Detailed Protocol Title: Behavior and brain responses to drugs

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Summary: Alcohol abuse and dependence remain significant public health issue, and there is a need to identify risk factors predicting excessive alcohol use. We and others have demonstrated individuals vary widely in their responses to an acute dose of alcohol: Some people experience mainly stimulant-like effects which are generally considered pleasurable, whereas others experience sedative-like effects which are rated more negatively (Holdstock and de Wit, 1998; King et el 2011). Moreover, the stimulant-like responses to alcohol appear to be predictive of an escalation in use (King 2016). An important question is whether the patterns of stimulant-like and sedative-like subjective effects correspond to differences in brain activation with the drug. We (Weafer et al, 2018) recently reported a good correspondence between stimulant-like subjective response to intravenous alcohol (0.8 g/kg) and activation of ventral striatal brain areas. In the present project, we wish to extend these interesting findings in two ways: i) to examine the dose-relationships between the mood-brain correlations by administering placebo and two doses of alcohol (0.4 and 0.8 g/kg), ii) to investigate the relationship when the drug is administered by the more naturalistic oral route. We propose to assess brain activation patterns in relation to subjective effects using fMRI in a counterbalanced, 3-session, placebo-controlled, double-blind, within-subjects design with placebo, 0.4 g/kg alcohol and 0.8 g/kg alcohol. During an initial drug challenge screening session, 50 potential scanning subjects will receive a single dose of 0.8 g/kg alcohol, to identify individuals who exhibit a pronounced stimulant effect (N=15) or a sedative effect (N=15) from the drug, and only these will participate in the two scanning sessions. We hypothesize that individual variation in the self-reported stimulant or sedative-like effects of alcohol will correspond with variation in activation patterns in reward-related brain regions.

Background: In humans, acute alcohol administration produces subjective stimulation and mood-enhancement in some individuals, but it produces sedative-like effects and dysphoria in others (e.g., Holdstock and de Wit, 1998; King et al 2011). These distinctive subjective effects are also associated with differences in the propensity to consume alcohol. In early studies (de Wit et al. 1987, 1989), we found that individuals who reported greater increases in elation and vigor and greater stimulant effects after alcohol consumed more alcohol-containing drinks in a choice test, whereas individuals who reported greater sedative effects were more likely to prefer placebo beverages over alcohol-containing drinks. These findings support the idea that individual variation in the subjective response to alcohol influences alcohol consumption and may therefore also influence the development of alcohol abuse and dependence. However, little is known about neural basis of these individual differences in mood effects of alcohol.

Functional imaging techniques have been used to localize the acute effects of psychoactive agents in the brain. In an early study, we (Metz et al, 1994; de Wit et al, 1990) assessed cerebral glucose utilization (FDG PET) after alcohol in individuals who varied in their liking of alcohol. Although we observed some correlations between subjective responses to alcohol and changes in regional glucose utilization, these were difficult to interpret given the small

number of subjects. More recently, a study used fMRI to show that oral alcohol suppressed brain activity during performance of simple cognitive tasks (Horn et al. 2006). However, few studies have examined the localized effects of alcohol in the brain in relation to its self-reported subjective effects. As noted above, we recently (Weafer et al, 2018) examined fMRI BOLD response after intravenously administered alcohol. As expected, we found that alcohol produced stimulant-like effects in a subset of individuals, and using region of interest analyses we showed that the time course of stimulation correlated with BOLD signal in the striatum. In the present study we aim to extend this finding i) using more naturalistic, oral administration of ethanol, ii) using two different doses of alcohol, and iii) adding ASL measures to monitor changes in blood perfusion to inform interpretation of neural activation changes. We hypothesize that inter-individual variation in the self-reported subjective effects of alcohol will correspond to variation in brain activation patterns. Stimulant-like subjective effects are expected to be associated with increases in the mesolimbic system (related to dopamine activity), whereas sedative-like effects are expected to be more associated with areas rich in GABA.

