Indiana University, Bloomington, IN

Temporal Interference Neurostimulation and Addiction

Joshua W. Brown, Indiana University Bloomington

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IRB Study # 1904451651

Revised Aug. 21, 2023

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Table of Contents:

- **Objectives:** Clearly stated specific aims aligned with well-defined endpoints and appropriate study design.
- **Scientific Merit/Background and Rationale:** Justification for conducting the study; results of similar or pilot data; current literature cited.
- **Design:** Cleary [sic] describes: how stated objectives will be achieved, methods to acquire data, and strategies to overcome anticipated barriers. Addresses randomization, minimization of bias, patient follow-up, and blinding (if applicable).
- **Eligibility Criteria:** Specific inclusion/exclusion requirements and stratification factors (if applicable).
- **Outcome Characteristics and Endpoint Definitions:** Clearly defined primary and secondary endpoints/outcomes.
- **Statistical Analysis and Sample Size:** Appropriate and adequate study design statistical analysis plan. Prospective analysis plan, including sample size justification to achieve study objectives and plans to minimize missing data.
- **Data Management:** Practices and procedures in order to manage data analysis, quality, cleaning, and storage.
- **Principal Investigator and Study Site Qualifications and Resources:** Has the necessary skills, experience, time, and resources to ensure that the study can be successfully completed, including identification of personnel to provide statistical computations and statistical expertise. A plan to register protocol with clinicaltrials.gov.

1.0 Objective

New approaches to treating substance use disorders (SUDs) are desperately needed. We aim to develop novel neurostimulation using temporal interference technology to treat SUDs, with the long-term goal of developing a lightweight, inexpensive headband that can suppress the wearer's cravings and support drug abstinence indefinitely. To do this, we will explore newly developed non-invasive deep brain electrical stimulation methods that allow penetration to deep brain structures, especially those that are central to reinforcement of addiction, without stimulating the overlying cortex. We will test our methods first in subjects with nicotine use

disorders. We propose to compare feasibility and tolerability of temporal interference stimulation against existing transcranial direct current stimulation, which has been studied in SUDs, but has limited efficacy given its inability to stimulate deep brain regions.

Specific Aim: To investigate whether stimulation with a mild current from temporal interference non-invasive deep brain stimulation (TI-NDBS) to the Anterior Cingulate Cortex (ACC), the anterior insula (AI), or the nucleus accumbens (NAcc) will reduce nicotine craving and seeking. The TI-NDBS is similar to the traditional transcranial direct current stimulation (tDCS), a method approved for use in a number of other studies in our department. Other studies have shown there have been some effects of reducing craving with tDCS (Fregni, Liguori, et al., 2008), however, tDCS cannot stimulate structures such as the ACC very effectively because tDCS cannot stimulate deeper brain regions. Thus, the Specific Aim ultimately will compare TI-NDBS with tDCS and sham stimulation. The first phases (Phases 1 and 2) of this aim investigate the effects of TI-NDBS on sensations, craving, and brain activity. The second set of phases examine the effects of TI-NDBS on nicotine seeking using a Nicotine Delivery Device (NDD) and craving in comparison with sham (Phase 3) and tDCS and sham (Phase 4).

2.0 Background

This project aims to develop a line of research using new non-invasive neurostimulation technology to treat adults with substance use disorders (SUDs). SUDs are a severe, current problem in Indiana and across the US, with many lives lost daily to overdoses and other medical complications. In the short term, we aim to identify novel target brain regions for neurostimulation treatment and characterize their effects behaviorally and neurally. A number of case reports in humans describe complete, permanent, and near effortless disruption of SUDs due to direct effects on specific brain regions and circuits known to be involved in the addiction process, such as the insula, the nucleus accumbens (NAcc), the dorsolateral prefrontal cortex (DLPFC), and the amygdala (Naqvi & Bechara, 2014). For instance, Naqvi et al. (2007, Science) described cases in which smokers spontaneously lost all interest in cigarettes following stroke damage to the bilateral anterior insula (AI). Similarly, Müller et al. (2009, Pharmacopsychiatry) describes cases of permanent remission of alcoholism due to deep brain stimulation of the NAcc after years of 2+ liter/day hard liquor consumption. The AI assists with predictions of future affective bodily states, such as satiety, pain, craving, etc. (Craig, 2002).
Given these findings, it is likely that the AI represents internal affective states related to drug use, such as craving, drug reward, withdrawal, adverse health effects, successful self-control and abstinence, and the anticipation of each of these states. Likewise, error-related activation of the nearby amygdala is greater in subjects who are more likely to fail treatment for addiction (Forster et al., 2017).

When considering cases of significant damage caused by clinical pathology (e.g., lesion from stroke), deep brain areas have shown to exhibit a variety of outcomes. In the anterior cingulate (ACC), the most consistent and substantial report has been an expression of akinetic mutism; those with ACC lesions are un-willing/motivated to produce voluntary motor responses (Devinsky et al., 1995). Damage to AI regions through stroke lesions have presented with widely varying effects, including a slower capacity in switching between different cognitive tasks (set-

switching; Varjacic et al., 2018), or a higher pain sensitivity to noxious stimuli (e.g., cold tolerability; Starr et al., 2009). Therefore, the lesions to AI exhibit a large variety in changes to cognitive and behavioral states. In terms of the NAcc, the understanding regarding the effects of impact to humans is based almost exclusively on trials using deep brain stimulation of the NAcc in clinical populations, such as obsessive compulsive disorder (Huff et al., 2010), alcohol dependency treatment (Kuhn et al., 2007), and addiction to smoking (Kuhn et al. 2007). The effects of altering NAcc through stimulation have shown a variety of results, including cessation of smoking or alcohol dependency (Kuhn et al., 2007), or increased risky decision making during cognitive tasks (Nachev et al., 2015). Therefore, alteration of NAcc function through DBS has shown a variety of outcomes. These types of findings, as well as those previously discussed, have led to a possible link to underlying addiction states. Importantly, these examples are extreme clinical cases in which substantial affliction to these brain areas or deep brain implantation (which uses larger levels of voltage exceeding 3 V/mm). Thus, methods that offer a safe and non-invasive, reversible modulation of neural activity in the AI, NAcc, and ACC in particular are likely to be effective at treating addiction without inducing any of the effects subsumed by lesions.

