Protocol Name: Disinhibition and alcohol reward (called "Behavioral tendencies and responses to drugs" on the consent form for blinding purposes)

Identifiers: NCT03930446 Unique Protocol ID: IRB16-0015

Date: 10/6/2015

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Study Location: The University of Chicago Medical Center

Version Date: October 6, 2015

Background and Aims: Poor inhibitory control is a known risk factor for alcohol dependence. Prospective studies show associations between poor inhibitory control in childhood and alcohol use disorders in adolescence and adulthood (Dawson et al., 2010; McGue et al., 2001). Additionally, greater impulsive action on the stop task in a sample of heavy drinkers (N=380) prospectively predicted the development of alcohol dependence 4 years later (Rubio et al., 2008). In laboratory animals, drug-naïve mice bred to be high alcohol preferring exhibit higher levels of impulsive action compared to non-alcohol preferring lines (Bowers and Wehner, 2001; Logue et al., 1998; Wilhelm et al., 2007). Together these studies suggest that poor inhibitory control plays a causal role in alcohol abuse.

Greater sensitivity to alcohol's rewarding effects has also been associated with risk for abuse. In early studies, we showed that stimulant effects of alcohol were associated with alcohol choice in a controlled laboratory setting (Chutuape and de Wit, 1994; de Wit et al., 1987). More recently, we showed that a greater stimulant response to alcohol was prospectively associated with increased binge drinking at a 2 year follow-up (King et al., 2011). Moreover, individuals who are genetically at increased risk for alcohol abuse (i.e., Family History Positive) also report greater positive, stimulant-like effects of alcohol (Newlin & Thompson, 1990; Quinn & Fromme, 2011), providing further support for the link between sensitivity to alcohol reward and propensity for excessive use.

Initial reports have investigated associations between impulsive personality and response to alcohol. These suggest that individuals scoring higher on self-report measures of impulsivity also report greater stimulation and less sedation after drinking, and that this association is stronger at higher doses (Hendershot et al., 2013; Leeman et al, 2013). These promising new findings further emphasize the need to probe this association with a behavioral measure of impulsive action.

Study Aim: ***To examine the degree to which impulsive action predicts rewarding effects of alcohol.*** In this study we will examine the degree to which impulsive action predicts sensitivity to the rewarding effects of alcohol in healthy adults. To attain this objective, we will test the *working hypothesis* that individuals high in impulsive action, but matched on drinking history, will report significantly greater euphoria and arousal after alcohol than those low in

impulsive action, and that they will exhibit greater preference for alcohol over placebo in a choice test. We will test our working hypotheses by comparing individuals high and low in impulsive action in both subjective reward and choice for alcohol vs placebo. The primary measures of euphoria and arousal with alcohol will be BAES Stimulation (see below), as well as ARCI A (arousal) and MBG (euphoria), and DEQ Drug Liking. The measure of choice will be the choice for alcohol over placebo and the number of alcohol servings consumed on the last session. Successful completion of this study will provide important information regarding the degree to which poor inhibitory control is linked to alcohol reward, as measured by both subjective and behavioral measures. Taken together with our other concurrent study with amphetamine, it will also provide information about the generalizability of associations between poor inhibitory control (i.e., impulsive action) and drug reward. Further, evidence that individuals with poor inhibitory control are more sensitive to the rewarding effects of alcohol, a drug that is often co-abused with stimulant drugs, will set the stage for future studies to examine neurobiological substrates underlying poor inhibitory control and both stimulant and alcohol reward. This will provide valuable information regarding potential risk factors for poly-drug abuse in these individuals.

Research Design and Methods:

Design: The study will use a between-subjects design to test two measures of reward (subjective effects and drug choice) in participants pre-selected based on their performance on the stop task (Logan et al., 1997), a standardized measure of impulsive action. Participants will be eligible to participate if they score in the upper (stop reaction time > 325ms; N=30) or lower (stop reaction time < 270ms; N=30) quartiles on stop task performance (calculated from over 500 previous subjects in our lab) during the screening session. Subjects will then participate in a 5-session choice procedure, consisting of 4 sampling sessions and one choice session. During the sampling sessions, participants will consume beverages containing 0.8 g/kg ethanol (divided into 4 servings of 0.2 g/kg each) or a matching placebo under double blind conditions. During the choice session, they will choose the beverage they prefer, and drink the number of servings (from 1-4) they prefer. The primary outcome measures are subjective ratings of stimulation, drug liking, “euphoria”, and “arousal” (see below) on the sampling sessions, and choice and number of servings of alcohol or placebo on the choice session.