Design: We will measure individual differences in brain activity after two doses of alcohol (0.4 g/kg, 0.8 g/kg) or placebo using fMRI. Participants (N=50) will first be pre-selected ('ascertained') based on their responses to a single dose of alcohol (0.8 g/kg) in the behavioral laboratory. Individuals who exhibit either a clear stimulant-like response or a clear sedative-like response to alcohol will be invited to continue to the three fMRI scanning sessions. From the 50 participants tested, we will select 15 stimulant responders and 15 sedative responders. The three imaging sessions will be at least 72 h apart. At each session, subjects will receive the beverage containing alcohol or placebo, and then be placed in the fMRI scanner. Order of the three drug conditions (0, 0.4 and 0.8 g/kg ethanol) will be randomized and the drug will be administered under double-blind conditions. Immediately before and after the scan, subjects will complete standardized questionnaires to assess mood and subjective drug effects. We hypothesize that stimulant-like subjective effects will be associated with increases in activation in the striatum and regions related to the mesolimbic dopamine circuit. To minimize variability related to body composition and cycle phase, only males will be recruited for this preliminary study. Later, we will extend the study to include female participants.

Subject Recruitment and Screening

Screening interviews and orientation sessions will be conducted in the Human Behavioral Pharmacology Laboratory (HBPL; 5841 S. Maryland Ave., L484-496). Forty healthy male social drinkers aged 21-35 years will be recruited from the university and surrounding community using posters, newspaper advertisements and word-of-mouth referrals. To qualify subjects must report having consumed 4 drinks on a single occasion at least once in the last three months. Subjects will be recruited without regard to race or ethnicity, provided they meet the screening criteria. Potential subjects will be screened under protocol 13681B. Initial eligibility will be ascertained in a telephone interview conducted by the recruiter (age, current drug use, medical conditions), and appropriate candidates will be scheduled for an in-person interview. Eligible candidates will undergo a structured clinical psychiatric interview to exclude persons with major psychiatric disorders (DSM V; APA 2016). Subjects will complete a psychiatric symptom checklist (SCL-90; Derogatis 1983), the Beck Depression Inventory (BDI; Beck 1996), the Michigan Alcoholism Screening Test (MAST; Selzer 1971), the Barratt Impulsiveness Scale-11 (BIS11: Patton et al. 1995). Individuals will be excluded if a contraindication for MRI is present, including claustrophobia or metal implants. Individuals will receive a physical examination and electrocardiogram that will be approved by a physician. Subjects must have at least a high school education, be fluent in English, have a body mass index between 19 and 26, report no regular flushing response from alcohol and be in good physical and mental health. Subjects will not be accepted if they have a major psychiatric

disorder, serious medical condition, history of cardiac or liver disease, high blood pressure, history of drug or alcohol dependence (as determined in the diagnostic interview), work a night shift, counter-indication for MRI scanning (i.e. claustrophobia, pacemaker, heart valves) or are left handed. Candidates who drink more than 4 alcoholic or caffeinated beverages every day will be excluded. Subjects will report past month drinking using the Timeline Follow Back (TLFB; Sobell and Sobell, 2003) and alcohol problems using the Alcohol Use Disorders Identification Test (AUDIT; Babor *et al,* 1989).

Consenting Procedures:
At the orientation session subjects will read and sign the consent form, which outlines the procedures and lists the classes of drugs subjects might receive and their possible effects. Participants will be informed that they might receive a placebo, stimulant/anorectic, sedative/tranquilizer, opiate/analgesic, alcohol or a cannabinoid/marijuana-like drug. This use of mild deception in this study is necessary to prevent expectancy effects. Subjects will be told the purpose of the study is to investigate the effects of psychoactive drugs upon brain activation. In the consent form subjects agree not to use any drugs except for their normal amounts of caffeine for 24 hours before and 6 hours following each session, and not to operate any machinery requiring concentration for 6 hours following the sessions. They will also agree to fast for 4 hours prior to each session. Participants will also practice completing the questionnaires to be used in the study. They will be allowed to view the fMRI scanners, undergo a mock scan and be instructed on the imaging procedures which will be employed. We will query subjects about any prior history of claustrophobia or anxiety in small spaces. Each subject will complete a detailed questionnaire regarding the presence of any metal implants or metal objects in their body.

