Document Coversheet

Study Title: Neurobiological Factors Underlying Sex Differences in Risk for Alcohol Abuse

Institution/Site:	University of Kentucky
Document (Approval/Update) Date:	1/27/2024
NCT Number:	NCT04543942
IRB Number	50301
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IRB Approval
1/27/2024
IRB # 50301
IRB1
CLOSED

PROTOCOL TYPE (VERSION 4)

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Which IRB

◉ Medical ○ NonMedical

Protocol Process Type

○ Exemption
○ Expedited (Must be risk level 1)
◉ Full

IMPORTANT NOTE: You will not be able to change your selections for "Which IRB" and "Protocol Process Type" after saving this section. If you select the wrong IRB or Protocol Process Type, you may need to create a new application.

See below for guidance on these options, or refer to ORI's "Getting Started" page. Please contact the Office of Research Integrity (ORI) at 859-257-9428 with any questions prior to saving your selections.

Which IRB

The **Medical IRB** reviews research from the Colleges of:

- Dentistry
- Health Sciences
- Medicine
- Nursing
- Pharmacy and Health Sciences
- and Public Health.

The **Nonmedical IRB** reviews research from the Colleges of:

- Agriculture
- Arts and Sciences
- Business and Economics
- Communication and Information
- Design; Education
- Fine Arts
- Law
- and Social Work

Note: Studies that involve administration of drugs, testing safety or effectiveness of medical devices, or invasive medical procedures must be reviewed by the **Medical IRB** regardless of the college from which the application originates.

Which Protocol Process Type

Under federal regulations, the IRB can process an application to conduct research involving human subjects in one of three ways:

- by exemption certification
- by expedited review.
- by full review;

The investigator makes the preliminary determination of the type of review for which a study is eligible. Please refer to ORI's "Getting Started" page for more information about which activities are eligible for each type of review.

The revised Common Rule expanded exemption certification category 4 for certain secondary research with identifiable information or biospecimens. The regulations no longer require the information or biospecimens to be existing. For more information see the Exemption Categories Tool.

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PROJECT INFORMATION

0 unresolved comment(s)

Title of Project: (Use the exact title listed in the grant/contract application, if applicable).
If your research investigates any aspect of COVID-19, please include "COVID19" at the beginning of your Project Title and Short Title

Neurobiological factors underlying sex differences in risk for alcohol abuse

Short Title Description
Please use a few key words to easily identify your study - this text will be displayed in the Dashboard listing for your study.

Sex differences alcohol

Anticipated Ending Date of Research Project: 2/28/2024

Maximum number of human subjects (or records/specimens to be reviewed) 60

After approval, will the study be open to enrollment of new subjects or new data/specimen collection? ○ Yes ◉ No

Are you requesting that the UK IRB serve as the lead IRB for a multi-site study, or that the UK IRB defer review to another IRB? [Click here for "IRB Reliance" help]
○ Yes ◉ No
If "Yes," before completing your IRB application, fill out the Reliance Request Form and submit it to irbreliance@uky.edu.

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INFORMED CONSENT/ASSENT PROCESS/WAIVER

0 unresolved comment(s)

For creating your informed consent attachment(s), please download the most up-to-date version listed in "All Templates" under the APPLICATION LINKS menu on the left, and edit to match your research project.

Additional Resources:

- Informed Consent/Assent Website
- Waiver of Consent vs. Waiver of Signatures
- Sample Repository/Registry/Bank Consent Template

Consent/Assent Tips:

- If you have multiple consent documents, be sure to upload each individually (not all in a combined file).
- If another site is serving as the IRB for the project, attach the form as a “Reliance Consent Form” so the document will not receive a UK IRB approval stamp; the reviewing IRB will need to stamp the consent forms.
- Changes to consent documents (e.g., informed consent form, assent form, cover letter, etc...) should be reflected in a 'tracked changes' version and uploaded separately with the Document Type "Highlighted Changes".
- It is very important that only the documents you wish to have approved by the IRB are attached; DELETE OUTDATED FILES -- previously *approved* versions will still be available in Protocol History.
- Attachments that are assigned a Document Type to which an IRB approval stamp applies will be considered the version(s) to be used for enrolling subjects once IRB approval has been issued.
  Document Types that do NOT get an IRB approval stamp are:
  - "Highlighted Changes",
  - "Phone Script", and
  - "Reliance Consent Form",
  - "Sponsor's Sample Consent Form".

How to Get the Section Check Mark

1. You must:

   a) provide a response in the text box below describing how investigators will obtain consent/assent, and
   b) check the box for at least one of the consent items and/or check mark one of the waivers

2. If applicable attach each corresponding document(s) **as a read-only PDF**.
3. If you no longer need a consent document approved (e.g., closed to enrollment), or, the consent document submitted does not need a stamp for enrolling subjects (e.g., umbrella study, or sub-study), only select "Stamped Consent Doc(s) Not Needed".
4. After making your selection(s) be sure to scroll to the bottom of this section and SAVE your work!

Check All That Apply

- ☐ Informed Consent Form (and/or Parental Permission Form and/or translated short form)
- ☐ Assent Form
- ☐ Cover Letter (for survey/questionnaire research)
- ☐ Phone Script
- ☑ Informed Consent/HIPAA Combined Form
- ☐ Debriefing and/or Permission to Use Data Form
- ☐ Reliance Consent Form
- ☐ Sponsor's sample consent form for Dept. of Health and Human Services (DHHS)-approved protocol
- ☐ Stamped Consent Doc(s) Not Needed

Attachments

Informed Consent Process:

Using active voice, describe how investigators will obtain consent/assent. Include:

- the circumstances under which consent will be sought and obtained
- the timing of the consent process (including any waiting period between providing information and obtaining consent)

- who will seek consent
- how you will minimize the possibility of coercion or undue influence
- the method used for documenting consent
- if applicable, who is authorized to provide permission or consent on behalf of the subject
- if applicable, specific instruments or techniques to assess and confirm potential subjects' understanding of the information

Note: all individuals authorized to obtain informed consent should be designated as such in the E-IRB "Study Personnel" section of this application.

Special considerations may include:

- Obtaining consent/assent for special populations such as children, prisoners, or people with impaired decisional capacity
- *Research Involving Emancipated Individuals*
  If you plan to enroll some or all prospective subjects as emancipated, consult with UK legal counsel **prior to submitting this application to the IRB**. Include research legal counsel's recommendations in the "Additional Information" section as a separate document.
- *Research Involving Non-English Speaking Subjects*
  For information on inclusion of non-English speaking subjects, or subjects from a foreign culture, see IRB Application Instructions for Recruiting Non-English Speaking Participants or Participants from a Foreign Culture.
- *Research Repositories*
  If the purpose of this submission is to establish a research repository describe the informed consent process. For guidance regarding consent issues, process approaches, and sample language see the Sample Repository/Registry/Bank Consent Template.

