

Neural mechanisms of high-risk decisions-to-drink in alcohol-dependent women

Lindsay R. Arcurio¹, Peter R. Finn¹ & Thomas W. James^{1,2,3}

Department of Psychological and Brain Sciences,¹ Program in Neuroscience² and Cognitive Science Program,³ Indiana University, Bloomington, IN, USA

ABSTRACT

A hallmark of alcohol dependence (AD) is continually drinking despite the risk of negative consequences. Currently, it is not known if the pattern of disordered activation in AD is more compatible with an over-sensitive reward system, a deficit in control systems or a combination of both to produce the high risk-taking behavior observed in alcohol dependents (ADs). Here, alcohol cues were used in an ecological decisions-to-drink task that involved high- and low-risk scenarios where the chance of serious negative imagined consequences was varied. Non-alcohol cues were included as control stimuli. Functional magnetic resonance imaging (fMRI) was used to measure blood oxygen level-dependent (BOLD) signal change in 15 alcohol-dependent and 16 control women. This design allowed us to address two major questions concerning AD: first, is there a specific pattern of disordered activation that drives the heightened endorsement of high-risk decisions-to-drink in ADs? And, second, is that pattern specific to decisions-to-drink or does it generalize to other appetitive and/or neutral cues? The results showed that, during high-risk decisions-to-drink, alcohol-dependent women activated reward circuits, cognitive control circuits and regions of the default-mode network (DMN), while control women deactivated approach circuits and showed enhanced activation in regions of the DMN. Group differences were found only for decisions-to-drink, suggesting that they are specific to alcohol cues. Simultaneous activation of reward networks, cognitive control networks and the DMN in alcohol-dependent women suggests that over-endorsement of high-risk drinking decisions by alcohol-dependent women may be due to a problem with switching between different neural networks.

Keywords Alcohol dependence, central executive network, default-mode network, reward, risk, salience network.

Correspondence to: Lindsay R. Arcurio, Department of Psychological and Brain Sciences, Indiana University, 1101 E. Tenth St., Bloomington, IN 47405, USA. E-mail: ldachill@uemail.iu.edu

INTRODUCTION

A hallmark of alcohol dependence (AD) is continually drinking in situations that are associated with a high risk of serious negative consequences. Negative outcomes related to high-risk drinking in our society occur at an alarming frequency (such as car accidents related to driving under the influence of alcohol or sexually transmitted infections related to unprotected sex) and the rate of binge drinking is increasing (Centers for Disease Control and Prevention 2013). This reality underlines the importance of understanding the factors behind decisions-to-drink in low- and high-risk situations. Importantly, understanding the neural mechanisms involved in decisions-to-drink may provide crucial insights into understanding AD that would be unattainable without such neural measures. In turn, these insights may lead to

novel applications targeted at decreasing drinking in situations where the risk of negative consequences is high. Studies investigating the neural correlates of AD have focused on a dual-process account of addiction where addictive behavior is considered to be the outcome of two independent neural systems—a reward-driven, bottom-up, approach system versus a cognitive control-driven, top-down, avoidance system (Goldstein & Volkow 2002; Kalivas & Volkow 2005; Bickel *et al.* 2007; Cousijn *et al.* 2012; Volkow *et al.* 2013).

A large body of research demonstrates that reward systems become hypersensitive in AD. Specifically, heavy drinking is associated with increased sensitivity of dopamine reward circuitry to alcohol and cues predicting alcohol use (Robinson & Berridge 2008). Functional magnetic resonance imaging (fMRI) studies have found a relationship between AD and increased activation with

drug-related cues in regions implicated in reward processing (Heinz *et al.* 2009; Ihssen *et al.* 2011) and a relationship between cue-induced reward activation and the level of attention directed at drug-related cues (Vollstadt-Klein *et al.* 2012). In a review article, Heinz *et al.* (2009) outlined core brain regions that were activated across most alcohol cue-reactivity studies that used fMRI. These regions include the anterior cingulate cortex (ACC), medial prefrontal cortex (PFC), orbitofrontal cortex (OFC), amygdala, and ventral and dorsal striatum. In addition, the anterior insula has been strongly implicated in drug craving (Naqvi & Bechara 2010). Many of these regions belong to the salience network (SN), which is primarily involved in detecting and orienting to salient or rewarding stimuli (Menon & Uddin 2010; Menon 2011). The core regions of the SN are the anterior insular cortex (AIC) and dorsal ACC (dACC). Other regions in the SN include the pre-supplementary motor area (pre-SMA), dorsal and ventral striatum, substantia nigra, OFC (BA47) and frontal pole (BA10) (Seeley *et al.* 2007). Taken together, this previous work suggests that brain regions that are more strongly cue-reactive in relation to AD are involved with detecting and orienting to highly motivating stimuli, i.e. involved with processing stimulus salience. This would include stimuli associated with high reward, and for people with alcohol dependence [alcohol dependents (ADs)], would include alcohol cues.

There is also a large body of research demonstrating that ADs have deficits in central executive function, suggesting that hypersensitive reward processing may not be the only issue associated with AD. Central executive function describes the ability to store and manipulate information over time, in accordance with behavioral goals (Kimberg, D'Esposito & Farah 1997). ADs perform significantly worse across many measures of central executive function compared with controls, including short-term memory, executive working memory, intelligence and conditional associative learning (Finn 2002; Sullivan *et al.* 2002; Crews & Boettiger 2009; Finn *et al.* 2009). Deficits in executive control are also related to greater impulsivity and ADs are typically more impulsive than controls (Bobova *et al.* 2009; Gunn & Finn 2013), with greater impulsivity also being associated with greater drinking problems (Finn 2002; Gunn & Finn 2013). The brain regions implicated reliably in central executive function have been termed the central executive network (CEN). The core regions of the CEN are the dorsolateral prefrontal cortex (dlPFC) and the lateral posterior parietal cortex (lPPC). Other regions of the CEN include the ventrolateral PFC (vlPFC), frontal operculum (BA44) and frontal eye fields (FEFs) (BA8/9) (Seeley *et al.* 2007; Menon 2011).

Together, these two bodies of research suggest that both a hypersensitive reward system and deficits in

central executive function may contribute to the inflated rate of high-risk decisions-to-drink associated with AD. Thus, tasks that tap general reward processing and executive control [e.g. temporal discounting tasks and the Iowa Gambling Task (IGT)] may be able to dissociate the exact role of these opposing systems in AD. On temporal discounting tasks, ADs have been shown to discount the future significantly more than controls, suggesting that ADs prefer smaller immediate rewards compared to larger delayed rewards relative to controls (Bickel *et al.* 2007). ADs also have poorer performance on the IGT compared to controls. On the IGT, ADs make more disadvantageous decisions, which reflect choices that favor immediate larger rewards at the cost of long-term losses (Mazas, Finn & Steinmetz 2000; Fein, Klein & Finn 2004; Kim, Sohn & Jeong 2011). The neural mechanisms associated with performance on the IGT and temporal discounting tasks have been studied in healthy controls (Li *et al.* 2010; Liu & Feng 2012), but to our knowledge, have not compared ADs to controls. It is clear that ADs have behavioral deficits related to these tasks, but it is not known whether these deficits are primarily related to hypersensitive reward processing, possibly due to a disorder of the SN, or deficits in executive function, and hence due to a disorder of the CEN.

