Official title: Subjective Response to Alcohol and Associated Neural Systems in Bipolar Disorder

NCT number: NCT04063384

Document last approval date: 8/28/2023

Document information: Overall study protocol and change in behavior and functional connectivity (primary outcomes) statistical analysis approach.

1 Research Hypothesis

To input text, click in the light grey area below.

We hypothesize that:

a) Individuals with bipolar disorder will show a low response to alcohol (decreased self-report of feeling intoxicating and experiencing stimulating/sedative effects of alcohol) and a low response to alcohol will be associated with higher alcohol intake.

b) Individuals with bipolar disorder, compared to healthy comparison subjects, will show smaller alcohol-induced changes in regional responses of, and functional connections between, the amygdala, striatum, and the dorsal and ventral prefrontal and anterior cingulate cortices. Smaller change in regional responses of, and functional connections between, these regions will be associated with a self-reported low level of response to alcohol.

2 Study Background

To input text, click in the light grey area below.

Disease progression in bipolar disorder is very heterogeneous and our understanding of mechanisms associated with differences in disease progression is limited. Bipolar disorder has a high rate of comorbidity with alcohol use disorders (AUDs) [1-3], with estimates as high as 60% [4]. Comorbidity with AUDs is related to more severe illness outcomes in bipolar disorder, including increased impulsive risk-taking [5-8], more severe mood episodes [9, 10], cognitive deficits [11-13], decreased quality of life and a higher risk for suicide [14-17]. These associations highlight the importance of understanding how this comorbidity develops and the relationship with disease progression in bipolar disorder. However, there has been little study in this area; neuroimaging studies in bipolar disorder have not focused on alcohol use, and related differences in disease progression and, in fact, often exclude subjects with this comorbidity from study.

There is substantial overlap in mechanisms implicated in bipolar disorder and AUDs. Anxiety- and stress-related mechanisms are implicated in both bipolar disorder and AUDs with bipolar disorder comorbidity with anxiety disorder itself suggested to elevate the risk for comorbid AUDs [18]. This suggests changes in mechanisms and neural regions underlying stress modulation may be one path mediating the development of comorbid AUDs in bipolar disorder. There is significant genetic overlap across these disorders. For example, the 5'promoter region of the serotonin transporter gene (SLC6A4) has been associated with both bipolar disorder and anxiety disorders [19] and is suggested to be related to individual differences in responses to alcohol—an endophenotype that identifies young adults with high risk for alcohol use disorders [20]—including differences in the subjective high one feels following alcohol consumption [21] and reported number of drinks needed to feel intoxicating effects of alcohol [22]. These multiple (and potentially shared) mechanisms of disease may contribute to differences in disease progression that potentially may be targeted for treatment.

With these considerations in mind, the proposed research will focus on one mechanism for altering disease progression in adolescents and young adults with bipolar disorder. We will investigate whether differences in neural and self-reported subjective responses to alcohol, including stimulation and sedation responses, exist within individuals with bipolar disorder, compared to age-and sex-matched healthy comparison participants. Cognitive and behavioral data will be collected to control for appropriate factors and explore how cognitive (or other behavioral constructs) may be associated with these processes. Participants will first complete baseline structural and resting state functional magnetic resonance imaging (rsfMRI) and return within days of their baseline scan to participate in an alcohol challenge study that will directly investigate differences in neural and subject responses to alcohol, compared to placebo, in young adults with bipolar disorder and healthy comparison young adults. Identifying differences in neural responses to alcohol may enhance our understanding of why AUDs are more prevalent in bipolar disorder than the general population and may reveal novel therapeutic targets that can be targeted in future studies.

Our goals are to:
a) identify differences in subjective responses to alcohol between young adults with bipolar disorder and healthy comparison young adults. This will be measured through self-report surveys and physiological measures during controlled alcohol/placebo administration sessions,

b) identify differences in neural responses between young adults with bipolar disorder and healthy comparison young adults. This will be measured through a fMRI scan during controlled alcohol/placebo administration sessions (same session as in a above),

3 Design and Methodology

Provide information regarding study design or data collection methodologies. Details regarding protocol specific research procedures will be discussed in a later section.