On Oct. 12, 2018 we received funding from the IU Grand Challenge Addictions program to examine the effects of neurostimulation on nicotine/drug craving and seeking, which is the focus of this protocol. We will be stimulating specific brain areas that we have found to be centrally involved in nicotine seeking (with our approved companion protocol on gambling for nicotine inhalations) using the nicotine delivery device (NDD) that we use in the MRI scanner with smokers. Our companion protocol studies found so far that activation in the dorsal ACC (anterior cingulate cortex) occurred just prior and right after the subject gambled to obtain a nicotine dose; once satiated on nicotine, the ACC was no longer activated and the subject did not seek more nicotine. In addition to the ACC, the ventral striatum also was activated while seeking nicotine. The overarching purpose of this project is to test the feasibility and effectiveness of stimulating these brain areas using temporal interference non-invasive deep brain stimulation method (referred to here as TI-NDBS) with the idea that such stimulation may be ultimately used as a treatment component for nicotine addiction, and eventually for opiate addiction, since these brain areas are centrally involved in addiction in general. TI-NDBS is similar to other commonly used low voltage/current brain stimulation approaches, such as transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS), which, to date, have only shown the side-effect of mild skin irritation in tDCS but not tACS (reviewed in Matsumoto and Ugawa, 2017). Thus, non-invasive electrical neurostimulation methods including TI-NDBS all induce such a low level of voltage in the brain (0.8 V/m) that these methods can only modulate ongoing neural activity in a weak manner. Because TI-NDBS is identical in delivery type and amount of energy to tACS and no previous studies have reported a side effect with tACS, this indicates there is little to no risk for adverse reactions to TI-NDBS. Essentially, to date, there is no reported negative side-effects for any non-invasive electrical neurostimulation method, demonstrating their safety (Matsumoto and Ugawa, 2017). The IRB has already approved tDCS/tACS for ongoing studies in other labs at IU, for example the Hetrick lab. The difference between TI-NDBS and tDCS/tACS is that stimulation can be localized better with TI-NDBS; *notably, TI-NDBS being more localized does not mean it is stronger, the stimulation is just more confined to the intended brain region*. TI-NDBS stimulation consists of multiple electrode pairs administering tACS, except

it is far superior as the localization of stimulation to deep brain sites is much better.

Because TI-NDBS is essentially identical to tACS (and almost identical to) tDCS stimulation, which both have been applied to deep brain regions previously and found no side effects. This indicates there is no historical evidence for any expected negative consequence of using TI-NDBS on the same brain regions. For example, tACS directed towards ACC (Onoda et al., 2017) found weak, non-persistent changes in reports to emotionally valanced stimuli. Other studies of tACS on the ACC have found no adverse effects (Chander et al. 2016), nor have studies that broadly target the prefrontal cortex and would likely affect the nucleus accumbens and insula (Vanneste et al. 2013). Along these lines, tDCS directed at AI (Li et al., 2018) only had a reported effect of increasing participant alertness and mild and transient changes in brain network activity assessed using fMRI. With respect to TI-NDBS, previous testing has been completed with animals at currents equivalent to that normally applied in human studies (~ 2 mA), and the histological assays looking for tissue damage found no evidence of harm (Grossman et al., 2017). Together, the commonality between TI-NDBS and existing methods, and the complete absence of any reports of damage or harm from more common methods (tACS/tDCS), this indicates that TI-NDBS should be equally safe and tolerable for neurostimulation.

Given that other studies have shown effects of reducing craving with tDCS (Fregni, Liguori, et al., 2008) when stimulating deep brain areas, while tDCS lacks the focal control afforded to TI-NDBS, our proposal aims to employ TI-NDBS as a more accurate means to stimulate different brain targets previously linked to addiction. There are 4 phases to the protocol. Phase 1. A pilot study of acceptance of TI-NDBS (assessing the subjects subjective mood and sensations during stimulation), Phase 2. A pilot localization study where TI-NDBS will be done in the MRI scanner and the exact location of stimulation will be established with specific scalp electrode placements. Phase 3 will examine the effects of TI- NDBS and sham on nicotine craving and inhalations using our nicotine inhalation device already approved in another of our IRB protocols and Phase 4 will compare the effect of TI-NDBS, with traditional tDCS, and sham on nicotine craving and inhalations.

3.0 Design

The project proposes to test the effects of electrical neurostimulation as a treatment for addiction. Stimulating the brain to treat SUDs is not entirely novel. Transcranial direct current stimulation (tDCS) is a very cost-effective method that may provide longer-lasting reduction in substance use disorder symptoms in human adults with, for example, effect sizes of Cohen's d'=0.71 for reduction of cigarette consumption following 5 days of tDCS (Fecteau et al., 2014; Wing et al., 2013). The problem with most tDCS studies is that they have focused on stimulation over bilateral dorsolateral prefrontal cortex (left cathodal), around F3 and F4 in the 10/20 system. This may not be the most effective approach. Instead, we would like to target the bilateral anterior insula and the nucleus accumbens, as they are far more integral to the process of starting and maintaining SUDs. Likewise, disruption of the insula often results in complete spontaneous loss of addiction (Naqvi et al., 2007); thus we hypothesize that neurostimulation to the insula may disrupt its function and thereby disrupt addiction, resulting in fewer cravings and milder withdrawal. The insula and accumbens may perform complementary functions, with the accumbens driving reward seeking and craving, and the insula driving behavior that reduces withdrawal symptoms.

The Brown lab has developed finite element simulation software that will be used to determine

electrode placement. The software simulates the electrical fields generated given a set of electrode locations in the 10/20 coordinate system. With this, we are able to specify a target brain region, then run a software optimization routine that determines the optimal electrode placement to target the desired brain region. After some *in silico* testing, we found that the electrode placement can be determined in the standard 10/20 coordinate system using a standard brain image template (the Montreal Neurological Institute or MNI template.) Furthermore, once the electrode locations are calculated, they can be applied to all subjects without subject-specific structural MR images, because the between-subject variation in 10/20 coordinates vs brain regions is small relative to the extent of the temporal interference region. Put another way, the marginal increased accuracy due to optimization on a subject-specific structural MR image vs. an MNI template brain is negligible. This will allow us to determine the electrode placements with high accuracy, so that we can specifically target the desired brain regions.

