigger the urge to engage in NSSI, (Nock, Prinstein, & Sterba, 2009). Studies using fMRI have shown that patients who frequently engage in NSSI also have heightened BOLD responses to social rejection in regions associated with subjective distress, such as the anterior insula (AI) and dorsal anterior cingulate cortex (dACC) (Brown et al., 2017; Groschwitz, Plener, Groen, Bonenberger, & Abler, 2016). This sample also exhibited abnormal responses in the ventrolateral prefrontal cortex, a key region for inhibitory control over emotions and response tendencies. The vlPFC has been shown to exert top-down influence on the amygdala and nucleus accumbens (Berkman, Kahn, & Merchant, 2014; Berkman & Lieberman, 2009; Cohen, Berkman, & Lieberman, 2013; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008; Wagner & Heatherton, 2013), subcortical regions involved in emotion-generation, during emotion regulation tasks such as reappraisal. During social rejection, activity

in the vlPFC negatively correlates with both subjective reports of distress as well as BOLD activity in the AI and dACC (Eisenberger, Lieberman, & Williams, 2003; Eisenberger, Way, Taylor, Welch, & Lieberman, 2007; Kawamoto et al., 2012; Onoda et al., 2010), demonstrating its importance in shaping emotional responses to social stimuli. Collectively, these data suggest that the vlPFC may be a promising target for NSSI treatment.

Novel brain stimulation approaches may modulate vlPFC activity and, in so doing, could potentially exert therapeutic effects on NSSI. Transcranial direct current stimulation (tDCS) is an inexpensive, portable, non-invasive form of brain stimulation that has demonstrated efficacy in major depressive disorder (Brunoni et al., 2013), cognitive difficulties (Hoy, Arnold, Emonson, Daskalakis, & Fitzgerald, 2014), and chronic pain (Villamar et al., 2013). By modulating the activity of neural regions involved in emotion regulation, tDCS may facilitate adaptive emotional responses to the environment. Recent studies have shown reductions in emotional distress and aggression following social rejection in healthy participants by stimulating the right ventrolateral prefrontal cortex (vlPFC) using tDCS (Riva, Lauro, DeWall, & Bushman, 2012; Riva, Lauro, DeWall, Chester, & Bushman, 2014; Riva, Lauro, Vergallito, DeWall, & Bushman, 2015). In her doctoral work, Dr. Yttredahl found reductions in rumination following social rejection due to vlPFC tDCS were directly related to trait emotion regulation abilities whereby participants with poorer regulation benefitted the most (Yttredahl, 2019).

The primary aim of this study is to examine the tolerability and effectiveness of tDCS in treating NSSI and urges to engage in NSSI. For this experiment in which we are examining the effects of anodal vLPFC tDCS on NSSI behavior and the neural correlates of social rejection assessed by fMRI, we plan to enroll up to 50 individuals who engage in frequent NSSI to obtain a sample of 23 subjects who complete the study procedures. Participants will be randomized to receive active anodal vs. sham tDCS to right vlPFC for two twenty-minute applications on each of six alternating days over approximately two weeks. During the stimulation, participant behavior will be standardized by having all participants engage in the same Attention Training Technique administered over headphones. NSSI behaviors and urges will be recorded for three weeks using Ecological Momentary Assessment (EMA), a novel procedure that minimizes recall bias by capturing the thoughts, feelings, and behaviors of subjects in real time. This will allow measurement of NSSI urges and behaviors for the weeks before, during, and after the tDCS intervention. Our first goal in this study is to characterize tolerability and acceptability of this intervention in this population. Secondly, we wish to identify changes in BOLD responses to social rejection from pre- to post-tDCS using fMRI. We hypothesize that activity in the AI, dACC, and amygdala during rejection will be attenuated by tDCS. Lastly, it is hypothesized that tDCS directed to the right vlPFC will lead to reductions in both NSSI and in urges to engage in NSSI. This pilot work may pave the way for larger controlled trials to examine differential target engagement and clinical efficacy between active and sham conditions.

In order to continue to conduct research with patients who engage in NSSI, given the current state-instituted shutdown of in-person research activities, we are adding a remote-tDCS arm to our study. Remotely supervised, at-home tDCS has been gaining traction in clinical research in order to broaden the reach of clinical trials and reduce burdensome travel for patients receiving multiple tDCS sessions (Charvet et al., 2015; Cucca et al., 2019). Specialized tDCS devices, such as the Mini-CT (Soterix, Inc) used in this study, have been developed to allow researchers to strictly control the dosing and timing of self-administered tDCS in the clinical setting (Charvet et al., 2015; Cucca et al., 2019; Shaw et al., 2017). These devices, combined with validated protocols, enable researchers and clinicians to provide safe, reliable, reproducible tDCS

stimulation to patients outside of the clinic (Charvet et al., 2015, 2020). Patients who enroll in our study are monitored regularly by a psychiatrist who provides open treatment for three months at the conclusion of tDCS procedures (and sooner in the event of clinical worsening). By creating a remote tDCS arm, we will be able to continue to enroll participants in research procedures, offer treatment following research procedures, and add valuable data to the literature on the feasibility and efficacy of at-home remotely-supervised tDCS in this clinical population. This same equipment and procedure will be used in the neuroimaging arm of the study as well, so that participants who feel comfortable enough to receive MRI scanning at NYSPI can still receive all other assessments and tDCS remotely.

Heart rate variability: The autonomic nervous system (ANS) plays an intrinsic role in the coordinated brain-body activity that gives rise to subjective emotional states and enables regulation of ongoing emotional experience. Increased heart rate, which may be parasympathetically and/or sympathetically driven, contributes somatic cues necessary to discern emotional feeling states and mount an appropriate response (Levenson, 2003). Cardiac innervation from the parasympathetic branch of the ANS enables rapid and flexible modulation of the heart rhythm, allowing swift adjustment to complex emotional demands (Thayer & Lane, 2000). By adding acquisition of ECG data concurrent with the fMRI social feedback task, we will be able to analyze these real-time sympathetic and parasympathetic responses to social rejection. Concurrent autonomic measurement may also aid in interpreting neural responses to task-relevant stimuli. These data will complement our investigation of the effectiveness of tDCS in facilitating adaptive emotion regulation in individuals with NSSI.

Specific Aims and Hypotheses

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Aims/Hypotheses 1 through 3 pertain to the sample of patients with NSSI. Aim 4 pertains only to the non-clinical sample who will pilot our social feedback task. Aim 5 pertains to the remotely-supervised no-contact arm of the study.

1. Evaluate the tolerability and acceptability of a tDCS intervention in a sample of individuals engaging in frequent NSSI. We hypothesize that 6 treatments of tDCS (two times per day for three days over right vlPFC) will be well-tolerated by study participants who engage in frequent NSSI.
2. Characterize changes in BOLD responses to social rejection from pre- to post-tDCS sessions in the active tDCS group compared to the sham tDCS group using fMRI and a social exclusion task called Cyberball. Hypothesis: BOLD activity in the dorsal anterior cingulate cortex, the anterior insula, the amygdala, and the medial PFC/rostral ACC will scale with different percentages of exclusion in Cyberball. Furthermore, there will be a significant interaction effect whereby participants in the sham stimulation group will show greater changes in these three regions during scan 2 compared with those in the active group.
3. Gather pilot data on the effectiveness of tDCS in treating NSSI and the urge to engage in NSSI in patients currently suffering from NSSI on a regular basis. Hypothesis: tDCS directed to the right ventrolateral prefrontal cortex will lead to greater reductions in both NSSI and in urges to engage in

NSSI, as assessed by self-report measures as well as real-time monitoring using ecological momentary assessment, than sham tDCS.
4. Assess feasibility of the behavioral and neural responses to a social feedback task in a non-clinical sample.
5. Assess the feasibility of using remotely-supervised tDCS self-administration in a sample of patients who engage in NSSI.