Experimental Procedure:
Subjects will first participate in a 4-hour drug-challenge screening session conducted in the HBPL, where they will receive the 0.8 g/kg dose of ethanol. The purpose of this session is to select 'stimulant responders' and 'sedative responders' to alcohol, and secondarily to ensure that they can tolerate the alcohol dose. Any subjects who experience nausea or other ill effects from the alcohol will be discontinued. Upon arrival at the HBPL, subjects will provide breath and urine samples to detect recent use of alcohol (Alco-sensor III, Intoximeters, St. Louis MO) and drugs (OnTrak TestStik, Roche Diagnostics Indianapolis, IN). Subjects will be instructed that a positive test will result in exclusion from the study. Subjects will complete baseline self-report and drug effect questionnaires, which will be repeated at 15-30 min intervals throughout the session. Heart rate and blood pressure will be assessed at these same times. After the baseline measures subjects will ingest the dose of alcohol, administered in a gelatin vehicle. Breath alcohol levels (BAL) will be obtained at 15-30 min intervals through the session. Subjects will complete two standardized questionnaires of alcohol effects, the Biphasic Alcohol Effects Scale (BAES; Martin et al, 1993) and the Subjective Effects of Alcohol Scale (SEAS; Morean et al 2013). Both of these include subscales assessing stimulant and sedative effects. Based on their combined responses we will select the 15 subjects who report the greatest stimulant effects and the 15 who report the least stimulant effects from the challenge dose to proceed to the three scanning sessions. Subjects who complete only the initial challenge dose session will receive $25.

The three scanning sessions will begin in the HBPL for screening measures, and then subjects will be escorted to the Magnetic Resonance Imaging Research Center (MRIRC) for alcohol administration and the fMRI scan. The three sessions will be conducted between 5 and 7pm at least 3 days apart. The end of the session will depend on BAL level; subjects will remain in the laboratory until levels fall below 0.04 g%, as per NIAAA guidelines. Participants will complete the fMRI safety questionnaire to confirm that they do not have any medical condition that

would preclude their participation and remove any metal on their person. They will complete pre-drug mood questionnaires and then ingest a dose (0, 0.4 or 0.8 g/kg ethanol) under double blind conditions and be placed in the scanner. Subjects will complete questionnaires rating their subjective state every 5 min, using a key pad. Heart rate will be recorded manually from the scanner control room every 2 min. BAL will be measured immediately after the scan. The fMRI scan is expected to take 60 min. After the scan they will be escorted to the HBPL until BAL levels return to 0.04 g%, and where they will complete final self-report ratings, physiological indices. After completing all three experimental sessions, the senior investigator will explain the purpose of the study. Participants will be told that the drug they received was alcohol and they will be paid $300. If subjects drop out before completing all three sessions they will receive $25 for each session completed.

Alcohol dose preparation

Alcohol and placebo will be administered in individual servings of black cherry sugar-free jello (Weafer et al, 2016). The doses of 0.4 and 0.8 g/kg ethanol are equivalent to 2 or 4 standard drinks, and are expected to yield BAL's of 40 and 80 mg/100 ml. The effects are expected to peak within 20 min. Alcohol will be administered in jello to mask the taste (Ralevski et al., 2006) and for fast consumption and absorption. The alcohol jello will be prepared with 3 parts 95% alcohol and 5 parts of water, mixed together with the jello powder and then refrigerated overnight. Placebo jello will be prepared with 8 parts of water. Participants will receive jello servings (5 g alcohol each) in black opaque 2 oz cups. The number of servings required to reach a dose of 0.8 g/kg alcohol will be determined for each participant based on body weight. Placebo will be administered in an equivalent number of jello servings.

fMRI Data Acquisition and Analysis

fMRI experiments will be performed using a 3T GE MRI scanner in the MRIRC. During the fMRI scan, the subject will be positioned supine inside the bore of the magnet and the head will be immobilized using padding. A 32 channel head coil will be used. A T2*-weighted gradient-echo echo-planer imaging (EPI) pulse sequence (TE (echo time) = 30ms; TR (repetition time) = 2000ms; flip angle = 70 degree; image matrix = 64 x 64; FOV (field of view) = 20cm x 20cm) will be used for functional scan.

EPI images will be processed and analyzed using AFNI (Cox 1996), FSL5.0.9 (FMRIB Software Library), and SPM12 (Wellcome Trust Centre for Neuroimaging). The time series will be volume registered to the median image to reduce motion artifact using 3dvolreg within AFNI. Motion outliers will be identified and censored from analyses. Subjects will be excluded if at least one of their scans showed motion >10mm total displacement in any one direction or if more than 50% of volumes within any time point window (see below) were censored.
fMRI analyses. Imaging data will be temporally downsampled to the behavioral data by taking a windowed average including the 35 time points before and after the time of the subjective response measurement, resulting in a downsampled dataset at the same temporal resolution as the behavioral data. We chose this relatively long time period because subjective responses are slow-changing, and averaging over a larger window allow for better signal to noise ratio. The windows do not overlap for any time point. The downsampled fMRI data will be voxel wise correlated with the subjective response data (across all time points) using AFNI's 3dfim+, with the resultant coefficients converted to z-scores using Fischer's transformation. The correlation maps will then be coregistered to the participant's anatomical data and warped to MNI space, resampled to 2mm isotropic voxels and smoothed with an 8 mm FWHM isotropic Gaussian kernel.

