Study Protocol

Study Title: Brain Responses to Environmental Influences on Drinking Decisions

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ClinicalTrials.gov: NCT04067765

Principal Investigator: Dr. Michael Amlung
Department of Applied Behavioral Science and Cofrin Logan Center for Addiction Research and Treatment, University of Kansas, Lawrence, KS 66045
Email: mamlung@ku.edu
Phone: 785-864-6148

Local Principal Investigator: Dr. James MacKillop
Department of Psychiatry & Behavioural Neurosciences, McMaster University;
Peter Boris Centre for Addictions Research, St. Joseph's Healthcare Hamilton, Hamilton, ON L8N 3K7
Email: jmackill@mcmaster.ca
Phone: 905-552-1155, x39492

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St. Joseph's Healthcare Hamilton West 5th Site

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I. Lay Project Summary

Alcohol use disorder is a major public health issue and development of novel treatments and improved screening/diagnostic measures depends on advances in understanding the intersection between brain and behaviour in this disorder. This study uses techniques from an area of research known as neuroeconomics, which integrates concepts and methods from psychology, neuroscience, and economics to better understand how people make decisions and how these decisions are supported by the brain. One neuroeconomic concept that is especially relevant in the area of addictions is substance demand, or how consumption of a commodity (e.g., alcohol, tobacco, or drugs) is influenced by price and other factors. Previous studies have shown that alcohol demand is related to severity of alcohol misuse, drinking quantity/frequency, and treatment outcomes. In addition, we know that alcohol demand can also fluctuate in response to environmental cues such as alcohol-related stimuli (e.g., people report wanting to consume more alcohol and placing higher value on alcohol when in the presence of alcohol-related beverage cues relative to non-alcoholic beverage cues). This increase in consumption and value is clinically significant because it helps us understand how people with alcohol use disorders are negatively impacted by environmental stimuli related to drinking and how this prompts increases in craving and motivation to drink.

What remains unclear, however, is how the brain responds in these situations and whether these responses differ as a function of severity of alcohol misuse. Therefore, this study will use functional magnetic resonance imaging (fMRI) to understand brain activity patterns associated with changes in the value of alcohol in the presence of alcohol-related beverage cues relative to neutral-related beverage cues. Participants will be non-treatment-seeking adult heavy drinkers who are recruited from the community to participate in two testing sessions at St. Joseph's Healthcare Hamilton: 1) a baseline eligibility screening session and 2) an fMRI scan at the Imaging Research Centre. During the fMRI scan, participants will make decisions about how many alcohol beverages they would consume (hypothetically) at various prices while their brain activity during those decisions is measured. The experimental manipulation involves an in-scanner alcohol cue exposure task in which the drinking decisions will be made after viewing high-quality images of alcoholic (beer/wine/liquor) beverages or neutral (water/juice/soft drinks) beverages. This project has important clinical implications. Determining the neural signatures of change in alcohol demand in response to these real-world external influences has high potential to increase our understanding of how the brain supports decisions to control drinking (or inability to control drinking) in real-world drinking situations.

II. Background and Rationale

Neuroeconomics integrates principles from psychology, economics, and cognitive neuroscience to understand the neurobiology of decision making[1–3]. In alcohol research, neuroeconomics has unique potential to increase the ecological validity of functional neuroimaging by investigating cost-benefit decisions related to alcohol use disorder[4–6]. Our group has recently validated a novel functional MRI paradigm for measuring a behavioral economic index of reinforcing value of alcohol known as alcohol demand[7]. This refers to the process of making choices about alcohol consumption across a range of prices, in order to characterize both trait and state-based variation in alcohol value.

From a behavioral economic perspective, pathological motivation for alcohol reflects both generally high reinforcing value and acute phasic (or state-based) changes in alcohol value. These changes include increases resulting from potent environmental triggers, such as alcohol cues. In general terms, the working hypothesis is that individuals who are experiencing problems with alcohol may have difficulties refraining from or reducing their drinking when they encounter personally-relevant alcohol cues, such as their preferred drink or driving past a bar or liquor store. This change in motivation is captured on hypothetical alcohol purchase tasks in laboratory studies, whereby people report wanting to consume greater amounts of alcohol and are willing to spend more money on alcohol when they are in the presence of alcohol cues relative to neutral cues. Prior research has supported this hypothesis, including studies showing that demand is increased following exposure to alcohol cues in a simulated bar laboratory, or consumption of alcoholic beverages in a self-administration paradigm [8–10].

Despite increasing evidence from the behavioural literature suggesting that alcohol value dynamically increases in the presence of personally-relevant alcohol cues, how the brain responds in these situations remains unclear. Therefore, an important question is how do the brain processes supporting alcohol-related decisions change when people are making those choices in the presence of potent alcohol-related stimuli compared to when the choices are made under neutral conditions. Our group has validated a neuroeconomic task to measure brain activity related to alcohol demand decisions[11]. Our previous study using this task revealed significant neural activation in regions implicated in reward salience (ventral striatum), interoception/subjective desire (anterior insula), subjective awareness (posterior cingulate), conflict monitoring (anterior cingulate), and executive control (dorsolateral prefrontal cortex) in male heavy drinkers.

The current study will extend these initial findings by examining the neural correlates of changes in alcohol demand via an experimental manipulation that models motivational factors in real-world drinking decisions. We hypothesize that acute increases in alcohol value will be subserved by changes in areas associated with reward salience, interoceptive processing, and perceived value. Furthermore, the proposed studies will include both males and females allowing for systematic examination of sex differences. Finally, the study will examine whether severity of alcohol misuse moderates behavioural and neural responses to the alcohol cues.