An important concern about studying reward and control in ADs with typical generic decision-making tasks—tasks that reward points or money—is that they are not ecologically valid insofar as their relevance for actual decisions to *drink* is unclear (Bogg & Finn 2009). An assumption of using generic decision-making tasks is that they serve as trait-like measures of decision-making biases, associated with broad reward sensitivities and/or control problems, and that such tasks would predict decision-making problems across a wide range of appetitive behaviors, including drinking. However, dual-process models of self-regulation (Wiers *et al.* 2010) emphasize that impulse control problems are usually very specific to certain behaviors and contexts, with alcohol consumption being a prime example. Wiers *et al.* (2010) noted that general measures of trait impulsivity, and by implication, generic decision-making task measures, do not predict specific impulsive behaviors as well as more specific measures of impulsive processes.

With this in mind, the current study was designed to specifically investigate decisions to drink in young women with AD. The intent was to examine decision-making biases of ADs as well as the brain activation correlates of those decisions. This was carried out using a task that included hypothetical contexts regarding alcohol, food (appetitive control) or household/stationary items (neutral control) that non-independently varied the level of risk and potential reward. In addition, each participant was scanned twice to control for potential hormonal

effects due to menstrual cycle phase, and as part of the larger project, participants also made decisions about low- and high-risk sexual scenarios. Sexual decisions were not examined in the current study (see the Methods section for rationale). In a study using a similar drinking decision task (without the use of appetitive and neutral control stimuli), ADs reported that they would drink more than controls in hypothetical contexts that combined increased risk of negative consequences and high reward probabilities (Bogg & Finn 2009). We hypothesized that alcohol-dependent women will chose to drink significantly more high-risk alcoholic beverages compared to control women. We also hypothesized that alcohol-dependent women would show differential patterns of neural activation for alcohol stimuli compared to appetitive and control stimuli and compared to controls. Specifically, we hypothesized that alcohol-dependent women would show hyperactivation in reward regions for alcohol compared to control stimuli and compared to controls. We also hypothesized that alcohol-dependent women would show less activation in central executive regions for high-risk alcohol compared to high-risk control stimuli and compared to controls. Importantly, because one of the most compelling problems for ADs is continuing to drink in high-risk situations, the main focus of the study was on patterns of brain activation produced during the high-risk decisions-to-drink scenarios.

METHODS

Participants

Recruitment

Participants were recruited using Indiana University list serves and by placing flyers around the Indiana University campus and in local bars. They were also recruited from a large sample of alcohol-dependent women in the Bloomington, IN, area, whom Dr. Finn recruited for another NIAAA funded project and who met the group criteria for this study. Participants from Dr. Finn's project were contacted directly if they indicated that they would like to be contacted for other studies. Three types of flyers were used to recruit participants. The first type of flyer/email was neutral with regard to the level of drinking and was designed to attract responses from controls and alcohol abusers/dependents (Wanted: Women currently interested in participating in an fMRI research study). The second type of flyer/email was designed to recruit control women with low levels of drinking (Wanted: Light drinking women currently interested in participating in an fMRI research study). The third type of flyer was used to recruit women who are self-identified as heavy drinkers (Wanted: Heavy drinking women interested in

participating in an fMRI research study). In all cases, responses were requested from women who were 18–28 years of age; were not currently under treatment or taking medication for mental disorders, including depression and anxiety; who had regular 28- to 32-day menstrual cycles; and who were not using hormonal contraceptives.

Telephone screening interview

All participants calling in response to flyers/emails or who were contacted through Dr. Finn's project underwent an initial eligibility screen that began with a general description of the study, followed by questions that assessed whether they met the basic requirement of the study (described under study exclusion criteria). Next, we asked a series of questions to determine whether they met the criteria for our control or alcohol dependence group (described under group inclusion/exclusion criteria), followed by questions to rule out psychosis or traumatic brain injuries (TBIs). Finally, we asked a series of MRI safety questions to determine whether or not they would be eligible to participate in the fMRI portion of this experiment. Potential participants were told that they would come into the laboratory for a diagnostic interview and that only those who met the diagnostic criteria would be allowed to continue in the study. They were also told that they would need to refrain from drinking alcohol or using any illicit psychoactive drugs for a period of at least 24 hours before each test session. In addition, they were told that they would need to not engage in any sexual activity with a partner for 24 hours prior to each test session and not eat within four hours of testing.

Study exclusion criteria

Participants were excluded from this study for the following reasons: (1) they were not female; (2) they were not between the ages of 18 and 28; (3) they were currently undergoing treatment for depression or anxiety; (4) they were not heterosexual; (5) they did not experience regular 28- to 32-day menstrual cycles; (6) they were pregnant; (7) they used hormonal contraceptives within the last 3 months; (8) they currently used any drugs except for occasional marijuana use; (9) they had any contraindications for MRI; (10) they were currently seeking treatment for alcohol abuse; (11) they reported symptoms of psychosis or TBI; (12) they had never had a full drink of alcohol; and/or (13) they were currently abstaining from alcohol use.

Group inclusion/exclusion criteria

Control women had the following inclusion criteria: (1) no recreational drug use in the last three months; (2) no history of drug use besides marijuana in their lifetime;

(3) have used marijuana less than 25 times in their lifetime; (4) are social drinkers; and (5) report no history of drug or alcohol abuse or dependence and not meeting DSM-IV [Fourth Edition (DSM-IV); American Psychiatric Association 1994] criteria for current or past alcohol abuse or dependence. Alcohol and drug use were measured by using a reduced version of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz *et al.* 1994). Alcohol-dependent women had the following inclusion criteria: (1) meeting the DSM-IV criteria for AD; (2) not currently using opiates, sedatives or be stimulant-dependent; (3) past use of psychoactive drugs and past or present marijuana is allowed due to high rates of co-occurrence between alcohol and drug dependence (Finn *et al.* 2009); and/or (4) not marijuana dependent.

Test session exclusion criteria

Test session included the following exclusion criteria: (1) did not refrain from drinking alcohol and/or using any illicit psychoactive drug for a period of at least 24 hours before testing; (2) did not refrain from sexual activity with a partner for 24 hours prior to the test session; and (3) did not refrain from eating within 4 hours before the test session. At each test session, participants submitted to a breath alcohol test using an AlcoSensor IV (Intoximeter, Inc., St. Louis, MO, USA) and a urine drug screen, and answered questions that determined whether they had participated in any sexual activity with a partner with the past 24 hours or ate food within the past 4 hours. If participants' breath alcohol concentration was greater than 0.0%, or there were any positives on their urine drug screen, or they did not meet our other test session requirements, they were asked to reschedule the test session.