Description of Subject Population

Sample #1

Specify subject population
Patients with NSSI receiving M1 tDCS and PET (no longer recruiting)
Number of completers required to accomplish study aims
3
Projected number of subjects who will be enrolled to obtain required number of completers
10
Age range of subject population
18-60

Sample #2

Specify subject population
Patients with NSSI receiving M1 tDCS without neuroimaging (no longer recruiting)
Number of completers required to accomplish study aims
10
Projected number of subjects who will be enrolled to obtain required number of completers
20
Age range of subject population
18-60

Sample #3

Specify subject population
Sample of healthy volunteers for fMRI pilot
Number of completers required to accomplish study aims
10
Projected number of subjects who will be enrolled to obtain required number of completers
10
Age range of subject population

18 - 60

Sample #4

Specify subject population
Patients with NSSI receiving VLPFC tDCS and fMRI
Number of completers required to accomplish study aims
22
Projected number of subjects who will be enrolled to obtain required number of completers
50
Age range of subject population
18-60

Sample #5

Specify subject population
Remotely-Supervised Patients with NSSI
Number of completers required to accomplish study aims
24
Projected number of subjects who will be enrolled to obtain required number of completers
50
Age range of subject population
18-60

Gender, Racial and Ethnic Breakdown

Patients with NSSI:
a. Gender: Based on previous clinical trials and biological studies in our research division recruiting individuals with self-injury, 60% of participants were female.
b. Ethnicity: No ethnic/racial group is excluded. Since subjects will be recruited by advertisement in the same fashion as we have done for previous studies, we expect that the sample will be similar to those who have responded to our advertisements in the past. Based on previous clinical trials and biological studies in our research division recruiting individuals with self-injury, we anticipate that our study population will be approximately 15% Hispanic, 85% non-Hispanic; 75% white, 22% black, and 3% Asian.
Description of subject population

Patients with NSSI undergoing tDCS and fMRI:
Our sample will be defined by a symptom/pattern of behavior, and not by a DSM-V diagnosis. Specifically, we seek to recruit individuals engaging in frequent NSSI, because that is the symptom that we will attempt to target with this treatment. We aim to recruit 22 subjects who complete all study procedures. Based on recent brain imaging studies in our division, we estimate that we will need to enroll 50 subjects to achieve this number of completers, due to subject ineligibility, subject withdrawal prior to study completion, and failure to attend appointments.

Sample of healthy volunteers for fMRI pilot:

We will recruit up to 10 healthy volunteers currently or previously enrolled in IRB #6786 or 7653 or 7172 to complete the social feedback task twice during fMRI.

Patients with NSSI undergoing remote tDCS:
Our sample will be defined by a symptom/pattern of behavior, and not by a DSM-V diagnosis. Specifically, we seek to recruit individuals engaging in frequent NSSI, because that is the symptom that we will attempt to target with this treatment. We aim to recruit 24 subjects who complete all study procedures. Based on recent brain imaging studies in our division, we estimate that we will need to enroll up to 50 subjects to achieve this number of completers, due to subject ineligibility, subject withdrawal prior to study completion, and failure to attend virtual appointments.

Recruitment Procedures

Describe settings where recruitment will occur

Sample of patients with NSSI:
Participants may be recruited from the New York Presbyterian Hospital emergency room, referrals for inpatient and outpatient treatments from the community, a large network of referring doctors, and the extensive outpatient depression clinics at NYSPI (e.g., Depression Evaluation Service and the Late Life Depression Center). Participants will also be recruited via advertisements. Printed advertisements will be posted and distributed around the medical center and in surrounding areas and may be given to affiliated clinicians. Online advertisement is described below.

Sample of healthy volunteers for fMRI pilot:
Healthy volunteers will be previously or currently enrolled in IRB #4185 or 6786 or 7653 or 7172 and will be contacted by phone.

How and by whom will subjects be approached and/or recruited?

Sample of patients with NSSI:
Clinical inpatients and emergency room patients will not be approached by research staff until clinical staff has ascertained that they are willing to discuss possible research participation. Participants will be recruited through printed as well as online advertisements. Subjects who have completed other protocols in our division may also be contacted and asked about study participation. Providers in the community may be contacted by email to refer patients who are interested and potentially eligible.

Sample of healthy volunteers for fMRI pilot:
Only participants who checked the box agreeing to be contacted for other studies on a consent form for IRB #4815 or 6786 or 7653 or 7172 will be contacted and offered the option of participating in these study procedures. Participants will be contacted by telephone by our research coordinator, Dr. Miller, or Dr. Yttredahl.

How will the study be advertised/publicized?

Sample of patients with NSSI:
Online advertisements will be placed on websites that may include Craigslist, in sections including volunteers, gigs, and jobs, Google Ads, Facebook, Research Match, RecruitMe, and others including our own IRB-approved website: https://tdcsresearch.wordpress.com . We will advertise this study to Columbia-affiliated clinicians on the Columbia University PsychoPharmacology (CUPP) list-serve and will email local providers. The Google Ad includes the following link to a description of the study on the Columbia Recruitme Website:
https://recruit.cumc.columbia.edu/clinical_trial/1324
where participants can learn more about the study and contact us if possibly interested in participating.

We would like permission to change contact information (name, phone #s) on internet-based advertisements (craigslist ads, CUPP posting, etc...) as needed. Any individuals listed as a contact for recruitment will have previously completed CITI training.

Do you have ads/recruitment material requiring review at this time?
No
Does this study involve a clinical trial?
No

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement

Sample of patients with NSSI:
Participants will be screened through our division's screening protocol:
IRB # 6879R: Molecular Imaging and Neuropathology Clinic Studies Initial Evaluation (formerly #5880R)

Participants will co-enroll in our division's umbrella protocol:
IRB #4815: Biological and neurocognitive measures for genetic studies of psychiatric populations (PI: Maria A. Oquendo, M.D.)

Participants who previously enrolled in studies who may meet study eligibility criteria for the current study may be re-contacted to ask about their interest in current study participation. This includes studies in which participants have already given written consent to be re-contacted about future studies, including:

IRB #6777R: Treating of Suicidal Behavior and Self-Mutilation in BPD: Predictors of Change (PI: Barbara Stanley, Ph.D.)

IRB # 5792R: Prospective Study of Predictors of Suicidal Behavior in Borderline Personality Disorder

(BPD) - Biological Measures (formerly # 4728)

If we seek to re-contact subjects from protocols that do not include consent for re-contacting subjects, we will submit a ward-off letter to the IRB for approval.

Sample of healthy volunteers for fMRI pilot:
Participants who previously enrolled in IRB #4815 or 6786 or 7653 or 7172 as a healthy volunteer may be re-contacted to ask about their interest in current study participation, if they have already given written consent to be re-contacted about future studies.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Neuroimaging participants
Create or insert table to describe the inclusion criteria and methods to ascertain them

	Neuroimaging participants with NSSI: Inclusion Criteria	Method of Ascertainment
1.	Age 18-60	Remote interview
2.	Frequent current NSSI (including cutting in which the skin is broken; self-hitting in which there is bruising; or burning in which there is evidence of a burn. Will not enroll if skin-picking or scratching is the only form of self-injury): has engaged in ≥2 episodes of NSSI in the two months prior to enrollment	Remote Self Injurious Thoughts and Behaviors (SITBI) scale and remote clinical interview
3.	Capacity to provide informed consent	Remote clinical interview
4.	If carries a diagnosis of bipolar I or II disorder, taking **or willing to begin** a therapeutic dose of a mood stabilizer*	Remote SCID, remote clinical interview, therapeutic blood levels if applicable
5.	Normal hearing	Remote interview
6.	Physical capacity (e.g., manual dexterity) to set-up and self-administer tDCS	Remote interview

* If not currently taking a mood stabilizer, the participant will have the option of beginning mood stabilizer with a psychiatrist on our team. We would perform any necessary blood testing to screen for appropriateness of mood stabilizer treatment and to monitor blood levels. We would provide psychiatrist visits and any necessary blood testing, but would not cover the costs of mood stabilizer medication. If participants continue to meet all other eligibility criteria upon achieving a therapeutic dose of mood stabilizer, we would proceed with research participation. If they do not, we would forego research procedures and offer 3 months of open treatment.