III. Purpose

The core scientific purpose of this project is to use our novel fMRI paradigm to investigate the neural correlates of increases in alcohol demand resulting from exposure to alcohol cues. The specific aims are as follows:

Primary Aim #1: Characterize neural activity associated with increases in alcohol demand resulting from exposure to alcohol cues. Hypothesis: Increases in alcohol value following alcohol cues will be associated with significant increases in activity in ventral striatum, anterior insula, and posterior cingulate.

Secondary Aim #1: Investigate severity of alcohol misuse as a moderator of the manipulations. Hypothesis: Based on previous behavioral findings, we predict that increased AUD severity will enhance reactivity to cues both in terms of behavioural response and brain activity associated with alcohol decisions.

Secondary Aim #2: Examine patterns of functional connectivity underlying alcohol demand. Based on recent evidence supporting network-based perspectives in the neuroscience of decision making, we will conduct functional connectivity analyses to characterize the underlying neural networks that subserve alcohol demand in general and alterations in connectivity from the alcohol cue exposure.

IV. Design

This study will utilize a within-subjects design to compare heavy drinking individuals (N = 70, 50% female) in alcohol demand following an active (i.e., viewing alcohol-related cues) and a control (i.e., viewing neutral beverage cues) manipulation. Participation will involve one remote session and two in-person sessions, including a two-part eligibility screening and an fMRI scanning session. The in-person session will also include a validated laboratory alcohol cue exposure in the Peter Boris Centre for Addictions Research Simulated Bar Laboratory, although no actual alcohol will be consumed.

V. Settings

This study will primarily be conducted in the Peter Boris Centre for Addictions Research under the direction of Dr. MacKillop (LPI). The Peter Boris Centre for Addictions Research (PBCAR) is located at the SJHH West 5th site. The PBCAR has several private testing rooms, research assistant work space, private washroom, and a kitchenette. Dr. MacKillop's office is located within the PBCAR.

The laboratory-based alcohol cue exposure component will be conducted in the simulated bar laboratory within the PBCAR. The simulated bar room is equipped with a bar and bar stools, alcohol bottles, and alcohol-related artwork. Participants are also monitored via a closed circuit video camera

system to ensure compliance with study procedures and participant/staff safety. The bar lab component is described in detail in Section VIII. Study Procedures.

MRI data will be collected at the Imaging Research Centre (IRC) at the SJHH Charlton site. The IRC is home to a research-dedicated MRI scanner with MRI compatible patient monitoring and projection/response systems. The IRC also has a participant waiting room, private assessment rooms, an MRI simulator, and an MRI physics lab. The IRC is staffed by multiple licensed MRI technologists and an on-site MRI physicist.

VI. Sample Characteristics

Eligibility Criteria

Heavy drinking adults will be recruited from the Hamilton community. Participants will be required to consume alcohol in quantities equal to or above the NIAAA recommended weekly drinking limits of 14/7+ drinks for males/females. Participants who are currently in treatment for alcohol problems, or those who are currently seeking treatment for alcohol problems are not eligible for this study. Inclusion and exclusion criteria are summarized in **Table 1**.

Table 1. Eligibility Criteria

General Inclusion Criteria
1) 21-55 years old; 2) right-handed; 3) fluent English speaker; 4) heavy drinker (i.e., on average > 14/7 drinks per week for males/females in past three months; 5) > 1 heavy drinking episode weekly (heavy drinking episode = 5+/4+ for males/females) over past three months
General Exclusion Criteria
1) Currently receiving treatment, or seeking treatment, for alcohol related problems; 2) Current DSM-5 substance use disorder other than alcohol or tobacco; 3) Weekly or more frequent use of recreational drugs other than cannabis; 4) History of schizophrenia-spectrum disorders, psychotic disorders, bipolar disorder, or PTSD; 5) History of neurocognitive disorder or impairment; 6) MRI contraindications (e.g., metal in body, history of seizure, etc.); 7) history of serious brain injury; 8) currently taking psychotropic medications or medications that could affect cerebral blood flow; 9) pregnancy (females); 10) attending any study session with a positive breath alcohol concentration (BrAC > 0.00g%)

Sample Size

Sample size was determined via a power analysis based on our previously conducted proof-of-concept study. The power considerations pertain to within-subjects contrasts between choices made after acute exposure to neutral cues compared to alcohol cues. We based our effect sizes on a previous study that most resembles the proposed study cue exposure. Effect sizes for cue effects varied from medium to large, fs = .44-.56.A sample size of 70 (35 females) would be sufficiently powered to detect a conservative medium effect size ($f = .35$, $\alpha = .05$, $1-\beta = .80$). We anticipate oversampling on in-person screenings to account for ineligible participants and no-shows (estimated total number of screenings = 84). We will also oversample scans by 10% to account for the possibility of excessive head motion (N = 77).

VII. Assessments

Telephone Screening Interview

Initial eligibility for the current study will be assessed via a telephone interview conducted by a trained research assistant using a standardized script. The phone interview consists of the following:

- A brief description of the study.
- Questions assessing the inclusion and exclusion criteria for the study (**Table 1**).
- Statement concerning outcome (Positive vs. Negative) or follow-up if outcome is ambiguous (i.e., responses that require clearance from the study PI).

- For eligible and interested participants, scheduling of in-person session and providing information about lab location and other details pertaining to the study sessions.

Physical Measurements

During the in-person screening and scan session, physical measurements of participants will be completed. Physical assessments are provided in **Table 2.**

Table 2. Physical Measurements		
Variable	**Measure**	**Format**
Body Composition	Bioelectrical Impedance Analysis (BIA) Scale: weight, body fat percentage, total body water percentage, muscle mass, physique rating, BMR, metabolic age, bone mass, visceral fat	Electronic scale

Clinical Interview

During the in-person screening, participants will undergo a clinical interview assessing drinking behaviour, alcohol use disorder symptoms and personality disorder symptoms. Interview assessments are provided in **Table 3**.