To input text, click in the light grey area below.

A total of 60 bipolar and healthy comparison subjects (n=30 per group, 21-26 years of age, 50% women, with no history of a severe AUD) will be recruited from the greater Austin area. We included individuals with a history of mild/moderate AUDs as doing so is more generalizable since it is common that individuals in this age group experiment with alcohol use. We will exclude individuals with a history of symptoms suggesting dependence (which is what you see in individuals with severe AUDs). Subjects will be recruited through multiple venues to optimize subject enrollment. Once recruited and enrolled, subjects will undergo detailed structured clinical evaluations to verify inclusion and exclusion criteria followed by structural MRI assessments. Following standard beverage administration procedures, they will then complete measures of subjective response to alcohol and fMRI scans while under the influence of alcohol or a placebo condition (counter-balanced). All subjects will be euthymic and alcohol/placebo sessions will occur within 3 days of each other. FMRI assessments will include a continuous performance task with emotional and neutral distractors (CPT-END) and resting state scans. Participants will first complete the CPT-END task at baseline (outside the scanner) before their alcohol or placebo session. Our recent data suggest differences in ventral brain networks when viewing emotional stimuli for the first time compared to the second time (associated with habituation of emotional networks), but that there are minimal differences between the second and third viewings. We will investigate (Aim 1) differences in subjective response to alcohol between bipolar and healthy participants and associations with recent drinking patterns and (Aim 2) differences between bipolar and healthy young adults in alcohol-induced changes, compared to placebo, in regional activation in vPFC emotional networks and connectivity among these regions.

4 Data Analysis

Describe the data analysis plan, including any statistical procedures or power analysis.

To input text, click in the light grey area below.

Aim 1: Between Group Differences in Subjective Response to Alcohol

Group (bipolar, healthy)-by-condition (alcohol, placebo)-by-time of subjective response interactions on subjective response to alcohol will be modeled, covarying beverage condition order, biological sex, and age with SEAS and DEQ subscale scores as the dependent variables. Time of subjective response (pre- and post-scan) and beverage condition (alcohol, placebo) will be within-subject factors and group an independent between-subject factor. Following no group-by-condition-by-time of subjective response interaction, the three-way interaction term will be dropped and group-by-condition interactions investigated. Following no two-way interaction, the two-way interaction term will be dropped and main effects of group and condition assessed. Findings for these planned analyses will be considered significant at $p<0.05$.

Between Group Differences in Functional Connectivity to Alcohol

Using the CONN Toolbox, we will perform region of interest (ROI)-to-ROI bivariate correlation first-level analysis to calculate fisher transformed correlation coefficients (measure of functional connectivity (FC)) between a priori ROI-to-ROI connections during placebo and alcohol condition CPT-END fMRI sessions. We will extract Fisher transformed correlation coefficients between ROI-to-ROI connections during emotional stimuli and during squares for analysis. We will calculate the contrast: FC during emotional stimuli minus FC during squares for alcohol and placebo conditions, in line with prior studies. A priori ROIs will be defined using the FSL Harvard Oxford Atlas in the CONN toolbox, and included bilateral insula, amygdala, nucleus accumbens (NAcc), ventromedial PFC (vmPFC), lateral orbitofrontal cortex (OFC), subcallosal cortex (SCC), and inferior frontal gyrus pars triangularis (IFG.tri). We will examine ROI-to-ROI connections between limbic/subcortical regions (insula, amygdala, or NAcc) with ventromedial PFC (vmPFC or SCC) and ventrolateral PFC (OFC or IFG.tri) regions.

We will use a mixed model to examine group by condition by hemisphere (left, right) interactions on ROI-to-ROI FC response to emotional stimuli (contrast: emotional stimuli - squares). Group will be an independent between-subject factor, condition and hemisphere within-subject factors, and ROI-to-ROI FC the dependent variable. Results of primary models will be considered significant at $p \leq 0.004$ (Bonferroni correction for twelve ROI-to-ROI connections).