Create or insert table to describe the exclusion criteria and methods to ascertain them

	Neuroimaging participants with NSSI: Exclusion Criteria	Method of Ascertainment
1.	Unstable medical conditions based on medical history or medical assessment	Medical history (by a physician), medical assessment as conducted in IRB #4815
2.	Current psychotic disorder, mania, hypomania, intellectual disability	Remote psychiatric interview and SCID
3.	Dermatologic condition resulting in non-intact skin on the scalp	Medical history
4.	Significant suicidal ideation with a plan and intent that cannot be managed safely as an outpatient	Remote C-SSRS, remote clinical interview
5.	Pregnancy, currently lactating, or planning to conceive during the course of study participation*	Urine HCG on days of MRI scans prior to scanning
6.	A neurological disease or prior head trauma with evidence of cognitive impairment. Subjects who endorse a history of prior head trauma and score ≥ 1.5 standard deviations below the mean on the Trailmaking A&B will be excluded from study participation.	Remote clinical interview and medical history, Trailmaking A & B as

		needed.
7.	Current alcohol or substance use disorder that is severe according to DSM-5 criteria	Remote SCID and clinical interview
8.	Individuals who initiated or increased the dose of concurrent psychiatric medications (including antidepressants, anxiolytics, antipsychotic medications, and mood stabilizers) within two weeks prior to enrollment	Remote clinical interview and medical history
9.	Individuals who initiated psychotherapy within two weeks prior to enrollment	Remote clinical interview
10.	Current seizure disorder	Remote clinical interview and medical history
11.	Use of anticonvulsant medications that target the GABA system (e.g., gabapentin)	Remote clinical interview and medical history
12.	Individuals currently using benzodiazepines who are unable or unwilling to refrain from the use of benzodiazepine medications for at least 72 hours before the first tDCS session and throughout the duration of the 2-week tDCS intervention**	Remote clinical interview and medical history
13.	Metal implants or paramagnetic objects contained within the body (including heart pacemaker, shrapnel, or surgical prostheses) which may present a risk to the subject or interfere with the MRI scan, according to the guidelines set forth in the following reference book commonly used by neuroradiologists: “Guide to MR procedures and metallic objects,” F.G. Shellock, Lippincott Williams and Wilkins NY 2001. Additionally, transdermal patches will be removed during the MR study at the discretion of the investigator.	Remote clinical interview, MRI safety screening forms
14.	Claustrophobia significant enough to interfere with MRI scanning	Remote clinical interview and medical history
15.	Weight that exceeds 325 lbs or inability to fit into MRI	Weight and

	scanner	maximal body circumference (if necessary) as self-reported; visit to the MRI suite if necessary***
16.	**Suicide attempt within the past 3 months**	**Remote clinical interview and medical history**
17.	**Serious self-harm resulting in hospitalization within the past 3 months.**	**Remote clinical interview and medical history**

*For females of childbearing age: Urine pregnancy test is performed during the screening procedure and urine pregnancy test is repeated on MRI scanning day. Since this test cannot detect the very early stage of pregnancy (the10-day period between fertilization and implantation), an effective birth control method or sexual abstinence is required during the 15 days before the scans.

**Individuals currently using benzodiazepines will be converted to an equivalent dose of a short-acting benzodiazepine, which they may continue to use until 72 hours before the first tDCS session.

***In cases where there is a question about whether a participant's dimensions are compatible with the MRI scanner, a subject's circumference may be measured to determine if the subject's circumference is less than the MRI scanner limit, 200 cm. The subject also may be brought to the MRI center so that the MRI technologist can assess whether or not the subject will fit safely inside the MRI scanner. Metal screening and urine pregnancy testing will be done before this brief visit. Subjects who cannot safely enter the scanner will not be eligible to participate in the scanning portion of the study but may elect to remain in the study as a non-imaging subject.

Inclusion/Exclusion Criteria #2

Name the subject group/sub sample
Participants without Neuroimaging (not currently recruiting)
Create or insert table to describe the inclusion criteria and methods to ascertain them

	Participants with NSSI without Neuroimaging: Inclusion Criteria	Method of Ascertainment
1.	Age 18-60	Interview
2.	Frequent current NSSI (including cutting in which the skin is broken; self-hitting in which there is bruising; or burning in which there is evidence of a burn. Will not enroll if skin-picking or scratching is the only form of self-injury): has engaged in ≥ 2 episodes of NSSI in the two months prior to enrollment	Self Injurious Thoughts and Behaviors (SITBI) scale and clinical interview
3.	Capacity to provide informed consent	Clinical interview
4.	If caries a diagnosis of bipolar I or II disorder, taking a therapeutic dose of a mood stabilizer	SCID, clinical interview, therapeutic blood levels if applicable

Create or insert table to describe the exclusion criteria and methods to ascertain them

	Participants without Neuroimaging: Exclusion Criteria	Method of Ascertainment
1.	Unstable medical conditions based on medical history of physical examination	Medical history (by a physician), physical exam, screening lab tests as performed through co-enrollment in IRB #4815
2.	Current psychotic disorder, mania, hypomania, intellectual disability	Psychiatric interview, SCID
3.	Dermatologic condition resulting in non-intact skin on the scalp	Medical history, physical exam
4.	Significant suicidal ideation with a plan and intent that cannot be managed safely as an outpatient	C-SSRS, clinical interview
5.	Pregnancy, currently lactating, or planning to conceive during the course of study participation	serum HCG at time of screening
6.	A neurological disease or prior head trauma with evidence of cognitive impairment. Subjects who endorse a history of prior head trauma and score ≥ 1.5 standard deviations below the mean	Clinical interview and medical history, Trailmaking A&B as needed

	on the Trailmaking A&B will be excluded from study particpation	
7.	Current alcohol or substance use disorder that is moderate or severe according to DSM-5 criteria	SCID, urine drug test, clinical interview
8.	Current opiate use disorder	SCID, urine drug test, clinical interview
9.	Current medical or recreational use of any opiate medication	Clinical interview, urine drug test
10.	Individuals who initiated or increased the dose of concurrent psychiatric medications (including antidepressants, anxiolytics, antipsychotic medications, mood stabilizers, and benzodiazepines) within two weeks prior to enrollment	Medical history, clinical interview
11.	Individuals who initiated psychotherapy within two weeks prior to enrollment	Clinical interview
12.	**Suicide attempt within the past 3 months**	**Remote clinical interview and medical history**
13.	**Serious self-harm resulting in hospitalization within the past 3 months**	**Remote clinical interview and medical history**

Inclusion/Exclusion Criteria #3

Name the subject group/sub sample
Sample of healthy volunteers for pilot (not currently recruiting)
Create or insert table to describe the inclusion criteria and methods to ascertain them

	Sample of healthy volunteers for fMRI pilot	Method of Ascertainment
1.	Current or past enrollment in IRB #4815 or 6786 or 7653 or 7172 as a healthy volunteer. *	chart review
2.	Written consent to be contacted about additional studies	chart review

*Note: if participant's enrollment occurred more than 6 months prior to consent for this protocol, they will re-enroll in IRB #4815 to have medical and psychiatric assessments updated.

Create or insert table to describe the exclusion criteria and methods to ascertain them

	Sample of healthy volunteers for fMRI pilot	Method of Ascertainment
1.	Pregnancy, currently lactating, or planning to conceive during the course of study participation. *	urine HCG on days of MRI scans prior to scanning
2.	Metal implants or paramagnetic objects contained within the body (including heart pacemaker, shrapnel, or surgical prostheses) which may present a risk to the subject or interfere with the MRI scan, according to the guidelines set forth in the following reference book commonly used by neuroradiologists: "Guide to MR procedures and metallic objects," F.G. Shellock, Lippincott Williams and Wilkins NY 2001. Additionally transdermal patches will be removed during the MR study at the discretion of the investigator.	Interview, MRI safety screening forms
3.	Claustrophobia significant enough to interfere with MRI scanning	Clinical interview
4.	Weight that exceeds 325 lbs or inability to fit into MRI scanner	Weight and maximal body circumference (if necessary) as part of physical exam; visit to the MRI suite if necessary **

* For females of childbearing age: Urine pregnancy test is performed during the screening procedure and urine pregnancy test is repeated on MRI scanning day. Since this test cannot detect the very early stage of pregnancy (the10-day period between fertilization and implantation), an effective birth control method or sexual abstinence is required during the 15 days before the scans.

** In cases where there is a question about whether a participant's dimensions are compatible with the MRI scanner, a subject's circumference may be measured to determine if the subject's circumference is less than the MRI scanner limit, 200 cm. The subject also may be brought to the MRI center so that the MRI technologist can assess whether or not the subject will fit safely inside the MRI scanner. Metal screening

and urine pregnancy testing will be done before this brief visit. Subjects who cannot safely enter the scanner will not be eligible to participate in the scanning portion of the study but may elect to remain in the study as a non-imaging subject.