Table 3. Clinical Interview Assessments		
Variable	**Measure**	**Format**
Drinking Quantity/Frequency	30-day Timeline Follow Back: Participants will report their alcohol consumption on a daily basis for the last 30 days.	Interview
Clinical Interviews	The Diagnostic Assessment Research Tool (DART) will be used for AUD diagnostic status[12]. The Structured Clinical Interview for DSM-IV Axis Two Disorders (SCID-II) will be used to assess cluster B personality disorders[13].	Interview

Questionnaires and Neurocognitive Measures

The majority of questionnaires will be administered electronically using REDCap software (using the McMaster University instance of REDCap), with a few paper-pencil questionnaires. We will also administer three neurocognitive tests via REDCap or Inquisit software. The list of questionnaires and neurocognitive tests, including the construct being assessed, the measure name (if applicable), and format, is provided in **Table 4**.

Table 4. Questionnaire Measures		
Variable	**Measure**	**Format**
MRI Safety / Compatibility	Imaging Research Centre Screening Form: MRI safety and contraindications.	Paper-Pencil
Study-Specific Data Sheet	Paper-pencil data sheet for MRI testing session. Used to record information about time since last use of alcohol/tobacco/drugs, date of last menstrual period, medications, etc.	Paper-Pencil

Demographics	Self-reported gender identity, sex, age, race, ethnicity, education, income, etc.	REDCap
Alcohol History	Self-report questionnaire assessing personal drinking history, family history of alcohol problems, and prenatal alcohol exposure	REDCap
Alcohol Craving	Penn Alcohol Craving Scale (PACS); self-report assessment of alcohol craving over the last week	REDCap
Alcohol Use Disorder Severity	Alcohol Use Disorders Identification Test (AUDIT); 10-item self-report screening for alcohol problems	REDCap
Nicotine Use	Fagerstrom Test of Nicotine Dependence (FTND); 6-item self-report screening for nicotine dependence	REDCap
Drug Use Frequency	NIDA Modified ASSIST; Self-report checklist assessing frequency of drug use in last 3 months	REDCap
Drug Use Severity	Drug Use Disorders Identification Test (DUDIT); 11-item self-report screening for drug use severity	REDCap
Cannabis Use	Cannabis Use Disorder Identification Test (CUDIT-R): self-report screening for cannabis use	REDCap
Depressive Symptoms	Patient Health Questionnaire-Depression; 9-item self-report measure of depression symptoms	REDCap
Anxiety Symptoms	Generalized Anxiety Disorder 7-item (GAD-7); self-report measure of anxiety symptoms	REDCap
COVID-19 Questionnaire	Self-report measure of the effect of COVID-19 on daily life	REDCap
Sobriety Questionnaire	5-item self-report measure of sobriety	REDCap
Personality Traits	Personality Inventory for DSM-5 Short Form (PID-5-SF); 100-item self-report measure of personality traits	REDCap
Criminal History	4-item self-report measure of criminal history	REDCap
Traumatic Experiences	Brief Trauma Questionnaire (BTQ); 10-item self-report measure of trauma	REDCap
PTSD Symptoms	PTSD Checklist for DSM-5 (PCL-5); 20-item self-report assessment of DSM-5 PTSD symptoms	REDCap
Neurocognitive Tests		
Working Memory	**Working Memory Span;** Computerized digit span test	Computer task
Verbal IQ	Verbal reasoning subscale of **Shipley Institute of Living Scale**	Computer task
Inhibitory Control (Two tasks)	**Go/No-Go Task;** computerized response inhibition task assessing ability to suppress prepotent/automatic behavioural responses to visual cues presented in rapid succession on the screen.	Computer task

	Flanker Task: computerized inhibition task assessing response selection under conditions of visual and cognitive interference.	

Cue Reactivity Measures

During the laboratory cue exposure, we will administer several assessments to measure the effects of neutral and alcohol cues on drinking motivation, positive and negative affect, and subjective arousal. The list of assessments is provided in **Table 5**.

Table 5. Cue Reactivity / Motivational Measures

Variable	Measure	Format
Alcohol Demand	Alcohol Purchase Tasks-State Versions (e.g., "how many drinks would you consume right now if they cost $3 each?". All choices are hypothetical.	REDCap
Alcohol Craving	Craving visual analog scales (e.g., three items assessing subjective alcohol craving; "How much do you want a drink?" "How high is your urge for a drink?" and "How much do you crave a drink?"; Rated from 0-100)	REDCap
Subjective Affect	Six 100-point affect circumplex items, from −50 to +50: Tense-to-Calm, Sad-to-Happy, Nervous-to-Relaxed, Bored-to-Excited, Stressed-to-Serene, and Depressed-to-Elated.	REDCap
Physiological Arousal	Blood pressure; heart rate	Electronic blood pressure monitor