Upon arriving at the lab, all participants' proof of age will be checked and each will be asked to sign an informed consent form describing the nature of the experiment and outlining all of the conditions for participation. Consent will be obtained by the Principal Investigator. The consent form provides the potential volunteer with information about the study (e.g., who is conducting it, contact information for the investigators and medical staff, how it is funded, where it will take place, and the purpose of the study), what will be required of the volunteer (e.g., time commitment, alcohol administration, and dietary, drug, and alcohol use restrictions prior to sessions), the risks to the volunteer (e.g., MRI scanning), the rights of the volunteer (e.g., confidentiality and voluntary participation), and the benefits of participating (e.g., monetary compensation and scientific knowledge). The informed consent form will be explained thoroughly and signed on-site. Each volunteer will receive a copy of their informed consent document and will sign a document indicating its receipt. The PI will review all screening materials and sign off on consent forms. After consent is obtained, participants will provide a breath sample to verify a zero BrAC and urine sample to test for pregnancy and other drug use. Anyone disqualified for a positive test result, or declining to continue at any time after appearing at the research site, will receive a prorated payment for sessions completed and dismissed. Transportation will be provided.
Our previous research in this area finds that participants are quite comfortable with the testing protocol and the reporting of information. Any complaints from the participants regarding the administration of this protocol will be responded to immediately. The PI will be informed of these issues, which will also be documented.

☐ Request for Waiver of Informed Consent Process

If you are requesting IRB approval to waive the requirement for the informed consent process, or to alter some or all of the elements of informed consent, complete, Section 1 and Section 2 below.

Note: The IRB does not approve waiver or alteration of the consent process for greater than minimal risk research, except for planned emergency/acute care research as provided under FDA regulations. Contact ORI for regulations that apply to single emergency use waiver or acute care research waiver (859-257-9428).

SECTION 1.

Check the appropriate item:

☐ I am requesting a waiver of the requirement for the informed consent process.

☐ I am requesting an alteration of the informed consent process.

If you checked the box for this item, describe which elements of consent will be altered and/or omitted, and justify the alteration.

SECTION 2.

Explain how each condition applies to your research.

a) The research involves no more than minimal risk to the subject.

b) The rights and welfare of subjects will not be adversely affected.

c) The research could not practicably be carried out without the requested waiver or alteration.

d) Whenever possible, the subjects or legally authorized representatives will be provided with additional pertinent information after they have participated in the study.

e) If the research involves using or accessing identifiable private information or identifiable biospecimens, the
not practicably be carried out without using such information or biospecimens in an identifiable format.

- Private information/specimens are “identifiable” if the investigator may ascertain the identity of the subject or if identifiers are associated with the information (e.g., medical records). This could be any of the 18 HIPAA identifiers including dates of service.
- If not using identifiable private information or identifiable biospecimens, insert N/A below.

Request for Waiver of Signatures

If you are requesting IRB approval to waive the requirement for signatures on informed consent forms, **your research activities must fit into one of three regulatory options**:

1. The only record linking the participant and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., a study that involves participants who use illegal drugs).
2. The research presents no more than minimal risk to the participant and involves no procedures for which written consent is normally required outside of the research context (e.g., a cover letter on a survey, or a phone script).
3. The participant (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm, the research presents no more than minimal risk to the subject, and there is an appropriate alternative mechanism for documenting that informed consent was obtained.

Select the option below that best fits your study.

*If the IRB approves a waiver of signatures, participants must still be provided oral or written information about the study. To ensure you include required elements in your consent document, use the **Cover Letter Template** as a guide. There is an English and a Spanish version.*

Option 1

Describe how your study meets these criteria:

a) The only record linking the participant and the research would be the consent document:

b) The principal risk would be potential harm resulting from a breach of confidentiality (i.e., a study that involves subjects who use illegal drugs).

Under this option, each participant (or legally authorized representative) must be asked whether (s)he wants to sign a consent document; if the participant agrees to sign a consent document, only an IRB approved version should be used.

Option 2

Describe how your study meets these criteria:

a) The research presents no more than minimal risk to the participant:

b) Involves no procedures for which written consent is normally required outside of the research context (i.e. a cover letter on a survey, or a phone script):

Option 3

Describe how your study meets these criteria:

a) The subject (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm.

b) The research presents no more than minimal risk to the subject.

c) There is an appropriate alternative mechanism for documenting that informed consent was obtained.

RESEARCH DESCRIPTION

0 unresolved comment(s)

You may attach a sponsor's protocol pages in the "Additional Information" section and refer to them where necessary in the Research Description. However, each prompt that applies to your study should contain at least a summary paragraph.

Pro Tips:

- **Save your work often to avoid losing data.**
- **Use one of the attachment buttons in this section or under the Additional Information section to include supplemental information with your application. During the document upload process, you will be able to provide a brief description of the attachment.**

Background

Include a brief review of existing literature in the area of your research. You should identify gaps in knowledge that should be addressed and explain how your research will address those gaps or contribute to existing knowledge in this area. For interventional research, search PubMed and ClinicalTrials.gov for duplicative ongoing and completed trials with same condition and intervention(s).

Alcohol abuse inflicts enormous physical, emotional, and financial burdens on the individual and society at large. Knowing who is at risk for alcohol abuse, and why, is crucial for the development of effective prevention and treatment strategies. Alcohol abuse has been traditionally considered a male-oriented problem and as a consequence research on risk factors specific to women has been minimal. However, the sex gap in substance abuse is closing rapidly, and findings from both animal and human studies suggest that females are actually more vulnerable to drug use than males. As such, there is an urgent need to identify sex differences in risk factors for alcohol abuse in order to develop sex-specific prevention and treatment efforts. One clear candidate risk factor is poor inhibitory control, both in terms of baseline levels of inhibition and sensitivity to the disinhibiting effects of alcohol. Recent studies suggest that sex hormones affect inhibitory control in drug-free individuals, potentially contributing to sex differences in baseline levels of inhibition. However, the degree to which fluctuations in sex hormones influence sex differences in inhibition-related brain function in sober and intoxicated individuals is not known. The proposed project will determine the neural and hormonal mechanisms underlying sex differences in sensitivity to the disinhibiting effects of alcohol in heavy drinkers.

Objectives

List your research objectives. Please include a summary of intended research objectives in the box below.

The overall objective of the research is to identify hormonal determinants of alcohol effects on brain activation during response inhibition (BARI) in young adult female and male drinkers. BARI will be assessed using fMRI during performance of the stop signal task. This task reliably activates right-lateralized prefrontal regions implicated in inhibitory control. We will assess BARI during IV alcohol (60mg%) and saline infusion in women during the early follicular and mid-luteal phases and in men at matched intervals.
Aim 1: To determine the influence of circulating sex hormones on BARI responses to alcohol. Based on the positive relation between estradiol and BARI in sober heavy drinking women, we hypothesize that baseline levels of estradiol will be positively related to BARI following alcohol.
Aim 2: To determine the effects of menstrual cycle phase on BARI responses to alcohol. We hypothesize that women will be more sensitive to the impairing effects of alcohol on BARI in the early follicular phase, when hormone levels are low.
Aim 3: To determine the degree to which alcohol effects on sex hormones influence alcohol effects on BARI. We hypothesize that less alcohol-induced increase in estradiol will predict greater alcohol-induced decrease in BARI.
Aim 4: To determine sex differences in BARI responses to alcohol. Based on our previous findings that heavy drinking women show less BARI than men when sober, we hypothesize that women will display greater alcohol-induced decrease in BARI than men, and that the sex difference will be most pronounced for women in the early follicular phase.

Study Design

Describe and explain the study design (e.g., observational, secondary analysis, single/double blind, parallel, crossover, deception, etc.).

- *Clinical Research*: Indicate whether subjects will be randomized and whether subjects will receive any placebo.
- *Community-Based Participatory Research*: If you are conducting community-based participatory research (CBPR), describe strategies for involvement of community members in the design and implementation of the study, and dissemination of results from the study.
- *Qualitative research*: Indicate ranges where flexibility is needed, if a fixed interview transcript is not available, describe interview topics including the most sensitive potential questions.
- *Research Repositories*: If the purpose of this submission is to establish a Research Repository (bank, registry) and the material you plan to collect is already available from a commercial supplier, clinical lab, or established IRB approved research repository, provide scientific justification for establishing an additional repository collecting duplicate material. Describe the repository design and operating procedures. For relevant information to include, see the UK Research Biospecimen Bank Guidance or the UK Research Registry Guidance.

