Causal Lesion Network Guided Treatment of Bipolar Mania With Transcranial Electrical Stimulation

NCT #: NCT05445466

June 23, 2025

Protocol Number:	2022P000295
Title:	Causal Lesion Network Guided Treatment of Bipolar Mania With Transcranial Electrical Stimulation
Design:	Double blind, design with baseline, day 5, 1 month and 3 month follow up visits during which transcranial electrical stimulation (tES) was delivered to the right orbital frontal cortex (rOFC) from baseline to day 5 each day (5 days) twice a day for 20 mins. Participants were randomly assigned to either cathodal transcanial direct current (tDCS), 10hz or personalized transcranial alternating current (tACS) conditions to test the effectiveness and feasibility of stimulating the rOFC using a novel targeting methodology consisting of a lesion network guided brain target linked to mania symptoms.
Objectives:	Evaluate the effectiveness and safety of transcranial electrical stimulation for improving the mania symptoms
Enrollment:	14 Individuals
Clinical Sites:	Beth Israel Deaconess Medical Center, Boston, MA
Patient Population:	Male or female outpatients 18-65 years of age patient's diagnosis with either bipolar or schizoaffective disorder, or history of mania as defined by DSM-5 or DSM-IV-TR criteria
Primary and Secondary Outcomes:	Primary Outcomes: Young Mania Rating Scale (YMRS); Altman Self-Rated Mania Scale (ASRM); Average Hospitalizations Secondary Outcomes: Balloon Analogue Risk Task (BART); The Go/No Go Task; Reinforcement Learning Task (RLT); Social Functioning Scale (SFS); Positive and Negative Syndrome Scale (PANSS); Global Assessment of Functioning (GAF); Barret Impulsiveness Scale (BIS); Resting State EEG; Brief Assessment of Cognition (BAC); Montgomery-Asberg Depression Rating Scale (MADRS)
Inclusion Criteria:	1. Aged 18-65 years of age 2. Proficient in English 3. Able to give informed consent 4. Meet diagnostic criteria for bipolar disorder or schizoaffective disorder, bipolar type as verified by the SCID 5. History of mania (>1 lifetime episode) 6. Experiencing mild to moderate symptoms of mania 7. No changes to mood stabilizing medications for a period of 2 weeks prior to participation 8. Has not recently participated in tES/TMS treatments

	In addition to the criteria above, participants for this stimulation procedure will be included if they have a history of mania and may or may not be experiencing symptoms currently.
Exclusion Criteria:	1. Substance abuse or dependence (w/in past 6 months) 2. Those who are pregnant/breastfeeding 3. History of head injury with > 15 minutes of loss of consciousness/mal sequelae 4. DSM-V intellectual disability 5. Having a non-removable ferromagnetic metal within the body (particularly in the head) 6. History of seizures
Statistical Methodology:	Within and between comparisons to statistically detect differences in symptoms, tasks and electrophysiology measures before and after treatment conditions (cathodal tDCS, 10hz and personalized tACS). To determine the effectiveness and feasibility of targeting the rOFC with a novel targeting methodology to engage target outcomes.

Statement: The design, conduct and reporting of this trial shall be conducted in accordance with the protocol, the United States 45 Code of Federal Regulations (CFR) part 46 known as "The Common Rule", 45 CFR 164.502(d), and 164.514(a)-(c) known as "The Privacy Rule" of the Health Insurance Portability and Accountability Act (HIPAA), and the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP). All Investigators will have documented training in The Collaborative Institutional Training Initiative (CITI Program) in Biomedical Research and GCP.

Background: Mania is a core symptom of bipolar disorder involving periods of euphoria. Decreased inhibitory control, increased risk-taking behaviors, and aberrant reward processing are some of the more recognized symptoms of bipolar disorder and are included in the diagnostic criteria for mania. Current drug therapies for mania are frequently intolerable, ineffective, and carry significant risk for side effects. Presently there are no neurobiologically informed therapies that treat or prevent mania. However, using a newly validated technique termed lesion network mapping, researchers demonstrated that focal brain lesions having a causal role in the development of mania in people without a psychiatric history can occur in different brain locations, such as the right orbitofrontal cortex (OFC), right dorsolateral prefrontal cortex (DLPFC), and right inferior temporal gyrus (ITG). This lesion network evidence converges with existing cross-sectional and longitudinal observations in bipolar mania that have identified specific disruptions in network communication between the amygdala and ventro-lateral prefrontal cortex. The OFC is associated with inhibitory control, risk-taking behavior, and reward learning which are major components of bipolar mania. Thus, the association between

OFC with mania symptoms, inhibitory control, risk-taking behavior, and reward processing suggests that this region could be targeted using non-invasive brain stimulation.