Functional Magnetic Resonance Imaging (MRI) Scan

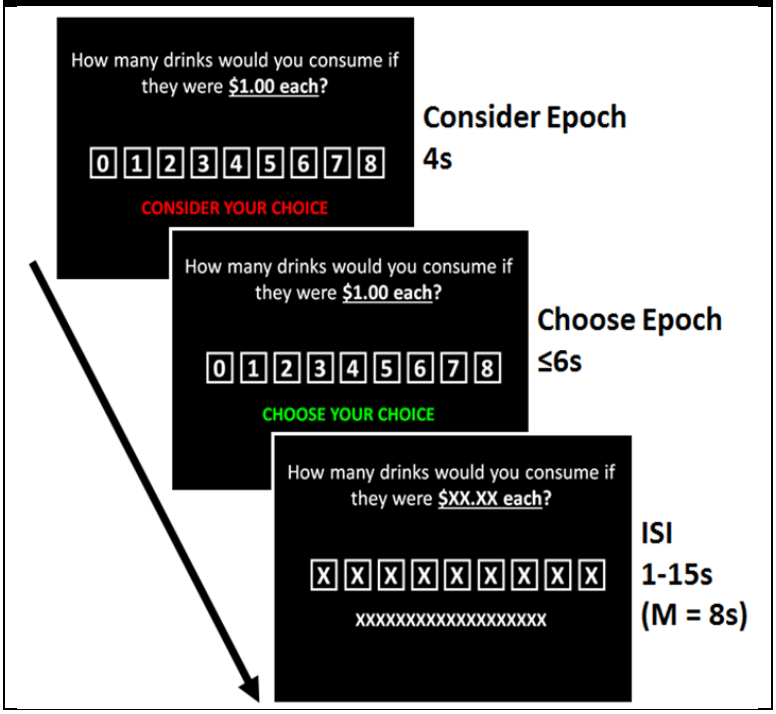
Participants will undergo a 60-minute fMRI scan at the Imaging Research Centre at SJHH on a research-dedicated 3-Tesla General Electric Discovery 750 MRI system. Scans will be administered by a licensed MRI technologist at the IRC.

1. Functional imaging will comprise T2*-weighted echo planar imaging scans with a gradient echo pulse sequence.
2. Structural imaging will comprise high-resolution T1-weighted fast spoiled gradient echo scan
3. Resting state functional connectivity scans will comprise T2*-weighted echo planar imaging scans with a gradient echo pulse sequence.

The in-scanner behavioural task is our fMRI alcohol demand paradigm (Alcohol Purchase Task; APT). A schematic depiction of the paradigm is presented in **Figure 1**. On each trial, participants are asked how many standard-sized drinks of their preferred alcoholic beverage that they would consume at a range of prices (e.g., "How many drinks would you consume if they cost $4 each?"). Each run will comprise 22 trials in a randomized order. An important aspect of the paradigm is its fractionation of the choice process into two discrete units: a stimulus processing Consider period (4 sec) and an active selection Choose period (<6s). In the Consider epoch, participants process the drink price for that trial and mentally decide how many drinks they want to purchase. In the Choose epoch participants' behaviorally select their consumption level. This permits dissociation of the cognitive processing part of the decision from the motor response of inputting the choice. The Consider period is considered the

primary period of interest. A jittered inter-stimulus interval (ISI) screen is presented in between trials (M = 8 sec, range 1-15sec)[14].

Figure 1. fMRI alcohol purchase task stimuli.
ISI = interstimulus interval, s = seconds



In this study, 4 runs of the paradigm will be administered (run duration = ~7 min). Each of the first two runs will be preceded by blocks of cues from one condition (either two runs of alcohol cues or two runs of neutral cues), and the final two runs will each be preceded by cues from the other condition. Example cues are presented in **Figure 2**. The order of cue conditions will be counterbalanced across participants.

Figure 2. Alcohol and neutral stimuli for in-scanner cue exposure.

Example Neutral Cue **Example Alcohol Cue**

The paradigm is programmed in E-Prime software and displayed via MRI-compatible stimulus presentation system. Participants make their responses using MRI-compatible button boxes. Specifically, participants use their dominant (more dexterous) right hand buttons to select the number of drinks and submit their choice by pressing a button with their left hand.

In addition to the APT, participants will complete a 9-minute resting state paradigm. During this scan, participants are asked to sit still with their eyes open (focusing on a fixation cross on the screen).

Breathalyzer Test & Urine Screen

Alcohol sobriety (i.e., breath alcohol concentration = 0.00%) at the beginning of the study visit will be assessed via a commercial breathalyzer device (e.g., Alco-Sensor; Intoxometers, Inc).

We will also assess recent drug use via a commercial urine drug screen (e.g., ToxCup 5-panel urine drug screen). Results of the drug screen will be recorded on the data sheet and kept strictly confidential. Collection of urine drug screen will follow laboratory SOPs.

VIII. Study Procedures

Participant Recruitment

Participants will be recruited from the Hamilton, Ontario community via advertisements/tear-off flyers posted on bulletin boards in public areas around Hamilton, such as libraries, university campuses, bus/train depots, grocery stores, etc. Flyers will also be posted on bulletin boards inside SJHH campuses. We will also post advertisements on online classified websites (e.g., Kijiji). We have also had success in prior studies with placing professional advertisements on Hamilton city busses and will use those methods as needed to increase recruitment.

Participants may also be recruited from the Population Assessment for Tomorrow's Health (PATH) Research Registry research registry in the Peter Boris Centre for Addictions Research (PI: Dr. James MacKillop). We will only contact participants in the PATH study who have agreed to be contacted for future studies. After identifying viable participants, we will provide a list of PATH subject IDs to the PATH Project Coordinator to request names and phone numbers. Then, a research assistant from the current study will contact the participants and conduct our telephone screening to formally determine eligibility for the current study.

Additionally, participants may be recruited from the Access Research Program at St. Joseph's Healthcare Hamilton (a database of patients who have consented to being contacted for research

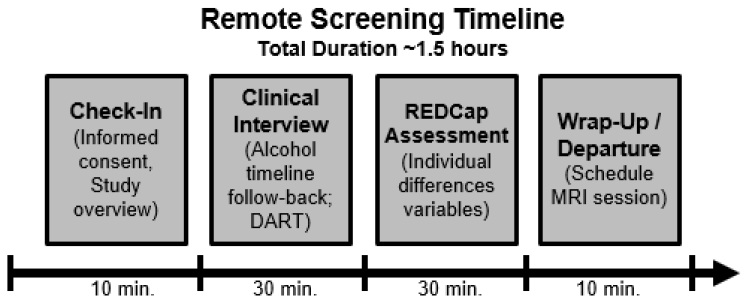
studies). A research assistant from the current study will contact the potential participants and conduct our telephone screening to formally determine eligibility for the current study.