Phase 1. Tolerablility. In phase I, we will test the safety of the temporal interference non-invasive deep brain stimulation (TI-NDBS) device on non-smokers (n=3). Subjects will be administered a questionnaire to assess their physical experiences and sensations using a 5-point Likert-scale (Stimulation experience scale attached in Notes & Attachments and is the same scale used in all four stages of the protocol). After baseline measures, subjects will be sitting in a chair and have the electrodes (measuring approximately 2 cm by 2 cm) attached to the scalp.
TI-NDBS will be a very small electric current applied to the brain through the scalp electrodes. The subjects will receive stimulation for 30 minutes. Electrodes will be placed around the head in positions designed to maximize focal stimulation of the anterior cingulate cortex, anterior insula, or nucleus accumbens. The skin beneath the electrodes will be cleaned prior to application, and a saline solution or gel will be used to help to attach the electrode to the scalp. There will be a small current of electricity (2 mA peak-to-peak alternating current per electrode pair) that will run through the electrodes. There will be a maximum of 2 mA per electrode pair and no single region will receive more than 2 mA, although there will be two pairs of electrodes, which each apply up to 2mA at separate sites. At the beginning of every period of stimulation, the current will increase slowly at a constant rate for 30 seconds until it reaches the appropriate intensity. At the end of the stimulation, the current will decrease slowly for 30 seconds until it reaches zero. Some tingling under the electrodes may be felt, and subjects may also see flashing lights. Subjects will also be able to stop the experiment at any time if the subject wants to stop or indicates significant discomfort. Right after half the stimulation period has elapsed, the subject will complete the stimulation experience scale again at the end of the stimulation period (condition assignment based). Then the subject will go to the restroom to clean off any gel that remains on the skin. The gel washes away easily with water. Ten minutes after the end of the stimulation, the subject will complete the stimulation experience scale again reporting on their feelings and sensations at that moment. The entire testing process will last about 1.5 hour. Phase 1 will be completed before we begin Phase 2. Testing will take place at IU Bloomington, Department of Psychological and Brain Sciences.

Safety and Monitoring:
(1) **Comfort:** Subjects will be asked to rate (1-5 scale) severity, location and quality (self described) of any discomfort immediately prior to the stimulation, at 5 and 15 minutes during stimulation, immediately after the stimulation and at 10 minutes after the stimulation. If any discomfort persists at 10 minutes after stimulation, treatment and ongoing assessment will be arranged as needed by the study physician.
(2) **Cognitive Effects:** Baseline memory, attention and verbal reasoning will be assessed using the Digits span test from the WAIS, which assesses short-term memory and attention. This will be repeated 10 minutes after the stimulation. Subjects will also be asked open ended

questions about any changes in their thinking or cognitive status. Research staff will contact subjects between days 2 and 5 after scanning to query the persistence or emergence of any cognitive changes.

(3) **Psychiatric Effects**: Emotional, motivational and behavioral symptoms will be assessed before stimulation and immediately following stimulation. Subjects will be contacted to follow up between days 2 and 5 after scanning to query the persistence or emergence of any changes to their emotions, motivation or behavior. This testing will involve using the PANAS-SF test of positive and negative affect.

In the unlikely event of serious adverse events occurring in Phase 1, the study team will report back to the DSMB and the IRB to assess whether or not the study could proceed to Phases 2-4.

Phase 2. Neural effects. In Phase II, subjects will complete the MRI safety screen questionnaire and the stimulation experience scale (the same scale from phase 1) prior to entering the MR scanner. The electrodes (2 cm x 2 cm) will be attached and subjects will enter the MR scanner and the TI-NDBS stimulation will be administered while in the scanner, alternating 2-minute stimulation and 2-minute no-stimulation periods. Subjects may alternatively receive stimulation from all electrodes at the same frequency in order to make comparisons to temporal interference stimulation. For every two minute period of stimulation, the current will increase slowly at a constant rate for 30 seconds until it reaches the appropriate intensity. At the end of the stimulation, the current will decrease slowly for 30 seconds until it reaches zero. For sham stimulation, the current will increase during a 30 second interval and then immediately decrease back to zero over a 30 second interval, for a total of 60 seconds of stimulation.This will allow us to identify immediate neural activation due to stimulation, while controlling for any scalp sensations with the sham condition. The electrodes will be placed to target stimulation at either anterior Cingulate or nucleus accumbens. Immediately following the stimulation session, subjects will complete the stimulation experience scale and then will clean off residual electrode gel. The stimulation experience scale is administered again 30 minutes later. The subject will be in the scanner for about 1 hour.

Safety and Monitoring:

1. **Comfort:** Subjects will be asked to verbally rate (1-5 scale) severity, location and quality (self described) of any discomfort immediately prior to the scan, after each block during the scans, immediately after the stimulation session and at 10 minutes after the stimulation sessions. If any discomfort persists at 10 minutes after stimulation, treatment and ongoing assessment will be arranged as needed by the study physician.
2. Cognitive Effects: Baseline memory, attention and verbal reasoning will be assessed using the Digits span test from the WASI, which assesses short-term memory and attention. This will be repeated 10 minutes after the stimulation. Subjects will also be asked open ended questions about any changes in their thinking or cognitive status. Research staff will follow up with participants in the second and third sessions and 5 to 14 days after the third session to query the persistence or emergence of any cognitive changes.
3. Psychiatric Effects: Emotional, motivational and behavioral symptoms will be assessed using the PANAS (Positive and Negative Affect Scale) before stimulation and immediately following stimulation.

Phase 3. Neural effects on behavior. In Phase 3, we will test the effectiveness of Temporal Interference-NDBS on reducing smoking and cigarette craving in heavy smokers. To test this, we will proceed with two stages. In the first stage (pilot), we will recruit heavy smokers into three groups, then ask them to abstain from smoking. One group will receive TI-NDBS to the left and

right insula. Another group will receive TI-NDBS over the nucleus accumbens. Another group will receive TI-NDBS to the anterior cingulate cortex. We will not target these brain areas in any particular order. Prior to stimulation, subjects will be administered a questionnaire to assess their physical experiences and sensations using a 5-point Likert-scale. Subjects will also be given the Nicotine Dependence Syndrome Scale to assess baseline Nicotine Dependence. In addition, we will measure total real-time ad lib nicotine vapor inhalation during a 60 minute stimulation session. At the start of the stimulation, the current will increase slowly at a constant rate for 30 seconds until it reaches the appropriate intensity. At the end of the stimulation, the current will decreased slowly for 30 seconds until it reaches zero. Every ten minutes, we will ask subjects to self-report their level of craving on a Likert scale of 1-10. We will identify whether TI-NDBS to the insula or nucleus accumbens or cingulate is more effective stimulation at decreasing cravings. In the second stage of Phase 3, we will take the two most promising of the three brain regions and repeat the procedure of stage 1, but with a larger sample size. The third group will receive sham stimulation as a control. In both stages, immediately after stimulation, subjects will complete the stimulation experience scale and then again 30 minutes later. We will then follow up with subjects every day, up to three times per day, for a period of 1 week afterward using Ecological Momentary Assessment (EMA) via a smartphone app (LifeData) to monitor cigarette and/or vaping use and craving. The questions that will be used in the app are in a script attached (see EMA follow up questions). In Phases 1, 2, and 4 subjects are paid $25/hr. In Phase 3, subjects are paid $40/hr. In addition, in Phases 3 and 4, subjects are paid $5/day for providing ecological momentary assessment data outside of the lab sessions, and $10 bonus for completing 7 consecutive days of ecological momentary assessment (EMA). Payment will be made at the end of each day's lab session in cash, and for phase 3, by check after the EMA period ends.

