Study Protocol

Official Title:

Theta Burst Stimulation to Reward Circuitry in Young Adults with Depression

ClinicalTrials.gov ID (NCT number):

NCT03737032

Protocol Date:

3/31/2023

Scientific Background

Our work has consistently found that depression and related mood states are associated with high dmPFC response to reward and altered functional connectivity between dmPFC and ventral striatum (e.g., Healey et al., 2014; Morgan et al., 2016; Romens et al., 2015). The emerging literature on dmPFC as a target for repetitive TMS treatment for depression also focuses on this region (Dunlop et al., 2015), and intrinsic dmPFC connectivity has recently been identified as a biomarker for an anhedonic subtype of depression (Drysdale et al., 2017).

Innovative rodent research involving a combination of optogenetics and neuroimaging has indicated that mPFC plays a causal role in anhedonia, a feature of depression involving disrupted motivation toward and enjoyment of pleasant experiences (Ferenczi et al., 2016). Anhedonia includes neural, behavioral, and subjective components, and it is evident in reward-driven mood (e.g., low positive affect, low enjoyment of rewards) and behavior (e.g., low motivation, low effort to obtain rewards). Thus, the clinical and basic neuroscience literatures support our guiding hypothesis that reducing dmPFC response via TMS will increase VS

response, reduce strength of dmPFC-VS functional connecitivity, and increase reward-driven mood and behavior in adults with depression.
Clinically and developmentally, early adulthood represents an optimal time for investigating the disruption of dmPFC and related circuitry in depression, as it is early in the clinical course of depression, close to a mature state of brain system organization, and a foundational period for the skills critical to healthy adult functioning (Arnett, 2000). TBS, a next-generation form of noninvasive brain stimulation, requires shorter duration of stimulation and provides perhaps stronger clinical efficacy than traditional repetitive TMS for depression (Chung et al., 2015). It is thus an appropriate technique for the study.

Study Objectives

This study will use theta burst stimulation (TBS), a form of neuromodulation based on transcranial magnetic stimulation, to investigate frontostriatal brain function in young adults with depression.
The goal of the study is to understand the pathophysiology of depression by taking an experimental approach to testing the role of dorsomedial prefrontal cortex and related reward circuitry in mood, behavior, and brain function.
Aim 1. Investigate the feasibility of stimulation to decrease activity of the dorsomedial prefrontal cortex (dmPFC) using TBS. We will use an fMRI-TBS-fMRI design with counterbalanced sessions of continuous (inhibitory) TBS, intermittent
(excitatory) TBS, and sham TBS.
Aim 2. Examine whether TMS targeting dmPFC will increase response in the VS and decrease functional connectivity between dmPFC and VS. We predict that circuit-level changes will occur with acute TBS to influence task-related VS response and dmPFC-VS functional connectivity, such that VS response will increase and mPFC-VS will decrease with continuous but not intermittent TBS.
Aim 3. Examine (a) whether TMS targeting dmPFC will influence reward-related mood (i.e., anhedonia, positive affect) and behavior and (b) whether TMS influence on mood and behavior occurs through changes in dmPFC, VS, or their functional connectivity. We will test acute changes with TBS, with the hypothesis that anhedonia will decrease and positive affect and reward-motivated behavior will increase after continuous but not intermittent TBS. If associations are found, we will test the mediating effects of changes in frontostriatal function detected by analyses in Aims 1 and 2. We will include covariates as appropriate (e.g., COVID

experiences, stressful life events, age, gender) to address potential confounds or influences on the associations of interest.