Transcranial Electrical Stimulation (tES): tES is a non-invasive brain stimulation technique which modulates cortical excitability by a weak electrical current [< 4 milliamps (mA)] between two electrodes via direct current (DC), alternating current (AC), random noise (RN) or oscillatory current (OC). This study will utilize cathodal tDCS, 10hz and personalized tACS. Five days of twice a day (2x20min) of tES will be used during the week.

Electroencephalography (tES): EEG is a routine, non-invasive procedure to record brain activity. EEG electrodes will be attached to the skin indirectly. Most of the electrodes are mounted in an elastic cap, which is fitted over the head and held in place with elastic straps. Some additional electrodes are placed next to the eyes, on the forehead, or behind the ears, and are held in place with adhesive collars. Electrical contact between the skin and the electrodes is achieved via a water-soluble electrode gel.

Study Rationale: Mania is a core symptom of bipolar disorder involving periods of euphoria, delusions, and overactivity. Mania occurs in multiple medical and psychiatric illnesses and can be refractory to existing treatments. Two recent studies using brain lesion mapping of psychiatrically healthy individuals presenting with mania identified causal locations in the brain, including the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), and inferior temporal gyrus (ITG), that were associated with new onset mania symptoms. Moreover, these identified brain regions have also been implicated in bipolar mania with specific disruption in network communication between the amygdala and ventro-lateral prefrontal cortex. The OFC is of particular interest because it is a brain structure that is associated with inhibitory control, risk-taking behavior, and reward, which are major behavioral components of mania. Thus, the association between OFC with mania symptoms, inhibitory control, risk-taking behavior and reward suggests that this region could be targeted using noninvasive brain stimulation. While several studies have non-invasively targeted the DLPFC for mania, no study to date has non-invasively stimulated the OFC with either transcranial direct current stimulation (tDCS) or alternating current (tACS) in bipolar disorder and examined its effects on mania, inhibitory control, or risk-taking behavior. However, a study in healthy volunteers showed that cathodal stimulation to the OFC enhanced inhibitory control and decreased risk-taking behavior. Recently, research have showed that targeting the OFC with tACS, personalized to the individual's intrinsic beta-gamma frequency of the reward network, that individuals showed rapid, reversible, frequency-specific modulation of reward-guided choice behavior and learning. Here we aim to answer the question of whether noninvasive brain stimulation when optimally targeted and personalized to an individual's beta-gamma frequency to the OFC can improve emotional cognitive processing and mania symptoms compared to tDCS or sham targeting. The knowledge gained from this study will provide a marker for clinical response and allow personalized treatment for patients with bipolar disorder.

Study Protocol:

Study Timeline

Study Visit Timeline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 (1-month follow up)	Visit 7 (3-month follow up
Consent	X						
Clinical Evaluation	X				X	X	X
Tasks/Cognition Testing	X				X	X	X
EEG	X				X	X	X
tES	X	X	X	X	X		
Sensation Questionnaire	X	X	X	X	X		
Self-Reports	X				X	X	X

Study Visits and Details:

Participants will complete baseline clinical, neuropsychological, behavioral tasks and neurophysiological assessments (day 0), short-term follow-up (day 5) and long-term follow-up (1 & 3 month).

Pre-Screening
Subjects will be prescreened. If the subject appears to qualify for the study, they will be invited in for a screening and a baseline visit.

Screening and Baseline Procedures (approximately 3-4 hours)
Screening and baseline procedures will be conducted in the Massachusetts Mental Health Center (MMHC)/ Beth Israel Deaconess Medical Center (BIDMC) in Boston, MA. The urine toxicology screen and pregnancy test will be completed at MMHC or within BIDMC.