Inclusion/Exclusion Criteria #4

Name the subject group/sub sample
Remote Participants with NSSI
Create or insert table to describe the inclusion criteria and methods to ascertain them

	Remote participants with NSSI: Inclusion Criteria	Method of Ascertainment
1.	Age 18-60	Remote Interview
2.	Frequent current NSSI (including cutting in which the skin is broken; self-hitting in which there is bruising; or burning in which there is evidence of a burn. Will not enroll if skin-picking or scratching is the only form of self-injury): has engaged in ≥2 episodes of NSSI in the two months prior to enrollment	Remote Self Injurious Thoughts and Behaviors (SITBI) scale and clinical interview
3.	Capacity to provide informed consent	Remote clinical interview
4.	If carries a diagnosis of bipolar I or II disorder, taking a therapeutic dose **or willing to begin** a mood stabilizer*	Remote SCID, remote clinical interview, therapeutic blood levels if applicable
5.	Normal hearing	Remote interview
6.	Physical capacity (e.g., manual dexterity) to set-up and self-administer tDCS	Remote interview

*If not currently taking a mood stabilizer, the participant will have the option of beginning mood stabilizer with a psychiatrist on our team. We would perform any necessary blood testing to screen for appropriateness of mood stabilizer treatment and to monitor blood levels. We would provide psychiatrist visits and any necessary blood testing, but would not cover the costs of mood stabilizer medication. If individuals continue to meet all other eligibility criteria once on a therapeutic dose of a mood stabilizer, we

would proceed with research procedures. If they do not, we would forego research procedures and offer three months of open treatment.

Create or insert table to describe the exclusion criteria and methods to ascertain them

	Remote participants with NSSI: Exclusion Criteria	Method of Ascertainment
1.	Unstable medical conditions based on medical history	Medical history and remote medical evaluation
2.	Current psychotic disorder, mania, hypomania, intellectual disability	Remote psychiatric interview and SCID
3.	Dermatologic condition resulting in non-intact skin on the scalp	Medical history and remote medical evaluation
4.	Significant suicidal ideation with a plan and intent that cannot be managed safely as an outpatient	Remote C-SSRS and clinical interview
5.	Pregnancy, currently lactating, or planning to conceive during the course of study participation*	Urine HCG prior to first tDCS session
6.	A neurological disease or prior head trauma with evidence of cognitive impairment. Subjects who endorse a history of prior head trauma and score ≥ 1.5 standard deviations below the mean on the Trailmaking A&B will be excluded from study participation	Remote clinical interview and medical history, Trailmaking A & B as needed
7.	Current alcohol or substance use disorder that is severe according to DSM-5 criteria	Remote SCID and clinical interview
8.	Individuals who initiated or increased the dose of concurrent psychiatric medications (including antidepressants, anxiolytics, antipsychotic medications, and mood stabilizers) within two weeks prior to enrollment	Remote clinical interview and medical history
9.	Individuals who initiated psychotherapy within two weeks prior to enrollment	Remote clinical interview

10.	Current seizure disorder	Remote clinical interview and medical history
11.	Use of anticonvulsant medications that target the GABA system (e.g., gabapentin)	Remote clinical interview and medical history
12.	Individuals currently using benzodiazepines who are unable or unwilling to refrain from the use of benzodiazepine medications for at least 72 hours before the first tDCS session and throughout the duration of the 2-week tDCS intervention**	Remote clinical interview and medical history
13.	**Suicide attempt within the past 3 months**	**Remote clinical interview and medical history**
14.	**Serious self-harm resulting in hospitalization within the past 3 months.**	**Remote clinical interview and medical history**

*For females of childbearing age: Urine pregnancy test is mailed to the participant with instructions for performing the test. Results are captured with a photo and sent to the experimenter through REDCap or attach.nyspi.org.

**Individuals currently using benzodiazepines will be converted to an equivalent dose of a short-acting benzodiazepine, which they may continue to use until 72 hours before the first tDCS session.

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
4815
Describe Study Consent Procedures

Sample of patients with NSSI:
Following preliminary determination of eligibility, informed consent procedures will be conducted by the physicians listed in the following section. Initial screening will completed as detailed in IRB #4815**.** For all remote procedures, the consenter will connect with the subject over the phone or a videoconference and will go through all relevant documents, including the HIPAA form and consent form, with the participant. Participants will provide an electronic signature through RedCap's e-signature option. Consent for remote clinical or research procedures will be documented, and the consent discussion process will include discussion of the technology HIPAA-compliant platforms to be used and any concerns the patient may have, such as access to a private space in which to take calls, or accessibility—access at home to adequate devices, cell signal, or Wi-Fi. There will be a consent procedure note that includes that there was a discussion of risk related to COVID-19 during travel. Consent discussions will include informing participants of the option to reschedule if travel does not seem safe and/or the study team may offer alternative transportation, such as Uber or Lyft.

Sample of healthy volunteers for fMRI pilot:
Initial screening will be completed as detailed in IRB #4815 through current or past enrollment in IRB #6786 or 7653 or 7172. If 6 months or more have passed since the initial screen, participants will be re-screened using the procedures detailed in IRB #4815. Informed consent procedures will be conducted by one of the researchers listed in the following section.

Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Grunebaum, Michael, MD
Lan, Martin, MD
Miller, Jeffrey, MD
Sublette, M, MD
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

I attest to follow the COVID-19 Safety Guidelines for Columbia Psychiatry and NYSPI Re-Entry outlined in the NYSPI Director's June 1st memo, which include but are not limited to:

• Infection Control/PPE – Guidelines
• Research participants will only come on-site if absolutely necessary for study procedures.
• No volunteers/externs on-site during Stage 1.
• Clinical research teams will screen their participants for COVID symptoms (night before and day of onsite visit, documenting this in the chart), and escort them in and out of the building.
• COVID/COVID-like symptoms in participants will be reported to the IRB via PRISM as an SAE.

Sample of patients with NSSI:
All of the study procedures are listed below. Participants who enroll in the arm of the study without neuroimaging will follow all procedures described below with the exception of the neuroimaging-related procedures (MRI). Participants will follow all procedures described below remotely, with the exception of the neuroimaging-related procedures (MRI). For females of childbearing age, a urine HCG test will be sent by mail with instructions detailing how to use the test. Participants will be asked to photograph the results of the test and upload them through RedCap or attach.nyspi.org. For both arms of the study, participants will have the option of receiving tDCS in-person or remotely.

Subjects who frequently engage in NSSI will be recruited as described above and will co-enroll in the brief medical assessment arm of IRB Protocol #4815. Following informed consent for participation, screening evaluation will be performed at study entrance through IRB protocol #4815 and will include a complete medical history and remote clinical examination to exclude significant physical illness.

Psychological Assessments

Psychological assessments and their timing are described in the "Assessment Instruments" section.

Real-Time Monitoring of NSSI, Stressors, and Urges

In addition to using retrospective reports of NSSI, we will also employ a recently developed assessment, Ecological Momentary Assessments (EMA). EMA records thoughts, feelings and behaviors and the circumstances preceding these experiences in real time, which may allow for a more accurate understanding of mood and behavior than retrospective reporting (Nock et al., 2009).

In this study, we will use EMA to have participants rate the frequency, duration, and severity of urges to engage in NSSI, the frequency and nature of actual NSSI, as well as suicidal ideation, relevant affects, stressors and behaviors, and possible triggers for these events, for one week prior to treatment, through the duration of the course of tDCS treatments, and one week following completion of tDCS, to measure the persistence of any observed effects. These items will be presented to each participant on an iPod device during each momentary assessment. We will enter each subject's self-reported typical waking and bedtime

into the software. Using this information, the program will stratify waking hours into six intervals, then randomly select one moment within each interval to deliver a prompt of an audible beep. This beep will be repeated every 30 seconds for up to 5 minutes. Collected data will be downloaded when the device is synced with a computer and can be easily imported into standard spreadsheets or statistical packages. If the participant records the presence of treatment emergent suicidal ideation, an open-ended question allowing the subject to record descriptions of their experience with this development will be presented. Subjects will also be reminded about emergency procedures to contact staff if they are concerned about suicidal ideation or risk.

We have used this procedure in a NIMH-funded study of actively suicidal patients without adverse effects and with good adherence.

