LIBR #2025-005

10/9/2025

i. Cover Sheet:

Decoding Emotional Dynamics Driving Mood Instability in Bipolar Disorder

Funding Source: National Institute of General Medical Science (NIGMS)

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Summary of Changes from Previous Version:

Version Information	Summary of Revisions Made	Rationale
V2 10/13/2025	1. Section D, Inclusion Criteria:** Added PHQ-9 to inclusion criterion #8. 2. Section D, Exclusion Criteria (#4):** Revised to read: “Drug or alcohol intoxication (based on a positive UTOX or breathalyzer test at screening or study session), or reported alcohol/drug withdrawal. Last cannabis use must be >48 hours prior to the study session.”	1. To accommodate the practical screening procedures and maintain consistency with a previous project. PHQ-9 is included in the NeuroMAP Core data collection, which all participants will be recruited through (Section E). A PHQ-9 score ≥10 is considered equivalent to a MADRS score ≥15 in depressive severity. 2. To make the exclusion condition more practical and operationally.

	3. Section D, Exclusion Criteria (#9):** Removed the criterion: “Prescription of a medication outside of the accepted range, as determined by the best clinical practices and current research.” 4. Section F, Table 1:** Moved the clinician-administered depression and mania assessments (MADRS and YMRS) to the day of scanning. 5. Section F, Figure 1:** Removed the second resting-state scan from the MRI session. 6. Section F, Think and Regulate Affective States Task (TReAT):** Increased the number of attention trials from four 3-second trials to six 2-second trials. 7. Section J, Psychiatric or Behavioral Risk:** Added “Current DSM-5 diagnosis of” before “moderate-to-severe substance use disorder.”	3. This exclusion is beyond the scope of the study’s monitoring and cannot be reliably assessed within the study’s procedures. 4. To ensure that symptom ratings reflect participants’ clinical status at the time of imaging, as symptoms may change between the preparation visit and the scan day. 5. To ensure the total MRI session is completed in under two hours and to prioritize scans most relevant to the study aims. The second resting-state scan was deemed least essential. 6. To increase task demand and more effectively clear participants’ thought states between affective task periods. 7. To clarify and specify the diagnostic basis for determining exclusion due to substance use disorder.

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A. Purpose of the Study

The purpose of this study is to investigate the neural mechanisms underlying mood instability in individuals with bipolar disorder (BD) by decoding moment-to-moment emotional states using functional magnetic resonance imaging (fMRI) and advanced computational methods. Mood instability is a defining and impairing feature of BD, yet its dynamic neurobiological underpinnings remain poorly understood.

This research seeks to understand how emotional states fluctuate over time, how these fluctuations differ between individuals with BD and healthy controls (HC), and how the brain supports or disrupts emotional self-regulation. Findings from this study are expected to inform the development of personalized, neurobiologically informed treatments that adapt to an individual's emotional state.

B. Specific Aims

(1) Decode momentary emotional states from whole-brain fMRI data using machine learning.

(2) Quantify dynamic fluctuations in brain state using complexity science (e.g., metastability, fractal scaling) and network control theory.

(3) Evaluate the impact of positive emotion amplification strategies on emotional state stability and associated brain dynamics in BD.

Hypothesis 1: A machine learning classifier can decode different thinking states with statistically significant accuracy from fMRI brain activation signals. The decoded state trajectory in BD will be more unstable and fluctuating (i.e., exhibit greater temporal irregularity) compared to healthy controls (HC).

Hypothesis 2: Individuals with BD will exhibit more unstable emotional state trajectories (lower metastability and fractal scaling) compared to HC.

Hypothesis 3: Positive affect amplification will stabilize emotional dynamics and engage cognitive control regions in BD participants.

The outcome of these aims will help the investigators develop a personalized intervention approach to stabilize mood fluctuations.

C. Background and Significance

Bipolar disorder (BD) is a serious mental health condition marked by significant mood instability, which impairs emotion regulation and leads to functional difficulties [1]. Unlike unipolar depression, BD involves rapid and intense mood fluctuations, including difficulty sustaining negative emotions [2]. These patterns suggest that BD is defined more by dynamic instability than by persistent mood states.

Neuroimaging studies have revealed abnormalities in emotion-related brain circuits, including decreased activity in regulatory regions like the anterior cingulate cortex (ACC) and prefrontal cortex (PFC), and increased activity in emotion response regions (e.g., amygdala) [3, 4]. BD is also associated with altered connectivity in the default mode and frontoparietal networks [5]. Dynamic functional connectivity studies show increased variability in brain states, but these methods are limited by low temporal resolution and interpretability [6, 7].

To address these gaps, this study will decode emotional states from whole-brain fMRI patterns using machine learning [8, 9] and quantify emotional dynamics using complexity science and network control theory [10, 11]. We will also evaluate how positive emotion amplification strategies influence emotional stability, informed by evidence from Amplification of Positivity (AMP) psychotherapy and neurofeedback [12, 13]. This approach offers a novel framework for understanding mood instability in BD and identifying targets for personalized, adaptive interventions.