STUDY PROCEDURE DESCRIPTION

5 Procedure Description

Describe all study procedures, including a step-by-step outline of what participants will be asked to do or how data will be used. Be sure to describe all of the following in detail, as applicable:

- Provide a description of all research procedures being performed and when they are performed, in sequential order.
- All research measures/tests that will be used and state if questions or measures are standardized or published (upload copies of all surveys, scripts and data collection forms)
- Secondary data or specimens that will be obtained, how they will be collected, and how they will be used
- Where each activity will take place, the duration of each, and who will perform each activity
- Include time commitment of participants

To input text, click in the light grey area below.

General Overview: After informed consent from subjects is obtained, diagnostic interviews and cognitive/behavioral testing (about 3 – 3.5 hours) will be performed. Saliva samples will be collected for genetic testing requiring subjects to spit into a tube until it is filled to a certain level. Subjects do not have to consent to give a saliva sample to take part in the study. Urine will be collected for urine toxicology with results discussed only with the subject. Baseline scanning will be performed on the 3 Tesla (3T) Siemens VIDA scanner at the UT-Austin Biomedical Imaging Center (BIC) formerly named the Imaging Research Center (IRC) at the Health Discovery Building (HDB). Before scanning, subjects will be assessed for ferromagnetic objects (all subjects) and pregnancy (female subjects). The scanning session will be 45 minutes long. We anticipate that total participation will take approximately 4.5-5 hours to complete baseline assessments. This time can be divided into different days if preferred by the subject (i.e. clinical assessments and scan occuring on different days).

Within days of baseline clinical assessment, participants will return for alcohol/placebo MRI sessions (counter-balanced). These sessions will occur on the 3T Siemens Vida at the UT-Austin's BIC in the HDB similar to baseline scanning. Urine toxicology (and pregnancy test for females) and re-assessment for ferromagnetic objects will be completed before each session. Following alcohol (and placebo) consumption, these individuals will complete a 30 minute fMRI scan session. A within subject comparison

between MRI scans while under the influence of alcohol and those collected during the placebo session will be examined and alcohol-induced changes compared between individuals with bipolar disorder and healthy comparison subjects.

General Overview of Data Collected:
Data is collected on paper (clinical assessments) and on an experimental computer or on standardized instruments (e.g. standardized behavioral self-reports). MRI data is collected at the 3T MRI systems at UT Austin.

Location of Data Collection:
Clinical assessments are conducted in the PI's research space in the Health Discovery Building (HDB 4.208A) or (in light of COVID-19 precautions and to decrease density of research participants on UT Austin's campus) can be conducted remotely. Baseline MRI scans will be conducted at the UT BIC located in the Health Discovery Building on the Dell Medical School campus. Alcohol/placebo sessions will occur in the PI's research space in HDB (HDB 4.208A) or UT BIC in HDB at Dell Medical School.

Written Informed Consent: The study objectives, requirements, and risks are explained as part of the review of the consent form and the informed consent process. The subject is then encouraged to ask questions. If the subject agrees to participate, a consent form is signed.

Diagnostic Interviews: Subjects will first complete diagnostic interviews and be diagnosed as bipolar disorder or a healthy comparison participant. Validated instruments include *Structured Clinical Interview for DSM-V axis I Disorders* (SCID). Clinically relevant information (i.e. mood state at the time of assessment, etc.) is also obtained from these diagnostic interviews. If a participant is depressed or in an elevated (hypomanic, manic, mixed) mood state at the time of their baseline assessment they will be sent home and invited to return at a later date when they are euthymic.

-*Structured Clinical Interview for DSM-V axis I Disorders (SCID):* a semi-structured diagnostic interview that provides assessment of present episode and lifetime history of DSM-V psychiatric illness in adults [23].

- The *Hamilton Anxiety Rating Scale (HAM-A)* and *Hamilton Depression Rating Scale (HAM-D):* clinician-administered scales validated for assessing anxiety and depression in adolescents and adults [25, 26]. *The Young Mania Rating Scale (YMRS):* an 11-item clinician-administered scale validated for both children and adults to quantify manic symptoms [27]. These measures are used to assess mood symptoms over the last week at the time of baseline clinical assessment.

- Additionally, mood state will also be measured by self-report surveys, i.e. the *Beck Depression and Anxiety Inventories* [28, 29]. These self-report surveys will be completed before beverage consumption during the alcohol and placebo MRI sessions.