Sample characteristics

A total of 72 participants were recruited for this study after completing the phone interview. Of the 72 participants, 28 (10 alcohol dependent and 18 controls) were excluded after the initial phone interview session. Of those participants, two ADs and five controls did not qualify for the study after completing the interview, and the remainder did not follow up with scheduling the fMRI sessions. Of the remaining 44 participants (25 controls, 19 ADs), 6 controls and 4 ADs completed only one of the two required fMRI sessions. Of the 34 participants (19 controls, 15 ADs) that completed both fMRI sessions, 2 controls had motion that was too excessive for inclusion in our analyses, and data were corrupted for 1 control. Thus, a total of 31 participants (16 controls, 15 ADs) completed the interview and 2 fMRI sessions, constituting our sample for all reported analyses. The ethnicity of

our sample was 71% Caucasian, 13% African American, 10% Hispanic and 6% Asian. The majority of our sample had at least some college education (87%), indicating that college educated persons are over-represented in this sample (see Table 1).

Assessment materials

Recent alcohol and other substance use

In an interview, participants were asked if they regularly consumed alcohol or other drugs on each day of the week, and if yes, how much they usually consumed. Alcohol use was quantified as the sum of the usual amount of alcohol consumed for each day of the week, and the number of days per week where drinking usually occurred within the past 3 months. Drug use was quantified as the number of times used ever in their lifetime.

Diagnostic interview

The SSAGA (Bucholz *et al.* 1994), which uses the criteria from the DSM-IV (American Psychiatric Association 1994), was used to determine whether participants satisfied diagnostic criteria for AD, marijuana dependence and drug dependence. Problem counts for alcohol and marijuana were also calculated from the SSAGA.

Questionnaires

Questionnaires were given to participants to complete directly after the diagnostic interview. Questionnaires were given regarding (1) demographics; (2) general health; (3) menstrual cycle; (4) eating patterns (Three Factor Eating Questionnaire, TFEQ); and (5) mood [Positive and Negative Affect Schedule (PNAS); Beck Depression Inventory II (BDI-II)] (Table 1). Specifically, participants provided recent dates and typical lengths of their menstrual cycles, as well as previous or current use of hormonal contraceptives, in addition to information about past or current psychiatric treatment, including use of psychotropic medications. The TFEQ (Stunkard & Messick 1985) contains three subscales; we used the first subscale, Cognitive Restraint, which is a 21-item index of conscious control of eating. The PNAS (Watson, Clark & Tellegen 1988) is a 10-item mood questionnaire widely used and validated as a measurement of positive and negative mood. The BDI-II (Beck, Steer & Brown 1996) is a 21-item depression questionnaire also widely used and validated as a measurement of depression. Participants also completed other questionnaires related to the larger project that were not a part of the current study.

Appetitive and neutral cues

There were four categories of cues, alcoholic beverages, food and household/stationary items, plus faces, which

Table 1 Participant demographics, SSAGA problem counts, substance use, mood ratings and eating patterns.

	Control (n = 16)	Alcohol dependent (n = 15)	Sig.
Age (years)	20.25 (1.57)	21.20 (2.08)	n.s. ^a
Education (n)			
High school graduate	1	3	
Some college	13	9	
College graduate	2	3	
Ethnicity (n)			n.s. ^b
Caucasian	12	10	
African American	2	2	
Hispanic	2	1	
Asian	0	2	
SSAGA problem counts			
Alcohol problems	0.94 (1.34)	7.87 (3.07)	< 0.001 ^a
Marijuana problems	0.00 (0.00)	1.67 (3.37)	n.s. ^a
Recent substance use			
Alcohol frequency (days/week)	1.50 (1.21)	4.20 (1.15)	< 0.001 ^a
Alcohol quantity (drinks/week)	4.47 (4.62)	36.57 (18.10)	< 0.001 ^a
Mood			
PANAS negative affect	12.19 (3.31)	13.50 (4.83)	n.s. ^a
PANAS positive affect	24.44 (7.74)	25.08 (6.97)	n.s. ^a
BDI	7.94 (9.59)	6.67 (5.88)	n.s. ^a
Eating			
TEFQ factor 1 (dietary restraint)	19.13 (3.50)	19.20 (3.12)	n.s. ^a
TEFQ factor 2 (disinhibition)	20.69 (2.57)	19.00 (3.30)	n.s. ^a
TEFQ factor 3 (perceived hunger)	17.63 (2.31)	16.00 (2.36)	n.s. ^a

Note. ^at-test. ^bChi-square test. BDI = Beck Depression Inventory; n.s. = not significant; PANAS = Positive and Negative Affect Schedule; SSAGA = Semi-structured Assessment for the Genetics of Alcoholism; TEFQ = Three Factor Eating Questionnaire.

were not the focus of this article and were not included in any of the current analyses. Faces were not included in the current analyses because there is no prior literature examining the neural correlates of sexual decision making in alcohol-dependent women. The hypotheses to be tested for sexual decisions are completely separate from the hypotheses tested in the current study.

Forty-five pictures from each category were normed with measures of arousal, valence and desirability. Arousal and valence were acquired using the same procedures as for the International Affective Picture System (IAPS; Lang, Bradley & Cuthbert 1997). Desirability was acquired using a similar nine-point scale as arousal, but participants were instructed to rate the desirability or attractiveness of the cue. A set of negative valence IAPS pictures was included only in the norming procedure to ensure that participants used the full range of rating values for the three measures. The a priori hypothesis was that alcohol, food and face stimuli would be treated as appetitive cues and would be rated with positive valence and above average arousal and desirability, whereas items would be considered neutral and would be rated with low arousal and desirability and neutral valence. Thirty-six pictures were chosen from the 45 in each category based on the mean ratings using selection criteria meant to

further bias the a priori categorization into appetitive and neutral sets and to attempt to equate the various appetitive cue categories on measures of arousal, desirability and valence. Selection criteria were prioritized as follows: (1) the valence of each alcohol and food cue was at least 4; (2) the mean valence of alcohol cues and the mean valence of food cues were as similar as possible; (3) the mean desirability of each alcohol and food cue was at least 4; (4) the mean desirability of alcohol cues and the mean desirability of food cues were as similar as possible; (5) the mean desirability and arousal of item cues was as close to 1 as possible; (6) the mean valence of item cues as close to 4 as possible. The mean (SD) desirability ratings of the resulting pictures sets were alcohol 5.2 (0.87), food 5.3 (0.55) and item 2.8 (0.44). The mean (SD) valence ratings were alcohol 5.7 (0.81), food 5.9 (0.52) and item 4.2 (0.34). The mean (SD) arousal ratings were alcohol 5.2 (0.81), food 5.6 (0.31) and item 1.9 (0.31). The face cues (not included in the current analyses) had mean desirability of 4.0 (0.49), arousal of 4.6 (0.45) and valence of 5.2 (0.44).