D. Criteria for Participant Selection

Target Recruitment:

- 32 individuals with BD (BD-I or BD-II, currently in a depressive or mixed state)
- 32 healthy control participants

Inclusion and Exclusion

Inclusion Criteria

1. Age 18 to 65 years
2. Male or female
3. BMI between 18.5 and 38.0 kg/m^2 at Screening
4. Capable of understanding and complying with study requirements
5. Fluent in English
6. Able to provide informed consent

BD Group:

7. Meet the DSM-5 diagnostic criteria for BD-I or BD-II who are currently depressed or mixed state defined by the Mini-International Neuropsychiatric Interview (MINI) [14]
8. Moderate or greater depressive symptom severity (MADRS ≥ 15 or PHQ-9 ≥ 10)

HC Group:

9. No current or past psychiatric disorder (verified by MINI)

Exclusion Criteria

1. No telephone or easy access to telephone
2. Significant medical problems as identified by the medical screening questionnaire: e.g. a history of unstable liver or renal insufficiency; glaucoma; significant and unstable cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, or metabolic disturbance; or any other condition that, in the opinion of the investigator, would make participation not be in the best interest (e.g., compromise the well-being) of the participant or that could prevent, limit, or confound the protocol-specified assessments
3. A positive test for drugs of abuse, including alcohol (breath test), cocaine, opiates, amphetamines, methamphetamines, phencyclidine, benzodiazepines, barbiturates, methadone, and oxycodone
4. Drug or alcohol intoxication (based on positive UTOX or breathalyzer test at screening or study session) or reported alcohol/drug withdrawal, last cannabis use must be >48 hours prior to study session.
5. Current DSM-5 diagnosis of a psychosis spectrum disorder or moderate to severe substance use disorder
6. Moderate to severe traumatic brain injury or other neurocognitive disorder with evidence of neurological deficits, neurological disorders, or severe or unstable medical conditions that might be compromised by participation in the study (to be determined by primary care provider)
7. Current significant suicidal ideation or suicide attempt within the past 3 months.

8. Change in the dose or prescription of a medication within the 6 weeks before enrolling in the study that could affect brain functioning, e.g., anxiolytics, antipsychotics, antidepressants, or mood stabilizers
9. Taking drugs that affect the fMRI hemodynamic response (e.g., methylphenidate, acetazolamide, excessive caffeine intake > 1000 mg/day)
10. MRI contraindications as documented on the MR Environment Screening
11. Unwillingness or inability to complete any of the major aspects of the study protocol, including magnetic resonance imaging (i.e., due to claustrophobia), or behavioral assessment. However, failing to complete some individual aspects of these assessment sessions will be acceptable (i.e., being unwilling to answer individual items on some questionnaires or being unwilling to complete a behavioral task)
12. Non-correctable vision or hearing problems

Rationale for Sampling Plan

A final sample size of 32 per group (after accounting for ~10% attrition) provides sufficient power (80%) to detect a medium effect size (d = 0.71) based on pilot findings, particularly in measures like fractal scaling.

E. Recruitment and Retention Plans

Recruitment Strategy

Participants will be recruited through:

- The NeuroMAP Recruitment and Assessment Core at LIBR (WCG IRB# 20231660)

During NeuroMAP Core study procedures, initial eligibility screening will occur via phone. Individuals who meet preliminary criteria will be invited for an in-person screening session, where they will undergo a structured psychiatric assessment using the MINI interview and standardized self-report measures. No identifying information will be collected prior to voluntary contact with LIBR research staff. Once NeuroMAP Core data collection is complete, study staff will screen subjects against the eligibility criteria listed above. Trained study staff will contact individuals who are determined to be initially eligible to confirm eligibility and interest in discussing the informed consent.

Retention and Compensation

Participants will complete two sessions: (1) Preparation visit and (2) MRI scan visit. Participants will be compensated $20 per hour for time spent completing written and oral tests, and $50 per hour for time spent in the scanner (scanning time will not exceed 2 hours). The detailed payment structure is described in Section L. Compensation for Participation. Retention is further supported by flexible scheduling, reminder calls/emails, and a structured and respectful participant experience.

F. Study Procedures and Protocol

Study Site

Participants will complete the study procedures at the Laureate Institute for Brain Research (LIBR) in Tulsa, OK. All data will be collected by LIBR staff trained on the study protocol and in research and good clinical practices. Data will be stored electronically using REDCap on LIBR networks and IT security.

Overview of Study Design

This is a cross-sectional, neuroimaging-based study designed to assess emotional state dynamics in individuals with bipolar disorder (BD) and healthy controls (HC) using:

- fMRI-based Think and Regulate Affectivate states Task (TReAT)
- Resting-state fMRI
- Structural MRI and white matter tractography
- Self-report questionnaires
- Computational metrics (e.g., metastability, fractal scaling, network controllability)

Session Timeline

The study sessions consist of two visits: one preparation session and one MRI scanning session. Table 1 describes the overall outline of this study and measures obtained at different points in time.

Table 1. Experimental procedure and Assessments

Content	Procedures/Assessments	Visit1	Visit 2 1-7 days after Visit 1		
			Before MRI	During MRI	After MRI
Informed Consent		X			
Mania	Young Mania Rating Scale (YMRS)		X		
Depression	Montgomery–Åsberg Depression Rating Scale (MADRS)		X		
Trait Rumination	Ruminative Response Scale (RRS) [15]	X			
State Rumination	Brief State Rumination Inventory (BSRI)	X	X		
Hedonic	Temporal Experience of Pleasure Scale (TEPS)	X			
Emotion Regulation	Emotion Regulation Questionnaire (ERQ)	X			
Emotion Regulation	Difficulties in Emotion Regulation Scale (DERS)	X			
Positive/ Negative Valence	Positive and Negative Affect Schedule-X (PANAS-X)	X	X		X
Depression	16-item Quick Inventory of Depressive Symptomatology (QIDS)	X	X		
Social Functioning	Sheehan Disability Scale (SDS)	X			
Trait-anxiety	State Trait Anxiety Inventory (STAI-T)	X			
State-anxiety	State Trait Anxiety Inventory (STAI-S)		X		X
Depression	PROMIS Depression	X			
Anxiety	PROMIS Anxiety	X			
Hedonia	PROMIS General Self-Efficacy Scale	X			
Anger	PROMIS Anger	X			