Telephone Screening (10-15 Minutes)

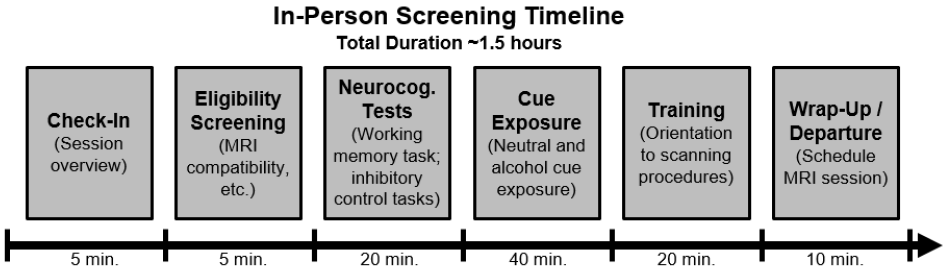
Prospective participants will contact the PBCAR via telephone and leave a voicemail message with their contact information. A research assistant will contact participants to conduct the telephone screening. Individuals who screen positive will be scheduled for the in-person screening session. Individuals who have an ambiguous outcome will be re-contacted after consultation with Dr. MacKillop. Individuals who do not qualify for the study will be thanked, and their data will be destroyed.

In-Person Screening (3 Hours; Peter Boris Centre for Addictions Research)

Figure 3



Participants who pass the initial telephone screening will complete two screening sessions to collect baseline data. The first screening session will be conducted remotely using the Zoom app and will last approximately 1.5 hours. The session will occur in a private laboratory room. Participant sobriety will be assessed at the outset of the session. Participants will then be given a verbal overview of the study, read a Participant Information Sheet, and provide electronic informed consent for the screening portion of the study. They will complete the clinical interview (Timeline Follow-Back, DART, SCID-II), and questionnaires administered via REDCap.



The second screening session will be conducted in-person and will last approximately 1.5 hours (**Figure 3**)**.** The in-person session will take place in Dr. MacKillop's lab in the Peter Boris Centre for Addictions Research at SJHH West 5th site. The session will occur in a private laboratory room. Participant sobriety will be assessed at the outset of the session. They will complete the MRI safety screening form, and computerized neurocognitive tests. Final eligibility will be based on participant responses during the screening sessions. This decision will be made by the research assistant in consultation with Dr. MacKillop.

Participants will next undergo a standardized neutral and alcohol cue exposure protocol Importantly, these procedures (see Appendix A) have been used extensively in over three decades of laboratory

alcohol research [15,16], including several studies by Dr. Amlung and colleagues[17–19]. The protocol is identical to a prior study approved by HIREB (Project #1001; PI: Dr. Michael Amlung) and involves exposure to neutral (water) cues and alcohol-related cues. Importantly, the present protocol will not involve any actual alcohol consumption (see Potential Risks Section IX.3 and Appendix B for procedures in the event that participants deviate from protocol and consume alcohol).

In the neutral cues portion, participants will interact with a neutral water beverage in a neutral laboratory room (**Figure 4**)**.** The participant will be seated at a small table and a bottle of water and glass will be placed on the table in front of them. The experimenter will open the bottle and slowly pour the water into the glass. Participants are told to not drink the beverage. The experimenter will instruct the participant to pick up the glass, hold it up to their nose, and take 5 deep breaths to inhale the small of the beverage. The experimenter will then ask the participant to put on a pair of headphones and listen to a pre-recorded imagery script using the iPad (recording duration ~5 minutes). The recording will ask the participant to periodically pick up the drink, take five deep breaths to inhale the smell of the drink. They will also be asked to pay attention to the physical attributes to the drink (e.g., the coolness of the glass, the color of the beverage, etc.). After the recording finishes, the experimenter will return and administer the post-cue assessments (e.g., blood pressure, craving, alcohol demand, affect).

In the alcohol cues portion, the participant will be escorted to the Boris Centre bar laboratory where they will interact with an alcohol beverage in a simulated bar environment (**Figure 4**). Participants are told that they are not permitted to go behind the bar or handle/drink any of the alcohol in the bottles. The procedures for the alcohol cue exposure (e.g., picking up and smelling the drink, listening to the recording, etc.) are identical to the neutral cue exposure except that the beverage will be a standard sized drink of the participant's preferred alcoholic beverage. Participants are once again told to not drink the beverage. Following the completion of the recording, the experimenter will return and administer the post-cue exposure assessments (e.g., blood pressure, craving, alcohol demand, affect). During both cue exposures, participants will be monitored for compliance to the instructions via a closed-circuit camera system.

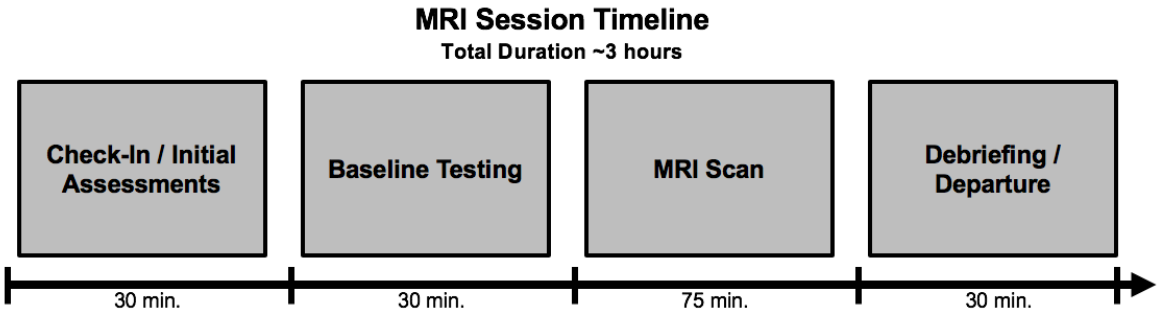
For those participants who qualify for the study, we will provide a detailed description of the full study, training on the in-scanner alcohol purchase task, and a description of a typical MRI procedure. Then, if they want to continue in the study, a research assistant will schedule the appointment for the MRI session. Participants will be given a debriefing, during which they can ask any questions that they may have about their experience in the screening. At the conclusion of the debriefing, participants will receive their gift card and sign a payment receipt.