Additionally, after consenting, subjects in all phases will be asked to fill out a contact form detailing their email address, home address, and phone number, as well as their preferred method of contact. This form will be used to pay subjects via mail as well as contact them for potential participation in future studies if they are interested.

Safety and Monitoring:

1. **Comfort:** Subjects will be asked to rate (1-5 scale) severity, location and quality (self described) of any discomfort using the attached stimulation experience scale immediately prior to the stimulation, immediately after each 10 minute stimulation block, and at 10 minutes after the stimulation session. If any discomfort persists at 10 minutes after stimulation, treatment and ongoing assessment will be arranged as needed by the study physician.
2. **Cognitive Effects:** Baseline memory, attention and verbal reasoning will be assessed using the Digits span test from the WASI, which assesses short-term memory and attention. This will be repeated 10 minutes after the stimulation. Subjects will also be asked open ended questions about any changes in their thinking or cognitive status.
3. **Psychiatric Effects:** Emotional, motivational and behavioral symptoms will be assessed using the PANAS (Positive and Negative Affect Scale) before stimulation and immediately following stimulation.
4. **COVID-19 safety:** Subject and experimenter, both wearing masks, enter the testing room. Experimenter places electrodes on subject's head and adjusts them. Experimenter gives the subject an e-cigarette mouthpiece and an exhaust device to exhale into (which has a carbon and HEPA filter to filter the subject's exhaled breath and nicotine vapor), with instructions for the subject to remove their facemask after the experimenter has left the room, inhale from the e-cigarette per protocol, and exhale into the exhaust device. Experimenter leaves the room, after which subject removes their own facemask. Subject proceeds to do the experiment and puts their facemask back on before the experimenter again enters the room.

Phase 4. Relative effectiveness of stimulation. In phase 4, we will compare TI-NDBS vs.

conventional transcranial direct current stimulation for smoking reduction. To test this, we will recruit another group of subjects who are heavy smokers into three groups, then ask them to abstain from smoking. Prior to stimulation, subjects will be given the NDSS to determine baseline nicotine dependence. The first group will receive standard transcranial direct current anodal stimulation of the right DLPFC and cathodal stimulation of the left DLPFC (F3 and F4 in the 10/20 system). The second group will receive TI-NDBS to either the nucleus accumbens or anterior insula or anterior cingulate, depending on which is found to be more effective in Phase 3. The third condition will be sham. The strength of the stimulation and duration will be the same as in previous phases. Prior to stimulation, subjects will be administered a questionnaire to assess their physical experiences and sensations using a 5-point Likert-Scale. Immediately after stimulation, subjects will complete the stimulation experience scale, then complete the scale again 30 minutes later.In addition, we will assess craving levels every 10 minutes during the stimulation period. We will repeat this for five consecutive days. We will then follow up with subjects every day, up to three times per day, for 1 week after starting the tDCS, using EMA via a free smartphone app (ilumivu.com) to monitor cigarette use and craving. The questions that will be used in the app are in a script attached (see EMA follow up questions). We will compare the sham vs. tDCS vs. TI-NDBS groups to identify differences in craving and relapse. We expect to find that TI-NDBS leads to reduced craving and drug use relative to sham or tDCS. The procedure in this phase will not add anything new, except testing subjects with tDCS in addition to TI-NDBS and sham.

Safety and Monitoring:

1. **Comfort:** Subjects will be asked to verbally rate (1-5 scale) severity, location and quality (self described) of any discomfort immediately prior to the scan, after each block during the scan, immediately after the stimulation session and at 10 minutes after the stimulation session. If any discomfort persists at 10 minutes after stimulation, treatment and ongoing assessment will be arranged as needed by the study physician.
2. Cognitive Effects: Baseline memory, attention and verbal reasoning will be assessed using the Digits span test from the WASI, which assesses short-term memory and attention. This will be repeated 10 minutes after the stimulation. Subjects will also be asked open ended questions about any changes in their thinking or cognitive status.
3. Psychiatric Effects: Emotional, motivational and behavioral symptoms will be assessed using the PANAS (Positive and Negative Affect Scale) before stimulation and immediately following stimulation.

New technology.

Temporally-interfering non-invasive deep brain stimulation (TI-NDBS) is a form of transcranial alternating current stimulation (tACS) which allows focal stimulation and disruption of deep brain structures, without invasive measures, and without disrupting overlying brain regions (Grossman et al., 2017, Cell). Temporal interference tACS (TI-NDBS) has been used since at least the 1970s in humans to treat pain, and devices and software to stimulate the human brain with temporal interference tACS is now FDA approved for investigational use and sold commercially https://soterixmedical.com/research/interferential-stimulation.

TI-NDBS works by applying two or more alternating current electric fields to the scalp at frequencies above those necessary to cause stimulation (e.g. 2KHz). The field frequencies differ by a small amount (e.g. 2000 Hz vs. 2010 Hz), so that the differences causes a 10 Hz beat frequency where the fields overlap, similar to the beat frequency of two guitar strings which are slightly out of tune with each other. The location can be tuned to anywhere in the brain, and with any beat frequency, even within deep structures (Figure 1, from Grossman et al., 2017). In our study, subjects will also receive stimulation from all electrodes at the same

frequency (e.g. 2000 Hz) in order to make comparisons to temporal interference stimulation (e.g. 2000 Hz vs, 2010 Hz).

As the technology is very new, we do not yet have sufficient data to estimate an effect size of TI-NDBS on nicotine or opiate use or craving. We specifically hypothesize that tDCS neurostimulation to the dorsolateral PFC will reduce nicotine intake and craving, and that TI-NDBS to the insula will be more effective than tDCS at reducing both nicotine intake and craving. The electrodes will be placed according to the standard EEG 10/20 system.