During the fMRI procedure, each appetitive or neutral cue was presented simultaneously with text providing the participant with information for gauging the potential risk of negative consequences associated with the cue in

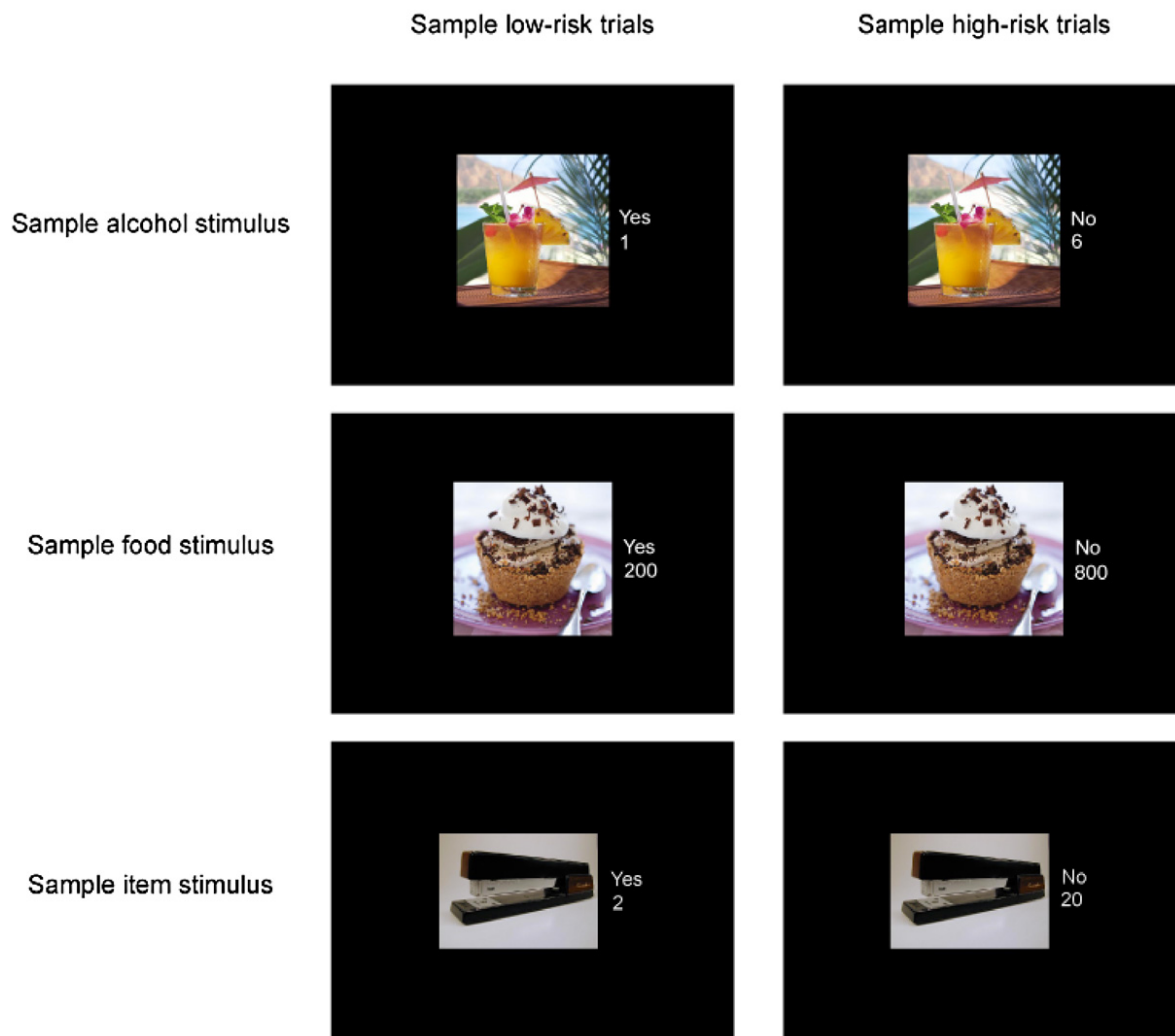


Figure 1 Examples of stimulus cues and risk information. Sample pictures of alcohol, food and household/office items presented with high- or low-risk information to create high- and low-risk decisions. The same pictures were used across high- and low-risk conditions. See the Methods section for the meaning of the numeral and the yes/no risk information

the picture (Fig. 1). This 'risk' information was used to create both a low- and a high-risk context for each picture. There were two parts to the 'risk' information, either the word 'yes' or 'no', and also a single number. Both were presented to the right side of the picture with the yes/no above the number. The risk information conveyed the different contexts depending on the type of cue: for alcohol cues, whether or not the participant had a designated driver and how many alcohol units (1 unit = alcohol content in 1 shot, 1 glass of wine or 1 beer depending on whether the alcohol cue depicted a cocktail, glass of wine or beer) the drink contained [low, 1 ± 1 (mean \pm SD); high, 6 ± 1]; for food cues, whether or not the food establishment passed its latest health and safety inspection and the caloric content (low, 200 ± 10 ; high, 800 ± 10); for item cues, whether or not the store had a return policy and the cost in dollars (low, 2 ± 1 ; high, 20 ± 1); and for face cues (not included in the current

analyses), whether or not the male usually uses condoms and the number of sexual partners (low, 2 ± 1 ; high, 8 ± 1). Specific number values were selected randomly on each trial, with a minimum value of 0 and no maximum value. The two pieces of 'risk' information were non-independently varied such that all low-risk situations contained 'yes' and low-risk numbers and all high-risk situations contained 'no' and high-risk numbers (Fig. 1).

The high-risk context was clearly considered more risky in previous similar work (Rupp *et al.* 2009), but it is also likely that it was considered somewhat more rewarding. Although the major difference between high- and low-risk contexts was the chance of a negative outcome, another mediating difference was reward (see the Discussion section). Likewise, although the appetitive stimulus types were selected to be equally appealing and desirable, it is likely that the perceived risk of negative outcomes associated with the decisions (sex, drinking, eating) even

in the low-risk condition were somewhat different across types. Even with these limitations of the stimulus sets and tasks, the behavioral data (see the Results section) show that manipulation of 'risk' information had a strong effect on endorsement, suggesting that all subjects deemed the high-risk context more risky.

Procedure

After the first interview session, where participants reported recent alcohol and drug use, underwent a diagnostic interview, and answered questionnaires, as described earlier, participants were scheduled for two fMRI sessions. As part of the larger project, each participant was scanned specifically at the follicular and luteal phases of their menstrual cycles with the order of the two sessions for each participant determined by which of the two phases was most imminent. Determination of menstrual phase for test scheduling was performed using a counting method and verified by later hormone assay from urine samples. Testing for the ovulatory phase session occurred between day 10 and day 14 after the women report menstruation began and testing for the luteal phase occurred between day 19 and day 23 following menstruation.

The procedure was conducted with a script programmed in Matlab 7.6 and the Psychophysics Toolbox (<https://www.mathworks.com>; <http://www.psychtoolbox.org>; Brainard 1997; Pelli 1997) on a Apple MacPro laptop. Before each fMRI session, participants reported their recent alcohol and drug use for the last week and provided a small urine sample (20 ml) for later hormone assay. This urine sample was also used for a drug screen and pregnancy test. The urine samples remained in the refrigerator for the remainder of the session, at which point they were transferred to deep freeze storage (-20°C). Samples were sent to the University of Wisconsin's National Primate Research Center Assay laboratory for estradiol, testosterone and progesterone measurement to verify the phase of menstrual cycle at the time of testing and whether naturally cycling women had ovulatory cycles (Israel *et al.* 1972), in addition to obtaining absolute measures of hormone levels. Following the urine sample, if the drug screen and pregnancy tests were negative, participants were introduced to the task that they were asked to perform in the fMRI scanner and given the opportunity to practice it on a laptop.