MRI Scans:

MRI images will be acquired at the New York State Psychiatric Institute on a GE SIGNA Premier 3T MRI scanner. Subjects will undergo T1-weighted structural imaging and a functional EPI, during which the Cyberball task will be presented (described below). If time allows, they may undergo diffusion tensor imaging (DTI) as well as a resting-state fMRI scan. Scans will not last more than 60 minutes. Because these MRI scans are being performed for research purposes only, they may not show problems that would normally be found in a typical clinical MRI scan ordered by a doctor for a specific medical problem. The T1-weighted images acquired in this study, regardless of resolution of other image characteristics, do not, in general, yield adequate information for a clinical quality read. However, gross structural abnormalities such as the presence of mass effects or hydrocephalus will be examined and documented by an appropriately qualified radiologist. Upon request, results will be shared with research subjects or a physician designated by them. When there is evidence of a mass lesion, hydrocephalus or other significant abnormality, a qualified clinician will call the subject and then a letter will be sent, depending on the urgency, and at the discretion of the investigator and neuroradiologist.

Heart Rate Variability:

Participants will be outfitted with MR-safe ECG leads in a lead II configuration before entering the scanner. The lead II configuration places the positive electrode near the lower left rib and the negative electrode near the right arm, just below the clavicle. This configuration maximizes the R spike of the QRS wave complex. A third reference lead can be placed on either the lower right rib or near the left arm. Placement on the trunk rather than limbs will minimize artifacts due to movement.

tDCS:

All tDCS sessions for participants who do not participate in neuroimaging, may occur either remotely (see section below on "Remote tDCS") or at the M.I.N.D. Clinic at NYSPI and will be conducted by Dr. Miller, who has completed training in tDCS with Dr. Javitt and his staff, by Dr. Yttredahl, who has previous experience administering and training in the use of tDCS, or by another staff member listed in the study personnel after they complete training in tDCS by Dr. Miller or Dr. Yttredahl. Dr. Miller or Dr. Yttredahl will be available at all times during tDCS administrations. 1.5mA of stimulation will be applied for up to 20 minutes at each treatment. Participants will be randomly assigned to receive either sham stimulation, which consists of a ramp-up to 1.5mA followed by an immediate ramp-down and 20-minutes of no-stimulation, or

active stimulation which consists of 20-minutes of stimulation at 1.5mA between the ramp-up and ramp-down. Both participants and researchers will be blind to the tDCS assignment. The anode will be positioned over right ventrolateral prefrontal cortex (vlPFC), and the cathode will be positioned over the left supra-orbital area. Non-metallic, conductive rubber electrodes will be used, as recommended by Nitsche and Paulus, 2000. Electrode sponges will be kept moist in order to avoid skin irritation and will be secured using non-conductive elastic bands. If using paste, an even application of Ten20 paste will be spread on the electrodes to sit between the electrode and the skin to avoid skin irritation. If contact quality becomes suboptimal during tDCS, additional conductive gel may be applied to the electrodes. tDCS administrations will be performed using the Mini-CT from Soterix Medical Inc. Soterix is a well-established company creating and supplying research- and clinical-grade tDCS devices that have been used in over 200 published studies since 2012 and is currently involved in 29 different clinical trials worldwide. The Mini-CT was designed specifically for use in clinical trials and has built-in safety features that can even allow remotely-supervised self-administration by participants. tDCS will be administered two times per day for six alternating days, for a total of 12 sessions. If scheduling conflicts prevent sessions over three alternating days exactly, we will administer tDCS as close to this schedule as possible.

Participants will have the option to receive tDCS either remotely or in-person at NYSPI. tDCS administered in-person will be applied in an office suite while the tDCS administrator remains socially distanced, maintaining visual and auditory contact throughout the session, in an adjacent room. Both the participant and the research staff member will don face masks for the duration of the tDCS session. Participants receiving tDCS in-person will be scheduled with no less than 1 hour between appointments. During the time between participants, researchers will disinfect all surfaces in the participant area and the tDCS device with Super Sani Cloths or similar alcohol-based disinfectant cloths.

Attention Training Technique:

During tDCS, participants will undergo the Attention Training Technique (ATT). This task involves listening to an approximately 12-minute audio file at a comfortable volume over a pair of headphones, earbuds, or stereo speakers. Participants are asked to focus on a visual fixation point in the room and engage in three attention exercises: 1)selective attention (focusing on indivisual sounds), 2) attention switching (shifting attention between different sounds), and 3) divided attention (attending to sounds simultaneously).

Open Treatment:

Beginning one week after the conclusion of the tDCS treatment week, participants will be offered 3 months of medication-based treatment with a psychiatrist in our division.

Cyberball:

Participants will be presented with animated drawings depicting the participant's avatar and two other 2 cartoon figures tossing a ball between each other and the participant. When the participant's avatar receives the ball, they will press one of two buttons indicating which of the other two cartoons will receive the ball next. The number of times the ball is tossed to the participant will vary each block, such that the participants feel excluded from the game to varying degrees. Participants will be told before the study that the other characters are not real people and that they are not really playing the game with other people, but asked to imagine it as though it were real. At the end of each scan, an investigator will check in with the participant

to make sure the task did not cause significant, lasting distress. If the participants are upset following the task, a clinician will be available to speak with the participant. After scan 2, the check-in will include a full debriefing about the purpose of the task, including an explanation that Cyberball is a simulation of social exclusion. During debriefing, participants will be reminded that the task was only a computer game and the other players were not real people.

Remote tDCS:

Following consenting procedures, remote patients with NSSI will participate in all above procedures with the exception of in-person medical assessment and neuroimaging-related procedures (MRI). All assessments, clinical interviews, and procedures will be administered remotely. Cyberball will be presented through the computer outside of an fMRI scan. Participants will be provided with a tDCS device, headgear, and supply kit through the mail, and will be trained on tDCS self-administration over a HIPAA-compliant video-conferencing software **(**either CUIT-supported Zoom or NYS WebEx**)** by Dr. Yttredahl or Dr. Miller. Participants may be provided a laptop or tablet and headphones in their tDCS kit to ensure access for those who may not otherwise have the ability to use the videoconferencing software at home. The Mini-CT, our tDCS device, is intended for home use; it can be controlled via single-use codes that will be provided before each session once the researcher supervising the session confirms proper placement of the electrodes through visual inspection over the secure video-conferencing platform. Using these codes, the dose and timing will be controlled remotely, and the device will not operate without a code. Each tDCS session will be supervised over a HIPAA-compliant video conferencing platform by either Dr. Yttredahl or Dr. Miller. The participant will be trained in how to terminate the tDCS stimulation at any time should they experience significant adverse effects during stimulation. The audio file for the ATT will be sent to participants who may then use their own (or researcher-provided) speaker or headphone system to listen to the task during each tDCS session. Audio setup will be tested with a test audio file (not the ATT) to confirm that the audio system is functioning properly prior to initiating tDCS. In addition to instructions received by the research staff member (Dr. Miller or Yttredahl) during the videoconference, participants will also be provided with detailed instructions and diagrams explaining the setup and use of the device. Participants will be instructed to re-package the device, accessories, and any other borrowed equipment (e.g., tablet) in the provided box and mail the package back to the experimenters using a prepaid label included in the kit.

Sample of healthy volunteers for fMRI pilot:
Following consenting procedures, volunteers will participate in the social feedback task listed in the previous paragraph during fMRI scanning. MRI images will be acquired at the New York State Psychiatric Institute on a GE SIGNA Premier 3T MRI scanner. Subjects will undergo T1-weighted structural imaging using the same procedures listed above. Participants will also undergo functional imaging during the task presentation. The entire scan session is expected to last approximately 30 minutes but may take up to one hour. Participants will undergo fMRI twice on separate days with at least 5 days between scan sessions.

Personnel and Responsibilities

1. Medical exam and history: physician
2. Psychiatric Interview: physician or psychologist
3. Semi-structured interview: physician, psychologist or research interviewer

4. tDCS administration: Jeffrey Miller, M.D., Ashley Yttredahl, PhD, **Sarah Herzog, PhD,** at NYSPI;
5. Radiologists designated to read MRI research scans: radiology staff at Imaging On Call (www.imagingoncall.com)

6. Psychologists conducting psychological ratings

a. Masters or doctoral-level research psychologists within our division

7. Staff assisting Dr. Miller or Dr. Yttredahl with tDCS at NYSPI:

a. Sarah Herzog, PhD
b. Olivia Kolodka
c. Rachel Velasquez
d. Sophia Capri

e. Evan Lieberman
f. Lisette Thurkill
g. Ella Sudit

Data and safety monitoring plan:

Overview: Given that we are conducting a small pilot trial of a minimal risk intervention in which concurrent ongoing treatments are permitted, we have developed a data and safety monitoring plan, as described below, to ensure and oversee the safety of participants.