Assessment for Ferromagnetic Objects: Participants will be carefully screened for implanted devices and previous exposure to metallic fragments. Screening involves verbal discussion with the researcher (and/or Safety Officer), as well as completion of a checklist maintained by the Imaging Research Center. All ongoing participants will be required to fill out a screening form at the beginning of their participation, after every revision to the form's criteria, at the beginning of every semester, and after any changes to their medical/health status that may be relevant to MRI safety. Subjects having or suspected of having foreign metal objects will be excluded. This exclusion may be confirmed, with a subject's consent, either by obtaining and examining the subject's medical chart and/or contacting their physician if there is any question.

Assessment of Pregnancy: The risks of study with pregnancy and the possibility of pregnancy will be discussed with each menstruating female subject by an investigator of the study. A urine screening will be required for all female subjects with childbearing potential within 24 hours prior to scanning to verify

pregnancy status. Pregnant women will be excluded from participating in this protocol. If there is any question that a pregnancy could exist, but is at too early a stage for detection by this test, the woman will also be excluded from study.

Because full confidentiality regarding pregnancy cannot be entirely guaranteed, these testing requirements and the limited scope of confidentiality will be made known to all subjects during the consent procedure. In this manner, young women who would not be comfortable with pregnancy testing or sharing the results of such testing can opt out of the study at the time of the initial consent, without having to declare specific reasons.

<u>Magnetic Resonance Imaging (MRI) Acquisition:</u> In an MRI study, some education on the nature of the stimulus sequence, its presentation, and the response required, may be necessary. The subject is instructed to remove jewelry, wallet, and any metallic objects from their person. Baseline MRI scans will be performed at the UT-Austin BIC on a 3 Tesla (3T) Siemens VIDA scanner. The alcohol/placebo session will occur on the 3T Siemens Vida imaging system in the Dell Medical School's Health Discovery Building. The alcohol/placebo session will take place in HDB as the PI's research space is in this building and there will be comfortable and private space for participants to detox after their alcohol/placebo sessions. The 3T field strength falls within FDA limits and is now widely used clinically; the scanner also allows us to work within conventional research limits for dB/dT and SAR (the other FDA-monitored criteria related to aspects of the intensity of the MR imaging). Although this system provides the standard operating range for research, we also carefully monitor each participant for possible discomfort related to MR imaging (details are discussed in Section VI, D).

The subject is fitted with earplugs and/or headphones. The subject is positioned inside the MRI scanner, instructed to lie motionless during the procedure, and told that he/she can communicate with the operator through the intercom system and can be seen by the operator via window. The time period of the baseline MRI examination is approximately 45 minutes. Subjects can be removed at any time from the scanner by simply requesting to be. All scanning sessions include collecting anatomical images. Generally, scanning sessions include acquisition of standard localizer images to allow subsequent slice prescriptions (i.e., to find where the head/brain are positioned relative to the bore of the MRI scanner).

The baseline 50 minute protocol will include acquisition of high resolution structural MRI (sMRI) data, diffusion tensor imaging (DTI) data, and resting state functional MRI (rsfMRI) data. Durinig structural scans, participants will be told they can close their eyes. We will also project a utube video of fish swimming. We have found this facilitates participants lying still in the scanner and creates a more enjoyable experience while in the scanner.

Scans will include an "MPRAGE" sequence or a similar conventional anatomical protocol. These scans are relatively quick to acquire (~5 min) and provide a high resolution view of the brain's anatomy. This permits subsequent registration of each session's functional data with data collected from the same subject in other scanning sessions. A variant of MR imaging called DTI allows us to obtain data that informs us about how various brain areas are structurally connected to one another. DTI allows the MRI scanner to detect directional differences in the diffusion of water molecules, which indicates the orientation of white matter pathways in the brain. No additional equipment is required for DTI. Single shot EPI sequences for measuring diffusion-weighted data sets with up to 256 directions of diffusion weighting are also a part of the Siemens Skyra 3T system′s capability. It provides diffusion tensor imaging and parametric maps derived from fractional anisotropy calculated in real time, automatically. High quality, high angular resolution DTI is relatively quick to acquire (~5-10 minutes). fMRI sessions will collect large numbers of T2*-weighted image volumes. These volumes are obtained using various MR techniques for fast gradient-recalled echo (GRE) imaging. Most commonly, we utilize variants of functional imaging that utilizes a raster-like acquisition trajectory called echo-planar imaging (EPI). Additional fMRI pulse sequences are continually under development to improve such qualities as signal-to-noise ratio and spatial resolution. In general, fMRI sequences are "gradient heavy", meaning that their specific absorption ratio (SAR) levels are very low, but they operate at or near magnetic-field slew rate