Hedonia	PROMIS Positive Affect and Well-being	X				
Subjective cognitive abilities	PROMIS Applied Cognition-Abilities	X				
Subjective cognitive concerns	PROMIS Applied Cognition-General Concerns	X				
Physical function	PROMIS Fatigue	X				
Sleep	PROMIS Sleep Impairment and Disturbance	X				
Thought collection work sheet (study original)		X				
Emotion Intencity of events	Likert scale for positive or negative emotions	X	X			
MRI screening	MRI safety-screening questionnaire		X			
Alcohol and drug	Breathalyzer and urine drug screening test		X			
Pregnancy (only for female)	Urine-screening pregnancy test		X			
Emotional State	Affective slider (emotional valence and arousal)			X		
Fatigue	Likert scale (study original)			X		
Comfort during the session	Feedback Questionnaire† (study original)				X	
Physiological measurement (Cardiogram, Respiration)				X		

†The Feedback Questionnaire assesses the participant's overall comfort during the session. It includes the following items: 1) How pleasant was the current MRI session for you? 2) How unpleasant was the current MRI session for you? 3) How challenging was the current MRI session for you? 4) How successful do you feel you were in following the instructions and tasks? 5) How did you feel about the amount of time you spent in the scanner?

Preparation Session

Informed Consent Process

Informed consent will be obtained by a member of the research team who has received training specific to this study. All participant interactions will take place in private interview or exam rooms, or via private virtual meetings. The consent review process may be conducted either in person or virtually.

Documented informed consent will be obtained once the consent form has been reviewed and the individual agrees to participate using the IRB-approved informed consent document. Participants will be provided with a copy of the signed consent prior to conducting study related activity. All volunteers will be at least 18 years old and will be asked to give fully informed, documented consent, following procedures already approved by the IRB. Care will be taken to explain the study thoroughly, and the process will be documented with signatures from both the participant and the individual obtaining consent.

Protection Against Coercion

The researcher will remind participants that participation is strictly voluntary and that they have the right to withdraw at any time without penalty. Family members may be present during the consenting process and may assist in discussing the study with the participant, if requested.

Participant Capacity

All individuals enrolled in this study will have the capacity to consent. As noted previously, individuals with moderate to severe neurocognitive disorders will be excluded from the study.

Participant/Representative Comprehension

During the written informed consent process, the participant's understanding of the study protocol will be assessed and documented by trained study staff. If a participant is unable to demonstrate adequate understanding of the protocol, they will not be enrolled in the study.

Self-Report Measures

After the informed consent document is signed during Visit 1, the study participants will be asked to complete a series of questionnaires either in-person using a LIBR iPad or computer, or remotely using a link sent to the participant's email. Data collected from these questionnaires will be used to characterize the study population and examine how individual differences relate to brain activation metrics.

Participants will be asked to complete several questionnaires related to mood, clinical symptoms, traits and personality characteristics, daily life functioning, and medical and mental health history. These self-report questionnaires are listed in Table 1. Self-report measures may be completed at home using a link from REDCap, as needed.

Participants will recall eight autobiographical events, each clearly associated with one of two thinking patterns: rumination (past negative events) or reminiscence (past positive events), which will be used in the MRI task. They will generate four events per category and write brief, keyword-based descriptions to assist with memory recall inside the MRI scanner. Details of each event will not be requested, allowing participants to provide personal events honestly.

MRI Scanning Visit

Participants will be scheduled for Visit 2 one to seven days after Visit 1 is complete. The following instruments and scans will be conducted during the MR scanning visit.

Pre-scan Assessments and MRI Preparation

Prior to scanning, participants will receive task instructions and complete a brief training session (15–30 minutes) to ensure understanding. They will rate distress levels related to autobiographical memories used in the task via a Lickert Scale. Participants will also be instructed on enhancing positive emotion during the regulation block using brief strategies adapted from Amplification of Positivity (AMP) psychotherapy [12, 16]. MRI eligibility will be confirmed before study entry. On the day of the scan, participants will complete the standard MRI Environment Screening Form. Alcohol and drug use will be screened using a breathalyzer and urine drug screening kit. Female participants will also undergo a urine pregnancy test. Vision correction will be provided if needed.

All standard MRI safety and comfort measures will be implemented: removal of ferromagnetic items, communication setup, ear protection, and physical stabilization (e.g., neck pillow, knee support). Participants will be positioned in the scanner, fitted with physiological monitoring devices (pulse oximeter and respiration belt), and given an emergency squeeze ball. The scan operator will ensure comfort, verify task screen visibility, and initiate communication before starting the scan.

MR Safety Screening

An MR Environment Screening questionnaire will be completed by each participant. The MRI safety-screening questionnaire is developed and distributed by the Institute for Magnetic Resonance Safety, Education, and Research (IMRSER) in Los Angeles, CA*. The safety-screening questionnaire probes for possible occupational exposure to metal slivers or shavings (remnants of which may remain lodged in a participant's head or neck), surgical clips or shrapnel, cochlear implants, or any other form of ferrous metal implanted in or on the participant's body. Participants answering in the affirmative to any of these conditions will be excluded. All subjects with any form of implanted wires, metal, or electronic devices will be excluded. All persons involved in this protocol will receive MR safety training conducted at the LIBR.