Further analyses will follow the plan we used in our previous study (Weafer et al, 2019). We compared correlation maps between the time course of subjective response ratings and the time course of BOLD signal following alcohol to those following placebo using paired *t*-tests. In order to control for typical alcohol consumption, we entered average drinks per week

from the TLFB as a covariate. Based on previous associations between subjective alcohol response and striatal activity, we focused our analyses within three hypothesis-driven anatomically-focused bilateral striatal regions of interest (ROIs): the nucleus accumbens, caudate, and putamen. We also included bilateral primary visual cortex to serve as a negative control ROI. The striatal ROIs were defined via the AAL atlas and created using MARINA (www.bion.de/eng/MARINA.php; Walter *et al,* 2003). The primary visual cortex ROI (Brodmann area 17) was created using the WFU PickAtlas tool (Maldjian *et al,* 2004; Maldjian *et al,* 2003). We extracted parameter estimates/ß weights representing the correlation between BOLD signal and subjective ratings in z-scores from each ROI following alcohol and placebo and conducted paired *t*-tests in SPSS to compare the two drug conditions. We applied a Bonferroni correction across the four ROIs tested, and so the p-value was set at $p < 0.0125$. We also conducted exploratory, whole-brain analyses of correlations between BOLD signal and stimulation and sedation ratings using SPM12 (cluster-forming voxel-wise height of $p < 0.001$, $k = 50$). Statistical inferences were based on cluster level significance, corrected for family wise error (FWE, $p < 0.05$).

ASL Analysis

ASL data will be acquired using a pseudo-continuous sequence (TR = 4700 ms, voxel size= 3.4x3.4x5mm, FOV = 220x220x145mm, flip angle = 90 degrees, TE = 13 ms , bolus time = 1800 ms, TI = 3600 ms) with 35 control-label pairs. A proton density (PD) image (TR = 10000 ms , TE = 13 ms, voxel size = 3.4x3.4x5mm) will be acquired and used as a calibration image for cerebral blood flow (CBF) quantification in addition to the T1-weighted structural scan used for registration. Data will be preprocessed and analyzed using FSL analysis tools (Smith et al., 2004). Each data set will be preprocessed using a pipeline including motion correction, registration of ASL to the structural image, partial volume correction and distortion correction. Quantification of CBF will be completed using FSL's BASIL tool (Chapell et al., 2009). CBF will be quantified in units of ml/100g/min using a kinetic model and defaults for the parameters consistent with the formula in the ASL consensus paper (Aslop et al., 2015). For group analysis, quantified CBF images will be normalized to MNI space, smoothed and adjusted to account for individual differences in global CBF and voxelwise within-group ANOVAs will be conducted to assess for drug effects. Voxels showing differential perfusion will be converted to masks and used to interpret drug effects found from fMRI analyses.

Dependent Measures:

- **Subjective Effects.** Participants will complete comprehensive subjective effects questionnaires during the initial baseline session to determine their subjective alcohol profile. They will complete the three questionnaires described below at 15-30 min intervals during the baseline session. During the scanning sessions they will complete only the 5 questions of the DEQ (below) at 5 min intervals.

Biphasic Alcohol Effects Scale (BAES; Martin et al, 1993): 14-item questionnaire on which subjects rated the degree to which they feel subjective stimulant and sedative responses to alcohol on 11-point likert-type scales.

Subjective Effects of Alcohol Scale (SEAS; Morean et al, 2013): also a 14-item questionnaire on which subjects rated the degree to which they feel subjective stimulant and sedative responses to alcohol on 11-point likert-type scales.

The Drug Effects Questionnaire (Morean et al 2013) consists of four adjectives describing subjects' current subjective state, each associated with a 100mm line that is anchored at one end with "not at all" (0) and the other with "extremely" (100). The VAS will contain five questions; "Do you feel a drug effect right now?" (none at all to extremely), "Do you like the

effects you are feeling now?" (rated from "dislike" to "like very much"), "Are you high?" (rated from "not at all" to "very"), and "Feeling lively and talkative" (rated from "not at all" to "very much"), and "Feeling relaxed or sluggish" (rated from "not at all" to "very much").