(dB/dt) limits. These general procedures have been regularly used in the BIC for approved neuroimaging protocols.

When subjects return for their alcohol/placebo sessions they will complete a fMRI task that involves presenting visual stimuli related to cognitive or emotional functions. Responses are required and made by button press response (see appendix C for description of the CPT-END fMRI task that will be employed). They will not complete this task in the scanner at their baseline MRI scan, however, they will complete the task outside of the scanner at baseline (i.e. before they come to lab for their alcohol or placebo session). Our recent data suggest differences in ventral brain networks when viewing emotional stimuli for the first time compared to the second time (associated with habituation of emotional networks), but that there are minimal differences between the second and third viewings. The PI and trained staff will evaluate each participant during and following the MRI scan. During all MRI scans, a *MRI Run Sheet* is completed. At the end of the baseline MRI examination, the subject is removed from the magnet, assisted to his/her feet, and escorted to the Patient/Subject Room from where he/she is discharged. If there is no unusual occurrence and the subject feels well, he/she is released following their baseline scan. Post-scan procedures following the alcohol/placebo sessions below.

Throughout study involvement, participants will be referred for psychological counseling if needed or if subjects request a referral for psychological counseling. Research staff will emphasize mental health resources are available to all participants.

<u>Laboratory Alcohol Challenge Procedures:</u> The Principle Investigator will review baseline clinical assessments of individuals before they participate in the alcohol/placebo sessions. During phone screening, participants are screened so that any individuals who might have an adverse reaction to alcohol can be identified. Participants will be scheduled for their alcohol/placebo laboratory sessions that will begin in the afternoon. They will receive a reminder email and/or call the day prior to their laboratory session. Participants will be instructed to abstain from alcohol for 24 hours before the session and from caffeine and tobacco for 3 hours before the session and to eat a full meal 4 hours before arrival at the laboratory. They will also be informed that they will not be able to drive themselves home at the end of the session and must receive a ride from a friend or family member. Specifically, each participant will be told that they should NOT drive to their laboratory sessions and will not be allowed to drive after their laboratory sessions. The transportation requirement will be explained when the participant is invited to participate in the study and the day before the actual lab alcohol/placebo sessions in order to ensure the participant understands that they will need to be driven home after participating in the study. We encourage participants to take the bus or get a ride to the laboratory and NOT to drive their own vehicle because: 1) parking is scarce around the University; and 2) their cars will have to remain overnight because they will have to be driven home after the experiment. If the participant is unwilling to comply with this requirement, they will not be eligible to participate in the study because it is unsafe and against policy. In addition, at the laboratory sessions, participants will be asked whether they drove to the laboratory. Based on their response, the participant will have to agree to leave their vehicle overnight or will be informed they will have to be rescheduled for a different study session.

Upon arriving for their session participants will receive breathalyzer tests (Also-Sensor IV Handheld Breath Alcohol Tester (Intoximeters Inc. St. Louis, MO) to ensure a .00 % breath alcohol concentration (BrAC). Participants will have their heart rate and blood pressure measured and be weighed (for purposes of beverage preparation, see below). Female participants will be required to test negative for pregnancy. The participant will be informed that the test results will be confidential. If a participant should test positive for pregnancy, a research assistant or the PI will immediately take the participant in to a private room and inform them of the test results in a sensitive manner. The participant will be informed that they should discuss the results with their doctor, and will be provided with a list of referrals should they want to discuss the impact of the results with a counselor. The participant will not be allowed to continue with the alcohol/placebo administration sessions but will be provided transportation home either by a sober friend or family member.