*INSTITUTE FOR MAGNETIC RESONANCE SAFETY, EDUCATION, AND RESEARCH 7511 McConnell Avenue, Suite 100, Los Angeles, CA 90045, http://www.imrser.org

Although there are no known risks of MR to pregnant women, there may be unknown risks. Therefore, females who are pregnant will not participate in this study. To ensure that female subjects are not pregnant at the time of the MRI procedure, all female participants will undergo a standard urine-screening pregnancy test prior to participation in any MRI scanning.

Physiological Monitoring

Physiological signals will be acquired through physiological monitoring of pulse rate using a finger-tip pulse oximeter throughout the MRI session [17]. A respiration belt that fits comfortably between the participant's chest and waist to measure respiratory changes. The concurrent information on pulse rate will be used to remove physiological fluctuations from the fMRI data.

MRI scanning

The MRI scan session includes a structural brain scan (T1-weighted image), field map scans (phase-encoding direction-flipped images with echo-planar imaging [EPI]), functional scans (T2*-weighted images using EPI to acquire blood-oxygenation-level-dependent [BOLD] functional MRI time-series data), and diffusion-weighted imaging (for diffusion tensor imaging [DTI] and white matter tractography). Figure 1 (upper panel) illustrates the sequence of scans. The total scan time is expected to be under 2 hours.

Functional MRI scans include both resting-state scans and scans acquired during the Think and Regulate Affective states Task (TReAT). The resting-state scan is 12 minutes and participants are instructed to stay still while fixating a cross sign displayed on the screen. Participants' motion will be monitored in real time during the MRI scan. If frequent significant motion is observed, the scan will be paused, the participant will be reminded of the importance of remaining still, and the scan will be restarted from that session.

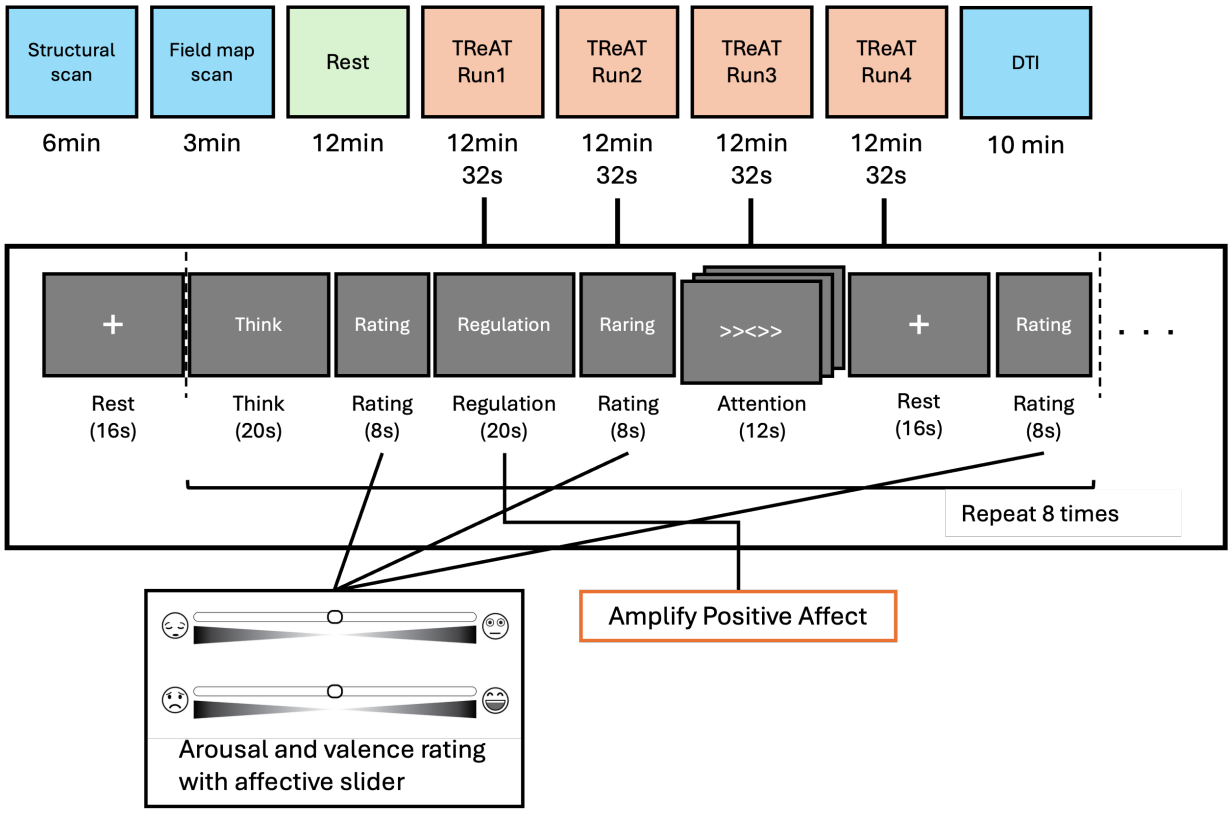

Figure 1

Think and Regulate Affective states Task (TReAT)