For tDCS to the dorsolateral prefrontal cortex, we will place electrodes over F3 and F4. For TI-NDBS, we will use finite element methods (simnibs.org or sim4life) to determine where to place each of four electrodes (two pairs) in order to target the desired brain region. Each smoking subject will be allowed *ad lib* intake from our custom e-cigarette, which measures total inhaled vapor and thus nicotine intake (as we verified in Velez et al., 2015). As a measure of short-term neurostimulation effectiveness, we will compare total nicotine inhaled during stimulation for tDCS, TI-NDBS, and sham subjects. We will also ask for periodic self reports of craving during stimulation, i.e. “How much do you want to smoke?”, on a Likert scale of 0-10. We will compare self-reported craving across different stimulation conditions. For long-term assessment, we will use ecological momentary assessment, with the Ilumivu.com system. Subjects will be prompted 3 times a day (morning, afternoon, and evening) between neurostimulation sessions and for the next two weeks following neurostimulation to report how many cigarettes they smoked in the preceding time period, and how much they are craving cigarettes at the moment. We will use this information to assess how strong the effect of stimulation is even after the stimulation session has ended. In the lab, we will measure recent smoking by measuring breath carbon monoxide (CO, Smokerlyzer PiCO).

Recruitment:
Participants are recruited by placing flyers around the community that ask for responses from “heavy smokers who are interested in research and are between the ages of 18-50 years”. Participants are also recruited via Craigslist using a post titled “Participants Needed for Psychology Study.” After calling or emailing the lab, interested participants complete a 5 minute phone screen to determine eligibility (e.g., smoking at least 15 cigarettes per day). These phone screens will be de-identified and retained to show eligibility to participate. Once in the laboratory participants also complete the nicotine dependence severity scale to quantify the severity of their nicotine dependence. Finn and Brown have successfully recruited populations of heavy smokers for fMRI studies in the past. Subjects who express interest by calling or emailing the lab will be contacted via telephone by the lab subject coordinator. They will be asked a series of screening questions to confirm that they meet the inclusion/exclusion requirements. This screening interview will be oral and no information will be recorded or retained, as it is for screening purposes only. If subjects meet the inclusion criteria, they will then be asked to provide a schedule of availability and placed on a list of interested subjects. They will be informed that they may or may not be offered a spot in our current study, depending on available timeslots and how many participants we will run in relation to how many interested respondents we have. As volunteers are needed for specific time slots, the research coordinator will contact them to schedule them, and the first subject that is available for the required session time will be scheduled. Interested participants who meet all screening criteria but who are not offered a slot in our current study will be informed that they have the option to be put on our contact list for future studies. Previously interested volunteers will be removed from the contact list immediately if they so request.

Temporal Interference neurostimulation methods
Equipment: *Temporal Interference (TI)* Temporal Interference (TI) is a stimulation method

that uses specific electrode arrangement patterns, to selectively stimulate a region of the brain (Grossman et al. 2017; *Figure 2*). This is accomplished by administering at least two different sinusoidal electric currents (i.e. transcranial alternating current stimulation, tACS) at frequencies too high to impact neural firing directly, but that create a specific frequency 'envelope' at the intersection of the currents. For example, electric frequency 1 (E1) could be a 2mA current, that oscillates at 2.00 kHz frequency, while electric frequency 2 (E2) could be a 2 mA current that oscillates at 2.01 kHz. The additive frequency of the stimulation 'envelope' would be 10 Hz (or .01 kHz). Higher oscillations outside of the envelope do not impact cellular firing, while the neurons within the envelope are stimulated by the additive frequency. This is achieved by altering the cell's resting membrane potential which is the mechanism of action for all tEs methods (Polanía, et al. 2018), and in particular for TI neurostimulation (Cao et al., 2017, biorxiv).

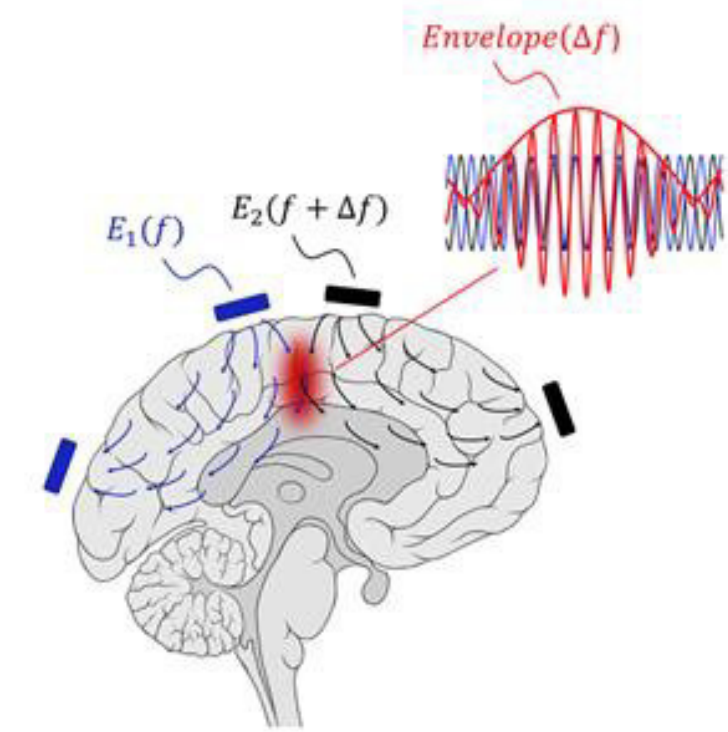

Figure 1. Frequency envelope created during Temporal Interference (TI). One current (blue arrows; E_1) is passed at a specific frequency (f) between one pair of electrodes (blue rectangles). A differing frequency (f + Df) current (black arrows) is passed between another pair of electrodes (black rectangles). The overlapping, red "envelope" demonstrates the area of stimulation, while the area covered by the individual currents (black and blue arrows) remains unstimulated.