This study will use a within- and between-subjects, placebo-controlled, single-blind design in a sample of female (N=30) and male (N=30) young adult heavy drinkers. Subjects will attend four fMRI sessions (two in the early follicular phase and two in the mid-luteal

phase for women, and at matched intervals for men) in which they perform the stop signal task and a resting state undergoing either IV alcohol (60mg%) or saline infusion (placebo). Alcohol and saline sessions within each phase will be separated by 24-48 hours. Dose and phase order will be counter-balanced. Blood samples will be collected at baseline and during infusion to assess levels of estradiol, progesterone, and testosterone. The primary outcome measure will be brain activation during response inhibition.

Attachments

Subject Recruitment Methods & Advertising

Describe how the study team will identify and recruit subjects. Please consider the following items and provide additional information as needed so that the IRB can follow each step of the recruitment process.

- How will the study team identify potential participants?
- Who will first contact the potential subjects, and how?
- Will you use advertisements? If so, how will you distribute those?
- How and where will the research team meet with potential participants?
- If applicable, describe proposed outreach programs for recruiting women, minorities, or disparate populations.
- How you will minimize undue influence in recruitment?
- Attach copies of all recruiting and advertising materials (emails, verbal scripts, flyers, posts, messages, etc.).

For additional information on recruiting and advertising:

- IRB Application Instructions - Advertisements
- PI Guide to Identification and Recruitment of Human Subjects for Research

The study will recruit subjects through flyers, brochures, posters, Research Spotlights, ads placed on campus and in the surrounding community and region (Study Team will place/remove ads), including but not limited to the UK Medical Center, UK Clinics, Good Samaritan Hospital, Student Center, UHS, the 5 UK Center for Clinical and Translational Research wall mounts, Cardinal Hill, monitor screens, and area facilities and businesses. Subjects may be recruited through paid print and digital advertisements, including brochures, magazines, newspaper (e.g., Herald Leader, Bluegrass Area, Courier Journal, Cincinnati Enquirer, Health & Wellness, Chevy Chaser, Hamburg Journal, Business Lexington, or other publications in the surrounding region e.g., Bluegrass Regional print & digital ads, may include Appalachian counties), Radio (e.g., Sirius, Clear Channel, Cumulus, LM Communications, Public Radio, Pandora, etc.), Television spots, scrolling information on community stations, and theater screens. Recruitment ads may also appear on billboards, Lextran buses, taxicabs, other transportation methods, and Craig'sList. The study will employ a pre-screening eligibility survey to determine if a volunteer meets basic inclusion/exclusion criteria. We will build and administer the eligibility survey on UK's REDCap which provides HIPAA compliant storage on UK servers and encrypted transmission of survey responses. The link will be included in study information sent to ResearchMatch participants who have indicated interest in the study. Before redirecting the volunteer outside of ResearchMatch and to the REDCap survey, the volunteer is once again asked to confirm their interest in completing the pre-screening survey. Interested individuals will contact the experimenter by phone. The following initial inclusion criteria will be obtained over the phone as preliminary screening to be verified at the intake session:
i) Confirmation of age (21-29). Volunteers will be told to bring proof of age to the laboratory (e.g., driver's license or passport).
ii) General health status. Callers will answer questions from the Telephone Screening Interview.
iii) Contraindication for fMRI. Callers will answer questions from the MR screening form to confirm that they do not have any metal in the body.
iv) Drinking status. Volunteers will be asked how many alcoholic beverages they consume in a typical week, and how often they consume 4/5 (for women/men) or more drinks in 2 hours. They will also answer questions from the Alcohol Use Disorders Identification Test.
v) No history of drug or alcohol use disorder. Callers will be asked if they are currently or have previously sought treatment for a drug or alcohol use disorder.
vi) Pregnancy. Women will be asked if they are currently pregnant or breastfeeding. It will be explained that no pregnant women or women who are breastfeeding can participate in the study. Women will be told that they will be required to submit a simple urine sample for a pregnancy test (testing human chorionic gonadotrophin (HCG) levels) and that a non-negative result would disqualify them from participation.
vii) Urine drug screen. It will be explained to subjects that they must submit a urine sample prior to each session that will be screened for drug use that would disqualify them from participating.
viii) Zero BrAC check. Callers will be informed in advance that they must have a zero BrAC and will be given a breath test when they arrive at the experimental site.
ix) Regular menstrual cycle and birth control. Women will be asked if they have regular menstrual cycles, and the typical length of their menstrual cycles. They will also be asked if they are using any type of hormonal contraception.
Any persons excluded from participation during phone screening will simply be thanked for their interest. Appropriate volunteers will be given a general description of the study and the criteria for participation will be explained. They will then be scheduled and instructed to abstain from alcohol and other drugs for 24 hours. Prospective subjects are also told that they could receive alcohol during the test sessions so that alternate transportation home is provided.
This study will be advertised on recruitment internet webpages in digital or video form (e.g., UKclinicalresearch.com, ResearchMatch.org, CenterWatch.com, CISCRP, UK, CCTS and may utilize Google Adwords). The study will be promoted via social media, including Facebook boost ads, UK_CCTS Facebook, UK_CCTS Twitter, UK_CCTS Instagram, UK and UKHC social media, and departmental/lab pages. If advertised on UKClinicalresearch.com, the online study flyer will include an option for interested individuals to enter and submit their contact information, they will be asked whether study team can contact them (Yes or No) via study-related text messages, and CCTS will also ask, 'How did you learn about the study? Internet and social media recruitment will follow the terms of use for each site utilized. The study will also be promoted through UK HC monitor screens. Potential participants may be

identified from registry databases, including but not limited to ResearchMatch.org, Wellness Health and You, Sanc
Aging, Infectious Disease, Dentistry, and the Markey Cancer Center. The CCTS attends outreach activities to promote research participation in general (e.g., Roots & Heritage Festival, Latino Festival, Eastern Kentucky University, Transylvania Health fairs, etc.) and will bring all relevant study flyers that are enrolling participants. This study may also go out on email distribution, listservs, or e-newsletters, e.g., the CCTS list serv, Markey Cancer Affiliates list servs, ResearchMatch.org, Wednesday's Word, Kentucky Office of Rural Health (KORH), Appalachian Translational Research Network (ATRN), etc. We may utilize physician referral letters to community physicians for patient recruitment. Articles and interviews about the researchers and research study may be promoted via UKNow, Kentucky living, and other media outlets. Research and study-related articles published on UKNow may contain standard language directing interested individuals on where to read more about research and current studies. UKPR, UK HealthCare marketing or the CCTS PRS may create videos to promote research, researchers and their studies to local, regional and national media venues and on internal hospital monitors. UK HealthCare may place study recruitment flyers on their internal and external racks (e.g., UK pharmacies, clinics, UK Libraries and Lexington Libraries) or on digital monitors. Participants may be recruited using newsletters, such as In the Loop, Health Matters, Making a difference, and external news letters. The study may also be advertised through UKPR and UKHC outreach activities. All of these sources will be used to recruit participants from the Lexington area and surrounding counties. Advertisements will invite moderate to heavy drinkers (age 21 - 29) to participate in a study of the effects of alcohol on brain activity. The investigators have extensive experience using this recruitment procedure in communities for alcohol and other drug studies. All advertisements will be approved by the UK Institutional Review Board (IRB) and the UK Office of Public Relations.