In an adjacent room, the participant will complete the Time Line Follow Back interview. Participants will have been fasting from food for 4 hours prior to their session, so before beginning consumption of their beverages, they will be provided with a light snack of pretzels. In addition to facilitating the participants' comfort, food intake delays the rate of alcohol absorption and increases the duration of the ascending limb of the BAC curve (when we will be conducting the MRI session). We will give participants a weight adjusted amount of pretzels based on their body weight so that they will receive 1 calorie per pound (e.g., a 150-pound participant would receive 150 calories; roughly 7 large pretzels. This has become standard practice for alcohol administration studies (e.g., [33, 34]). A gluten-free option will also be available.

Participants will consume their beverages in a private interview room at the BIC in the Health Discovery Building. A study staff member will be present at all times. Following 10 minutes for absorption, breathalyzer tests will be conducted until the participant reaches an ascending limb BrAC of 0.06%, at which time the first alcohol response measures will be collected (e.g. *Subjective Effects of Alcohol Scale*). Immediately following, participants will complete their MRI assessment. This is done to ensure we are imaging during the ascending limb of the BAC. For this study, we are focusing on imaging during the ascending limb of the BAC based on our pilot suggesting altered sensitivity to the stimulating, but not sedatative, effects of alcohol in bipolar disorder.

The MRI scan session will last approximately 30 minutes. Subjects will complete a neuropsychological task (i.e. the CPT-END). For each individual completing the alcohol and placebo sessions, functional MRI data during the alcohol session will be directly compared to placebo fMRI data.

Following scanning, the participant will be escorted back to a private interview room and subjects will immediately be given a breathalyzer test and BrAC recorded. They will complete alcohol response measures again). Participants will be escorted to a comfortable private room in the PI's research suite where they can watch television while they detox. Consistent with NIAAA guidelines for human alcohol studies, BrAC readings will be taken every 30 minutes until participants are below 0.04% at which time they will be allowed to leave the laboratory.

<u>Beverage Manipulation and Procedures:</u> Participants will use alcohol free mouthwash prior to the first breathalyzer test. Participants will be assigned randomly to the placebo or alcohol condition. Participants are told they will complete two alcohol sessions where they will be assigned a large dose of alcohol (alcohol condition) or a small dose of alcohol (placebo condition). These will be counter-balanced. A placebo condition will be used to model effects of alcohol expectancies. Using standardized alcohol administration procedures, study staff who are blind to beverage condition will calculate individual dose based on the participants' gender and weight, and will pour drinks from vodka bottles in full view of participants. Participants will be given 10 minutes to consume each of two beverages (20 minutes total time drinking) containing a 1:3 mixture of 80 proof vodka (mean: 2.389 ml/kg of body weight; women: 2.174 ml/kg of body weight) to mixer (diet 7-up, cranberry juice, and lime juice) to achieve a target breath alcohol concentration (BrAC) of 0.08%. In the placebo condition, the vodka bottle will contain decarbonated tonic. Consistent with standard procedures [35], the rims of the glasses will be moistened with vodka, and a squirt of 100 proof alcohol from a plastic lime juice container will be added to the top of each drink just prior to serving.

6 Research Participant Information

Describe the research population.

**For multiple research populations (e.g., teachers, students, and parents), copy this section as necessary to describe your population.*

a Participant Group Name

To input text, click in the light grey area below.

Participants include young adults diagnosed with bipolar disorder and typically developing young adults.

60 total participants will complete baseline assessment, alcohol and placebo sessions (30 diagnosed with bipolar disorder and 30 healthy comparison subjects). All subjects will be between 21 and 26 years of age. We plan to include equal numbers of males and females and minorities in proportions representative of the population in the greater Austin area. We expect many subjects will be students at University of Texas. We also expect to recruit approximately 10 participants who will not meet inclusion/exclusion criteria following initial clinical assessment (e.g., they do not meet criteria for bipolar disorder type I). These individuals will be compensated for completing the clinical interview but will not be invited to come in for the baseline scan or the alcohol/placebo MRI session. Total participants to be recruited includes 70 young adults.

b Minimum Age

To input text, click in the light grey area below.