Figure 1 (lower panel) illustrates the sequence of the Think and Regulate Affective states Task (TReAT). TReAT consists of seven types of blocks. In the **Think** block, a short description (keywords) of an autobiographical event is presented, and participants engage in self-relevant emotional thoughts for 20 seconds. These keywords are provided by the participants using a thought collection worksheet (study-specific) during Visit 1. The Think block is followed by a **Rating** block, during which participants use the Affective Slider [18] to rate valence and arousal based on the preceding Think block while viewing the same keywords. Eight seconds (four per measure) are provided for responses. In the **Regulation** block, participants are instructed to amplify positive mood for 20 seconds while continuing to view the same keywords. At the end of this block, another **Rating** block is presented for eight seconds to assess the affective state during the Regulation block. In the **Attention** block, an array of five arrows is presented, and participants must respond to the direction of the center arrow within two seconds per trial; each block contains six trials. In the Rest block (**Rest**), a fixation cross is displayed for 16 seconds, during which participants are instructed to clear their minds and avoid directed thoughts. A **Rating** block follows the Rest block to assess the affective state during resting. These blocks will be repeated eight times in one fMRI scan run, and four runs will be performed.

Post-Scan Assessments

At the end of each scanning run, participants are asked to evaluate their task performance, level of sleepiness, and fatigue using a Lickert scale in response to the following questions: 1) How difficult was it to engage with your thoughts during the thinking blocks? 2) How successful were you in engaging with your thoughts during

the thinking blocks? 3) How sleepy were you during the scan? 4) How emotionally drained do you feel right now? 5) How tired are you right now?

After the scanning session, participants complete the PANAS-X and STAI-S to assess their current emotional states. In addition, the Feedback Questionnaire is administered to evaluate the participant's overall comfort during the session (see Table 1).

Participant Discontinuation and Withdrawal

Participants will be informed that participation is completely voluntary and that they may withdraw from the study at any time. If a participant withdraws or is discontinued, the reason and the method used to determine the need for discontinuation will be documented. Participants will be withdrawn if they revoke consent or if the investigator determines that continued participation is not in their best interest. This may include newly emerging or worsening suicidal ideation. Participants may also be withdrawn if they do not comply with staff instructions or are unable to remain still in the MRI scanner and continue to exhibit frequent motion despite guidance, as excessive motion renders the MRI data unusable. In the event of a system failure that prevents completion of the scanning session, we will attempt to reschedule the session within one week of the canceled appointment. If the participant is unavailable during this time, they will be withdrawn from the study.

Lost to Follow-up

A participant will be considered lost to follow-up if they fail to return for a scheduled 2nd visit and study staff are unable to contact the participant after 3 attempts.

The following actions must be taken if a participant fails to return for a 2nd session:

- The study staff will attempt to contact the participant, ascertain if the participant wishes to and/or should continue in the study, and as needed, reschedule the missed visit.
- Before a participant is deemed lost to follow-up, the study staff will make every effort to regain contact with the participant (where possible, 3 telephone calls, 3 text messages, or, if necessary, an email or certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's research record or study file.
- If there is any concern about the safety of a participant lost to follow-up (e.g., due to previously recorded suicidal ideation) and study staff are unable to reach the individual, then confidentiality may be broken and the COPES hotline (918-744-4800) may be called to help ensure safety of the participant.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

Estimated Time Commitment

- Visit 1: ~2.5 hours
- Visit 2: ~4 hours (2 hours MRI + 2 hours pre/post assessments)
- Total: ~6.5 hours per participant

G. Potential Risks and Anticipated Adverse Events

Risks Associated with Study Participation

The proposed study involves minimal to moderate risk. Potential risks include:

Psychological Risks

- Emotional distress may arise during the Think and Regulate Affective states Task (TReAT) when participants recall negative experiences.
- Participants with BD may experience temporary mood worsening due to emotional engagement.

Mitigation Strategies for Psychological Risks

- The task will be paused immediately upon participant request.
- Fatigue and emotional distress are assessed at the end of each TReAT run. If elevated distress is indicated in the participant's responses, we will ask the participant about their well-being and their willingness to continue the session.
- A clinical psychologist or trained clinical staff will be consulted if the participant reports significant emotional discomfort. If recommended by the LIBR staff psychiatrist or clinical staff, the participant may be referred to speak to their primary care provider or mental health practitioner, given a list of mental health resources, escorted to the Clinical Assessment Department at Laureate Psychiatric Clinic, or contact emergency services.

MRI-Related Risks

- Claustrophobia: Anxiety due to confined space
- Magnetic field hazards
- Peripheral nerve stimulation: Rare muscle twitches or discomfort during scanning
- Noise-related discomfort: MRI scanner produces loud sounds
- Dizziness

Mitigation Strategies for MRI-related Risks

- To reduce the risk of claustrophobia, participants will be thoroughly informed about the procedure and the scanner environment. If there is concern about a participant’s ability to tolerate the scanner, a mock scan may be conducted. If a participant is unable to tolerate the confined environment of the MRI scanner, their participation will be discontinued.
- Screening conducted to exclude participants with metal implants or devices.
- Participants will be monitored throughout the session; they can communicate with the MRI technician at all times. Any reported changes in skin sensations or symptoms like muscle twitching will prompt immediate assessment by the scan operator and possible removal from the scanner.
- Participants will wear earplugs and headsets that reduce scanner noise by approximately 20–40 dB. They will be instructed to inform staff if the noise causes any physical or psychological discomfort.
- To reduce the risk of dizziness, participants will be instructed to move slowly when rising from the scanner table.