Attachments

Attach Type	File Name
Advertising	Flyer.v2.PR_APPROVED.pdf
Advertising	PSYCH-063 APPROVED.pdf
Advertising	PSYCH-063 MON APPROVED.pdf
Advertising	PSYCH-063-rm APPROVED.pdf
Advertising	PSYCH-063-sm APPROVED.pdf
Advertising	SHIVA flyer females with QR codePR edit STAMPED.pdf
Advertising	SHIVA general flyer with QR code PR edit STAMPED.pdf
Advertising	SHIVA flyer female heavy drinkers sept 2021 Non-CCTS stamped.pdf
Advertising	ARCHE _Video_Stamped for IRB.pdf

Research Procedures

Describe how the research will be conducted.

- What experience will study participants have?
- What will study participants be expected to do?
- How long will the study last?
- Outline the schedule and timing of study procedures.
- Provide visit-by-visit listing of all procedures that will take place.
- Identify all procedures that will be carried out with each group of participants.
- Describe deception and debrief procedures if deception is involved.

Differentiate between procedures that involve standard/routine clinical care and those that will be performed specifically for this research project. List medications that are explicitly forbidden or permitted during study participation.

Orientation Session. During the first session, study procedures will be explained, and participants will read and sign the consent form. They will be told that the study is examining the influence of sex (male/female), sex hormones, and menstrual cycle phase on the brain's response to alcohol, and they will be informed that the infusion will contain alcohol or saline (inactive substance). Participants will complete self-report impulsivity measures, including the Barratt Impulsiveness Scale (BIS11; Patton et al. 1995) and the UPPS-P (Whiteside and Lynam 2001), as well as a practice round on the stop signal task. Female participants will be shown how to conduct the at-home luteinizing hormone (LH) tests (see below). Participants will agree not to use alcohol or drugs for 24 hours before each session, and fast for 2 hours before each session.
Determination of menstrual cycle phase. Women will complete a guided calendar-based interview to determine average menstrual cycle length and to estimate the onset of next menses (Roche and King 2015). Women will be randomly assigned to start in either the early follicular (2-7 days following the onset of menses) or the mid-luteal (5-10 days following ovulation) phase. Blood samples collected during each session will be used to retrospectively confirm that the targeted menstrual cycle phase was achieved. Ovulation will be confirmed by at-home urinary luteinizing hormone (LH) assays. Beginning on day 7 of their cycle, participants will complete the at-home LH assays every day, until a positive test is confirmed. They will be provided with small (2oz) cups and lids, as well as 20 LH tests. Each morning, they will use the cups to collect a small sample of urine. They will place the LH test (a short, paper stick) into the urine sample for 3 seconds, and then lie the test flat on the cup lid. Three minutes later, they will take a picture of the test and send it via text message to the Research Assistant. The RA will confirm whether the test is positive or negative. If negative, the RA will ask the participant to test again the next day, and if positive, the RA will inform the participant that she can stop the LH tests.

Brain Imaging Sessions. Sessions will take place in Kastle Hall, the Clinical Research Unit (CRU), and the Magnetic Resonance Imaging and Spectroscopy Center (MRISC) at the University of Kentucky. Participants will report to the lab in Kastle Hall and provide breath and urine samples to detect recent drug use or pregnancy. Positive pregnancy tests will result in exclusion. If a subject tests positive for a drug, and it is determined that the drug is not regularly used, the session is rescheduled. If subjects test positive a second time, they are discontinued. Participants will complete an MR scanner safety questionnaire and then complete a pre-scan practice round of the stop signal task. Subjects will be escorted to the CRU, where a nurse will draw a blood sample to assess baseline hormone levels. The nurse will then place an intravenous catheter in the dominant arm for delivery of infusion. Participants will then be escorted to the MRISC and positioned on the scanner bed. The nurse will connect the IV catheter via a length of tubing to the pump located outside the scanning room. Subjects will complete baseline subjective measures of drug effects: the Biphasic Alcohol Effects Scale (Martin et al. 1993) and the Drug Effects Questionnaire (DEQ). The infusion will begin, and 15 minutes later participants will complete the stop signal task (20 minutes), subjective measures (2 minutes), and a resting state scan (8 minutes). Pulsed arterial spin labeling (PASL) scans (6 min each) will also be acquired to measure regional cerebral blood flow (rCBF; ml/100 g/min) using a one-compartment model (Kareken et al. 2013; Wang et al. 2011) at baseline and following task performance. These scans will be conducted to ensure that alcohol infusion does not significantly affect global rCBF. Blood samples will be drawn for hormonal assays immediately prior to each PASL scan, and then placed on ice. During resting state scans, participants will be instructed to remain awake with eyes open, fixated on a crosshair, 'not think about anything in particular', and remain still. After resting state scans, participants will be asked to confirm that they did not fall asleep during the scan. Head movement will be minimized by detailed instructions to participants and a conformal pillow fitted to the participant's head using a vacuum pump to withdraw air from the pillow. Physiological sensors for heart rate and respirations will monitor participant status during scanning, and will be incorporated in reconstruction. Participants are told to immediately alert the technician if they experience discomfort or feel unwell, in which case the scan will be stopped and the participant removed from the scanner. The entire scan should require 1 hour. Immediately following the scan, the nurse will draw a second blood sample to assess acute alcohol effects on hormone levels.
Imaging Parameters. Imaging will be performed using a state-of-the-art Siemens Prisma 3T MRI scanner using a 64-channel head coil. BOLD echo-planar imaging (EPI) scans will be acquired for each task-based functional scan (XYZ dimension = 96*96*51; FOV [RL, AP, FH - mm] = 240, 240, 127; slice thickness [mm] = 2.5; gap thickness = 0; in-plane resolution [mm] = 2.5*25; echo time [ms] = 30; repetition time [ms] = 1500, flip angle [degrees] = 70; multiband factor = 3) and resting state scan (echo time [ms] = 29; repetition time [ms] = 760, flip angle [degrees] = 54; multiband factor = 5). High-resolution T1-weighted structural scans will also be acquired for co-registration and normalization to the Montreal Neurological Institute (MNI) coordinate system (XYZ dimension = 320*320*208; FOV [ap, fh, rl - mm] = 256, 256, 166; slice thickness [mm] = 0.8; gap thickness = 0; in-plane resolution [mm] = 0.8*0.8; echo time [ms] = 3; repetition time [ms] = 2000).
Infusion Procedure. The University of Kentucky Hospital Pharmacy Investigational Drug Service will prepare all infusion solutions (6% alcohol in half-normal saline and half-normal saline only), and alcohol and half-normal saline will be infused by a nurse from the CRU using the Computer-assisted Alcohol Infusion System (CAIS). The alternate method of administration in alcohol challenge studies is by oral ingestion. Due to uncontrollable gastric absorption kinetics, substantial variability in the time course of breath alcohol concentration (BrAC) is unavoidable with oral administration. Using IV alcohol infusion, we can provide precisely the same time course of brain exposure to alcohol in every subject. We have successfully administered alcohol intravenously in the scanner in the past

(Weafer et al. 2018). The infusion profile will be customized for each participant to achieve a linear ascension in B
min, followed by a clamping of BrAC at 60mg% for 40 minutes, allowing for constant exposure throughout BOLD imaging. Saline (placebo) infusions will follow the same time profile. This dose was chosen because it has been shown to reliably affect activation of inhibitory networks in previous fMRI studies (Gan et al. 2014; Kareken et al. 2013).
Once the scanning session is complete, the nurse will remove the intravenous catheters and the subject will be escorted back to Kastle Hall. We will obtain a breath alcohol sample and subjects will be allowed to leave the laboratory when BrAC is below 20mg% (NIAAA guidelines). If subjects are not able to arrange alternative transportation, we will provide transportation home. After the final imaging session, participants will attend a debriefing session, either in person or over the phone, in which the purpose of the study and the infusions they received will be told to them, and they can ask questions about the study.