Depression is a chronic, impairing form of psychopathology that is one of the world's leading causes of disability. An extensive literature on the neural mechanisms of depression has documented the disruption of function in reward circuitry as part of the pathophysiology of depression. Specifically, frontostriatal function is altered, with lower ventral striatal (VS) response, greater medial prefrontal cortex (mPFC) response, and stronger functional connectivity between the two regions. Yet few neuromodulatory approaches to depression have targeted this circuitry. Noninvasive neuromodulatory techniques such as transcranial magnetic stimulation (TMS) have been applied to depression and can elucidate the pathophysiology of this disorder by focusing on function in frontostriatal circuitry. This research fills the gap of understanding the brain networks underlying depression. It will investigate how frontostriatal function (especially functional associations between the dorsal mPFC and the VS) contribute to key symptoms of depression that involve altered positive emotions. The study will take an experimental approach to investigate how directly trying to modulate function in this brain circuit can influence mood, brain function, and behavior. Ultimately, this work can have relevance to developing or adapting treatments to improve response in people with depression.

Study Design & Methods

This experimental study examines response to theta burst stimulation (TBS) of the dorsomedial prefrontal cortex in a within-subjects crossover design with three conditions: intermittent TBS (excitatory to underlying cortex), continuous TBS (inhibitory to underlying cortex), and sham TBS (no cortical stimulation, with inactive placement of electrodes). All participants will complete all three TBS conditions, but in counterbalanced order and with randomization to order based on gender and baseline brain function.

The main variables are mood (especially anhedonia and positive affect), reward-related behavior, and brain function in frontostriatal reward circuitry. Brain function will include both BOLD response in specified brain regions (dmPFC, ventral striatum) and functional connectivity between those regions.

Study duration is a minimum of 4 weeks but may be longer due to scheduling constraints (will allow up to 10 weeks total, or more at the discretion of the PI).

Screening:

At the first lab visit, participants will go through the Core Modules of the Structured Clinical Interview for DSM-5, Research Version (SCID) with Research Associate staff. Between the subject's first visit and their second visit, the RA staff who completed the SCID interview will review the results of the interview with the Principal Investigator or one of the other clinical expert Co-Investigators (Dr. Ryan, Dr. Jones) to obtain their confirmation of subject eligibility prior to any TBS procedures.

Female participants will undergo a urine pregnancy test at the MRRC or SBNC, prior to MRI scans, to confirm the absence of pregnancy at each visit involving an MRI

(visits 2-5). All participants will be asked to undergo a urine drug screen at the SBNC on the day of their baseline MRI visit (visit 2), prior to any MRI or TBS procedures. At subsequent visits (3-5) the participant will be asked to self-report about recent drug use using a standard questionnaire.

Participants will complete a TMS Adult Safety Screening (TASS) questionnaire prior to any TBS procedures. The following responses on the TASS are considered unacceptable and would lead to exclusion from the study: a response of "Yes" to items 2 (seizure), 6 (metal in the head), or 7 (implanted devices), and/or "Yes" to item 11 (medications) and the medications being taken are exclusionary based on the study. In addition if the response to any other items is "Yes" and the corresponding characteristic or experience is determined by the MD, after review of the written details and/or discussion with the participant, to be a contraindication to TBS they may also be excluded from the study.

Study Procedures:

Participants will talk to a member of the research team on the phone for screening of eligibility, visit the lab for further evaluation of eligibility criteria and lab procedures, have MRI scans, and have 3 sessions of theta burst stimulation (TBS). Eligibility criteria will be assessed during Visits 1 and 2, with a complete determination of eligibility being completed during the first half of Visit 2, prior to having their motor threshold measured and prior to participating in an MRI scan. Visit 1 will include written informed consent, during which an MD/DO, a PhD-level licensed clinical psychologist, or a Master's-level licensed professional counselor explains exactly what the study involves, including risks and benefits of participation. During this visit, participants will also be asked about demographic characteristics (e.g., age and education) and clinical characteristics (e.g., depression symptoms). Sections of the research version of the Structured Clinical Interview for DSM-5