- **Physiological Measures**

Heart rate and blood pressure will be measured 15-30 min intervals throughout the initial challenge session, and following the scan on the scanning sessions. BAL will be assessed using (Alco-sensor III, Intoximeters, St. Louis MO) at 15-30 min intervals in the initial challenge session, and immediately after the scan in the fMRI sessions.

HUMAN SUBJECTS

***Human subjects involvement and characteristics*:** Subjects in these studies will be normal healthy males, aged 21-35 years. No special classes of vulnerable individuals will be included. Subjects will be accepted without regard to race or ethnicity as long as they meet inclusion criteria. Subjects will undergo extensive psychiatric and medical screening before participating, including a face-to-face interview with a trained interviewer to determine health history, current drug use and lifetime drug use history, and to screen for current and past psychiatric problems. Subjects complete the MAST (Seltzer, 1971) to detect alcohol problems. Subjects complete the SCL-90 to assess psychiatric symptomatology. All subjects will obtain an electrocardiogram, which must be normal, and are examined by a physician.
Exclusion criteria are:

1. any current medical condition requiring medication or abnormal electrocardiogram
2. current or past medical condition considered to be a contraindication for the study conditions
3. major psychiatric disorder or any history of psychosis
4. less than high school education
5. lack of fluency in English
6. night shift work
7. counter-indication for MRI scanning (i.e. claustrophobia, pacemaker, heart valves, body habitus too large for the MRI scanner bore).
8. left handedness

Inclusion of Minorities
Subjects will be accepted without regard to race or ethnicity.

Inclusion of Women:
Women will not be included in the study because sex differences in body composition introduce variations in the pharmacokinetics and hence subjective effects of alcohol. We aim to extend the study to women after this initial pilot study is complete.

Participation of children: Participants must be 21 because this study involves the administration of alcohol.

***Potential risks*:** The risks to subjects are minimal and involve risks of confidentiality, administration of alcohol, risks of fMRI scans and risk of being in a closed space when in the scanner. Laboratory personnel strictly maintain confidentiality, and records are kept in a secure location. Alcohol may produce side effects including constipation, drowsiness, coordination problems, memory loss, tiredness, depression, dizziness or faintness, rapid heart rate, raised blood pressure, restlessness, dry mouth, changes in sex drive, double or blurred vision, confusion, slurred speech, shakiness or tremor, headache and nausea or muscle weakness.

We have administered the proposed dose of alcohol in previous studies with no adverse effects. For the proposed study we will recruit subjects who report moderate drinking. Subjects will not be allowed to leave the lab unless their blood alcohol level is less than 0.04mg% and they will be instructed not to drive after the sessions. Subjects will be fully debriefed following the study.
Magnetic resonance imaging procedures are non-invasive, widely used and safe. The potential risks such as static magnetic field, radio-frequency field, magnetic field gradients, and acoustic noise are rarely dangerous or life threatening. Additional minor or rare risks include: 1) discomfort due to lying still for approximately an hour; 2) fast imaging sequences, such as those employed in this study, have the potential to induce peripheral nerve stimulation (PNS), which can be described as a light touching sensation on the skin surface and may cause mild discomfort but is not harmful to the subject; 3) anxiety reaction/panic attack induced by either confinement of the scanner or exposure to visual stimuli; 4) the magnetic resonance imaging may reveal a minor or significant lesion in the brain (e.g., tumor) previously unknown to the subject.

Adequacy of protection against risks:
Recruitment and informed consent: Subjects will be recruited from the university and surrounding community by posters, advertisements in the student newspaper and online, and word-of-mouth referrals. At the time of the initial screening interview and again during the orientation session preceding the study subjects will be required to read the consent form and may ask any questions they may have about it. After the study has been fully explained and questions have been answered by the Principal Investigator and/or Research Assistant, and before the first session, the subject will sign the consent form. Subjects agree in the consent not to take other drugs for 24 hours before each session. Subjects will be informed that breath alcohol levels and urines will be obtained before each session.