Attachments

Data Collection & Research Materials

In this section, please provide the following:

- Describe all sources or methods for obtaining research materials about or from living individuals (such as specimens, records, surveys, interviews, participant observation, etc.), and explain why this information is needed to conduct the study.
- For each source or method described, please list or attach all data to be collected (such as genetic information, interview scripts, survey tools, data collection forms for existing data, etc.).
- If you will conduct a record or chart review, list the beginning and end dates of the records you will view.

The research material consists of subjects' questionnaire scores, diagnostic test scores, urine analyses for drug metabolites and urine human chorionic gonadotrophin (pregnancy), fMRI data (BOLD, CBF), hormonal assays (estradiol, progesterone, testosterone), behavioral performance on the stop signal task, and subjective reports (BAES, DEQ). Drug metabolites tested include: amphetamine and amphetamine salts (e.g., methylphenidate), barbiturates, benzodiazepines, cocaine, opiates, and tetrahydrocannabinol. (No archival records or other data will be used). Authentication of drug and pregnancy tests is assured by purchase only from reputable commercial dealers who must adhere and document specific quality standards. The Timeline Follow-back (TLFB) and Alcohol Use Disorders Identification Test (AUDIT) will be used to provide valid and reliable assessments of drinking habits and problems, including typical frequency and quantity of alcohol consumption (number of standard drinks). These measures will be used to confirm that all participants meet criteria for heavy drinking (i.e., 10-30 drinks per week and at least two binge episodes (4/5 drinks or more for women/men in two hours) in a 30 day period on the TLFB and a score of 8 or above on the AUDIT). Trait impulsivity measures will also be assessed, including the UPPS-P and BIS-11.
Dependent Measures: Subjects will complete the following measures during each brain imaging session.
Stop Signal Task: While in the scanner, participants will complete three runs of the stop signal task, adapted and validated for use in fMRI (Kareken et al. 2013). Participants are instructed to respond as quickly as possible when a 'go' target appears (left or right arrow) by hitting the corresponding left or right button on the MRI-compatible keypad. They are also instructed to inhibit that response when a 'stop' signal (a red vertical arrow) occasionally occurs. Each run consists of 80 'go' trials and 40 'stop' trials. The duration of the delay to presentation of the stop signal following the go signal is adjusted until the participant is able to successfully inhibit the response on 50% of trials. The final mean delay of the stop signal, based on this 50% success rate criterion, is subtracted from the mean go reaction time, providing the stop signal reaction time (SSRT), which is the behavioral measure of response inhibition. The BOLD contrast of interest will be activation during correct inhibition trials compared to correct go trials [StopInh>Go].
Hormone assays: Serum assays of estradiol, progesterone, and testosterone will be analyzed by the CCTS Biomarker Analysis Lab.
Subjective Alcohol Effects: Subjective reports of mood and drug effects will be assessed using the BAES (a 14-item scale that measures stimulation and sedation) and the DEQ (a 100 mm visual analogue scale that measures the following: feel substance, like substance, and want more of the substance). Both scales have well-documented validity.

Attachments

Attach Type	File Name
DataCollection	UPPS-P-PaperCopy.doc
DataCollection	AUDIT.docx
DataCollection	BAESPaperCopy.doc
DataCollection	DEQ paper version.doc
DataCollection	TLFB.docx
DataCollection	BIS questionnaire.pdf

Resources

Describe the availability of the resources and adequacy of the facilities that you will use to perform the research. Such resources may include:

- Staffing and personnel, in terms of availability, number, expertise, and experience;
- Computer or other technological resources, mobile or otherwise, required or created during the conduct of the research;
- Psychological, social, or medical services, including equipment needed to protect subjects, medical monitoring, ancillary care, or counseling or social support services that may be required because of research participation;
- Resources for communication with subjects, such as language translation/interpretation services.

All of the equipment and space needed to conduct this study is available in Kastle Hall, the MRISC, and the CRU. Within Kastle Hall, there is a private room for testing volunteers, including a desktop computer. The MRISC houses a Siemens Prisma 3T scanner, along

with an AVOTEC SL-6011 LCD projection system used with Psychology Software Tools Inc. visual presentation s
MRA, Inc. 10 channel, fiber optic, patient response system with trigger interface and visual/auditory patient monitoring; Current Designs, Inc. patient response Interface Unit with 12 fiber optic cables and an MRI-compatible handheld, trackball mouse; Medrad, Inc. SHS200 Power Injector; InVivo Research, Inc. Press 3160 MRI compatible physiological monitoring unit with a pulse oximeter, blood pressure cuff, intravascular blood pressure, ECG, respiration and CO2 monitoring. The CRU is an NIH-funded research unit, and a fully equipped and professionally staffed medical unit. The CRU provides support for nursing staff. I will utilize the CRU for several key aspects of this project, including drawing blood samples for hormonal assays, inserting the IV catheters and tubing for IV alcohol and saline administration, and administering the alcohol and saline infusions using pumps.

Potential Risks & Benefits

Risks

- Describe any potential risks – including physical, psychological, social, legal, ability to re-identify subjects, or other risks. Assess the seriousness and likelihood of each risk.
- Which risks may affect a subject's willingness to participate in the study?
- Describe likely adverse effects of drugs, biologics, devices or procedures participants may encounter while in the study.
- *Qualitative research* - describe ethical issues that could arise while conducting research in the field and strategies you may use to handle those situations.
- Describe any steps to mitigate these risks.

Benefits

- Describe potential direct benefits to study participants – including diagnostic or therapeutic, physical, psychological or emotional, learning benefits. This cannot include incentives or payments.
- State if there are no direct benefits.
- Describe potential benefits to society and/or general knowledge to be gained.

Describe why potential benefits are reasonable in relation to potential risks. If applicable, justify why risks to vulnerable subjects are reasonable to potential benefits.