(SCID) will be completed with participants during this visit to further confirm diagnostic eligibility criteria that were asked about first during the phone screening call. With participant approval, these interviews may be audio- or videotaped and

reviewed by the research team to ensure consistency and reliability, and to provide training. If deemed eligible by the research team, participants will then complete a set of questionnaires.
Visit 2 will include a physical exam, motor threshold procedure, MRI scan, computer task, and questionnaires. The physical exam will include an MD assessing the participant's height, weight, Body Mass Index (BMI), blood pressure, pulse, respiration, and temperature. During the physical exam, the MD will also review the results of a urine drug screening test and a urine pregnancy test (for females). In addition, the MD will administer the TMS Adult Safety Screening form (TASS) and review participant's medical history by reviewing the "Medical History Form" and
"Medical Update Form" filled out by the participant at Visit 1 and Visit 2, respectively. The MD will initial on each of the medical history forms to confirm their review. After the physical exam, the information collected will be used to make a determination of subject eligibility. If the subject is deemed eligible, an MD will measure the participant's motor threshold, or the minimum amount of TBS power needed to make their thumb twitch. To do this, the MD will position the coil above the participant's motor cortex and deliver a single pulse of stimulation at a time. The MD will start at 55% (a low level of stimulation and standard in the field for finding motor threshold) and adjust the intensity in small increments (i.e., beginning with 1-2% at a time and not exceeding a 5% increase at each increment) until a motor response is elicited in the participant's hand. This is a process that is used as a basis for the TBS setting for each person, as it will be 80% of their motor threshold. Next, the participant will complete the first MRI scan in the study, which lasts approximately 30 minutes and will measure brain structure and function, used to identify the best location to place the TBS device. The MRI scan at Visit 2 will also include a number-guessing task that lasts 8 minutes and involves winning money. Participants will complete another computer task (outside of the MRI), and questionnaires about their mood.
Visits 3, 4, and 5 will each involve (1) questionnaires on recent medical history, depression, and recent life events, (2) an MRI scan before the TBS session, (3) a discomfort rating before the TBS session, (4) a TBS session, (5) a discomfort rating after the TBS session, (6) an MRI scan after the TBS session, (7) a computer task and (8) questionnaires about their mood.
An RA will review the "Medical Update Form" filled out by the participant before the TBS session and report any changes to an MD. An MD will review the "Medical Update Form" within 24 hours of each visit (3-5) to initial the document and provide comments on the clinical significance of any reported changes. At each TBS session, participants will have a magnetic coil placed on their scalp by carefully rained investigators, near the top of their forehead. The coil will send

pulses that can influence brain function in the region under that scalp location. There will be 3 sessions so that we can use 3 kinds of TBS: continuous (constant series of pulses) TBS, which tends to decrease brain function; intermittent (off and on) TBS, which tends to increase brain function; and sham TBS, which sounds and feels like TBS but doesn't send pulses or change brain function. TBS sessions will last from 40 seconds to 190 seconds, and the TBS influences brain function for up to 1 hour. The order in which participants receive these 3 kinds of TBS will be randomized and counterbalanced.

To accommodate participant schedules, activities listed under each visit may take place on separate days as possible and necessary. During the COVID-19 outbreak, written informed consent for all study activities as well as diagnostic interviews for eligibility, and participant completion of tasks and questionnaires may take place remotely. An approved video conference platform will be used to conduct and record diagnostic interviews to determine eligibility remotely. The study consent form would be emailed or mailed to the participant in advance, reviewed thoroughly during a phone or video call with an MD/PhD/DO, signed by the participant, and returned. Study activities would not begin until the signed consent form is received.

Measures and Devices:

The TBS sessions (Visits 3-5) will use the Cool-B65 Active/Placebo Coil and MagLink research software. The MRI scans (Visits 2-5) will be done on a Siemens 3T Prisma scanner. MRI scans will include brain structure, resting brain function, and task-based brain function at the first scan (visit 2); resting brain function before each TBS procedure (Visits 3-5); and resting brain function and brain function in response to a guessing task after each TBS session (Visits 3-5). The guessing fMRI task is a number-guessing task that lasts 8 minutes and involves winning money. The computer task completed at Visit 2 and after each TBS session involves pressing buttons to earn money. Self-report measures will be completed at each visit. The following questionnaires will be completed at Visit 1: the Alcohol and Drug Consumption Questionnaire (Cahalan, et al., 1969); the Center for Epidemiologic Studies Depression Scale (Radloff, 1977); the Young Mania Rating Scale (Young et al., 2000); the Barratt Impulsiveness Scale (Patton, et al., 1995); the Zuckerman Sensation-Seeking Scale (Zuckerman, 1971); the Youth Risk Behavior Survey
(CDC, 2015); the Revised Chapman Social Anhedonia Scale (Eckblad et al., 1982); the Snaith Hamilton Pleasure Scale (Snaith et al., 1985); the Temporal Experience of Pleasure Scale (Gard et al., 2006); the Behavioral Inhibition System/Behavioral Activation System Scales (Carver & White, 1994); the Altman Self-Rating Mania Scale (Altman et al., 1997); the Pittsburgh Sleep Quality Index