Participants: Healthy male and female volunteers, aged 21-29, will be recruited by posters, advertisements, and word-of-mouth referrals. Participants will provide consent under Protocol #13681B to undergo the screening procedure, which will include an EKG, physical exam, clinical psychiatric interview, and stop task performance. Participants will be moderate drinkers (7-30 drinks per week) who report at least one binge drinking episode (5 or more drinks on a single occasion for men; 4 for women) in the last month. Asian subjects who report a pronounced ‘flushing’ reaction will be excluded. Subjects who smoke >5 cigarettes/day will be excluded to avoid acute nicotine effects or withdrawal during the sessions. Additional exclusion criteria include any serious medical problems, Axis I psychiatric disorders including substance dependence (APA, 1994), pregnancy or lactation (females), lack of a high school education, and lack of fluency in English. Women not currently using hormonal contraceptives will only be tested during the follicular phase (days 1-14; White et al., 2002). We will monitor participant

characteristics throughout the study to ensure that the high and low impulsive groups are matched on sex, race, education, SES, alcohol drinking, cigarette smoking, and other drug use.

Qualifying participants will provide informed consent during an orientation session. They will agree to abstain from alcohol for 24 hours and other recreational drugs for 2 days before each session, to get normal amounts of sleep, and to consume their usual amounts of caffeine and nicotine prior to each session. For the sampling and choice sessions, they will also be asked to fast 4 hours prior. They will be told that breath and urine samples will be obtained on each session to verify abstinence. For blinding purposes they will be told that the beverages used in the study may contain a stimulant, sedative/tranquilizer, alcohol, or placebo.

Procedure: Sessions will be conducted in the afternoons, in comfortable rooms at the Human Behavioral Pharmacology Laboratory. At each visit, participants will provide breath (Alco-sensor III, Intoximeters, St. Louis, MO) and urine (ToxCup, Branan Medical Co. Irvine, CA) samples to detect recent drug use or pregnancy (women; Aimstrip, Craig Medical Vista, CA). Positive pregnancy tests will result in exclusion and positive drug tests will result in rescheduling or exclusion. All sessions will be conducted from 3 pm to 8 pm, and will be separated by at least 48 hours but no more than 7 days. Upon arrival pre-beverage mood and vital signs will be recorded, and beverage administrations will occur 30 min after arrival, at 3:30pm. Mood and vital signs will be recorded every 30 minutes post-beverage administration. Between measurements in the laboratory, participants may read or watch movies from an approved list, but will not be allowed to sleep or have access to internet or cell phones. Data collection will end at 8pm and participants will be provided with a snack and discharged providing they pass a sobriety test and breath alcohol concentrations are below 0.02mg% (as per NIAAA guidelines). If BrAC is above 0.02%, BrAC samples will be collected every 15 minutes until BrAC is below 0.02mg% after which participants will be allowed to leave. However, participants will not be allowed to drive themselves home. If using public transportation, participants will be accompanied by a lab member to the bus stop, and funds for public transportation will be given, if needed. If they are getting picked up, a lab member will wait with them until their ride arrives. Participants will be made aware of these travel requirements at their orientation session. In addition, we will confirm travel arrangements with the participant prior to drink administration at each of the sampling and choice sessions.

Orientation Session: Subjects will attend an orientation session during which study procedures are explained, and trait impulsive action is re-assessed. They will read and sign the consent form, complete self-report questionnaire measures of personality, and perform the stop task. Subjects will also perform additional behavioral impulsivity tasks, including a go/no-go task and a delay discounting task, to determine the specificity of these effects to impulsive action and the stop task. Finally, they will complete a sweet taste test to examine associations between alcohol reward and a non-drug reward.

Sampling Sessions: During the four sampling sessions, subjects will undergo the pre-session screening procedures described above, and then on each of four sessions they will receive 4 color-coded beverages in green or blue cups, containing alcohol (0.2 g/kg per dose, total dose

0.8 g/kg) or placebo. Within each session all the beverages will contain either alcohol or placebo, and the alcohol or placebo sessions will be scheduled in alternating order, with the initial drug randomized. For each subject the alcohol beverages will be in cups of one color, and the placebo in cups of the other color. Alcohol and placebo color-coding will be randomized across subjects. Subjects will be told that the drug and dose in each color will be the same on both days, and instructed to pay close attention to the color of the beverage container and to associate the color with how the drug makes them feel.

Choice Session: During the choice session, subjects will undergo pre-session screening and then complete an alcohol purchase task in which they choose between varying amounts of money and each color cup. The subject will then choose the color of the beverage cup they prefer (i.e., green or blue) to ingest and the number of servings they would like to consume (1-4). Mood and physiological measures will be obtained at regular intervals but the primary outcome measures will be whether they choose alcohol over the placebo, and the number of servings they choose to drink.