The potential risks in this study are minimal and involve risks of 1) confidentiality; 2) the fMRI procedure; 3) insertion of intravenous catheters and needles (for IV alcohol administration and blood draws); 4) administration of alcohol; and 5) pregnancy testing.
1. Confidentiality: Laboratory personnel strictly maintain confidentiality, and records are kept in a secure location. However, there is a risk that a volunteer's Protected Health Information (PHI) may be seen by others. PHI is considered individually identifiable health information transmitted or maintained in any form (i.e., electronic means, on paper, or through oral communication) that relates to the past, present, or future physical or mental health conditions of an individual that may be used or disclosed. The following PHI will be collected as part of this project: name, address, telephone number, Social Security number, dates (birth, admission, discharge), medical record numbers, mental and physical health history, drug use history, results from mental and physical health screening, and data from experimental measures. All data will be coded by participant number only and any personal identifiers linking participants to their reports on questionnaires will be detached and destroyed as soon as participation is completed or disqualification occurs.
2. fMRI procedure: fMRI is a non-invasive procedure that is widely used and safe. Potential risks such as static magnetic field, radio-frequency field, magnetic field gradients, and acoustic noise are rarely dangerous or life-threatening. The risks of the study are extremely small when exclusion criteria are observed and are outweighed by the large benefits of these studies to clinical and neuroscience research. Subjects will be asked questions about claustrophobia and the presence of metal in their body to make sure that the MRI scan is safe. If they have implanted metal of any kind, they will not be scanned. For their safety, they will be asked to remove any metal in their clothing before the scan (for example, belts and rings). Subjects will be given noise dampening head phones to reduce the discomfort due to the noise of the machines. Subjects are asked to report any discomfort immediately. They may discontinue the scan at any time if they are too anxious to continue, by communicating with the scanning operator that they would like to end the session. Additional minor or rare risks include: i) discomfort from lying still for 1 hour; ii) fast imaging sequences may potentially induce peripheral nerve stimulation (PNS) that may cause mild discomfort but is not harmful to participants; iii) anxiety or panic attack caused by close confinement in the scanner; iv) the MRI may reveal a minor or significant lesion in the brain (e.g., tumor) previously unknown to the subject. The CRC nurse and PI and also the Study Physician will be available and/or present during the fMRI scans in order to evaluate the emergence of any anxiety/panic attack, elevated levels of anxiety, or emotional discomfort during the procedure.
3. Insertion of needles/catheters: Some risks are associated with the insertion of intravenous catheters. These include bruising and pain at the site of the needle insertion, and a small risk of infection. A trained CRU nurse will perform blood draws and catheter insertion to minimize pain and standard sterilization techniques and other routine precautions will be utilized in order to minimize the risk of needle-site infections.
4. Intravenous administration of alcohol: The possible adverse effects of alcohol include pain at the injection site, disorientation, or sedation. Nausea and/or vomiting are extremely unlikely given the moderate dose administered. No serious adverse effects have been reported in healthy men and women following intravenous administration of a 6% alcohol solution (Blekher et al. 2002; Davidson et al. 1997; Ray and Hutchinson 2004; Yoder et al. 2005). We have successfully administered a higher dose (80mg%) than that proposed here (60mg%) intravenously both in and out of the scanner (Weafer et al. 2018).
5. Pregnancy testing. There is a risk of psychological discomfort from exposure to a pregnancy test or the upset that might result from an unexpected non-negative outcome. These tests do, of course, require the participant's consent and cooperation, and all potential female participants are given advance notice of this test during initial phone contact. The PI's standard operation procedures will call for the exclusive use of a trained Research Assistant (RA) to give instructions, process the samples, and report the results to participants individually. The RA will advise participants of the conclusiveness of negative results and also stress the ambiguity of non-negative outcomes. The RA will explain that rather than repeating non-negative tests to try to rule out a possible false-positive, any

ambiguous result is grounds for disqualification. The assistant will also immediately offer specific advice about wh
precise follow-up testing and provide information about how to get counseling if desired.
The risks to subjects are justified by the knowledge to be gained regarding sex-specific behavioral and brain-mediated processes related to alcohol use. Knowledge about sex-specific risk factors for alcohol abuse will inform our understanding of the development and treatment of drug and alcohol use disorders in men and women. Also, participants in the research derive considerable educational benefit from their participation. Subjects are genuinely interested in studies of alcohol and have many questions about how the drug may affect them. The feedback to participants includes written educational information about blood alcohol levels and the risks of impairment likely to result from drinking various amounts of alcohol. Participants in our studies often comment that this information is extremely helpful in judging the safety of their drinking practices and deciding about activities, such as driving after drinking. Given the potential educational benefits that subjects derive from participating in this research, the minimal risk to subjects in this research is reasonable.

Available Alternative Opportunities/Treatments

Describe alternative treatments or opportunities that might be available to those who choose not to participate in the study, and which offer the subject equal or greater advantages. If applicable, this should include a discussion of the current standard of care treatment(s).

There are no alternative treatments.

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Records, Privacy, and Confidentiality

Specify where the data and/or specimens will be stored and how the researcher will ensure the privacy and confidentiality of both. Specify who will have access to the data/specimens and why they need access.

Describe how data will be managed after the study is complete:

- If data/specimens will be maintained, specify whether identifiers will be removed from the maintained information/material.
- If identifiers will not be removed, provide justification for retaining them and describe how you will protect confidentiality.
- If the data/specimens will be destroyed, verify that this will not violate retention policies and will adhere to applicable facility requirements.

If this study will use de-identified data from another source, describe what measures will be taken to ensure that subject identifiers are not given to the investigator.

If applicable, describe procedures for sharing data/specimens with collaborators not affiliated with UK.

For additional considerations:
Return of Research Results or Incidental Research Findings
HIPAA policies
FERPA policies
Procedures for Transfer agreements
Information regarding multi-site studies
NIH Genomic Data Sharing (GDS) Policy
Digital Data

All research materials obtained from participants will be collected directly from them at the time of recruitment and participation. The research material consists of subjects' questionnaire scores, fMRI data (BOLD, CBF), hormonal assays (estradiol, progesterone, testosterone), behavioral performance on the stop signal task, and subjective reports (BAES, DEQ). No archival records or other data will be used. All data will be coded by participant numbers and any personal identifiers linking participants to their reports on questionnaires and computer tests will be maintained in a separate location by the PI. The data will then be transferred to computer files with all individual identifiers removed. All data will be stored in coded files and locked in the laboratory area. All information will be in the form of numerical data and used for research purposes only. Results will be reported only for groups, and no single individual will be identified. Personal identifiers, such as names, will be removed from the subjects' data records. Urine samples will be collected at screening, prior to a subject's participation in the experimental protocol. These urine samples will be tested for the presence of a full range of drugs of abuse. Drug urine screens and urine pregnancy tests will also be conducted daily during the experimental protocol. Expired air samples will also be taken at these times to detect the presence of recent alcohol consumption. Other research materials obtained from the volunteers include demographic information, mental and physical health screening information, experimental data, and non-intrusive staff observations. Experimental data include the stop signal task measures, fMRI BOLD/CBF data, hormonal assays, and self-reported responses on questionnaires.
Files will not contain the name of the volunteer. Instead, each volunteer will be assigned a unique identifying number. All written documents will be stored in locked cabinets in the PI's office (Kastle Hall Room 205). All data will be retained for a period of at least six years after the end of the IRB approval period. Key access will be limited to immediate laboratory personnel. Electronic information will reside on a stand-alone, password-protected computer.
To protect or minimize any possible risks, we will follow these procedures:
1. Subjects will be carefully screened to exclude those who are physically or psychiatrically at risk.
2. The study will be conducted in the MRISC and the CRU (both of which are located in the hospital), where emergency assistance, including the Study Physician (Dr. Lon Hays), is close at hand. Dr. Hays will provide medical consultation for the project and 24 hour on-call support from the Psychiatry Department. All laboratory technicians will have completed the training course on Human Subjects