Imaging took place at the Indiana University Imaging Research Facility. Participants were safety screened and completed a practice run of the task outside of the scanner. The practice run was a shortened version of the actual data collection runs and used pictures from all of the same cue categories, but the pictures were not the same ones used during scanning. After the participants

understood the task, they were comfortably positioned in an fMRI scanner (3T Siemens TRIO, Siemens AG, Erlangen, Germany). Functional scanning of 280 total trials was broken up into five ~7-minute runs to allow participants breaks. The protocol for each run was based on a rapid event-related design with 56 trials all separated by variable-length inter-trial intervals. Each interval was either 2, 4 or 6 seconds long and the different length intervals were used in a ratio of 4:2:1, respectively. On each trial, a stimulus from one of the four cue categories was pseudorandomly chosen without replacement, such that 14 cues from each category were presented during each run, 7 with low-risk information and 7 with high-risk information. The cue was presented simultaneously with the risk information for 4 seconds. Participants appraised the combination of cue and risk information and rated their likelihood to drink alcohol, eat food or buy the item (or have sex with the person/face) on a four-point scale, where 1 = very unlikely, 2 = unlikely, 3 = likely, 4 = very likely. Across the five runs, this protocol produced 35 trials for each of the eight combinations of cue category (4) and risk condition (2). In the current article, only three cue categories were analyzed (alcohol, food and items).

Imaging parameters

Imaging was carried out using a Siemens Magnetom Trio 3-T, whole-body MRI and collected on a 32-channel phased-array head coil. Each fMRI session took about an hour, during which the following scans were acquired: (1) three-plane scout used for choosing slice planes for the remaining scans (10 seconds); (2) gradient-echo T2* echo-planar imaging (EPI) scans for blood oxygen level-dependent (BOLD)-based functional neuro-imaging (duration ~7 minutes, five scans/session, ~35 minutes total functional scanning); and (3) T1 3-D turbo-flash structural scan of the entire brain at high resolution (1-mm isotropic voxels) (~5 minutes). The functional pulse sequence had the following EPI parameters: echo time (TE) = 30 ms, flip angle = 70° , field of view = 240×240 mm, matrix 96×96 , in-plane resolution = 2.5 mm slice thickness = 3.5 mm, gap thickness = 0 mm. A typical volume was 32 EPI slices acquired at a time of 62.5 milliseconds per slice for a total volume acquisition time of 2 seconds [repetition time (TR) = 2]. Slices were acquired approximately parallel to the anterior commissure/posterior commissure (AC-PC) plane to efficiently cover the entire brain. High-resolution T1-weighted anatomical volumes were acquired using Turbo-flash 3-D (TI = 900 milliseconds, TE = 2.67 milliseconds, TR = 1800 milliseconds, flip angle = 9°) with 160 sagittal slices with a thickness of 1 mm and a field of view of 224×256 (voxel size = $1 \times 1 \times 1$ mm).

Data analysis

Imaging data were analyzed using FSL v4.1.9 (FMRIB Software Library; online at <http://www.fmrib.ox.ac.uk/fsl>, August 2012). Generalized linear model (GLM)-based analysis in FSL was carried out with the fMRI Expert Analysis Tool (FEAT) (Woolrich *et al.* 2009; Jenkinson *et al.* 2012). Functional scans were co-registered to the MNI template (MNI-152 average brain). Functional scans were preprocessed using MCFLIRT for motion correction, the brain extraction tool (BET) for skull stripping, with a spatial smoothing full width at half maximum (FWHM) window of 5 mm, and a high-pass temporal filter (Smith *et al.* 2004). The first-level analysis used custom predictors based on the timing protocol of each of the eight combinations of cue category and risk information, convolved with a two-gamma hemodynamic response function. Outputs from the first-level analysis were contrasts among various cue and risk conditions. The second-level analysis combined first-level outputs from separate runs for each level of the menstrual cycle phase factor for each participant. Outputs from the second-level analysis were contrasts representing each phase, both phases combined and the difference between phases. The third-level analysis combined second-level outputs across participants within each group (controls and ADs). In addition, reaction time was included as a covariate for each participant (Grinband *et al.* 2008). The reaction time covariate was calculated separately for each first-level contrast by applying the same contrast to the mean reaction time across conditions. Before entry into the model, reaction time covariates were demeaned. Outputs from the third-level analysis were contrasts representing each group, both groups combined and the difference between groups. The higher level analyses were performed using a mixed-effects model (FLAME 1). The multiple testing problem was addressed by using a voxel-wise $z > 2.3$ threshold, which was then corrected at the cluster level with $\alpha = 0.05$ using random field theory (Worsley 2002).

RESULTS

Behavior

Likelihood of endorsement

Likelihood of endorsement was calculated as a dependent variable from the participants' responses during the scanning session by taking the average of their responses for each stimulus type. A repeated-measures ANOVA with endorsement rate as the dependent variable, stimulus and risk as within-subject factors, and group as a between-subject factor showed highly significant effects. There were main effects of stimulus [$F_{(2,58)} = 13.531$,

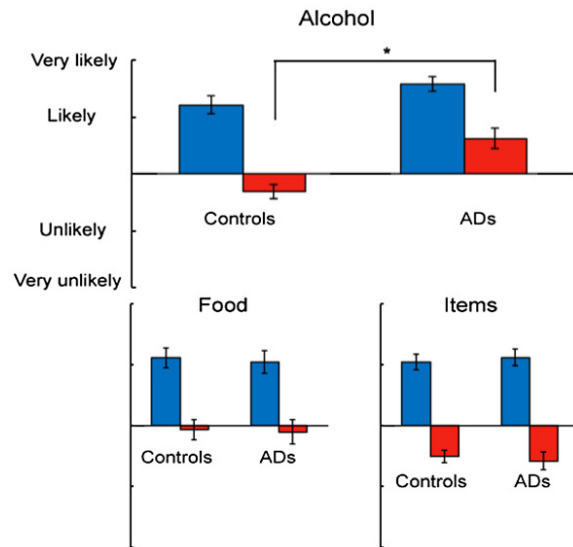


Figure 2 Mean endorsement rating as a function of stimulus cue, risk condition and group. Red bars: high risk; blue bars: low risk. * indicates a significant difference using Tukey's HSD

$P = 0.000$], risk [$F_{(2,29)} = 122.380$, $P = 0.000$] and group [$F_{(1,29)} = 4.347$, $P = 0.046$]; two-way interactions of stimulus type by risk [$F_{(2,58)} = 4.287$, $P = 0.018$], stimulus type by group [$F_{(2,58)} = 7.042$, $P = 0.002$] and risk by group [$F_{(2,58)} = 20.334$, $P = 0.000$]; and a three-way interaction of stimulus type by risk by group [$F_{(2,58)} = 3.994$, $P = 0.024$]. Importantly, the main effect of risk shows that our risk manipulation was successful for both groups, across all stimulus categories where all participants significantly reduced their endorsement of all high-risk stimuli compared to their endorsement of all low-risk stimuli.