21 years of age

c Maximum Age

To input text, click in the light grey area below.

26 years of age

d Inclusion Criteria

To input text, click in the light grey area below.

Eligibility will be determined by the staff consenting subjects, under the supervision of the Principal Investigator.

Inclusion Criteria:

All Subjects:

1. ages 21-26 years

2. male and female subjects from all racial and minority groups

Subjects with Bipolar Disorder:

1. diagnosis of bipolar disorder type I

7 Total Sample Size

To input text, click in the light grey area below.

Total study participants that will be recruited are 70 young adults (30 participants with bipolar disorder and 30 typically developing comparison young adults will complete the study and estimate 10 participants will not meet inclusion/exclusion criteria following initial clinical interview).

8 Sample size rationale

To input text, click in the light grey area below.

The proposed N in this study has the power to detect medium to large effects. At an alpha=0.05, 30 subjects per group will provide >80% statistical power to detect a within subject ES d≥0.5 and a between group ES d≥0.7. This compares favorably with large ESs calculated from between group differences in subjective response to alcohol in youth at risk for bipolar disorder (defined by previous hypomanic experiences; d>1.3) [53]. Our design

is sufficiently powered for both aims. In preliminary data, we observed large between group ESs when comparing differences in subjective response to alcohol (with cohen's d ranging from 0.7 to 1.3; Aim 1a), large within group ESs when performing correlations between response to alcohol and drinking patterns (r's ranging 0.7 to 0.9, Aim 1b), and large ESs in healthy participants (when comparing alcohol scan to baseline scan for Aim 2) with cohen's d ranging from 0.4 to 3.3. Conversely, we observed small ESs in bipolar disorder when comparing alcohol and baseline scans (with ESs as low as 0.03). Calculated sample size required to reach significance from pilot data ranged between N=3 to N=29 across both aims. The recruitment of 30 per group through this application ensures adequate power for testing our hypothesis.

OBTAINING INFORMED CONSENT

9 Consent and Assent Processes

Provide a detailed description of the consent process including who will obtain consent, where, and when consent will occur in such a manner that participants have sufficient time for adequate consideration.

To input text, click in the light grey area below.

Subjects are consented on a 1:1 basis with the PI, co-investigators, or research associates. The staff member reads the consent form aloud with the subject. The subject is encouraged to stop the staff member and ask questions along the way. In addition, the staff member anticipates questions and describes anything that seems unclear in more detail. After reading the consent form, the subject is asked again if they have any questions. Any questions are answered. They are then asked by the staff member whether he/she wishes to participate (consent). This enhances independent decision-making by never assuming the subject automatically wants to participate after reading the consent form.

Subjects will be asked if they will permit us to stay in contact with them in order to invite them to return for the second assessment and scanning session 1-year later. There may be some subjects who may only be willing to participate in the imaging component but will not wish to give a saliva sample and choose not to participate in the genetic component. In that case they will only be consented for the interview and the imaging component of the study.

It will be emphasized during the consent process that if a subject would like research data collected during their participation in the research study to be release to their physician that we will provide an authorization form for them to sign. We will have this form available if they would like one at the time of consent or they can contact us at any point after their study visit at which time we will provide the authorization form for them to sign (See Appendix I). After signing the authorization form an investigator from the study will provide the requested information to their physician.

Additionally, we recognize that informed consent is a process, not simply signing a form. Consequently, we regularly review the protocol and subject options as they participate.

In light of COVID-19 and to decrease density of research participants on UT Austin's campus consenting can be done remotely through redcap. Study personnel will send the consent form via email to the interested participant following a phone screen. The participant will then have time to review. Study staff

will schedule the enrollment visit. This enrollment visit can be done remotely. At the start of a remote enrollment visit, study staff will first go over the consent and allow time for questions as above. If the individual still wants to participate a link to the consent form in redcap will be sent to the participant. They will sign in redcap. Following consenting, they will complete their clinical assessments online or over the phone. They would then come to the laboratory on a day following completion of the clinical assessments for the alcohol/placebo MRI sessions (the baseline MRI scan would be collected at the beginning of the first beverage session).