Measures:

Stop Task (Logan et al., 1997) measures behavioral inhibition of a prepotent response. Participants are required to respond as quickly as possible when a ‘go’ target appears and to inhibit that response when a ‘stop’ signal (an auditory tone) occasionally occurs. 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 reaction time (stop RT), which is the primary measure of impulsive action.

The go/no-go task requires participants to respond as quickly as possible to ‘go’ stimuli and to withhold responses to ‘no-go’ stimuli. The dependent measure of interest is the number of inhibitory failures to no-go stimuli.

The delay discounting task requires participants to choose between a series of small hypothetical monetary rewards available immediately and large hypothetical monetary rewards available after a delay. A preference for smaller, sooner rewards over larger, later rewards is indicative of steeper discounting (i.e., greater impulsivity).

The Sweet Taste Test (Kampov-Polevoy et al., 1997) is a measure of preference for sweetness. Participants taste 5 concentrations of sweet solutions, and they rate each solution in terms of sweetness and pleasantness.

Biphasic Alcohol Effects Scale (BAES; Martin et al., 1993) is a 14-item measure on which subjects rate the degree to which they feel subjective stimulant and sedative responses to alcohol on 11-point Likert-type scales.

Drug Effects Questionnaire (DEQ) consists of questions on a visual analogue scale that are sensitive to the effects of drugs. Subjects are asked to rate the extent they feel a drug effect,

whether they like the drug effect, and if they would want to take more of the drug if given the choice. Scales range from ‘none’ to ‘a lot’.

Addiction Research Center Inventory (ARCI; Martin et al., 1971) is a 49-item true-false questionnaire that is a standardized measure of drug effects. We will focus on two empirically derived scales that measure drug-induced “euphoria” (morphine-benzedrine group: MBG) and stimulant-like effects (amphetamine: A).

Cardiovascular Measures will include heart rate (HR) and blood pressure (BP).

End of Session Questionnaire: subjects guess which drug they received, say if they would take the drug again in a recreational setting, and how much they would pay to take the drug again in a recreational setting.

Drug Choice (last session): Subjects will be given a choice of which color beverage to ingest (i.e., alcohol or placebo; green or blue color cups) and the number of servings they wish to ingest (1-4) during the choice session. Choice for alcohol or placebo and the total number of servings (1-4) will provide the measures of drug choice. This is a standardized procedure used in this and other laboratories (Evans et al, 1996). The amount of money they are willing to pay in the drug purchase task provides a secondary measure of drug choice.

Drugs: The 0.8 g/kg body weight dose of oral alcohol (190-proof ethanol) will be divided into 4 servings of 0.2 g/kg each. The 0.8 g/kg dose is equivalent to 4 standard drinks, where a standard drink is defined as one 12 oz beer, one 5 oz glass of wine, or one 1.5 oz shot of 80 proof alcohol. Women will receive a reduced dose (0.68 g/kg) to account for sex differences in total body water (Frezza et al., 1990; Sutker et al., 1983). Previous research using this adjusted dose has produced equivalent breath alcohol concentrations (BrACs) in men and women (Roche et al., 2015; Weafer and Fillmore, 2012). This dose was chosen because it is well-tolerated and produces reliable increases in subjective response measures and alcohol choice (Doty and de Wit, 1995; de Wit et al., 1987; Weafer et al., in press). With this dose we expect breath alcohol levels to return to 0.02mg% within about 4 hours (i.e., by 7:30pm). Subjects will be discharged at 8pm. To provide a context, the legal limit for driving is 0.08mg%. The individual alcohol servings will be served in a 10% solution by volume with either cranberry juice or orange juice, depending on the subject’s preference. The placebo beverage will consist of the cranberry or orange juice plus 1% alcohol added as a taste mask. All beverages will be sprayed with an alcoholic mist to provide a strong alcoholic scent. Beverages will be served in opaque (color-coded) lidded cups, and subjects will have a total of 15 min to consume the servings.