The significant three-way interaction of *group* \times *stimulus type* \times *risk* was interpreted before any of the other effects were considered. *Post hoc* pairwise tests were performed using Tukey's honestly significant difference (HSD). As expected, ADs endorsed high-risk alcohol stimuli significantly more than controls [$q_{(2,58)} = 4.46$], but the difference with low-risk alcohol stimuli was only marginal [$q_{(2,58)} = 1.73$]. Both ADs and controls significantly reduced their drinking in the high-risk alcohol condition compared to the low-risk alcohol condition [$q_{(2,58)} = 4.58$ and $q_{(2,58)} = 7.30$, respectively], demonstrating that manipulating risk information had the desired impact on both ADs and controls. ADs endorsed high-risk alcohol decisions less than low-risk alcohol decisions, but more than controls (Fig. 1). ADs and controls did not differ on endorsement of high- and low-risk food [$q_{(2,58)} = 0.16$ and $q_{(2,58)} = 0.60$, respectively] or high- and low-risk household items [$q_{(2,58)} = 0.38$ and $q_{(2,58)} = 0.35$, respectively] (Fig. 2).

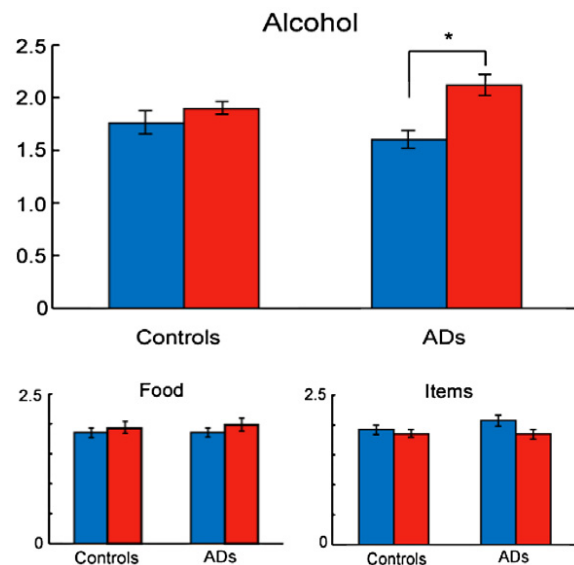


Figure 3 Mean reaction time as a function of stimulus cue, risk condition, and group. Red bars: high risk; blue bars: low risk. * indicates a significant difference using Tukey's honestly significant difference (HSD)

Reaction time

A repeated-measures ANOVA with reaction time as the dependent variable, stimulus and risk as within-subject factors, and group as a between-subject factor showed significant effects. There was a main effect of risk [$F_{(2,29)} = 4.325$, $P = 0.047$] where participants took a significantly longer amount of time to respond to high- compared to low-risk stimuli; two-way interaction of stimulus type by risk [$F_{(2,58)} = 20.334$, $P = 0.000$]; and a three-way interaction of stimulus type by risk by group [$F_{(2,58)} = 6.552$, $P = 0.003$].

The significant three-way interaction of *group* \times *stimulus type* \times *risk* was interpreted before any of the other effects were considered. *Post hoc* pairwise tests were performed using Tukey's HSD. ADs took a significantly longer amount of time to make high-risk alcohol decisions compared with low-risk alcohol decisions [$q_{(2,58)} = 3.84$]. There was also a marginally significant difference between ADs and controls for the difference in reaction time between low- and high-risk alcohol [$q_{(2,58)} = 2.81$]. Here, ADs tended to take a longer amount of time compared to controls to make a decision in the high-risk alcohol compared to low-risk alcohol conditions (Fig. 3).

The significant two-way interaction of *stimulus type* \times *risk* was driven by participants taking a longer amount of time to make high- compared to low- risk alcohol decisions compared to item stimuli where participants took a longer amount of time to make low- compared to high-risk decisions. The only significant *post hoc* comparison was in comparing the difference between

high- and low-risk alcohol decisions to the difference between high- and low- risk item decisions [$q_{(2,58)} = 3.45$].

fMRI

BOLD fMRI data were analyzed in a $3 \times 2 \times 2 \times 2$ full-factorial, whole-brain GLM analysis with stimulus cue (alcohol, food, item), risk (high, low) and phase (follicular, luteal) as within-subject factors and group (controls, ADs) as a between-subject factor. Procedurally, menstrual cycle phase was included as a factor due to hypotheses about its influence on face/sex decisions. Because face/sex decisions were not analyzed for this article, there was no specific hypothesis made about the influence of phase on stimulus cue activation. For completeness, phase was included as a factor in the overall analysis. However, for alcohol decisions, phase did not interact with risk, nor did it interact with group. As such, the results below are reported collapsed across phase (i.e. two sessions worth of data per participant).

Decisions-to-drink: low risk

Before describing the higher order effects, we first describe the lower order effects, particularly those for low-risk decisions, to establish a baseline from which the higher order effects deviate. The low-risk maps (Fig. 4) were generated by comparing alcohol decisions to food and item decisions in the low-risk condition [i.e. $2 \times (\text{ALC}^{\text{Low-risk}}) - (\text{FOOD}^{\text{Low-risk}} + \text{ITEM}^{\text{Low-risk}})$] for each group separately, and also for the two-way stimulus by group interaction. No clusters were found that showed a significant interaction, suggesting that patterns of activation across the whole brain in ADs and controls were similar for low-risk situations. This was confirmed by examining the separate groups maps. The pattern in both groups was mainly associated with greater activation of the 'default-mode network' (DMN) for alcohol decisions, including the precuneus BA7/31, posterior cingulate BA31, ventral anterior cingulate BA32, medial PFC BA9/10/11, right inferior parietal lobule BA40 and middle temporal gyrus BA39. Both groups also activated extensive regions of visual cortex, including the lateral occipital cortex (LOC) BA19 and fusiform gyrus (FG) BA 37. Activation of the hippocampus, nucleus accumbens and right caudate head and tail was also observed in both controls and ADs. Both groups significantly deactivated (i.e. produced less activation with alcohol decisions compared to food and item decisions) the medial occipital cortex, specifically the lingual gyrus, cuneus and intracalcarine cortex (BA18, BA17) (see Supporting Information Table S1 for list of low-risk ROIs for ADs and controls).