- Eligibility pre-screen will include a telephone pre-screening questionnaire that will assess basic inclusion and exclusion criteria.
- Eligibility screening will include a screening questionnaire that will assess more details related to inclusion and exclusion criteria and will be conducted in-person during the clinical diagnostic session (i.e., the first visit to the laboratory).
- Informed consent will be obtained
- Urine toxicology screen
- Urine pregnancy testing for females of childbearing age
  Subjects will be informed that if they do not pass the urine toxicology screen (other than prescribed medication), they will be withdrawn from the study and will not receive compensation for the initial visit. This will be made clear in the pre-screening questionnaire.
- tES screening questions for tES participation
- Demographics: Subjects will be asked to provide standard demographic information (age, sex, race/ethnicity, level of education, cohabitation status) using forms employed in previous studies.
- Psychiatric, medical, substance use history and medication review
- Signing a release to allow for access to recent psychiatric records, if confirmation of medications or psychiatric history is necessary

OBJECTIVES
Primary Objective
The primary objective of this study is to evaluate the effectiveness of tES for improving the mania symptoms (YMRS, ASRM and hospitalizations).

Secondary Objectives

The secondary objective of the study is to evaluate the safety and tolerability of tES targeting the rOFC as well as secondary clinical outcomes including depression, mania, cognition, impulsiveness, electrophysiology outcomes, social functioning and global functioning

Clinical and Cognitive Outcomes: Symptom ratings will be collected using the PANSS, ASRM, YMRS, MADRS, SFS, GAF, BIS and cognition with the BAC

Electrophysiology Outcomes: A reinforcement learning task will be implemented probing the reward feedback mechanisms related to the rOFC. A resting state task will be implemented to measure brain dynamics at rest.

Computerized behavioral tasks: The BART and Go/No Go task with be used to determine the effective targeting of the rOFC and impulsiveness behaviors.

Diagnostic Assessments

Structured Clinical Interview for DSM-IV (SCID)

This is a structured clinical diagnostic screening interview for subjects 15 and older. It is used to diagnose Axis I disorders including modules on depression, mania, psychosis, alcohol and substance use, anxiety, somatic and eating disorders.

Clinical Assessments

Positive and Negative Symptom Scale (PANSS)

The ratings are based on a clinical interview conducted by trained clinical staff, covering all of the items on the rating scale.

- This rating scale is meant to capture many different types of symptoms including positive, negative, and general psychopathology symptoms. The ratings are based on a clinical interview with the participants.
- Ratings should be based on the patient's condition in the past week.
- Always use the manual with anchor points when scoring and do not try to score from your memory of the anchor points or by their headings (mild, moderate or severe).

Altman Self-Rated Mania Scale (ASRM):

The Altman Self-Rating Mania Scale (ASRM) is a brief, self-report questionnaire used to assess the presence and severity of manic symptoms. It is a five-item scale where individuals rate their experiences over the past week, with higher scores indicating greater symptom severity. Self-administered in survey form.

Barret Impulsiveness Scale (BIS):

A brief, self-report questionnaire used to assess the presence and severity of manic symptoms. The scale contains 30 items that measure three main domains: attention impulsivity, motor impulsivity, and non-planning impulsivity.

Montgomery and Asberg Depression Rating Scale (MADRS)

Interviewer:

The questions in bold for each item ***should be asked exactly as written***. Often these questions will elicit enough information about the severity and frequency of a symptom for you to rate the item with confidence. Follow-up questions are provided; however, for use when further exploration or additional clarification of symptoms is necessary. The specified questions should be asked until you have enough information to rate the item confidently. In some cases, you may also have to add your own follow-up questions to obtain the necessary information.

Ratings should be based on the **patient's condition in the past week.*

Referent of "usual" or "normal" conditions. Several of the interview questions refer to the patient's usual or normal functioning. In some cases, such as when the patient has Dysthymia or Seasonal Affective Disorder, the referent should be to the last time they felt OK (i.e., not depressed or high) for at least a few weeks.

****Rate the highest level of psychopathology. When in doubt, rate up and record the higher score.***

Global Assessment Functioning (GAF)

Consider psychological, social, and occupational functioning on a hypothetical continuum of mental health-illness. Do not include impairment in functioning due to physical (or environmental) limitations.