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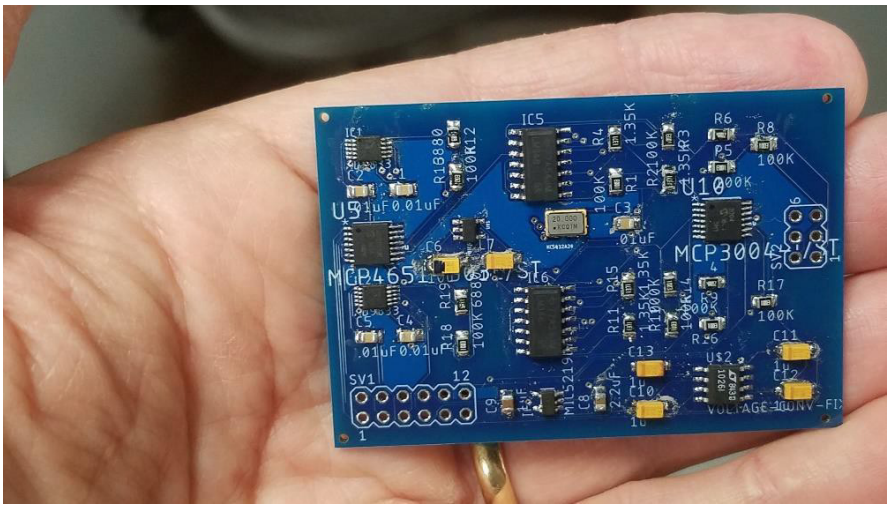

Figure 2. TI-NDBS prototype device, custom built by a senior electronics engineer in the Psychological and Brain Sciences electronic shop based on PI Brown's design. The neurostimulation is powered by a 9-volt battery, and the device is controlled and monitored by a separate microprocessor, typically a Raspberry Pi or Arduino. The control software ensures that the current remains within specified limits and that the stimulation waveforms remain sinusoidal.

Safety – Electrical Neurostimulation

Temporal interference tACS has been used since at least the 1970s in humans and safely at current levels over 10 times what we propose here (Venancio et al., 2013).

Grossman et al. (2017) determined the safety of TI by comparing the brain tissue of stimulated and unstimulated mice at currents of 125 mA per electrode pair (F1 = 2 kHz, F2 = 2.01 kHz) were applied in a 10 seconds-on, 10 seconds-off pattern for 20 min. Results showed no evidence of tissue damage. Notably, they found no tissue damage even when their tested stimulation of 125 ma was substantially larger than that applied normally in humans or will be applied in the proposed work. Grossman et al. (2017) found no differences in neuronal density, number of apoptotic cells, reactive microglia/astrocytes, or synaptic density, and no presence of DNA damage following stimulation vs. control. The current study proposes oscillatory frequencies of F1 = 2 kHz and F2 = 2.01 kHz, creating an envelope frequency of 10 Hz, with each current not exceeding a peak-to-peak amplitude of 2 mA. F2 may be varied up to 2.1 kHz to investigate the effects of different envelope frequencies. This creates a total of 4mA of alternating currents.
This alternating current amplitude was chosen based on recent findings that between 4-6 mA is required to reliably and efficaciously impact neural circuits, as 58 ± 7% of alternating current is blunted by skin and tissue and 16 ± 8% is attenuated by the skull (Vöröslakos et al., 2017). Other research has indicated that even 4 mA of direct current stimulation for 30 minutes has been safely tolerated (Bikson et al. 2016; Nitsche & Bikson, 2017). For transcranial alternating current stimulation as used by TI, there is also a question of what current frequencies can be safely applied. Chaieb et al. (2014, https://doi.org/10.1016/j.brs.2013.08.004) show that transcranial alternating current stimulation at a frequency up to 5KHz with a current of 1 mA for 10 minutes is safe, with no evidence of increased neuron specific enolase, a marker of neural injury. A recent review of adverse events of tACS and tDCS shows no serious adverse events. The potential minor side effects of tDCS include skin irritations, and no adverse effects of tACS have been reported (Matsumoto and Ugawa, 2017, https://doi.org/10.1016/j.cnp.2016.12.003). Stimulation with tACS at 2mA with frequencies of 10, 50, and 300 Hz for 5 minutes has been done with no adverse effects (Naro et al., 2016, https://doi.org/10.1016/j.brs.2016.02.005). Given these prior findings of safety for the types of stimulation we plan to administer, we do not expect adverse events beyond minor skin irritations in the rare case. There is some evidence that electrical neurostimulation may lead to effects that persist beyond 6 months. One study found that tDCS stimulation during learning may lead to lasting improvements in numerical abilities 6 months after training (Cohen Kadosh et al., 2010).

Safety – TI-NDBS device

The TI-NDBS device has the following safety features, designed to prevent malfunction and, if a malfunction were to occur, automatically reduce the electrical current to prevent injury to the patient:

1) **Intrinsic limits**: It has a 9 volt power supply, which limits the electrical stimulation power that can be delivered.
2) **Safety monitoring circuit:** It has a built in voltage monitor to detect malfunctions and take corrective action. The device is designed to deliver a fixed amount of current, up to 2 mA per channel. The voltage is constantly adjusted to compensate for the electrical resistance of the

head and maintain the desired electrical current. If the resistance increases such that the voltage reaches the maximum possible device voltage (e.g. due to a poor connection with the scalp), then the device will signal an error via an LED light and lower the set point current to avoid excessive voltage. In plain language, the device has a built-in monitor that will immediately detect malfunction and reduce the current.

MR safety of TI-NDBS device

Our MR physicist, Dr. Hu Cheng, assesses that the stimulator will be safe for the MR scanner, provided:

1) the stimulator circuit remains in the control room, and
2) the wires do not form loops, but go straight down the bore of the scanner, and
3) there are inductive RF filters along each wire, to filter out RF noise

Furthermore, prior to human subjects tests, we will test the MR safety of the stimulator by hooking it up to a phantom load (e.g., a piece of meat), running the stimulator while the scanner is running an fMRI sequence, and checking the actual current delivered (via an oscilloscope) to verify that the signal does not suffer from interference or produce overcurrent due to magnetic and/or RF interference.

TI device

The TI device was custom-built by the machine shop in the department of Psychological and Brain Sciences based off of schematics that Joshua Brown (PI) and Suha Lasassmeh (Ph.D., electrical engineer) devised based on the work of Grossman et al. 2017 (for device images and circuitboard diagram see the Notes & Attachments). The TI device contains a mechanism that constantly monitors the amount of current administered via the electrodes. The current study design is single-blind such that the experimenter will become aware of the amount of current administered to ensure the safety of experimental subjects. A prototype of the device is shown in Figure 2. The device has the following characteristics:

- The device is powered by standard 9-volt batteries that provides the energy to carry out the neurostimulation. The device may also be powered by a standard 9-volt power supply.
- There are two electrode pairs, with a total of 4 electrodes,that will connect from the device in Figure 2 to gel electrodes on the subject's head (as shown in Figure 1), typically of varying shapes approximately 2 cm x 2 cm. At 2 mA current, this will result in a maximum current density of 0.0005 A/cm^2. At 50Kohm scalp impedance, the total power dissipated by an electrode pair is I^2R = 200 mW, which is comparable to the power emitted by a cell phone.
- Each electrode pair generates a sinewave alternating current, with no DC component. The frequency can be varied continuously from zero to over 5 Khz. We will not apply alternating current frequencies over 5Khz. Typically, the frequencies will be around 2 Khz.