PI/IRB involvement: Approval for the proposed study and all amendments will be obtained by the NYSPI IRB before any procedures or changes in procedures take place. The PIs will be responsible for monitoring all procedures related to the study and ensuring safety of participants. The tDCS equipment will be operated under IDE exemption under the oversight of the NYSPI IRB. tDCS is considered a minimal risk procedure that may be associated with discomfort during stimulation (e.g. itching, tingling, burning) related to the scalp electrical fields but which has not been associated with lasting sequelae following completion of stimulation. The PIs, in conjunction with the relevant IRBs will maintain oversight of AEs. Serious adverse events, should they occur, will be reported by the PIs to the IRBs.

Staff Experience: Staff in the Division of Molecular Imaging & Neuropathology at NYSPI have extensive experience and training in the assessment of patients with suicidality and self-injurious behavior. Drs. Miller and Stanley will review principles of safety assessment with the staff involved in this research (research psychologists, research coordinators) prior to study initiation, and will conduct follow-up training and supervision as needed.

Independent safety officer: Because of potential discomfort induced by tDCS, a Columbia psychiatrist not involved with the study will serve as an independent individual/safety officer. This psychiatrist will periodically review reported side effects and will notify the PIs should there be significantly higher than anticipated incidence of side-effects, in which case appropriate adjustments will be made to the stimulation protocols, and case procedures would be reviewed. The psychiatrist will also review the Clinical Global

Impression rating, the Columbia Suicide Severity Rating Scale rating and adverse event reports to ensure that no unanticipated side effects are observed.

Annually, the PIs will prepare a summary of data safety monitoring activities, as requested, in the annual progress reports to the IRBs and will also provide this report to the psychiatrist who is serving as the independent reviewer. These reports will include: (1) whether participants' safety, privacy and confidentiality has been consistently assured by the investigators; (2) review of interim data analyses that bear on outcomes of the study and risk/benefit ratios to participants, including recommendations for statistical analyses; (3) judgment as to whether research instruments have been administered in a uniform manner and in a way that maintains the participants' privacy; (4) a review of the study's progress toward recruitment goals, quality of data (e.g., appropriate completion of forms), and participant retention/attrition rates; and, (5) a review of new scientific literature pertinent to the safety of participants or ethics of research participation.

There will be regular, ongoing communication between the PIs and the IRBs as well as with the independent psychiatrist. While no serious and unexpected adverse events are expected, any unanticipated study problems will be reported to both IRBs. The study personnel will take all clinically appropriate actions to prevent and treat psychiatric emergencies in participants.

Rationale for monitoring strategy: As per PHS guidelines (PHS SF424, section 4.15), other potential monitoring plans include a designated medical monitor; an Internal Committee or Board, or Data Safety and Monitoring Boards (DSMB). DSMBs are required for phase III and multisite studies, but, as per guidance, "smaller clinical trials may not require this oversight format and alternative monitoring plans may be appropriate". In the case of this study, we note that the number of subjects is small and that tDCS is considered a minimal risk device that has been extensively used in prior human research. Thus, we feel that a DSMB would entail unnecessary administrative burden, and use of an independent safety officer, as above, represents the most appropriate level of oversight.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

A CGI-Improvement score at any time point of 6 or 7 ("much worse" or "very much worse") will trigger clinical evaluation by the study investigators, Drs. Miller or Stanley, for possible study discontinuation. We will assess suicidal ideation and behavior weekly from the time of consent through the completion of tDCS procedures. If individuals endorse suicidal ideation that includes a plan and intent, or have made an actual suicide attempt, research procedures will be discontinued, and open clinical treatment will be initiated immediately at an appropriate level of care.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens

No blood is drawn through participation in this IRB protocol.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment

Sample of patients with NSSI:

Through co-enrollment in IRB #4815, participants will undergo a careful psychological assessment including characterization of DSM-IV diagnoses using the Structured Clinical Interview for DSM-IV (SCID, (First et al., 1995; First et al., 1997)). Recent suicidal ideation and behaviors will be assessed using the Columbia Suicide Severity Rating Scale (C-SSRS), which will be repeated on a weekly basis during tDCS administration to monitor emergent suicidal ideation (Posner et al., 2011). Selected items from the Self-Injurious Thoughts and Behaviors Interview (SITBI) will be used at baseline and on a weekly basis to monitor self-reported frequency, nature, motivations, and effects of NSSI, as well as urges to engage in NSSI, throughout study participation. Selected items from the Non-Suicidal Self-Injury Assessment Tool (NSSI-AT) will also be acquired at baseline to acquire additional information regarding history of NSSI behavior. The Clinical Global Impressions scale (CGI) (Guy et al., 1976) will be conducted on a weekly basis to monitor for clinical worsening. Possible mediators of treatment outcome that will be examined in the study include: emotion regulation using the Difficulties in Emotion Regulation Scale (DERS, (Gratz et al., 2004)) and the Cognitive-Attentional Syndrome Questionnaire (CAS-1; Wells, 2009); engagement with the ATT with the ATT-Scale; trait rumination with the Ruminative Responses Scale (RRS; Treynor et al., 2003) expectancy of clinical benefit, assessed with the Credibility/Expectancy Questionnaire (Devilly et al., 2000); and depression severity, as assessed by the Hamilton Depression Rating Scale (HDRS, (Hamilton, 1960)) and the Beck Depression Inventory (BDI, (Beck et al., 1961)). Tolerability of tDCS will be evaluated using the tDCS Adverse Effects Questionnaire (Aparicio et al., 2016).

Sample of remote-only patients with NSSI: Rater-administrated psychological assessments will be administered by phone or secure video-conference, and participants will be sent a link to complete self-report measures remotely through a secure platform (either REDCap, SIR, or Qualtrix). Cyberball will be remotely administered within one week before the first tDCS session and within one week after the final tDCS session. The original version of Cyberball was administered and validated for use as a digital task outside of the scanner (Williams, Cheung, & Choi, 2000).

Table: Timing of Psychological Assessments

Assessment	Enrollment	Baseline (prior to Session 1)	Post-Final tDCS Session	Following each tDCS session	One week Post-treatment	4 week Follow-up
Credibility/Expectancy Questionnaire (CEQ)		X				
Columbia-Suicide Severity Rating Scale (C-SSRS)		X	X		X	X
Selected items from the Self-Injurious Thoughts and Behaviors Interview (SITBI)	X	X	X		X	X
Selected items from the Non-Suicidal Self-Injury Assessment Tool (NSSI-AT)	X					
Clinical Global Impressions (CGI)		X	X		X	X
Difficulties in Emotion Regulation Scale (DERS)		X	X			
Hamilton Depression Rating Scale (HAM-D)		X	X			
Beck Depression Inventory (BDI)		X	X			
tDCS Adverse Effects Questionnaire				X		
Cognitive-Attentional Syndrome Questionnaire (CAS)		X	X			
ATT-Scale				X		
Ruminative Responses Scale (RRS)		X	X			

Criteria for Early Discontinuation

A CGI-Improvement score at any time point of 6 or 7 (“much worse” or “very much worse”) will trigger clinical evaluation by the study investigators, Drs. Miller or Stanley, for possible study discontinuation. We will assess suicidal ideation and behavior weekly from the time of consent through the completion of tDCS procedures. If individuals endorse suicidal ideation that includes a plan and intent, or have made an actual suicide attempt, research procedures will be discontinued, and open clinical treatment will be initiated immediately at an appropriate level of care.

State-Emotion Questions

During the social feedback task, participants will be asked to rate how they are currently thinking and feeling using select items from the PANAS (Watson et al., 1988), as well as some items used in a previous study (Yttredahl, 2019) assessing rumination and self-esteem.

Sample of healthy volunteers for fMRI pilot:

Criteria for Early Discontinuation

Non-patient participants can choose to discontinue participation at any time.

Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Device

Off label and investigational use of devices

Device #1

Name of the device
Soterix Mini-CT
Manufacturer and other information
Soterix Medical, Inc., New York City, NY.
Approval Status
No IDE is required
Choose one of the folowing options
Device is 'Non-significant risk'
Explain
No serious adverse events have been attributed to tDCS administration in over 10,000 subjects reported in any studies published in the modern era of tDCS, from 1998 to 2014 (Fregni et al, "Regulatory considerations for the clinical and research use of transcranial direct current stimulation (tDCS): Review and recommendations from an expert panel; Clin Res Regul Aff. 2015 Mar 1;32(1):22-35). The risks to human subjects directly associated with tDCS administration include a mild tingling sensation, slight epidermal irritation and mild temperature change at the site of application during administration (42); these do not tend to persist beyond the completion of the tDCS stimulation. Mild headache has been occasionally reported with tDCS, but typically responds to acetaminophen, ibuprofen, or aspirin. As such, devices used to administer tDCS have routinely been determined to be non-significant-risk devices by IRBs in the United States (Fregni et al, 2015). Moreover, standard tDCS parameters considered to be minimal risk have been published in terms of dose (<2.5mA), duration (≤60 minutes), frequency (≤2 treatments per day), and

electrodes employed (Fregni et al, 2015). The parameters proposed in this study are all well within these standard parameters.

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment
Study participants may continue with ongoing psychotherapeutic and/or pharmacologic treatment, as long as it was not started within 8 weeks of study enrollment. For participants not currently receiving psychiatric treatment, there may be a delay of up to 35 days prior to initiating tDCS through the study, in order to schedule baseline assessments, MRI scanning. For patients with bipolar 1 or 2 disorder not on a therapeutic dose of a mood stabilizer, evidence-based treatment with mood stabilizer treatment will be offered that would begin within 3 weeks of enrollment; tDCS research procedures would be further delayed in this case for the purposes of achieving a therapeutic dose of a mood stabilizer (prioritizing this clinical treatment ahead of research procedures).
Maximum duration of delay to standard care or treatment of known efficacy
Eight weeks
Treatment to be provided at the end of the study
One week following the conclusion of tDCS procedures, open medication-based treatment will be offered to study participants for a period of three months.

Clinical Treatment Alternatives

Clinical treatment alternatives
Alternative treatments for NSSI include a form of psychotherapy called dialectic behavioral therapy. While there are no FDA-approved medications for the treatment of NSSI, medications are sometimes used to treat NSSI based on previous research findings.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

Risk 1 applies only to the neuroimaging participants. Risks 2 through 5 apply to all participants.

Risks associated with participation in this study are related to 1) pregnancy; (MRI); 2) discomfort during scanning (MRI); 3) MRI scan; 4) transcranial direct current stimulation (tDCS); 5) psychological interviews

1. MRI Scan
The MRI scanner uses a large magnet (3 Tesla) to take pictures of the brain and is not associated with any known medical risks, except for persons who have a heart pacemaker, or have metal in their body (e.g.

shrapnel or surgical prostheses) which may be affected by the magnet. Subjects will be asked to notify us if this is the case. The long-term effects of being placed in a magnet of 3T are unknown. Although there are no known risks associated with pregnancy, we will not scan someone who is known to be pregnant. There is also the risk of burns from medicinal patches during the MRI; therefore, subjects will be asked to remove any patches prior to the scanning session. Some people have reported sensations during the MRI scan, such as "tingling" or "twitching" (or, very rarely, a painful sensation), which are caused by changes in the magnetic field that can stimulate nerves in the body. Occasionally, some people experience nervousness or claustrophobic feelings due to the scanner's small space. Despite these experiences, in our experience, no one has had sensations from the scanning that did not stop as soon as the scanning stopped. The MRI scan is not painful, but having to lie still in the enclosed space of the scanning table is uncomfortable for some people.

2. Transcranial direct current stimulation (tDCS)
The risks to human subjects directly associated with tDCS administration include a mild tingling sensation, slight epidermal irritation and mild temperature change at the site of application during administration (Brunoni et al., 2011); these do not tend to persist beyond the completion of the tDCS stimulation. Mild headache has been occasionally reported with tDCS, but typically responds to acetaminophen, ibuprofen, or aspirin. During the period of tDCS administration, the participant will be closely and regularly observed and asked to report any adverse effects. Subjects may opt to discontinue at any point. We will also regularly debrief subjects following tDCS sessions to detect patterns or procedures that might be associated with discomfort and will modify procedures as necessary. Similarly, we will continuously monitor the literature for procedures that might reduce risk of any discomfort. Participants will complete the tDCS Adverse Effects Questionnaire (Aparicio et al., 2016) following each tDCS administration to acquire systematic data regarding tolerability and side-effects. Any severe or intolerable side-effects will lead to the immediate cessation of the tDCS stimulation, and clinical monitoring and treatment by Dr. Miller or other M.I.N.D. division physicians, who will treat and monitor the symptoms until they resolve, and also closely follow up with the participant to ensure that the symptoms have not persisted. All adverse events, including serious ones, will be reported to the NYSPI IRB, with a review of procedures to determine whether the protocol should be modified accordingly. There are no specific risks related to using two different devices for tDCS in this study. Remote supervised self-administered tDCS has been successfully and safely performed in dozens of studies (Hordacre, 2018). All sessions will be supervised by Dr. Miller or Dr. Yttredahl, who will use the current best practices in remote administration of tDCS (Charvet et al., 2015, 2020; Shaw et al., 2017), with guidance and consultation from Dr. Leigh Charvet of NYU, an expert of remote administration of tDCS in clinical research, as needed. The device provided to participants in the remote arm of the study is intended for use with remote self-administration, and has been validated for this purpose (clinical uses include treatment for ALS (Sivaramakrishnan et al., 2019), MS (Charvet et al., 2018; Kasschau et al., 2016), and Parkinson’s Disease (Agarwal et al., 2018; Cucca et al., 2019)), and doses are strictly controlled by single-use codes that will be provided to the participants during each session once proper electrode setup and placement has been confirmed visually. Research has shown that the adverse events associated with at-home tDCS are the same as those of in-person tDCS and consist primarily of superficial, temporary discomfort such as itching, tingling, or burning sensations (Cucca et al., 2019).

3. Psychological Interviews
Psychological and neurocognitive assessments can be boring, tiring and sometimes disturbing.

4. EMA:
EMA may be mildly stressful. We have administered the EMA to >50 patients with Borderline Personality Disorder with recent suicide attempts and/or NSSI with no adverse effects. We obtained usable data from 98% of the participants. Data will be downloaded on the next visit to the institution. Once an assessment is completed the participant nor anyone else accessing the device will be able to see the responses.

5. Cyberball:
Participants may feel upset, annoyed, bored, or angry during the game, especially during exclusion trials.

6. Attention Training Technique:
The ATT could be boring, but is not associated with additional significant risks.

7. COVID-19
There is a risk of being infected with COVID-19 while traveling to and from the medical center.

Describe procedures for minimizing risks

1. MRI Scan
For women of childbearing years, urine pregnancy testing will be conducted the day of the MRI. If the subject experiences sensations and feels uncomfortable, the MR technologist will stop the scan immediately. Our research staff will be present at all times, and a staff psychologist or psychiatrist will be available at all times, should the subject experience any difficulties.

2. Transcranial Direct Current Stimulation
Routine safety procedures are in place to screen subjects prior to scanning, maintain security of the restricted access areas, and ensure that system security features are in good working order. A research physician will be present at all times to monitor patient safety. Operation of cellular (wireless) devices, telephones, or two-way radios may produce changes in device output, and thus should not be used in close proximity (< 1m).
We do not apply electrodes over broken or irritated skin. The use of other stimulation electrodes during the treatment period will be avoided. Lead wires are configured so that they cannot be plugged into power outlets such as wall sockets and line cord receptacles.
To ensure participants can safely self-administer tDCS, the following extra procedures will be added to the remote tDCS arm of the study:
a. All tDCS sessions will be monitored over a HIPAA compliant videoconferencing software (either NYS WebEx or CUIT-supported Zoom) by a trained researcher. We use secure videoconferencing software that is HIPAA compliant and approved for this use by our institution. While quite unlikely, there is a small risk that conversations that take place through videoconference could be intercepted, heard, or viewed by other individuals. Before beginning the tDCS, participants will be fully familiarized with all equipment, including how to immediately abort a stimulation session in the case of discomfort.
b. tDCS dosing will be strictly controlled by using a device that only starts a stimulation protocol when a single-use code is input. Thus, the device can only be activated by the participant once the supervising staff member has ensured all setup has been performed correctly, and the single-use codes will activate a montage with a pre-set intensity, duration, and condition (sham versus active). In addition, this device has

an automatic shut-off feature that will cause the stimulation to abort if the impedance goes above a preset threshold (a common cause of discomfort). In the case of an aborted session due to high impedance, participants will be guided to add additional saline to the sponges using syringes that have been prepared with saline and included in the tDCS kit.
c. A specialized headstrap (SNAPstrap), designed by Soterix to hold the electrodes at pre-determined positions on the scalp, will be used to ensure simple and consistent placement of electrodes on the scalp. The use of this strap will be further monitored by staff via a HIPAA compliant videoconferencing software before stimulation codes are provided.
d. For hygiene and to control the amount of conductive saline used during each session, single-use pre-soaked electrode sponges from Soterix will be provided to the participant. These sponges are packaged to include the correct amount of saline and designed to snap into the headstrap at the designated locations.
e. The protocol includes the following specific stop/go criteria for each step of the at-home administration, derived from the criteria published by Dr. Leigh Charvet (Charvet et al., 2020):

