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Can electrical stimulation reduce brain activity in brain regions involved in reward responses linked to risk-taking behavior in people with bipolar disorder?

Submission date
25/01/2019

Recruitment status
No longer recruiting

Registration date
13/02/2019

Overall study status
Completed

Last Edited
24/01/2020

Condition category
Mental and Behavioural Disorders

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol

Background and study aims
It is thought that people with bipolar disorder might have an increased response to the possibility of rewards. This might mean that they are more likely to show risk-taking behaviors and experience highs and lows of mood and activity. This study aims to investigate whether stimulating the parts of the brain involved in reward response with a low level of electrical current can change the activity in these brain areas in people with bipolar disorder and people without mental illness. If the activity can be reduced, this might be used as a treatment to reduce risk-taking behaviors and mood symptoms of bipolar disorder.

Who can participate?
Adults aged 18-45 years who are right-handed and either have bipolar disorder or have no mental illness and no family history of mental illness.

What does the study involve?
Participants will attend the clinic twice and will have their brain scanned during each visit using an MRI scanner while they are playing a card game that involves rewards. At one visit they will receive the electrical stimulation to their brain and at the other, they will receive a sham stimulation. The participants will not know which is the real or sham stimulation.

What are the possible benefits and risks of participating?
There are no direct potential benefits to participation in this study.
Participants might feel emotional discomfort (e.g. embarrassment or anxiety) as a result of clinical evaluations or assessments. The researchers are trained to administer evaluations and assessments in a way that will minimize discomfort. Participants may stop the evaluation or assessments at any time if they feel uncomfortable.
The risks associated with having an MRI brain scan are minimal. Although there are no known risks from exposure to the magnetic field used for these tests, if potential participants have metallic objects in their body, they would not be allowed to take part in the study because the

magnetic field in the scanner could cause these objects to move. No one knows if there is risk to an unborn child from the magnet, therefore, the researchers will not allow potential participants to take part in the study if they are pregnant. In rare cases, MRI scans can cause heating of the body and in severe cases cause redness of the skin or even burns. In most of these cases, the heating is due to the presence of a metallic object such as a wire, bracelet, medical device, or even some types of tattoos that contain metal. The safety questionnaire potential participants will fill out is designed to avoid these situations. However if for any reason a participant feels a sudden warming sensation during the scan they will be able to tell the technologist or scan operator immediately so that they can stop the scan.
The tDCS stimulation procedure itself should not be uncomfortable but owing to individual differences, it potentially could be, or the procedure could be emotionally stressful. However it should not be painful at all. It is common to experience mild skin sensations underneath the electrode (itching, prickling) and visual flickering. Much less frequently nausea, headache and more serious allergic skin reactions have been reported. These procedures (the scan itself and the stimulation) have been used in other studies without real harm. However since the tDCS device has not been tested in large scale studies, other unforeseen side effects cannot be presently ruled out.
In extremely rare instances, significant mood changes pre-post scan may be experienced, and the researchers will contact relevant emergency services (e.g., the Diagnostic Evaluation Center at WPIC), and/or the participant's primary care provider as necessary. In addition, the Re:solve Crisis Network in Pittsburgh can provide crisis intervention if needed. The clinical assessment team working on the study will be supervised by an experienced clinician, to assist in these circumstances. The participant must agree to this course of action in case of significant mood change. The study will be terminated at this point in this case.
Also extremely rare is that DCS may affect fluency of speech, but the effect is short-lived and will get better quickly. Because this side effect is very rare, it is difficult to estimate the amount of time this will last, but it should not remain after 30 minutes.
In addition, due to the potential for mild drowsiness or inattentiveness, researchers recommend taking the bus or walking to the visit rather than driving. Participants will be refunded for travel costs. Also, as there is some possibility of an interaction between the electrical stimulation device and the MRI scanner - researchers therefore will be very careful regarding what participants are wearing and what products they have used on their body.
Other possible discomforts participants might experience while participating in the scan include the following. They may become bored, tired, uncomfortable and/or frustrated during the scan. The MRI machine is loud when turned on, and may cause some discomfort so they must wear ear plugs. There is an intercom system that allows communication with the researcher during the scan. Participants will also be given a ‘squeeze-ball’ so that they can stop the testing if they become uncomfortable or anxious at any time. The space inside the MRI machine is fairly limited, so some people may feel claustrophobic. Participants will have the chance to look at this space before the test starts, but if they find the small space to be a problem during the procedures, they should will inform the researcher, and the scan will be stopped. Sometimes people feel anxious even after the scan is finished. If this happens the researcher will help the participant to calm down. Sometimes people feel lightheaded when they sit up after the scan, but this should go away quickly. In these events, or if the experiment makes the participant feel uncomfortable in any way, they can stop the procedures, without needing to fear any consequences. The researcher will help the participant leave the scanner and relax afterwards before they leave the facility.
Researchers will be able to view images of the participant's brain during the scanning session and there could be a slight possibility that they detect something unusual on the MRI scans. The MRI scans in this study are done to answer research questions and are not the type which would usually reveal medical conditions. In the unlikely event that the researchers detect an abnormality in your scan, the technician will refer your scans (without the participant's name) to