Indicate appropriate code for the **LOWEST level of functioning during the week of POOREST functioning in the past month.** (Use intermediate level when appropriate, i.e., 45, 68, 72).

Young Mania Rating Scale (YMRS)

General Instructions to the Clinician:

The purpose of each item is to rate the severity of that abnormality in the patient. When several keys are given for a particular grade of severity, the presence of only one is required to qualify for that rating.

The keys provided are guides. One can ignore the keys if that is necessary to indicate severity, although this should be an exception rather than a rule.

Scoring between the points given (whole or half points) is possible and encouraged after experience with the scale is acquired; this is particularly useful when severity of a particular item in a patient does not follow the progression indicated by the keys.

Social Function Scale (SFS):

Used to measure the degree of functioning across several domains. Social engagement/withdrawal (amount of time to spend alone, the likelihood to initiate conversation) Interpersonal behavior (number of friends, engagement in a romantic relationship) Prosocial activities (participation in social activities e.g. visit friends, play sports). Additionally, it provides competency scores for items.

Brief Assessment of Cognition in Schizophrenia (BACS)

Instructions (Atkins et al. 2017):

Verbal Memory (Verbal Memory & Learning Domain): *7 min*

Subjects hear a list of 15 words to remember. Words are presented by the App at a standard rate.

- Outcome measure: Total number of words recalled across 5 learning trials.

Digit Sequencing (Working Memory Domain): *5 min*

Subjects are presented with randomly ordered auditory clusters of numbers (i.e., 936) with steadily increasing trial length. Items are presented by the App at a standard rate. Subjects are asked to report the numbers in order, from lowest to highest.

- Outcome measure: Number of trials with all items in the correct order.

Token Motor Task (Motor Function): *3 min*

Subjects are presented with a virtual bowl and a supply of virtual tokens and asked to swipe a token from each side of the tablet with the index finger from each hand simultaneously and release them into the center container as rapidly as possible for 60 s.

- Outcome measure: Number of tokens correctly dragged into the container.

Semantic Fluency & Letter Fluency Tasks (Verbal Fluency Domain): *5 min*

During Semantic Fluency, subjects are given 60 s to generate as many words as possible within the category: *Animals*. Subjects are asked to generate as many words as possible beginning with a given letter. Subjects are administered two trials using letters F and S.

- Outcome measures: Total words generated for each fluency task in addition to total scores from both tasks combined to produce the Verbal Fluency domain score.

Symbol Coding (Speed of Processing): *3 min*

Subjects assign numbers to non-meaningful symbols with the use of a key that is provided. Numbers are entered on the digital keypad and appear in the location below the corresponding symbol. Following instructions and practice, subjects are given 90 s to complete as many items as possible.

- Outcome measure: Number items completed correctly within the 90 second test period.

Tower of London (Executive Functions/Reasoning and Problem Solving): *7 min*
Subjects are shown 2 images presented on opposite sides of the tablet screen. Each image shows a different configuration of 3 colored balls arranged on 3 pegs. The subject is required to accurately determine total number of times the balls in one picture would have to be moved in order to make the arrangement of balls identical to that of the other, opposing picture, while employing the standard rules employed in tower tests (balls are moved one at a time and balls on top of other balls must be moved first).

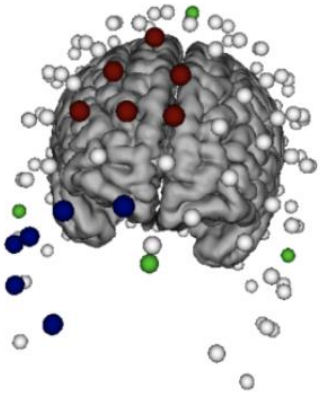
- Outcome measure: Number of correct responses.