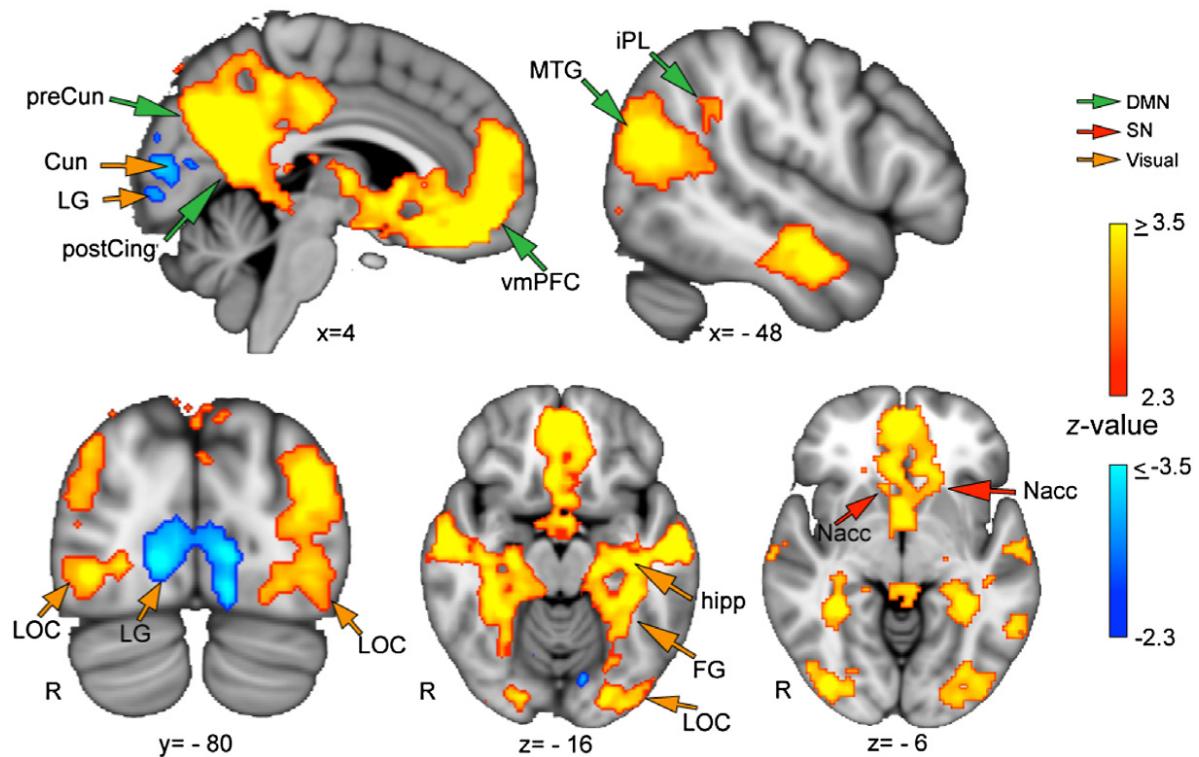


Figure 4 Statistical maps for low-risk decisions to drink alcohol in controls and alcohol dependents $[(2 \times \text{Alc_Lo}) > (\text{Food_Lo} + \text{ItemLo})]$. Green arrows mark regions associated with the default mode network (DMN); red arrows: salience network (SN); orange arrows: visual processing. Abbreviations: preCun, precuneus; Cun, cuneus; LG, lingual gyrus; postCing, posterior cingulate; vmPFC, ventromedial prefrontal cortex; MTG, middle temporal gyrus; iPL, inferior parietal lobule; LOC, lateral occipital cortex; FG, fusiform gyrus; hipp, hippocampus; Nacc, nucleus accumbens

Decisions-to-drink: high risk

The high-risk maps (Fig. 5) were generated the same way as the low-risk maps, except comparing all high-risk conditions [i.e. $(2 \times \text{ALC}^{\text{High-risk}}) - (\text{FOOD}^{\text{High-risk}} + \text{ITEM}^{\text{High-risk}})]$. The results for high-risk decisions were quite different from low-risk decisions. Here, ADs showed significantly greater activation for alcohol decisions compared to food and item decisions than controls in regions of the SN, including the substantia nigra, dorsal striatum, bilateral anterior insula and pre-SMA (Fig. 5a,b). ADs also showed significantly greater activation for alcohol decisions compared to food and item decisions than controls in regions of the CEN, including the mid-ventral lateral PFC (mid-vlPFC), which includes the inferior frontal sulcus (IFS) BA9, the inferior frontal gyrus (IFG) BA46/45/44 and the frontal operculum/insula, which will be referred to here as the fronto-insular cortex (FIC) (BA47/13) (Fig. 5a). In addition to greater activation in regions of the SN and CEN, ADs also showed significantly greater activation for alcohol decisions in the LOC (BA19), FG (BA37) and cerebellum (crus 1, bilateral) (Fig. 5b). There were no regions where controls

showed significantly greater activation for alcohol decisions than other decisions relative to ADs (see Supporting Information Table S2.3 for list of high-risk ROIs for ADs > controls).

Separate group maps for high-risk alcohol decisions (Fig. 5) were examined to determine what patterns of activation/deactivation were driving the interaction for different clusters. The map for controls only (top rows of Fig. 5a,b) represents the 'normative' pattern of activation for the high-risk alcohol decisions. It is worth noting that this normative control pattern for high-risk decisions was very similar to the control pattern for low-risk decisions; controls showed greater activation for alcohol decisions than other decisions in regions associated with the DMN (posterior cingulate and vmPFC). However, unlike with low-risk decisions, for high-risk decisions, controls also 'deactivated' (i.e. produced less activation with alcohol decisions than other decisions) core regions of the SN, including posterior and anterior portions of the insula, the dACC and pre-SMA. In addition, controls showed significant deactivation of the medial occipital cortex (see Supporting Information Table S2.1 for list of high-risk ROIs for controls-only).