Confidentiality Risks

- Potential loss of privacy due to sensitive data collection (psychiatric history, emotion ratings, neuroimaging)

Mitigation Strategies for Confidentiality Risks

- See mitigation plan in section I Data Confidentiality and Management below

Medical / Physical Risks

- Minor fatigue or discomfort due to long session duration
- Standard urine drug screening and pregnancy testing may cause mild embarrassment or inconvenience

Mitigation Strategies for Medical / Physical Risks

- The task will be paused immediately upon participant request.
- Fatigue and emotional distress are assessed at the end of each TReAT run. If elevated distress is indicated in the participant's responses, we will ask the participant about their well-being and their willingness to continue the session.
- If a pregnancy test is positive, the result will be discussed with the participant, and counseling will be offered if the result causes distress.

Contingency Plans for Suicidality

See Section M for contingency protocols regarding suicidality.

H. Potential Benefits

Benefits to Participants

There are no direct medical or therapeutic benefits to participants. However, participants may gain personal satisfaction from contributing to research on bipolar disorder, receive incidental health information (e.g., clinical MRI findings), and receive referrals for clinical services if needed (including mental health support).

Benefits to Society and Scientific Knowledge

This study has the potential to significantly advance our understanding of neural mechanisms underlying emotional instability in bipolar disorder, dynamic brain state transitions associated with mood regulation, and the impact of emotion regulation strategies, such as positive affect amplification. These findings may inform development of real-time, adaptive interventions and improved diagnostic tools and treatment personalization for mood disorders.

Risk–Benefit Assessment

The risks associated with the study (e.g., emotional discomfort, MRI-related risks) are minimal to moderate, and are well managed through protocol safeguards. The potential scientific and clinical value outweighs these risks.

I. Data Confidentiality and Management

Collection of Personally Identifiable Information (PII)

The following limited PII will be collected:

- Full name
- Contact information (address, phone, email)

This information is required solely for screening and scheduling purposes.

Data Collected:

- Clinical & cognitive: Table 1

- Behavioral: Emotional ratings (valence/arousal) during the TReAT
- Neuroimaging: T1-weighted anatomical, resting-state fMRI, TReAT task fMRI, DTI
- Physiological: Heart rate (measured via photoplethysmography [PPG]) and respiration (measured via a belt sensor)

The collection and processing of personal data will be limited to what is necessary to achieve the study objectives. Study records and urine samples will be assigned code numbers (combinations of letters and numbers) that do not directly identify individuals.

All data will be stored in a centralized repository using the Brain Imaging Data Structure (BIDS), a widely accepted standard that facilitates data sharing, export, and integrity validation.

Electronic data will be collected using REDCap (Research Electronic Data Capture), a secure, HIPAA-compliant software platform developed by Vanderbilt University and supported by a global consortium. REDCap projects use a detailed, study-specific data dictionary developed through an iterative process by the research team with IT support, resulting in a well-structured data collection strategy. REDCap servers are housed in a local data center at LIBR, with encrypted web-based transmissions, protected by firewalls and passwords.

Paper records containing PII, including consent forms and screening documents, will be stored in a secure medical records room accessible only to authorized personnel.

Privacy and Confidentiality Protections

- Participants will be assigned a unique ID code; names and identifiers will be stored separately in a secure, access-restricted database.
- All hard copy materials will be stored in locked cabinets, and electronic data will be stored on password-protected, firewall-secured servers.
- Only research team members and IRB-approved staff will have access to identifying information.

Participant confidentiality will be strictly maintained. Records will only be disclosed as required by law or as described in the informed consent document under “Confidentiality.” Authorized parties — such as the study doctor, sponsor representatives, the United States Food and Drug Administration (FDA), and the WCG Institutional Review Board — may inspect identifiable study records under specific regulatory conditions. However, participants will not be identified in any reports or publications.

J. Vulnerable Populations and Exclusion Criteria

This study does not include any federally recognized vulnerable populations, such as children (participants must be 18+), prisoners, or pregnant women/fetuses. All female participants will undergo a urine pregnancy test prior to MRI scanning. Pregnant individuals will be excluded from participation and referred for appropriate counseling if needed.

Cognitive or Decisional Impairment

Participants must demonstrate a clear capacity to understand the study procedures and must be able to provide informed consent independently. Individuals judged to be incapable of informed decision-making will not be enrolled.

Psychiatric or Behavioral Risk

Participants with any of the following will be excluded:

- Current psychosis
- Current DSM-5 diagnosis of moderate-to-severe substance use disorder
- Active suicidal intent or recent suicide attempt (past 3 months)

Ongoing monitoring of the participant's psychiatric status will occur throughout participation. Any new risk will trigger immediate mitigation listed in section G. Potential Risks and Discomforts and possible withdrawal from the study.

Additional Exclusions

- MRI contraindications (e.g., metal implants, pacemakers)
- Severe or unstable medical conditions
- Medications that alter fMRI signal (e.g., methylphenidate, excessive caffeine)
- Inability to complete core study procedures (e.g., cognitive tasks, emotional recall)

K. Compensation for Participation

Payment Structure

Participants will be compensated $20 per hour for time spent completing written and oral tests, and $50 for time spent in the scanner (the scanning time will not exceed 2 hours). Table 2 shows the details of compensation. Total compensation is up to $190 for full participation.