1. Stimulation will not proceed unless teleconferencing has been initiated with video and audio communication established. At least two forms of communication with the participant (e.g., telephone and videoconferencing) will be secured and tested before the first tDCS session. If the connection is lost during a session, the study technician will attempt to reestablish communication using the second form of connection. Participants will be instructed to abort the tDCS session if communication is lost. Training and practice on how to abort a session will occur before the first tDCS session.
2. Electrode preparation and position on the scalp has been visually verified by the study technician. Intact skin will be assessed through a visual inspection by the researcher through videoconferencing and verbally confirmed with the participant. Electrode preparation will be assessed by guiding and monitoring the participant on the setup of the electrodes and strap over videoconference. To position and hold the electrodes in place, we will be using a SNAPstrap from Soterix. This headgear was designed to be used in the home setting and is customized to fit electrodes at the correct anatomical locations needed for our specific montage. The strap has two holes, one for each electrode, that are placed in the correct location on the band and are color-coded to match the polarity of the electrode cables. Participants will be instructed to snap the electrodes into the color-matching holes and place the device on their heads so that the band lays across their forehead and an easily-visible marker on the front of the strap is centered between the eyebrows. The researcher will confirm that the strap is placed in the correct position by visually verifying the alignment of specified marks on the strap with anatomical landmarks on the head.
3. During the first 1-2 minutes of stimulation, following a complete ramp-up of current, participants will be asked to identify any physical sensations and rate them on a scale of 0-10. If any sensation is given a rating >4, participants will be asked whether the stimulation is tolerable. If necessary, the session will be aborted and the study technician will instruct the participant on how to adjust the electrode preparation to attempt to reduce impedance. If tolerability cannot be achieved, tDCS will not continue and the session may be rescheduled or the participant may be removed from the study, as needed.

3. Psychological interviews
Psychological interviews will be performed by trained staff who are sensitive to their potential effects. Subjects may become distressed during testing, in which case, testing will be postponed.

4. EMA: Subjects will not download EMA data themselves and they will not have access to it once a session is complete. We provide information about who to contact if the participant feels suicidal either during the EMA or at any other point.

5. Cyberball
Participants will be informed that they can stop the study procedures at any time without consequence. Participants will also be informed that the feedback they receive is not real, but is instead generated by researchers to study their responses to different types of feedback. In addition, a study clinician will be available as needed if the task causes substantial distress and patients will be carefully monitored for the duration of the study for any adverse effects of study procedures or worsening of symptoms. Social feedback paradigms have been administered safely in other studies of patients who engage in NSSI (Brown et al., 2017; Malejko et al., 2019).

6. Attention Training Technique
Participants will be informed that they can stop the study procedures at any time without consequence.

7. COVID-19
In order to minimize the risk of travel we will instruct all subjects in the importance of social distancing and wearing a mask at all times during travel to and from NYSPI as well as in NYSPI. On the days of the MRI scans we will offer to pay for an Uber ride for subjects living in the extended New York metropolitan area.

8. **Mood stabilizer treatment and associated blood monitoring (if applicable): If participants are diagnosed with bipolar 1 or 2 disorder and are not on a therapeutic dose of a mood stabilizer at the time of study enrollment, they may begin mood stabilizer treatment with a study physician. The risks of any mood stabilizer medication and alternatives will be discussed with participants in detail before initiating a trial. Mild discomfort can be expected from blood drawing that may be done to screen for medical conditions prior to beginning a mood stabilizer, and to measure blood levels of mood stabilizer medication. Sometimes a bruise will occur at the puncture site. Less than 40ml of blood will be drawn for this purpose.**

Methods to Protect Confidentiality

Describe methods to protect confidentiality
Personal information will be kept confidential and will not be released without the subject's written permission except as described in this section or as required by law. The subject's name or other identifying information will not be made known if the results of this study are published for scientific purposes. Clinical records, including the subject's name and other personal identifying information, and research data will be kept in secure storage at the New York State Psychiatric Institute. Information in paper format will be kept in locked files. Electronic data, including MRI images, will be protected by a firewall (programming that makes it virtually impossible to access the data from outside the New York State Psychiatric Institute) and by restricting access within the New York State Psychiatric Institute through use of a password known

only to authorized personnel. If information is transmitted electronically, it will be encrypted so that identifying information remains confidential.

All information that participants enter onto the iPod or iPhone will be encrypted and password-protected. If participants want to use their own iPhone for this study, they must agree to turn on the passcode (password) setting on their iPhone. If they do not have an iPhone, or do not wish to turn on the passcode (password) setting, they may use our iPod instead. Information stored on the iPod/iPhone app is associated with an ID number, and not with participants' names or other identifying information.

The subject's information will only be available to study research staff and other authorized individuals, including those at the New York State Psychiatric Institute, New York State and federal regulatory agencies such as the Food and Drug Administration who may review records as part of routine audits. There are also legal advocacy organizations that have authority under New York State law to have access to otherwise confidential subject records, although they cannot disclose this information without the subject's consent.

The subject's MRI will be interpreted and the results will be shared with the subject or physician who the subject may designate. The MRI report will be maintained as part of the clinical database at the Columbia Radiology MRI Center at the Neurological Institute along with the subject's name and will be accessible to clinicians at the New York State Psychiatric Institute. The subject's psychiatric diagnosis will not be a part of the report.

Will the study be conducted under a certificate of confidentiality?

No

Direct Benefits to Subjects

Direct Benefits to Subjects

This study was not designed for the direct benefit of the participants.

Participants will be offered three months of treatment visits with a psychiatrist for medication management at the conclusion of the tDCS procedures.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?

Yes

Please describe and indicate total amount and schedule of payment(s).

Include justification for compensation amounts and indicate if there are bonus payments.

Sample of patients with NSSI:

For neuroimaging participants: Subjects who complete all imaging assessments will be compensated a total of $150. Subjects who do not complete all imaging assessments will receive a partial payment prorated based on their participation in the study ($50 for each fMRI scan and $50 for the tDCS administrations).

For participants without neuroimaging: Subjects who are enrolled without neuroimaging and complete all clinical assessments will receive $150.

Payment procedures are initiated upon subject's completion of the study. Payment is in the form of a check, usually received in the mail about 4-6 weeks after completion of the study procedures.

Sample of healthy volunteers for fMRI pilot:
Participants in the fMRI portion of the pilot will receive $50 for each of the two scans at the completion of the scan, for a total of $100.

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STATISTICAL ANALYSIS PLAN

This is a double-blinded, randomized, sham-controlled pilot study examining the tolerability and effectiveness of repeated administrations of tDCS over right vlPFC in treating NSSI and its underlying neural correlates.

Primary analyses on behavior and clinical outcomes will be conducted using linear mixed effects models to account for repeated measures over time and individual variability. All tests will be performed using two-sided alternatives with alpha=0.05. Ecological momentary assessment data will be evaluated using mixed effects logistic regression. BOLD imaging data will be analyzed using generalized linear models comparing pre- and post- intervention neural responses to inclusion and exclusion trials during the Cyberball game. For all analyses, we will examine standard diagnostic plots to identify evidence of lack of model fit, presence of outliers or overly influential points, etc., and take appropriate remedies as indicated (e.g., review source data of outliers, transform data, etc.).

As this is a pilot study, additional exploratory analyses will be conducted for hypothesis generating purposes.