Protection and will be CPR and first-aid certified.
3. A technician or nurse is present during all sessions.
4. Subjects agree not to take any drugs for 24 hours before the sessions and compliance is monitored by breathalyzer and urine tests.
5. Subjects will remain in the laboratory until their BrACs have fallen below 20mg% (per NIAAA guidelines), and they will be provided with transportation home if needed.
6. Subject files containing confidential information will be maintained in a locked cabinet in the PI's office (Kastle Hall Room 205). 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.
7. 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.
8. 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 MR Safety form. Any individuals who have 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 1 hour will be minimized by custom pads and pillows to make the subject as comfortable as possible. Subjects will be constantly monitored for any side effects and will be treated appropriately by the available physicians and nurses. Earplugs may 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. Regarding the potential for PNS, the MRI machine is operated within FDA guidelines so the potential for PNS is low.
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 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 referral to a primary care doctor. If a subject has a primary care doctor, the Study Physician will contact the subject's doctor, at the request and with the permission of the subject, to inform him/her of the finding on the MRI scan and to help him/her to get the subject the appropriate follow-up. The decision as to whether to proceed with further examination or treatment lies solely with the subject and his/her primary care physician.
9. Alcohol Infusions: Subjects will be monitored carefully by the nurse and PI during infusions. Infusions and scans will be terminated and the subject removed from the scanner immediately if they report feeling nauseated. Subjects will fast for the 2 hours before scanning begins to minimize the possibility of aspiration of stomach contents. Additionally, the subject's head will be restrained only by a conformal pillow while in the scanner; they will be able to lift their heads at any time. Infusion solution will be prepared by the University of Kentucky Hospital Pharmacy Investigational Drug Service to ensure that the concentration of the infusate is not any higher than 6% alcohol, in order to reduce the risk of pain at the injection site. Infusion solutions will also be warmed using instant heat packs. The calculated pump rate will be close to the maximum rate of the pump and therefore accidental overdose due to the use of higher than calculated pump rates will be unlikely. Alarmed timers will be used by the nurse and PI to monitor the length of the infusion. All calculations will be double checked with the Senior MRI Research Technologist. We will exclude subjects who have not previously consumed alcohol and those who report less than regular moderate to heavy alcohol consumption.
10. A list of counseling and substance abuse treatment referrals will be provided to all participants. This referral will include psychological services such as The Harris Center at 859-257-6853.
11. The study will employ a pre-screening eligibility survey to determine if a volunteer meets basic inclusion/exclusion criteria. We will build and administer the eligibility survey on UK's REDCap which provides HIPAA compliant storage on UK servers and encrypted transmission of survey responses. The portable devices do not download the data, it is directly stored into the secure web-based connection (https) behind the firewall. All files are password protected once entered into the system. All project data is stored and hosted locally.

UK IRB policies state that IRB-related research records must be retained for a minimum of 6 years after study closure. Do you confirm that you will retain all IRB-related records for a minimum of 6 years after study closure?

◉ Yes ○ No

Payment

Describe the incentives (monetary or other) being offered to subjects for their participation. If monetary compensation is offered, indicate the amount and describe the terms and schedule of payment. Please review this guidance for more information on payments to subjects, including restrictions and expectations.

Participants will receive $75 for each brain imaging session attended, plus a $100 completion bonus, for a total of $400.

Costs to Subjects

Include a list of services and/or tests that will not be paid for by the sponsor and/or the study (e.g., MRI, HIV). Keep in mind that a subject will not know what is "standard" – and thus not covered by the sponsor/study – unless you tell them.

There are no anticipated costs to subjects.

Data and Safety Monitoring

The IRB requires review and approval of data and safety monitoring plans for greater than minimal risk research or NIH-funded/FDA-regulated clinical investigations.

- If you are conducting greater than minimal risk research, or your clinical investigation is NIH-funded, describe y
Monitoring Plan (DSMP). Click here for additional guidance on developing a Data and Safety Monitoring Plan.
- If this is a non-sponsored investigator-initiated protocol considered greater than minimal risk research, and if you are planning on using a Data and Safety Monitoring Board (DSMB) as part of your DSMP, click here for additional guidance for information to include with your IRB application.

The data and safety monitoring plan for this study follows the NIAAA guidelines for the administration of alcohol. The PI will be responsible for monitoring the safety and efficacy of the proposed study, executing the DSMP, and complying with the reporting requirements. The PI will be assisted by Dr. Lon Hays, the Study Physician, in the event that medical consultations are needed. A summary of the DSM report will be included in the annual progress report to NIAAA. The subjects' sociodemographic characteristics, expected versus actual recruitment rates, summary of AEs and SAEs, and any actions or changes with respect to the protocol will be included in this report.
Data Monitoring Plan: Subjective and behavioral data will be collected using standardized computerized measures. Brain imaging data will be identified with the study ID only and sent to a server owned by the PI by the MRISC staff. Hormonal data obtained from blood sample assays will also be sent to the PI by the analyzing laboratory. All subject data (subjective, behavioral, fMRI, and hormonal) will only be identified with the subject's ID. The PI will keep the codes that link the name of the participant and the study ID confidential in a password protected file on a password protected computer. Data from paper forms will be entered in the computer. Data will be analyzed using the general linear model and regression analyses within SPM and SPSS.
Safety Monitoring Plan: We will recruit healthy volunteers aged 21-29 years. Potential volunteers will be screened for physical and psychiatric health. Women will provide a urine sample for a pregnancy test before each session. Exclusion criteria are any serious medical conditions requiring medication, current or past medical condition considered to a be a contraindication for study condition, any current Axis I psychiatric disorder, including substance use disorders, any history of psychosis, less than a high school education, lack of fluency in English, and contraindication for MRI scanning (i.e., claustrophobia, pacemaker, heart valves). Women will be accepted only if they are not pregnant, lactating, or planning to become pregnant.
Subjects will attend an orientation session during which they will sign the consent form and be instructed on the procedures of the study. All subjects will be monitored for recent alcohol and drug use prior to each session. Those with positive tests will be rescheduled or dropped from the study. All fMRI sessions are conducted in a hospital setting. During the sessions, emergency medical assistance will be available by paging the Study Physician, the psychiatrist resident on call, or the general emergency number for the hospital. Alternately, the subject may be transported to the emergency room. All adverse events (AEs) and unanticipated problems occurring during the course of the study will be reported to the IRB by the PI. All AEs will be followed until resolved satisfactorily. If deemed necessary by a physician, a subject may be withdrawn from the study. AEs will be evaluated for serious adverse event (SAE) criteria (defined by the FDA). If an SAE should occur, it will be reported to the IRB, NIAAA, and the FDA. The initial report will be followed by a complete SAE report, sent to all three institutions. If a subject from the study or the investigator discontinues a subject's participation due to an SAE, the patient will receive follow-up medical care as necessary. Follow-up care will continue until the subject no longer requires hospitalization, the condition is stabilized with no future change expected, or the problem is determined to be unrelated to the alcohol administered in the study. The outcome of the SAEs will be reported to NIAAA. The annual progress report submitted to NIAAA will contain a summary of any SAEs occurring in the previous year.

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Future Use and Sharing of Material (e.g., Data/Specimens/Information)

If the material collected for this study will be used by members of the research team or shared with other researchers for future studies, please address the following:

- list the biological specimens and/or information that will be kept
- briefly describe the types, categories and/or purposes of the future research
- describe any risks of the additional use
- describe privacy/confidentiality protections that will be put into place
- describe the period of time specimens/information may be used
- describe procedures for sharing specimens/information with secondary researchers
- describe the process for, and limitations to, withdrawal of specimens/data

N/A

Are you recruiting or expect to enroll **Non-English Speaking Subjects or Subjects from a Foreign Culture**? (does not include short form use for incidentally encountered non-English subjects)

○ Yes ◉ No

Non-English Speaking Subjects or Subjects from a Foreign Culture

Recruitment and Consent:

Describe how information about the study will be communicated to potential subjects appropriate for their culture, and if necessary, how new information about the research may be relayed to subjects during the study.
When recruiting Non-English-speaking subjects, provide a consent document in the subject's primary language. After saving this section, attach both the English and translated consent documents in the "Informed Consent" section.