Table 2. Compensation

	Approximate Time in Hours	Estimated Compensation	Incentive Earned
Visit 1			
Consent	0.5	$10	
Symptom evaluations	1.5	$30	
Daily use of emotion regulation strategies (study original), Thought collection (study original)	0.5	$10	
Total for Visit 1	2.5	$50	
Visit 2			
Pre MRI symptom evaluations	1.0	$20	
Task instructions and practice (outside of MRI)	0.5	$10	
MRI scan	2	$100	

Post MRI symptom evaluations	0.5	$10	
Total for Visit 2	4	$140	
Total for completing the study		$190	

Conditions for Partial Payment

Participants who do not complete all study sessions will be compensated proportionally for the time they participated, including any portion of the preparation session and/or MRI session that was completed.

Incentive Justification

This compensation reflects:

- The time commitment (~6.5 hours total)
- The cognitive and emotional effort required
- Time spent in the MRI scanner (more intensive)

The compensation amounts are reasonable and not coercive, consistent with IRB-approved standards for similar research conducted at LIBR.

L. Adverse Event Reporting and Emergency Protocols

Monitoring for Adverse Events (AEs)

Participants will be monitored for physical, psychological, and behavioral distress throughout the study by trained research staff. This includes monitoring during screening, MRI procedures, and task performance. Potential adverse events include emotional distress, claustrophobia, dizziness, and any symptoms suggesting suicidal ideation or intent to harm self or others.

Response to Adverse Events

Minor events (e.g., mild distress or discomfort) will be addressed by pausing study procedures and offering participants appropriate support.

Serious Adverse Events (SAEs) will be promptly reported and evaluated by the Principal Investigator (PI) or a designated LIBR physician.

If an emergency arises, participants will be immediately referred to emergency medical care or psychiatric evaluation, in accordance with the LIBR Psychiatric Emergency Protocol.

Emergency Medical Protocol

The study will be performed at the Laureate Institute of Brain Research, 6655 S. Yale Ave, Tulsa OK, 74136. In the instance of an adverse event, the following standard procedures will be followed:

1. The participant will be directly evaluated by a LIBR study team member, and the severity of the adverse event will be determined in conjunction with the study principal investigator and a member of the LIBR physician team. A psychiatric and/or medical evaluation will be performed if the study personnel has concerns about the health of the individual. Depending on the severity of the adverse event, the study may be stopped.

2. In the event that a life-threatening medical emergency is detected, in which a participant becomes unresponsive, is not breathing, or is only gasping, the LIBR study team member will activate the LIBR medical emergency procedure. According to this procedure, if the LIBR study person is alone with the participant, they will call for a second rescuer. Once there are two rescuers present, Rescuer 1 (a Basic Life Support (BLS) certified member of the study staff) will immediately begin performing cardiopulmonary resuscitation (CPR). Rescuer 2 will coordinate help, which includes calling paramedics, getting a LIBR physician, getting the nearest automatic defibrillator, and assisting Rescuer 1 with CPR. They may rotate CPR with other Basic Life Support (BLS) certified members of the study staff including the study physician until the paramedics arrive.

3. Simultaneously, a member of the study staff will call for emergency response services by dialing 911. Based on prior experience, the response time is approximately 5 minutes for the Emergency Medical Services Authority (EMSA).

4. Immediately after calling for EMSA, the same study staff will bring the Automated External Defibrillator (AED) to the scene. LIBR possesses three AEDs. Each AED is positioned in the participant testing areas, immediately outside of testing rooms. There is an AED positioned 30 feet outside of the infusion room.

5. The study staff member will subsequently activate the LIBR emergency response alert, triggering a notification via overhead speakers throughout the building. This will call all other BLS certified staff members (physicians, and nurses) to the scene.

6. While awaiting EMSA responders (estimated response time: 5 minutes), all LIBR study staff present (BLS certified) will follow BLS protocol including performance of CPR if applicable, and AED deployment if applicable.

7. EMSA responders will determine the need for implementing the appropriate Advanced Cardiac Life Support (ACLS) protocol.

8. Emergency medical services responders will determine the need for transfer to the Saint Francis Healthcare System Emergency Department (located across the street) for further evaluation and management.

Contingency Plans for Suicidality

Individuals who report having a suicide plan or intent to attempt suicide at any point during the study will be excluded from participation. Any participant excluded for these reasons will be immediately referred for emergency care in accordance with the LIBR Psychiatric Emergency Protocol.

If a participant reports suicidal ideation while enrolled in the study, they will be immediately evaluated by a LIBR physician and referred for appropriate treatment per the LIBR Psychiatric Emergency Protocol. At any time during the study, if a participant reports increased psychological distress, suicidal ideation, or intent to harm themselves or others, LIBR physician or a licensed designee will be contacted immediately to ensure proper clinical care and to comply with mandated reporting requirements. Emergency services (911) or the Community Outreach Psychiatric Emergency Services (COPES, 918-744-4800) will be contacted if necessary and in all cases after hours (weekdays after 18:00) or on weekends. If such concerns arise while the participant is physically present at LIBR, a LIBR physician or psychiatrist will be available on site during regular business hours to address any concerns that arise. This team consists of three psychiatrists. Dr. Salvador Guinjoan MD, PhD, a LIBR principal investigator, is a board-certified psychiatrist with 20 years of experience in assessing and managing patients with mood and anxiety disorders including suicide assessment and management. Dr. Martin Paulus MD (NeuroMAP PI) is a board-certified psychiatrist with 25 years of experience in assessing and managing patients with mood and anxiety disorders including suicide assessment and management. Dr. Adrienne Taren, MD, PhD is a state licensed emergency medicine physician with 9 years of emergency medicine experience.. LIBR has set up a rotating coverage system so a board-certified physician is always reachable.