- The frequency difference between the electrodes will be varied between 1-100 Hz.
- The current for each electrode pair can be controlled continuously from zero to 2 mA. Each of the two electrode pairs may have a different current level, which allows the focal point of stimulation in the brain to be steered without moving the electrodes.
- For safety, the device includes an onboard current monitor to measure the amount of current actually delivered. The device can be powered down if for any reason the amount of current exceeds the specified setting, or if the voltage required to deliver the current exceeds the device's capacity.
- The device settings are controlled by a separate microcontroller, typically a Raspberry Pi zero, which communicates with the device via serial protocols, namely SPI and I2C. The raspberry pi is a fully functional computer that can be programmed to run timed stimulation protocols and control the neurostimulator.
- The four electrodes will be placed on the subject's scalp (Figure 1) at locations designated in the international 10/20 system, as used for EEG. The locations will be optimized by finite element modeling to target specific brain regions such as the dorsal anterior cingulate cortex (dACC), insular cortex, and nucleus accumbens.
- Should stimulation be terminated early for any reason, the same stimulation assessments will be conducted as if the session lasted the full 40 minutes including the EMA, stimulation experience scale, heart rate, blood pressure, psychiatric symptoms, nicotine craving, etc. The reason for termination will be recorded and an unanticipated event filed with the IRB. If the subject experiences as adverse reaction to the stimulation, this will be recorded and reported to the IRB and DSMB.

4.0 Eligibility Criteria

List the criteria:
Inclusion:

- between the ages of 18 and 50, must have at least a 6th grade education, ability to speak and read English for all phases.

Exclusion:

- if they are on psychotropic medications for ADHD, other mental illness or medication for cancer, epilepsy (i.e. individuals with any history of seizure disorder), migraines, or other neurological syndromes, or AIDs (which can cause cognitive deficits (Watkins & Treisman, 2015), history of head trauma, history of cognitive impairments, metal implants in the head or under the scalp, personal experiences consistent with symptoms of psychosis (i.e. hearing or seeing things that aren't there, being secretly controlled, or having special powers, seeing or hearing things that aren't really there).
- For phase 2, subjects will be excluded if they do not meet fMRI safety screening criteria (i.e. metal implants in their body, tattoo on head or neck, permanent jewelry, etc.) or if a participants uses an IUD for birth control they will be excluded unless the subject can document the model of the IUD and we can verify its safety for the MRI environment. Pregnancy should be self-reported, and a pregnant test will not be administered. Participants must weigh less than 440 lbs etc.
- History of holes bored into skull or known fissures in cranial bones
- Presence of pacemakers

- In phases three and four, subjects will be excluded if they do not smoke at least ¾ pack of cigarettes per day on average and if subjects do not have access to a cell phone (or loaner cell

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phone) with internet access.

5.0 Outcome Characteristics and Endpoint Definitions:

For Phase 1, we will determine if any participants report adverse reactions or any side effects from the TI-NDBS stimulation, using the Stimulation Experience Scale questionnaire. Some potential side effects include itching, unusual sensations, abnormal or unpleasant thoughts, or physical sensations. We will follow-up with participants after the stimulation session to determine if there were any side effects from TI-NDBS. For phase 2, we will measure the change in neural activity for each target area of the brain to be stimulated for TI-NDBS vs. no stimulation to determine if the activity is different for TI-NDBS stimulation, again using the Stimulation Experience Scale. For phase 3, we will determine whether TI-NDBS vs. sham leads to a difference in nicotine craving via self-report measures and corresponding reduced nicotine vapor inhalation in the MRI scanner. For phase 4, we will determine a difference in nicotine craving via self-report measures and corresponding reduced nicotine vapor inhalation in the MRI scanner between TI-NDBS and tDCS. We will also examine differences in neural activity measured by fMRI between TI-NDBS and tDCS.

6.0 Statistical Analysis and Sample Size:

In phase 1, we will assess tolerability with an initial cohort of 3 stimulation subjects. Our aim here is to identify any potential adverse effects, using two approaches. We will monitor the stimulation condition for clinically significant adverse effects such as seizures, prohibitive pain, etc, though we do not expect this based on all the literature from earlier studies.

In phase 2, we will conduct a pilot assessment to determine whether and how the stimulation immediately influences neural activity. As this is a within-subjects pilot design intended to estimate the effect size of neural activation, we will scan 10 subjects, comparing the neural activation in each subject during the stimulation period with neural activation in the same subject during the no-stimulation periods. We do not have a power analysis for this phase yet, because the whole point is to perform a pilot study in order to estimate the effect sizes. We anticipate that 10 subjects will be sufficient to estimate the effect sizes.

In phase 3, we will proceed in two parts. During the first pilot part, we will recruit 5 subjects in each of 3 groups, to identify which two of the three candidate brain regions seem most promising sites of stimulation to reduce nicotine craving and consumption. Once we identify the two more promising sites of stimulation, we will proceed to the second part. We do not have a power analysis for this part because again, we are looking to estimate the relative effect sizes for one stimulation site compared to another. For the second part, we will recruit 45 subjects who are heavy smokers into three groups of 15 each, then ask them to abstain from smoking for several hours prior to the session. The first group will receive TI-NDBS over the most promising site. The second group will receive TI-NDBS over the second most promising site. The third group will receive sham stimulation. We will measure total real-time ad lib nicotine vapor inhalation during a 60 minute stimulation session, and every ten minutes, we will ask subjects to

self report their level of craving on a Likert scale of 0-10. We will identify whether TI-NDBS over the insula or nucleus accumbens is more effective than sham stimulation. We will then follow up with subjects 1 week afterward, using ecological momentary assessment (EMA) via smartphone apps (ilumivu.com) to assess cigarette use and craving. We expect to find that TI- NDBS reduces craving and cigarette consumption relative to sham. **Analysis and predictions:** We predict that TI-NDBS will outperform tDCS at reducing smoking and cigarette craving, which in turn will outperform sham stimulation. We will sum the total inhaled nicotine vapor over the 60 minute session and perform pairwise t-tests to determine if total drug intake is lower with one of the stimulation groups vs. sham. Also, we will average the self reported craving levels across each subject during the 60 minute session, and we will perform pairwise tests to determine if stimulation lowers self reported craving. During the 7 days following the stimulation session, we will give subjects the ilumivu app on their smartphones (or a loaner phone if needed), and we will notify them daily to request a self report of their level of craving and cigarette use in the preceding 24 hours. We will average these measures for each subject and perform an omnibus ANOVA (time point by group), followed by post-hoc pairwise tests to determine whether the stimulation led to longer lasting effects relative to sham. We will perform post-hoc tests for each of the 7 days to identify any differences in the duration of stimulation effects. For a power analysis, we do not yet know how many subjects will be necessary to achieve statistical power in the second part of phase 3, because we do not yet know what the effect sizes are. Nevertheless we anticipate that 15 subjects per group will provide a solid estimate of the effect sizes of stimulation relative to sham, so that we can write a grant to scale up the number of subjects based on a power analysis.