Cultural and Language Consultants:

The PI is required to identify someone who is willing to serve as the cultural consultant to the IRB.

- This person should be familiar with the culture of the subject population and/or be able to verify that translated documents are the equivalent of the English version of documents submitted.
- The consultant should not be involved with the study or have any interest in its IRB approval.
- Please include the name, address, telephone number, and email of the person who agrees to be the cultural consultant for your study.
- ORI staff will facilitate the review process with your consultant. Please do not ask them to review your protocol separately.

For more details, see the IRB Application Instructions on Research Involving Non-English Speaking Subjects or Subjects from a Foreign Culture.

Local Requirements:

If you will conduct research at an international location, identify and describe:

- relevant local regulations
- data privacy regulations
- applicable laws
- ethics review requirements for human subject protection

Please provide links or sources where possible. If the project has been or will be reviewed by a local ethics review board, attach a copy in the “Additional Information/Materials” section. You may also consult the current edition of the International Compilation of Human Research Standards

50301
CLOSED

Does your study involve **HIV/AIDS research and/or screening for other reportable diseases (e.g., Hepatitis**
○ Yes ◉ No

HIV/AIDS Research

If you have questions about what constitutes a reportable disease and/or condition in the state of Kentucky, see ORI's summary sheet: "Reporting Requirements for Diseases and Conditions in Kentucky" [PDF].

HIV/AIDS Research: There are additional IRB requirements for designing and implementing the research and for obtaining informed consent. Describe additional safeguards to minimize risk to subjects in the space provided below.

For additional information, visit the online IRB Survival Handbook to download a copy of the "Medical IRB's requirements for Protection of Human Subjects in Research Involving HIV Testing" [D65.0000] [PDF], and visit the Office for Human Research Protections web site for statements on AIDS research, or contact the Office of Research Integrity at 859-257-9428.

PI-Sponsored FDA-Regulated Research

Is this an investigator-initiated study that:

1) involves testing a Nonsignificant Risk (NSR) Device, or
2) is being conducted under an investigator-held Investigational New Drug (IND) or Investigational Device Exemption (IDE)?
○ Yes ◉ No

PI-Sponsored FDA-Regulated Research

If the answer above is yes, then the investigator assumes the regulatory responsibilities of both the investigator and sponsor. The Office of Research Integrity provides a summary list of sponsor IND regulatory requirements for drug trials [PDF], IDE regulatory requirements for SR device trials [PDF], and abbreviated regulatory requirements for NSR device trials [PDF]. For detailed descriptions see FDA Responsibilities for Device Study Sponsors or FDA Responsibilities for IND Drug Study Sponsor-Investigators.

- Describe the experience/knowledge/training (if any) of the investigator serving as a sponsor (e.g., previously held an IND/IDE); and
- Indicate if any sponsor obligations have been transferred to a commercial sponsor, contract research organization (CRO), contract monitor, or other entity (provide details or attach FDA 1571).

IRB policy requires mandatory training for all investigators who are also FDA-regulated sponsors (see Sponsor-Investigator FAQs). A sponsor-investigator must complete the applicable Office of Research Integrity web based training, (drug or device) before final IRB approval is granted.

Has the sponsor-investigator completed the mandatory PI-sponsor training prior to this submission?
○ Yes ○ No

If the sponsor-investigator has completed equivalent sponsor-investigator training, submit documentation of the content for the IRB's consideration.

Attachments

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CLOSED

HIPAA

0 unresolved comment(s)

Is HIPAA applicable? ◉ Yes ○ No

(Visit ORI's Health Insurance Portability and Accountability Act (HIPAA) web page to determine if your research falls under the HIPAA Privacy Regulation.)

If yes, check below all that apply and attach the applicable document(s):

☐ HIPAA De-identification Certification Form
☐ HIPAA Waiver of Authorization

Attachments

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CLOSED

STUDY DRUG INFORMATION

0 unresolved comment(s)

The term drug may include:

- FDA approved drugs,
- unapproved use of approved drugs,
- investigational drugs or biologics,
- other compounds or products intended to affect structure or function of the body, and/or
- complementary and alternative medicine products such as dietary supplements, substances generally recognized as safe (GRAS) when used to diagnose, cure mitigate, treat or prevent disease, or clinical studies of e-cigarettes examining a potential therapeutic purpose.

Does this protocol involve a drug including an FDA approved drug; unapproved use of an FDA approved drug; and/or an investigational drug?

◉ Yes ○ No

If yes, complete the questions below. Additional study drug guidance.

LIST EACH DRUG INVOLVED IN STUDY IN THE SPACE BELOW

Drug Name:

ethanol

Note: Inpatient studies are required by Hospital Policy to utilize Investigational Drug Service (IDS) pharmacies (Oncology or Non-Oncology). Use of IDS is highly recommended, but optional for outpatient studies. Outpatient studies not using IDS services are subject to periodic inspection by the IDS for compliance with drug accountability good clinical practices.

Indicate where study drug(s) will be housed and managed:

☑ Investigational Drug Service (IDS) UK Hospital

Other Location:

Is the study being conducted under a valid Investigational New Drug (IND) application?

○ Yes ◉ No

If Yes, list IND #(s) and complete the following:

IND Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

☐ Checkmark if the study is being conducted under FDA's Expanded Access Program (e.g., Treatment IND) or if this is an Individual Patient Expanded Access IND (FDA Form 3926).

FDA's Expanded Access Program Information for Individual Patient Expanded Access INDs, and attach the following:

- FDA Form 3926;
- FDA expanded access approval or correspondence;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the Expanded Access SOP.

Complete and attach the required Study Drug Form picking "Study Drug Form" for the document ty applicable drug documentation (e.g., Investigator Brochure; approved labeling; publication; FDA correspondence, etc.) should be attached using "Other Drug Documentation" for the document type.

Attachments

Attach Type	File Name
Study Drug Form	Ethanol_ Side Effects, Dosages, Treatment, Interactions, Warnings.pdf
Study Drug Form	Study.Drug.Form.pdf
Study Drug Form	Alcohol_monograph.pdf
Study Drug Form	CofA Lot# 01RM1504A Ethanol.pdf
Study Drug Form	Ethanol_Label_Primary.pdf

Statistical Analysis Plan. *Statistical Analysis of Brain Activation:* The measures of brain activation during response inhibition (BARI) are activation in frontal ROIs (e.g., DLPFC, IFC, ACC, pre-SMA, SMA, and pre-motor cortex), as measured by BOLD % signal change, examined during response inhibition [StopInh>Go]. We will first check that men and women are matched on demographics and drug and alcohol use, and confirm that the [StopInh>Go] contrast activated the inhibitory network circuitry.

Statistical Analysis of Brain Activation: We will perform regression analyses in SPM12 to assess the degree to which baseline hormone levels predict change in BARI following alcohol compared to saline [StopInh>Go, Saline>Alcohol]. We hypothesize that greater baseline E2 will predict less activation following alcohol compared to saline. We will conduct a between-subjects t test to compare men and women on the StopInh>Go, Saline>Alcohol contrast. We hypothesize that alcohol effects on BARI will be greater in women compared to men. Finally, we will calculate change scores (alcohol minus baseline) for hormone levels, and perform regression analyses to predict [StopInh>Go, Saline>Alcohol] from change in hormone levels. We hypothesize that greater alcohol-induced increase in E2 will predict greater decrease in activation following alcohol.