a specialist for further examination as soon as possible after the scan. The participant will be contacted by phone immediately should the consulting specialist recommend further examination and will be given an opportunity to talk with the specialist. Then the participant and their primary care physician (PCP), if the participant agrees, will then decide if the participant should undergo further examination. The consulting specialist will be available to answer any questions the participant or their PCP might have about the findings of the scan. The results of the research MRI scan will not become part of the participant's hospital record. However, even with all procedures in place to prevent it, there is still a risk of breach of confidentiality. The researchers will follow strict procedures for record-keeping in order to maintain information that is related to the participant as confidential (private) as possible.

Where is the study run from?
Mood and Brain Lab, University of Pittsburgh (USA)

When is the study starting and how long is it expected to run for?
July 2015 to December 2018

Who is funding the study?
National Institute of Mental Health (USA)

Who is the main contact?
Dr Mary Phillips

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Protocol serial number
1R21MH108421-01A1

Study information

Scientific Title
Modulation of ventrolateral prefrontal cortical activity during reward processing by transcranial direct current stimulation

Acronym
IMPRES

Study objectives
The aims of this study are:
1. In 30 18-45-year-old remitted individuals with BD type I (BDI), and 30 age, gender ratio and IQ-matched healthy control individuals, to compare left ventrolateral prefrontal cortex (vlPFC), ventral striatum (VS) and amygdala activation and functional connectivity (FC) during uncertain outcome expectancy, and short-term risky decision-making, and examine across all individuals relationships among neuroimaging measures and short-term risky decision-making
2. To determine the impact of acute left vlPFC (vs. positive control left somatosensory cortex, SS) cathodal transcranial direct current stimulation (tDCS) on these neuroimaging measures and short-term risky decision-making, using individual neuroanatomy-targeted electrode montages
3. To determine if the impact of this intervention is greater in individuals with BDI than controls, given that in the former, abnormally elevated reward circuitry activation and FC may provide greater capacity for the effect of tDCS upon these measures

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 04/07/2016, University of Pittsburgh Human Research Protection Office (3500 Fifth Avenue
Hieber Building, Main Office, Suite 106, Pittsburgh, PA 15213, +1 (412) 383-1480, askirb@pitt.edu), ref: PRO16020366

Study design
Cross-sectional within-participant trial

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Bipolar disorder

Interventions
After determining eligibility at a visit 1 via clinical screening, the participants were scheduled for 2 scan visits (Visits 2 and 3). Scan visits comprised the same procedures except that participants who received actual cathodal stimulation at visit 2 received sham stimulation at visit 3 and vice versa. tDCS was administered concurrently with the reward paradigm in the scanner. The montage for left vlPFC stimulation employed left frontal cathodal stimulation and anodal stimulation on the shoulder (F7-EC). The montage for the “positive control” left SS cathodal stimulation condition employed left SS cathodal and right supraorbital region anodal

stimulation. Cathodal stimulation of -1 mA was applied for the duration of the reward task (an event-related card-guessing game for examining neural activation during expectancy and receipt of reward/loss feedback lasting approximately 20 minutes), being slowly ramped up to start and ramped down to end. Left vlPFC and left SS cathodal stimulation conditions were counterbalanced across participants, on separate days 1 week apart.

Intervention Type
Device

Primary outcome(s)
1. Reward expectancy (RE) activation assessed using blood-oxygen-level dependent (BOLD) signal change in MRI scan at the scan visit of left vlPFC, VS and amygdala,
using as regions of interest the left vlPFC mask created from previous studies of reward processing in BD, a VS mask based on prior reward-related activation loci with the same paradigm, and an amygdala mask, using the SPM atlas toolbox (http://fmri.wfubmc.edu/)
2. RE functional connectivity measured by extracted parameter estimates in the brain by MRI at the scan visit

Key secondary outcome(s))
1. Prediction error (PE)-related VS activation measured by BOLD signal change in the brain by MRI at the scan visit

Added 27/02/2019:
2. Risky decision making is measured by performance on a risky decision making task, which occurs after each scan
3. Affect is measured by the Hamilton Rating Scale for Depression (HRSD) and Young Mania Rating Scale (YMRS) at the screen visit as well as before and after each scan

Completion date
13/12/2018

Eligibility

Key inclusion criteria
All participants:
1. Right-handed (Annett criteria)
2. Aged 18-45 years
3. Able to give basic informed consent
4. Women of childbearing potential must agree to a urine pregnancy test

Adults with no psychiatric history (healthy controls):
5. No previous/present psychiatric history of any disorder including Substance Use Disorders (SCID-5 criteria)
6. No family history of psychiatric illness (Family History Questionnaire criteria)