Figure 4. Laboratory Cue Exposure Environments

Neutral Cue Environment	Alcohol Cue Environment
	

fMRI Session (2.5-3 hours; SJHH Imaging Research Centre)

Figure 5



The second laboratory session will ideally be scheduled within 1 week of the in-person screening. The session will last approximately 2.5-3 hours and will take place at the Imaging Research Centre at the SJHH Charlton site. The session timeline is provided in **Figure 5.**

Participants will arrive at the IRC at SJHH Charlton where they will be met by a research assistant and escorted to a private multipurpose testing room in the IRC. Participant sobriety will be assessed at the outset of the session. Participants will also provide a urine sample in a private washroom. Participants will read a second information sheet and provide informed consent for the full study.

Participants will then complete an initial assessment that will ask them about the time since last alcohol consumption, time since their last cigarette (if any), time since last drug use (if any), medications (if any), and the date of last menstrual period (for premenopausal women).

The MRI scan will be administered by an MRI technologist following standard IRC procedures. Participants will first meet with the technologist who will review the MRI safety form and answer any questions about the MRI procedure. The participant will change into a cotton gown in a private changing area. Participants will also remove all metal (i.e., jewelry, piercings, hair clips, etc.). The technologist will escort the participant into the MRI scanner room, position them on the scanner table, and insert the table into the MRI scanner. During the scan, participants will be asked to lay motionless and breathe and swallow normally. Research staff and the MRI technologist will maintain communication with the participant via an intercom system. The participant will be given a squeeze ball call alarm to hold during the MRI exam. This can be used to immediately stop the scan and speak to the technologist at any time during the procedure. When the scan is completed, the technologist will remove the participant from the scanner and participants will change back into their personal clothing.

The session will end with participants receiving a thorough debriefing about the purpose of the study. They will receive their gift card and sign a payment receipt prior to departing the session.

Incentives and Other Costs

Participants will receive a $20 gift card for completing each screening session of the study and a $40 gift card for completing the scan session; total compensation for completing both sessions = $80. Gift cards will be for local grocery / department stores. Participants will be required to sign a payment receipt. Participants will not have to pay anything out-of-pocket to participate in this study. Participants will be provided with parking/transportation vouchers, as needed.

IX. Potential Risks

This study does have several potential risks, and we have implemented several procedures to minimize these risks. Prior to enrolling in the study, all participants will be given a detailed overview of the study and will provide written informed consent for each session. Participants will be reminded that taking part in the study is voluntary and that they can withdraw at any time without penalty.

We anticipate the following potential risks:

1) **Risks associated with MRI scanning:** While all forms of diagnostic medical procedures involve some risk, the known risks of MRI are very low. However, accidents, injuries, and even deaths have occurred during MRI procedures. Serious consequences can occur in people who have metal pacemakers, metallic dust in their eyes, metallic prostheses, implants or surgical clips. MRI is also dangerous for anyone wearing metal objects (jewelry, hair clips, eyeglasses, metal on clothing, credit cards, loose change, etc.) Some participants might experience mild discomfort from the loud noise of the scanner and the confined space, which can bring on an anxiety reaction. Occasionally during scanning, participants may also experience slight warming of the skin due to increased energy absorption from radio waves used in magnetic resonance imaging.

   To reduce these risks, we will implement the following MRI safety and screening procedures:

   1. MRI scans will be administered by licensed MRI technologists at SJHH.
   2. Participants will be screened for MRI safety and compatibility as part of the telephone screening, again during the in-person screening, and confirmed with the MRI technologist on the day of the scan.
   3. Participants will change into a cotton gown prior to MRI scanning and will remove jewelry, hair accessories, piercings, etc. prior to entering the MRI room.
   4. Participants will be given earplugs to reduce risk of hearing damage due to scanner noise.
   5. Participants will be provided with a squeeze ball call alarm and will also be able to communicate with staff via the intercom/microphone. If participants have any heating or queasy feelings during the study, they can stop the scan by pressing the squeeze ball.
   6. All research staff administering the sessions and conducting the initial MRI safety screenings will complete the required MRI safety training course offered by the IRC.
   7. Finally, although there is no known risk to a fetus, it is the policy of the IRC to not scan women who report being pregnant.