(Buysse et al., 1989), and the Generalized Pain Questionnaire (Van Bemmel et al., 2019).
Visits 2-5 will include the following questionnaires: the Positive and Negative Affect Schedule (Watson et al., 1988), the Altman Self-Rating Mania Scale, a brief questionnaire on recent medical history, the Center for Epidemiologic Studies Depression Scale (Radloff, 1977), and an adapted version of the Life Events Scale for Students (Nikolova et al., 2012). Visit 2 will also include the TMS Adult Safety Screening (Keel et al., 2001). Visits 3-5 will additionally include a 0-10 discomfort rating.
Safety and Comfort:
We will conduct TBS according to the safety guidelines in our field. IFCN guidelines will be followed for training of the research team. Each person in the study will experience a much lower dose of TBS than the type of stimulation used to treat depression. During TBS participants will hear a series of clicking sounds and feel a tapping sensation under the location of the coil. Participants might experience a headache in the region of the coil or feel lightheaded during TBS. These usually end 30 seconds after TBS and feel like mild discomfort. Participants could also experience mood changes. Participants will stay in the lab for an hour after the TBS session, so we can make sure that they don't experience any lingering discomfort or mood changes.

Eligibility Criteria

Inclusion criteria are as follows:

- Age 18-25
- DSM-5 diagnosis of Major Depressive Disorder, Persistent Depressive Disorder, Other Specified Depressive Disorder, or Other Unspecified Depressive Disorder
- Eligibility confirmed by a physician associated with the study who will conduct a physical exam, review medical history, and conduct the TMS Adult Safety Screening (TASS) prior to TMS

Exclusionary criteria include:

- Bipolar disorder (lifetime diagnosis)
- Obsessive-compulsive disorder (lifetime diagnosis)
- History of psychosis
- Daily use of nicotine

- Past- month use of cocaine, amphetamines, MDMA, Phencyclidine (PCP), Ketamine, or gamma-hydroxybutyrate (GHB)
- Past 6 month substance use disorder
- Binge drinking (using NIAAA criteria) within the past week, more than 3 drinks/day in the past 3 days, alcohol use in the past 12 hours
- More than 3 uses of cannabis in the past month
- Neurological disorders: Epilepsy, Parkinson's Disease, brain tumor, brain injury, stroke
- History of head trauma with a loss of consciousness (eg. concussion)
- History of seizures
- MRI contraindications: body shape/size too large to fit in scanner, claustrophobia, and ferromagnetic forms of metal in the body
- Pregnancy
- Current use of Clozapine or Bupropion or prescription stimulants

Statistical Considerations

Our final sample size of N=36 (i.e., those who qualify and undergo all research procedures) gives adequate (80%) power to detect moderate-large effects (d>.5) of cTBS vs. iTBS and change in frontostriatal function. Meta-analytic review of iTBS and cTBS on motor cortex suggest large effect sizes (ES=1.5-2.2 for active vs. sham; Wischnewski & Schutter, 2015). In mPFC during a cognitive task, iTBS vs. cTBS produces a large effect size (ES=1.0; Grossheinrich et al., 2009). Recommendations for neuroimaging studies and effect sizes from our previous studies (eg., Cohen's d=.71 for depression association with striatal response) support this sample size, even with a loss of 15% of data due to movement.