Adults with Bipolar Disorder I (BDI):
7. In remission with a diagnosis of BDI (DSM-5 criteria; euthymic for more than 2 months)
8. Any antidepressant, any mood stabilizer, any atypical antipsychotic, or any combination of atypical antipsychotics and/or mood stabilizers and/or antidepressants taken for 2 months or longer or unmedicated individuals

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
45 years

Sex
All

Total final enrolment
58

Key exclusion criteria
All participants:
1. Not native English speaking or not fluent
2. History of head injury/severe concussion, neurological, pervasive developmental disorder (e.g. autism), or systemic medical disease (that could impact fMRI scans; from medical records and report by each potential participant)
3. Mini-Mental State Examination (cognitive state) score <24
4. Premorbid NAART IQ estimate <85
5. Visual disturbance (<20/40 Snellen visual acuity) with correction or either contacts or glasses
6. Left/mixed handedness (Annett criteria), to ensure a uniform hemispheric dominance for interpretation of neuroimaging data
7. MRI screening: to exclude individuals with ferromagnetic foreign objects, e.g., surgical implants, and individuals prone to claustrophobia; and a positive pregnancy test for females (performed at the MRRC) or self-report pregnancy; being too physically large to fit in the scanner (greater than 55 inches chest circumference)
8. Active suicidal ideation

Adults with Bipolar Disorder I (BDI):
9. Not being in remission with a diagnosis of BDI (DSM-5 criteria; euthymic for 2 months or less)
10. If medicated, not on any combination of atypical antipsychotics and/or mood stabilizers and /or antidepressants taken for two months or longer
11. History of alcohol/substance abuse/dependence (including nicotine) and/or illicit substance use (except cannabis) over the last 3 months, determined by Structured Clinical Interview for DSM-5 (SCID-5). Lifetime/present cannabis use (non-abuse levels) will be allowed, given its common usage in individuals with BD. Urine tests on the scan day will exclude individuals with current illicit substance use (except cannabis); salivary alcohol tests will exclude individuals who are intoxicated on the scan day. Alcohol/nicotine/caffeine/cannabis use (below SCID-5 abuse /dependence levels) per week will be allowed, recorded for all individuals
12. Score >7 on the Hamilton Rating Scale for Depression (HRDS)
13. Score >10 on the Young Mania Rating Scale (YMRS)
14. Psychotic: Score of 3 or more on suspiciousness, hallucinations, unusual thought content subscales of the Brief Psychiatric Rating Scale (BPRS)

Adults with no psychiatric history (healthy controls):
15. Lifetime history of alcohol/substance abuse/dependence (including nicotine) and/or illicit substance use (except cannabis), determined by Structured Clinical Interview for DSM-5 (SCID-5) (50). Urine tests on the scan day will exclude individuals with current illicit substance use (except cannabis); salivary alcohol tests will exclude individuals who are intoxicated on the scan day. Alcohol/nicotine/caffeine/cannabis use (below SCID-5 abuse/dependence levels) per week will be allowed, recorded for all individuals
16. Lifetime history of psychotropic medicine use
17. First degree relative with Axis I disorder
18. Present/previous personal history of psychiatric illness in childhood or after the age of 18 years (SCID-I)

Date of first enrolment
01/09/2016

Date of final enrolment
13/12/2018

Locations

Countries of recruitment
United States of America

Study participating centre
University of Pittsburgh
4200 Fifth Avenue
Pittsburgh
United States of America
15260

Sponsor information

Organisation
University of Pittsburgh

ROR
https://ror.org/01an3r305

Funder(s)

Funder type
Government

Funder Name
National Institute of Mental Health

Alternative Name(s)
Mental Health NIMH, NIH National Institute of Mental Health, Instituto Nacional de la Salud Mental, NIMH

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
Based upon the terms of award, the research data collected from this project was shared through the NIMH Data Archive (NDA, https://ndar.nih.gov/edit_collection.html?id=2432). Consent for sharing was obtained using approved NDA RDocdb language. Data is anonymized and no PHI is shared. Data submitted to the NDA was de-identified. Raw and analyzed data will be shared. Data submitted to NDA are shared based on the information provided in the Data Expected list, set according to the standard Data Sharing Regimen. Unless a specific schedule for data sharing has been defined in advance, raw data submitted to NDA are shared within 4 months of submission. During this time period, data remain in a private state to allow time for the quality of the data to be reviewed by the Collection owner and NDA staff. Analyzed data is typically shared when published. Summary information on the data shared in NDA is available on the NDA homepage without the need for an NDA account. The NDA provides basic descriptive and aggregate summary information for general public use. Such summary information may include summary counts and general statistics on completed assessment instruments. To request access to detailed human subjects data or subject level data, a requestor must be sponsored by an NIH recognized institution with a Federalwide Assurance and have a research related need to access NDA data. The request is reviewed by the Data Access Committee (DAC) established to oversee access to the NDA shared data. Those approved will have access to NDA for one year after which reapplying is necessary.

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	29/10/2019	24/01/2020	Yes	No