2) **Risks associated with exposure to alcohol-related cues:** The cue exposure involves exposure to several types of alcohol-related stimuli (visual cues, olfactory cues, imaginal cues). Exposure to these cues could trigger relapse or increased desire to drink in individuals who are in treatment or in recovery for alcohol-related problems. To minimize this risk, any participants who report seeking treatment for alcohol use disorders will be excluded. In addition, any participants who report actively trying to stop or cut down drinking will also be excluded.
3) **Risks associated with consuming alcohol against study protocol:** While it is highly unlikely based on the PI's previous experience conducting similar alcohol cue exposure studies, it is possible that participants may violate study protocol and drink alcohol and become intoxicated during the cue exposure portion of the screening session. This could result in increased risk to the safety of the participant, staff, and the public. We will implement a number of safeguards to mitigate this risk. These safeguards are described in detail in **Appendix B** and summarized here. First, the study policy prohibiting alcohol consumption will be explained and reiterated multiple times throughout the study (telephone screening, informed consent, cue exposures). Second, while in the bar lab, participants will be monitored by research staff from an adjacent control room via a closed circuit video system. This will allow research staff to immediately intervene in the event that a participant goes behind the bar and attempts to consume the alcohol stimuli. If the participant violates instructions and drinks the prepared beverage used in the cue exposure, the amount of alcohol that they would consume is likely less than they typically consume (i.e., all participants will typically drink heavily on a regular basis). Nonetheless, if a participant does become intoxicated during the session, the procedures outlined in Appendix B will be implemented.
4) **Risks associated with breach of confidentiality / loss of privacy**: A potential risk is loss of privacy due to inadvertent disclosure of personal information or which could lead to embarrassment or damage to reputation. In addition, some of the questions will ask about illegal behaviours such as drug use. We will strictly protect against these risks by keeping all data confidential and stored on password-protected servers or in locked file cabinets. Each participant will be assigned a unique

subject ID number that will be kept separate from their name. Finally, results will only be presented or published in aggregate form with no individual participant names.

5) **Risks associated with discomfort / distress in answering personal questions**: Participants may experience some discomfort resulting from answering some of the personal questions on the questionnaires and psychological tests, including questions about illegal activities (e.g., drug use). Participants will be reminded several times that they do not have to answer any questions that they do not want to answer. Participants will also be debriefed following both sessions to address any concerns that they may have about their experience in the study.

X. Incidental MRI Findings Policy

Procedures concerning incidental MRI findings will adhere to SJHH IRC policy (see IRC-MRI-6 "Incidental Finding MRI-IRC", dated 2012/05/08). An incidental finding on an MRI scan would include suspected pathology or unusual anatomical features which were not expected. Such findings may or may not impact the wellbeing of the individual and may warrant further medical investigation. In the best interest of the participant, the acquired images should be relayed to a radiologist for further assessment. The following procedures concerning incidental findings will be in place (see IRC Policy for further details):

- Participants will be informed that the MRI data collected in this study are for research purposes only and no clinical report will be issued for any research MRI scan.
- If in the course of the MRI scan procedure, the technologist notes a possible incidental finding, the action steps in the IRC policy above will be taken. Steps include notification of MRI radiologist on duty for review of images, contacting the study principal investigator, and relaying information regarding the incidental finding to the participant.
- If in the course of data analysis a researcher notes a possible incidental findings, the principal investigator will contact the IRC and request review of the images by the radiologist.

XI. Expected Study Timeline & Dissemination

The study is expected to take 36 months to complete. The study chronology is provided in **Table 6**. Following completion of the study, findings will be disseminated via peer-reviewed publications in scientific journals, presentations at local/national/international conferences, and presentations at local grand rounds and seminar series.

Table 6. Study Chronology

Year 1			Year 2			Year 3		
Qtr.	**Activities**	**N**	**Qtr.**	**Activities**	**N**	**Qtr.**	**Activities**	**N**
1	Start-up	-	1	Data Collection	14	1	Data Analysis	-
2	Data Collection	12	2	Data Collection	14	2	Data Analysis	-
3	Data Collection	12	3	Data Collection	13	3	Dissemination	-
4	Data Collection	12	4	Data Analysis	-	4	Dissemination	-
	Year 1 Total	**36**		**Year 2 Total**	**41**		**Year 3 Total**	**0**
							Overall Total	**77**

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Appendix A

Standardized Alcohol Cue Exposure Protocol used in Peter Boris Centre for Addictions Research

Approximate Duration: 20 minutes per condition (5 minutes preparation/instruction; 5 minutes exposure; 10 minute assessment); 40 minutes total for neutral + alcohol cue exposure

Note: Participants will be observed for compliance and completion via a video monitoring system installed in both rooms that feeds to a computer monitor located in an adjacent control room. Participants are not permitted to walk behind the bar and drink/interact with any of the alcohol stimuli.

Imaginal Script Methodology

The standard alcohol cue exposure protocol involves direct exposure to personally relevant alcohol cues, including visual, olfactory, gustatory, tactile, and proprioceptive cues. This involves preparation of the participant's typically consumed alcoholic beverage in front of the participant. The alcoholic beverage is a standard size beer (12oz.), glass of wine (5oz.), or mixed drink containing one shot (1.5oz.) of liquor. The beverage is presented in a prototypical glass for the type of alcohol provided (e.g., pilsner glass for beer, stemware for wine). The alcohol cue exposure is typically preceded by a neutral cue exposure involving a glass of water. The order of the exposures is typically not counterbalanced (i.e., neutral first, alcohol second) due to carryover effects from the alcohol cue exposure.

Following preparation of the beverage, the participant is given brief instructions on the inhalation procedure. This involves instructing the participant to pick up the drink and hold the glass 1/2 inch from their nose. They are asked to take five deep breaths and inhale the smell of the drink.

Next, the participant is instructed to put on a pair of headphones and listen to a pre-recorded audio script directing the cue exposure. The experimenter then leaves the room and the participant starts the recording (or the recording can be started by a staff member in an adjacent control room). The audio instructions repeatedly ask the participant to raise the beverage up to their nose and to take five inhalations of the smell of the beverage (total olfactory exposure = ~20s).

The same imaginal script will be used for both neutral (control) and alcohol cues. The methodology for the script is presented below. The duration of the scripts is approximately 3 minutes. The induction is 238 words and written at the 2nd grade level of reading comprehension.

Imaginal Script Structure

1. Introduction and instructions.
2. Initial olfactory exposure; ~5s direct olfactory exposure.
3. Second olfactory exposure; ~5s direct olfactory exposure.
4. Third olfactory exposure; ~5s direct olfactory exposure.
5. Fourth olfactory exposure; ~5s direct olfactory exposure.
6. Concluding instructions.