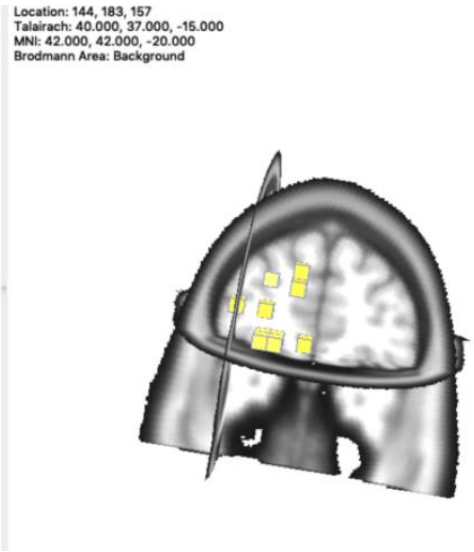
Self-Report tES Sensation Questionnaire

Given a participant after each tES session (2x20min), the questionnaire measures severity of sensations felt during the stimulation. Rated on a scale from 0 (none) to 4 (severe). In addition, the questionnaire has an open-ended question to allow participants to express any additional sensations felt during stimulation.

tDCS Montage:

Ensure to mark electrodes for stimulation and that correct settings are adjusted on tES device. A 30 second ramp should be set. All impedances should be checked before stimulation is delivered. Experimenters should remain blinded.





EEG Tasks Directions:

Resting State

For the next 5 minutes you will be asked to sit still and keep your eyes on a small white fixation cross at the center of the screen. Try to keep your eyes centered on that and try not to move excessively.

Reinforcement Leaning Task

The game is divided into 4 sessions, each comprising 90 trials and lasting 10 minutes. The first session will be used as a practice session before scanning. The three other sessions will be performed when we record the EEG.
The word 'ready' will be displayed 10 seconds before the game starts.

In each trial you have to choose between the two symbols displayed on the screen, above and below the central cross. Your choice will be circled in red after a 4 second delay.
As an outcome of your choice, you may
- get nothing
- gain +10
- lose -10
The two symbols displayed on a same screen are not equivalent in terms of outcome: with one you are more likely to get nothing than the other. Each symbol has its own meaning, regardless of where and when it is displayed.
The aim of the game is to win as much money as possible.

BART and Go/No Go:

These assessments will be conducted for all participants: These tests are run via **ePRIME.**

Set-Up:

BART

1. Connect eRPIME computer
2. Move the head and chin rest to be ***75 cm from the monitor*** *(marked with tape on the floor)*
3. Attach keyboard to computer and place on desk
4. Use alcohol wipe to clean:
    a. Forehead and chin rest
    b. Keyboard
5. Open up **"BART_2"** instructions
    a. You will use this to describe the tasks to the participant
6. Open up **"BART_2"**
    a. Load in program

Go/No Go

7. Connect eRPIME computer
8. Move the head and chin rest to be ***75 cm from the monitor*** *(marked with tape on the floor)*
9. Attach keyboard to computer and place on desk
10. Use alcohol wipe to clean:
    a. Forehead and chin rest
    b. Keyboard
11. Open up **"Go/No Go"** instructions
    a. You will use this to describe the tasks to the participant

12. Open up **“Go/No Go”**

a. Load in program

DATABASE Quality Assurance and Analysis

The clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures.

Description of Study Endpoints

Primary Endpoint

Change from baseline to day 5, 1 month and 3 month in clinical measures (PANSS, ASRM) and hospitalizations after 1 week of tES.

Secondary Endpoints

Change from baseline to day 5, 1 month and 3 month in GAF, SFS total score after 1 week of tES. Change from baseline to day 5 and 1 month in MADRS, PANSS, BIS after 1 week of tES. Change from baseline to day 5 and 1 month in voltage and peak frequency for reinforcement learning task measures after 1 week of tES. Change from baseline to day 5, 1 month and 3 month in cognition scores after 1 week of tES. Change from baseline to day 5, 1 month and 3 month in behavioral tasks (BART & Go/No Go) scores after 1 week of tES.

Safety and Tolerability Endpoint

A self-rated questionnaire related to sensations of tES is given to participants after each stimulation.

General Statistical Considerations

All collected study data will be collected on Redcap and processed using R and Matlab software. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be calculated by treatment group and sham group for continuous variables.

Primary Analyses

Primary Analysis of the primary, secondary, and additional efficacy endpoints: Mixed Model Repeated Measures analysis (MMRM)/non- parametric methods will be used to compare using within group differences as well as to determine the difference between the two treatment groups on the primary, secondary and safety endpoints depending on the distribution of the data.