Statistical analyses: First, we will check that the high and low impulsive groups are matched on sex, race, education, SES, cigarette smoking, alcohol drinking and other drug use. To test the hypothesis that individuals high in impulsive action will report significantly greater stimulation and euphoria after alcohol than those low in impulsive action, we will conduct 2 (Group) X 2 (Drug) mixed design analyses of variance (ANOVA), with dose order and sex included as covariates, for each of the subjective response measures (i.e., BAES, ARCI, and DEQ). Group (high or low impulsive action) will be the between-subjects factor, and will be determined at the orientation session (see above). The dependent measures of subjective stimulation and

euphoria will be calculated as area under the curve (AUC). An average AUC across the two alcohol sessions will be calculated, and an average AUC across the two placebo sessions will be calculated. If the overall F-test for the group X drug interaction is significant ($p<.05$), post hoc paired t-tests will be used to test for drug effects (relative to placebo) in the high and low impulsive action groups separately. To test the hypothesis that high impulsive individuals will exhibit greater preference for alcohol over placebo compared to low impulsive individuals, we will compare choice for alcohol or placebo in high and low impulsive individuals. We will perform a chi-square analysis to determine if the high impulsive action group is comprised of a higher number of choosers compared to the low impulsive action group, and a between-groups t test to see if the high impulsive action group chooses a greater number of alcohol servings than the low impulsive action group.

Sample size determination: Estimations of sample size were derived from our preliminary data with d-amphetamine. Between groups (high vs. low impulsive action) t tests for subjective response measures of Elation and Vigor (AUC; 20 mg vs. placebo) suggest a medium effect size (d=.60-.68). N=60 subjects would provide 80% power (alpha = .05) to detect a difference between high and low impulsive individuals.

HUMAN SUBJECTS

Risks to subjects:

a. Human subjects involvement and characteristics: Subjects in this study will be male and female adults, aged 21-29 years of any race or ethnicity, as long as they are fluent in English and meet other inclusion criteria. No special classes of vulnerable individuals will be included. Children younger than 21 will not be included because of ethical considerations and because the measures to be used are not validated for children. Subjects will undergo psychiatric and medical screening before participating, including a face-to-face interview with a trained interviewer to determine health history, current and lifetime recreational drug use history, and current and past psychiatric problems, according to DSM-V criteria. Subjects will also complete the MAST (Selzer, 1971) to detect alcohol problems, the SCL-90 and BDI to assess psychiatric symptoms, and women will complete a questionnaire concerning their menstruation history. Potential subjects will obtain an electrocardiogram and be examined by a physician. Exclusion criteria are: abnormal electrocardiogram, any current medical condition requiring medication or for which alcohol is contraindicated; any current Axis I psychiatric disorder (APA, 1994) including Substance Dependence, except Nicotine Dependence, any history of psychosis; less than high school education; lack of fluency in English; night shift work. Women who are pregnant or lactating will be excluded.

b. Sources of materials: Data collected will consist of demographic data obtained at intake, subjective (self-report), behavioral (e.g., task performance), and physiological measures (e.g., heart rate), and personality measures.

c. Potential risks: The risks to subjects are minimal. The drug used may produce side effects, including constipation, drowsiness, coordination problems, memory loss, tiredness, depression, dizziness or faintness, rapid heart rate, raised blood pressure, restlessness, dry mouth, changes in sex drive, double or blurred vision, confusion, slurred speech, shakiness or tremor, headache and nausea or muscle weakness. We have administered the proposed dose of alcohol in previous studies with no adverse effects. There is no evidence that alcohol administration in the laboratory increases drinking outside the laboratory. For the proposed study we will recruit subjects who report moderate drinking. Subjects will not be allowed to leave the lab unless their blood alcohol level is less than 0.02mg% and they will be informed not to drive after the sessions. Other risks involve risks of confidentiality. Confidentiality is strictly maintained by laboratory personnel, and records are kept in a secure location. Subjects will be fully debriefed following the study.

Adequacy of protection against risks:

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

b. Protection against risk: To protect against, or minimize any possible risks, we follow these procedures: Subjects will be carefully screened to exclude those who are physically or psychiatrically at risk (see above).

The study will be conducted in a laboratory located in a hospital, where emergency assistance (including the psychiatry resident on-call and a psychiatrist connected with the study) is close at hand. Subject files containing confidential information are maintained in a locked cabinet in the PI's office. Only personnel directly connected with the study have access to this information, and these individuals are instructed in the importance and procedures for maintaining confidentiality. 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

Potential benefits: The minimal risks to subjects are justified by the knowledge to be gained regarding the behavioral processes related to drug use. Knowledge about the risk factors for drug abuse in at-risk individuals (i.e., individuals with poor behavioral control) will inform our understanding of the development and treatment of drug abuse. Subjects will benefit from the information obtained during the screening procedure (e.g., physical examination and electrocardiogram, as well as psychiatric screening). This is particularly beneficial to individuals who are excluded during the screening because of some previously undiagnosed condition. These individuals are referred for treatment. Subjects are paid for their participation. They may

also request information about their performance and responses during the study. Smokers and individuals with other psychiatric disorders will be referred for treatment following their participation.