In phase 4, we will compare TI-NDBS vs. conventional transcranial direct current stimulation for smoking reduction. To test this, we will recruit another 45 subjects who are heavy smokers into three groups of 15 each, then ask them to abstain from smoking. The first group will receive standard transcranial direct current anodal stimulation of the right DLPFC and cathodal stimulation of the left DLPFC (F3 and F4 in the 10/20 system). The second group will receive TI-NDBS to the most promising site as determined in phase 3. The third condition will be sham. We will assess craving levels every 10 minutes during the 60 minute stimulation period. We will repeat this for five consecutive days. We will then follow up with subjects 1 week after starting the tDCS, using ecological momentary assessment (EMA) via smartphone apps (ilumivu.com) to monitor cigarette use and craving. We will compare the sham vs. tDCS vs. TI-NDBS groups to identify differences in craving and relapse. **Analysis and predictions:** We expect to find that TI-NDBS leads to reduced craving and drug use relative to sham or tDCS. We will carry out the same statistical tests as in Study 1. As before, we do not yet know the effect sizes but will aim to estimate them based on the initial 45 subjects.

7.0 Data Management

Data will be collected on secure computers and cloud services approved for handling confidential medical data. Ilumivu is an existing commercial EMA solution and is commonly used for collecting, storing, and transmitting sensitive health information. The exact form of the database has yet to be determined, but it will likely include CSV file intermediaries and will at all

times be stored and transmitted securely, using encryption such as TLS or SSH/SFTP protocols. We will use subject ID numbers to key the data. The data will mainly include self-reported craving scores. It will be stored and processed on PI Brown's internal lab server cluster, which gives secure nightly incremental backups to a separate location. We will use standard software tools for analysis, including PI Brown's existing fMRI processing software for the neuroimaging and nicotine vapor inhalation studies. The final archival data will be preserved in the IU Scholarly Data Archive.

The PI will monitor the quality of data, the number of subjects recruited, any adverse events, and any new information that comes to light that may impact the assessment of risk to the subjects. The PI will monitor the research as it is carried out, on a day-to-day basis. Formal monitoring evaluation will take place annually prior to continuing review or close-out. There are no statistical criteria that would lead to a premature end to the study, because a minimum sample size is necessary given the unknown statistical power. The study may be ended early if adverse events were to occur. The frequency and dates of monitoring will be reported, along with any adverse events and any new information that may impact the safety of participants or risk benefit ratio, along with any issues related to subject privacy and confidentiality.

8.0 Principal Investigator and Study Site Qualifications and Resources

The proposed protocol is for an IU grand challenge grant that was awarded to the PIs and funded over 10 months ago (October 2018). We have been requesting IRB and DSMB approval to begin work on the funded project since that time, first as a series of amendments to our existing protocol (1108006427) that uses the nicotine inhalation device as in phases 3 and 4, and at the IRB's request, we submitted this as a separate protocol.

The PIs (Brown, Finn, and Hulvershorn) have successfully collaborated on previous projects (Hulvershorn et al., 2015). Finn and Brown have collaborated successfully on a number of projects, with six resulting publications to date. The most recent collaboration included Centerstone Research Institute in Bloomington and showed that brief fMRI scans of those entering treatment for substance dependence could predict with high accuracy who would fail treatment over the next three months, and how often they would use drugs during that time (Forster et al., 2017).

Joshua Brown has extensive experience with studies of addiction, especially with fMRI, and has been funded by NIDA regularly since 2007. He has published a number of papers on computational neural models and fMRI of addiction, including various populations of polydrug users and heavy smokers. Current research in his lab focuses on understanding real-time neural mechanisms of drug use decisions, in which heavy smokers gamble for drugs and are allowed to inhale from an e-cigarette briefly when they win a gamble -- all while in the fMRI scanner. He also has a degree in engineering with the expertise necessary to develop and implement novel neurostimulation technology. For the current work, he has been in communication with the developers of the novel neurostimulation technology, who have tested their methods in humans with fMRI.

Peter Finn has over 35 years of experience in addiction research, with regular funding from NIDA and NIAAA. Dr. Finn's research focuses on behavioral and psychosocial processes in addiction and substance use disorders more broadly, including studies of cognitive and

decision-making processes, personality and motivational processes, and self-regulatory and self-control processes in addiction. Dr. Finn has been collaborating with Drs Brown and Hulvershorn on a range of studies of the neurobiological processes in addiction and the vulnerability to addiction for over 10 years. Dr Finn provides extensive experience and expertise in the recruitment, diagnostic ascertainment, and psychological and cognitive assessment of research participants and will oversee these functions. In addition, in collaboration with Drs Brown and Hulvershorn, Dr Finn will help coordinate the data management and analytics in these areas.

Leslie Hulvershorn is a board-certified, clinical addiction psychiatrist and has been funded by NIDA for addiction risk neuroimaging studies for > 10 years. Dr. Hulvershorn has extensive experience with clinical human subjects and clinical trials. She will oversee Aim 3 which will involve recruitment, assessment and provision of the intervention to adults with addictions. As a credentialed faculty member at IU Health and Eskenazi, Dr. Hulvershorn has access to recruit patients presenting in acute opiate withdrawal and these will be recruited in Aim 3 to test our new neurostimulation technology. She is also Indiana's Medical Director for the Division of Mental Health and Addiction, thus is familiar with all of the local facilities from which patients with addictions will present.

There will also be a DSMB from Dr. Hulvershorn's department to review the data collection and the subject safety. The DSMB will monitor the study biannually and will consist of two medical doctors/engineers and one physician that works with TMS, a similar form of brain stimulation. In the case of an event, with regard to participant safety, occurs before 3 months after any DSMB meeting, the PI will alert the DSMB and have that event reviewed within 3 months/quarterly. There is also a post-baccalaureate research technician on the research team that is familiar with TI-NDBS.

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