Imaginal Script Delivered by Audio Recording

"In a moment, I'm going to ask you to smell the beverage in front of you. When you are asked, please take five deep breaths inhaling the smell of the drink.

[7 seconds]

Please pick up the drink and take five deeps breaths, inhaling the smell of the drink with each breath. Keep the drink up to your nose. Take deep breaths and inhale the smell of the drink. Notice the how the glass feels in your hand and the color of the beverage. After you've taken five deep breaths, put the drink back down.

[7 seconds]

Please pick up the drink and take five deep breaths of the drink. Take your time and take deep breaths. Pay attention to the smell of the drink. Once you've taken five deep breaths, put the drink back down.

[7 seconds]

Please pick up the drink and take five deeps breaths, inhaling the smell of the drink with each breath. Keep the drink up to your nose. Take deep breaths and inhale the smell of the drink. Notice the how the glass feels in your hand and the color of the beverage. After you've taken five deep breaths, put the drink back down.

[7 seconds]

Please pick up the drink and take five deep breaths of the drink. Take your time and take deep breaths. Pay attention to the smell of the drink. Once you've taken five deep breaths, put the drink back down.

[7 seconds]

Please remove your headphones now.

Sample Step-by-Step Instructions

Note: The experimenter script is essentially identical for neutral and alcohol cue exposure. The key difference is the beverage that is prepared and presented to the participant. However, the experimenter should refer to the cues as "beverage" or "drink" and not "beer/wine/water/etc". Instructions/actions are presented in bold; verbal script is presented in italics. E = experimenter.

Prior to start of exposure protocol: Experimenter should ensure that both rooms are set up properly and that all beverages are out on the table/bar. Prepare audio recording on iPad or computer (also check volume level). Prepare iPad REDCap survey and any other assessments prior to participant arriving in cue exposure room.

E: *Now we're going to do the portion of the study that has various environmental cues. I'm going to take you to different rooms in the lab.*

Escort participant to the neutral cues room or bar laboratory

E: *I'm going to give you a moment to get situated* **(Time 60 seconds, then return).** *In a little while you will be asked to listen to a recording using these headphones. We will play the recording using the iPad. All you have to do is put on the headphones and press play when instructed to do so.*

Open and pour the beverage (water) into the glass while SLOWLY saying the following:

We will be using this beverage in this part of the experiment. However, it is important that you NOT drink the beverage under any circumstances. In a little while you will be asked to listen to the recording using the headphones. It is very important to listen carefully to the scene described in the recording and follow the instructions exactly. In addition to asking you to imagine certain things, the recording will ask you to inhale the smell of the beverage from time to time. I'd like to go through smelling the drink with you once before we go any further. Please pick up the drink and hold it a half an inch away from your nose. That's right **(when they complete it)**. *Now, please take five deep breaths and inhale the smell of the beverage. When you have taken five deep breaths, put the glass back down.*

Pause and count or at least wait until they are ready for the next instructions.

In a moment, I am going to ask you to put on the headphones and the recording will begin soon after. Please be sure to follow the instructions in the recording exactly, but do not drink any of the beverage under any circumstances.

Do you have any questions about anything I've told you so far? **Answer any questions.**

Now, I'm going to leave the room. Once I've gone, please put on the headphones and press play on the iPad to start the recording.

Leave room and close door. Confirm that participant has put on headphones and started recording. Monitor participant on video screen for compliance and completion of exposure activities. After the recording finishes and subject removes the headphones, enter room and administer assessment.

Appendix B

Procedures for Participants who Consume Alcohol during Session

Alcohol consumption is strictly prohibited in the *Brain Responses to Environmental Influences on Drinking Decisions* study. Participants are not allowed to consume the alcoholic beverage used during the cue exposure. They are also not permitted to go behind the bar and handle or drink any of the alcohol stimuli.

Nonetheless, it is possible that participants may violate study protocol and consume alcohol during the session. Importantly, the amount of alcohol that participants could potentially consume by drinking the cue exposure beverage is relatively modest (1 standard drink) given that participants will all be heavy drinkers who often consume much larger quantities of alcohol as part of their usual drinking patterns.

We will reduce risk of alcohol consumption and intoxication by reminded participants of the alcohol policy during the telephone screening interview, on the consent form, and during the cue exposure in the bar laboratory. We will also monitor participants via the closed circuit video camera system located in the adjacent lab room. This will allow research staff to intervene almost immediately after a participant begins to drink any alcohol.

In the unlikely event that a participant breaks protocol and consumes alcohol, the following procedures should be implemented:

1. Inform the study LPI (Dr. MacKillop) as soon as possible.
2. Remind the participant that alcohol consumption is not permitted and ask them to stop. If they refuse and continue to drink the alcohol, do not intervene further as this may put yourself or the participant at greater risk.
3. The testing session will be terminated immediately as participants will have violated study protocol.
4. If participants consume alcohol, research staff will monitor their blood alcohol concentration via a breathalyzer device. The participant will be asked to remain in the lab until their BAC is below 0.04 g%, which is the recommended safe level for departure from a research study per National Institute on Alcohol Abuse and Alcoholism's Recommended Guidelines for Alcohol Administration Studies.
5. Arrangements should be made for safe transportation home for the participants, including calling for a ride from a friend or family member or calling a taxi.
6. If participants refuse to remain in the lab and have a BAC > 0.04g%, hospital security will be notified and they will handle the situation.
7. If, at any time, participants become agitated, argumentative, violent, or pose any risk to the safety of staff or themselves, research staff should activate their personal alarms (signaling a Code White in the hospital) or contact the security office at extension 36204.