***Protection against risk*:** To protect against, or minimize any possible risks, we follow the following procedures:
i. Subjects will be carefully screened to exclude those who are physically or psychiatrically at risk (see above).
ii. Studies are conducted in a laboratory located in a hospital, where emergency assistance (including the psychiatry resident on-call and a psychiatrist connected with the study) is close at hand.
iii. A technician or nurse is present during all sessions. Heart rate and blood pressure will be monitored regularly.
iv. Subjects agree not to take any drugs for 12 hours before the sessions and compliance is monitored by breathalyzer and urine tests.
vi. Subject files containing confidential information are maintained in a locked cabinet in the PI's office. Only personnel directly connected with the study have access to this information, and these individuals are instructed in the importance and procedures for maintaining confidentiality.
vii. Data collected in the study are identified by subject codes only, and no data will be published in a form by which the subject can be identified.

MRI Scanning: Necessary precautions for safety for magnetic exposure will be taken and ensured in each subject and each will be screened for MRI safety with a standard MRIRC safety form. Prior to inclusion in the fMRI study, the presence of potential MRI risks, such as pacemakers, surgical clips, metallic surgical devices, and/or other irremovable ferrous-containing materials will be excluded. Minor risk of discomfort due to lying still for an hour will be minimized by custom pads and pillows to make the subject as comfortable as possible. The subjects will be constantly monitored for any side effects and will be treated appropriately be

physicians and nurses available. Earplugs will be used to reduce discomfort due to noise. The study may be aborted if the subject has any discomfort. The safety of the subjects will be continually monitored. The likelihood of PNS is low as the MRI machine is operated within FDA guidelines.

Discovery and disclosure of incidental finding or abnormality on MRI scans: First, all subjects will be instructed in their formal consent process about the potential risks (see consent form for details) of discovering an incidental finding or abnormality on their MRI scan. Second, if an abnormality is found in a subject's MRI scan, the study physician will contact the subject and refer the patient for medical follow-up for the problem if the subject requests, including a referral to a primary care doctor. If a subject has a doctor, the study physician will contact the subject's doctor, at the request and with the permission of the subject, to inform the participant of the finding on the MRI scan and to help to get the appropriate follow-up. The decision as to whether to proceed with further examination or treatment lies solely with the subject and physician.

Potential benefits: Subjects will benefit from the information obtained during the screening procedure (e.g., physical examination and electrocardiogram, as well as psychiatric screening). This is particularly beneficial to individuals who are excluded during the screening because of some previously undiagnosed condition. These individuals are referred for treatment. Subjects are paid for their participation. They may also request information about their performance and responses during the studies.
The minimal risks to subjects are justified by the knowledge to be gained. The findings will be important from a basic science perspective. The data will help us to elucidate the neural substrates of alcohol-induced subjective effects and how these vary between individuals which might determine individual susceptibility to alcohol abuse and dependence.

Confidentiality: Screening information and subjective and physiological data will remain in the lab at all times, and will only be accessible to personnel directly related to the study. Subjects will be identified only by assigned code numbers in all analyses, and publication of results will not identify any subjects by name. Data will not be shared unless a qualified scientist expressly requests it for re-analysis or verification purposes. In this event, no subject names will be included in shared data, only code numbers.

Recruitment and informed consent**:** Subjects will be recruited from the university and surrounding community by posters, advertisements in the student newspaper, and word-of-mouth referrals. At the time of the initial screening interview and again during the orientation session preceding the study subjects will be required to read the consent form and may ask any questions they may have about it. After the study has been fully explained and questions have been answered by the Principal Investigator or post-doctoral Research Associate, and before the first session, the subject will sign the consent form. The consent form outlines the procedures to be followed. Subjects agree in the consent not to take other drugs for 24 hours before and 12 hours following each session, and not to operate any machinery requiring concentration for 12 hours following the sessions. Subjects will be informed that blood alcohol (BAL) levels and urine samples will be obtained before each session.

Summary
We propose to compare responses to acute oral doses of ethanol in healthy young adults who experience mainly stimulant subjective effects from the drug (N=15) or mainly sedative effects (N=15). To identify stimulant and sedative responders we will first administer a single dose of alcohol (0.8 g/kg) to 50 healthy adults to characterize their responses. From the 50 subjects who complete this initial session we will select 15 stimulant responders and 15 sedative

responders, selecting individuals who report the largest and smallest increases on self-reported Arousal (Profile of Mood States). We anticipate some dropouts because of scheduling issues, illness, movement artifact during scanning and other technical problems. The subjects will participate in three scanning sessions, at least 3 days apart. Each scanning session will consist of an oral dose of alcohol (0, 0.4 or 0.8 g/kg), and a 60-min fMRI scan with resting state BOLD and ASL acquisition sequences.