For participants who are physically present at the LIBR facility and are deemed to be at serious risk for suicide, LIBR policy requires referral to the Clinical Assessment Department (CAD) at Laureate Psychiatric Clinic and Hospital (LPCH) for further evaluation and crisis support. If the participant agrees, a LIBR staff member may accompany them to CAD, which is located approximately 100 yards from the LIBR building. If a participant refuses escort and/or chooses to leave the premises, the study clinician will contact the Community Outreach Psychiatric Emergency Services (COPES, 918-744-4800), Oklahoma's only free mobile psychiatric crisis response service, available 24 hours a day to dispatch a mobile unit to the participant's location.

For participants with clinical concerns that do not represent an immediate psychiatric emergency, contact information will be provided during the informed consent process. This includes a phone number for reaching a LIBR clinician during regular business hours (Monday–Friday, 08:00–18:00), and a number for the 24-hour on-call psychiatric service provided by the Laureate Psychiatric Clinic and Hospital Call Center during evenings, nights, weekends, and holidays. Participants will also be reminded of the availability of the Mental Health Lifeline, which can be reached by dialing 988.

Upon completion of the study or early withdrawal, participants who are currently engaged in mental health treatment will continue with their existing treatment provider. Participants who do not have a treatment provider will be offered a referral to a community mental health provider from our community. Individually tailored referrals will be made for participants residing outside of the Tulsa region, so that they can receive psychiatric services that are located near their home or workplace.

Plan of Action for Incidental Scan Findings

To account for incidental findings, each participant's first scan session will include a clinical anatomical imaging series (T1-weighted, T2-weighted, and T2-FLAIR scans). These images will be reviewed by a clinical neuroradiologist. If an incidental finding is detected, a physician-researcher will verbally inform the participant. A written report will also be provided, advising the participant to follow up with their physician. LIBR will provide a digital copy of the relevant MRI images to the participant's physician upon request. The participant will complete a Release of Information if they choose for their provider to receive this information. Participants will be informed that only incidental findings will be reported, and LIBR does not provide comprehensive clinical evaluations.

Lost-to-Follow-Up Safety Concerns

If a participant who previously expressed suicidal ideation becomes unreachable, the study team may break confidentiality to contact COPES (Community Outreach Psychiatric Emergency Services, 918-744-4800) in order to ensure the participant's safety.

Emergency Contact and Support

Participants will receive contact information for:

- The Laureate Psychiatric Clinic and Hospital Call Center (available after hours and on weekends/holidays)
- The national Mental Health Lifeline (988) for 24/7 support

Reporting Requirements

Any applicable Serious Adverse Events (SAEs) or unanticipated problems involving risks to participants will be reported:

- Within 1 business day to the LIBR Human Protection Administrator
- Within 5 business days to the WCG Institutional Review Board

Reports will follow NIH and institutional guidelines, as applicable.

M. Data Sharing, Retention, and Publication

Data Retention

All study data, including neuroimaging, behavioral, physiological, and questionnaire responses, will be retained for a minimum of three years following the completion of the study, in accordance with institutional and federal guidelines. Data will be archived securely in both electronic and physical formats, where applicable.

Data Sharing

De-identified data may be shared with public research repositories such as the NIMH Data Archive (NDA). Shared datasets may include:

- Participant demographics (de-identified)
- Assessment scores and behavioral responses
- Functional and structural neuroimaging data
- Study participation details

To enable data sharing with NDA, information needed to generate a Global Unique Identifier (GUID) will be collected and processed according to NDA specifications.

All shared data will be compliant with HIPAA and institutional standards for de-identification. Identifiable information will never be shared outside of the research team or the approved IRB and regulatory bodies.

Publication and Dissemination

Study findings will be disseminated through:

- Peer-reviewed journal articles
- Scientific conferences and symposia
- Public data repositories, where applicable

Participants will not be identified in any report or publication. All results will be presented in aggregate or anonymized form. Clinical MRI findings deemed medically significant will be reported to participants per institutional protocol.

N. Scientific Importance and Potential Impact

Scientific Rationale

Bipolar disorder (BD) is a chronic psychiatric condition marked by mood instability, which significantly contributes to impaired functioning and reduced quality of life. While much is known about the neurobiology of static mood states (e.g., depression or mania), very little is understood about the neural mechanisms underlying dynamic mood transitions — the hallmark of BD.

This study applies innovative, time-resolved fMRI analysis, machine learning-based emotion decoding, and computational metrics (e.g., metastability, network controllability) to provide an unprecedented window into how emotional states evolve and shift in real time in the bipolar brain.

Innovative Contributions

This study is among the first to integrate:

- Fine-grained emotional state decoding from fMRI
- Complexity science metrics to quantify emotional lability
- Network control theory to identify brain regions that drive emotional state transitions
- Examination of positivity amplification as a potential stabilizer of mood dynamics in BD

Broader Impact

Findings from this research will:

- Improve our neurobiological understanding of mood instability
- Inform the development of real-time, adaptive interventions (e.g., neurofeedback, digital therapeutics)
- Support personalized treatment strategies based on brain state and emotional fluctuation patterns

This study will also provide preliminary data to support future R01-level funding and biomarker discovery efforts in mood disorders.

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