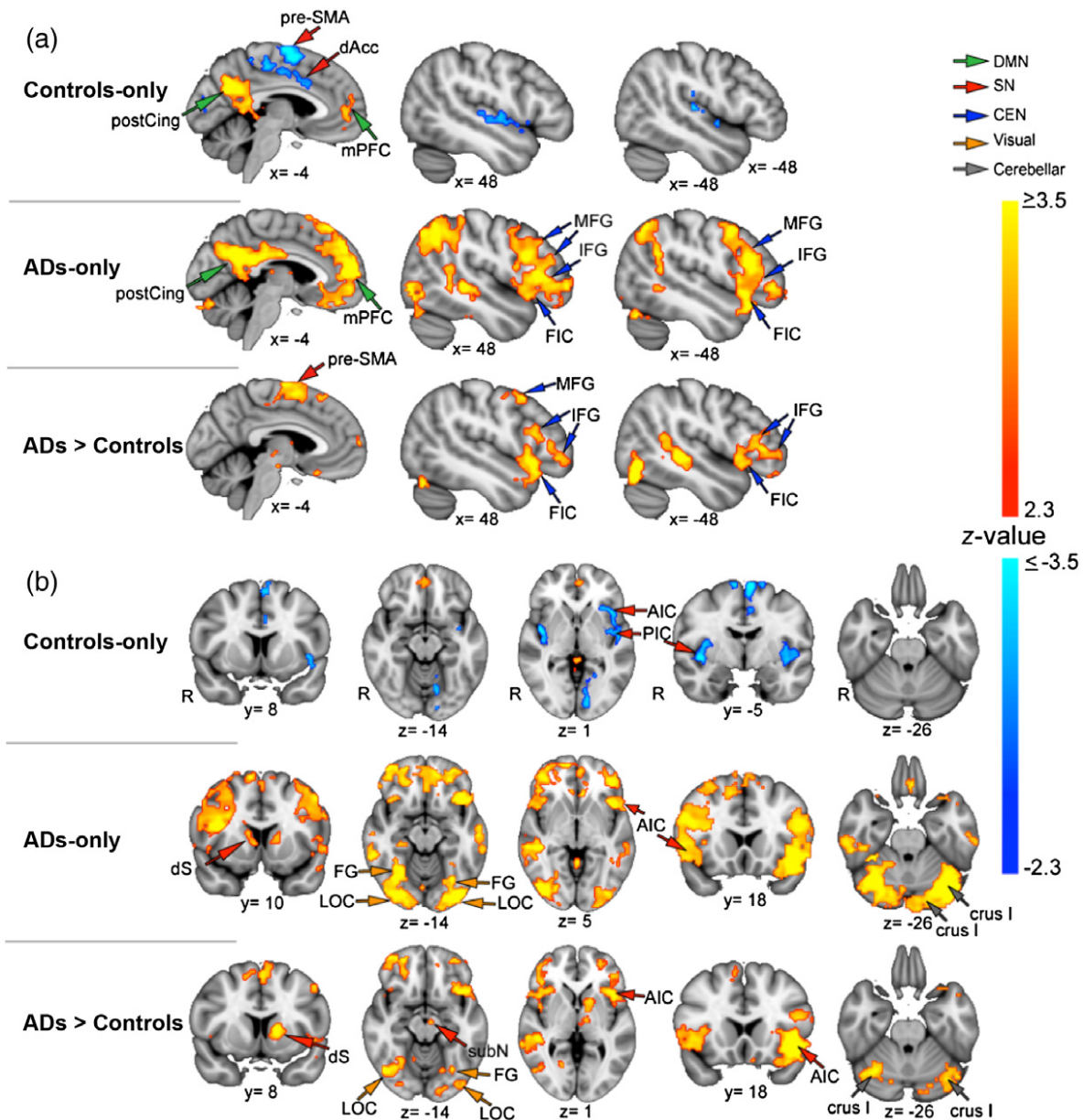


Figure 5 Statistical maps for high-risk decisions to drink alcohol [$(2 \times \text{ALC}^{\text{High-risk}}) - (\text{FOOD}^{\text{High-risk}} + \text{ITEM}^{\text{High-risk}})$]. Sagittal slices are shown in (a). Axial and coronal slices are shown in (b). Green arrows mark regions associated with the DMN; red arrows: SN; blue arrows: central executive network (CEN); orange arrows: visual processing; gray arrows: cerebellar processing. Abbreviations: postCing, posterior cingulate; pre-SMA, pre-supplementary motor area; dACC, dorsal anterior cingulate cortex; vmPFC, ventromedial prefrontal cortex; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; FIC, fronto-insular cortex; AIC, anterior insular cortex; PIC, posterior insular cortex; FG, fusiform gyrus; LOC, lateral occipital cortex; dS, dorsal striatum; subN, substantia nigra

Because controls showed 'deactivation' in some regions that also showed a significant stimulus by group interaction, it is possible that the interaction in those regions was driven by controls' deactivation for alcohol decisions relative to other decisions, rather than ADs' greater activation with alcohol decisions relative to other decisions. The AD-only map for high-risk alcohol decisions (Fig. 5a,b) showed significant activation for ADs in bilateral anterior insula, but not the pre-SMA. This suggests that the greater activation for alcohol decisions

compared to other decisions in the pre-SMA for ADs over controls (i.e. the *stimulus* \times *group* interaction) was driven by controls' 'deactivation' (Fig. 5a) rather than ADs' 'activation'. However, in the anterior insula, the same two-way interaction appears to be a combined effect of ADs' greater activation with alcohol decisions over other decisions and controls' greater 'deactivation' with alcohol decisions relative to other decisions. The AD-only map also showed another significant pattern of activation was not revealed in the *group* \times *stimulus* interaction,

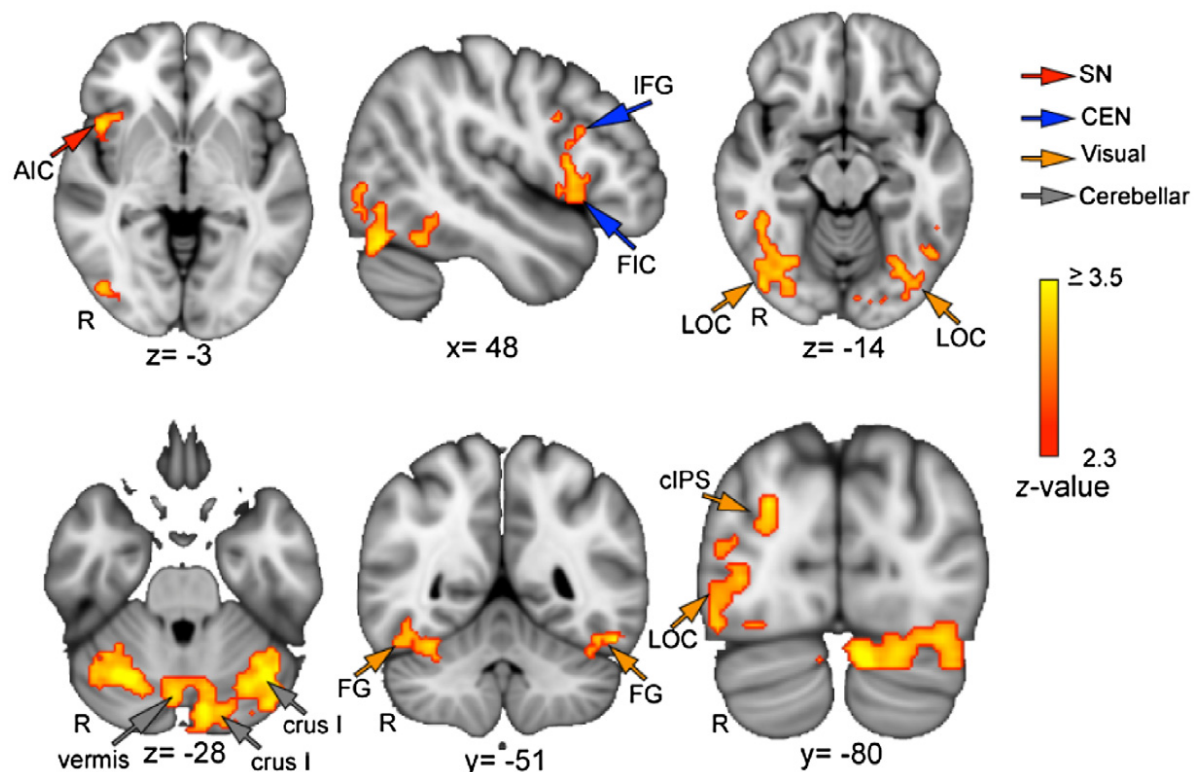


Figure 6 Statistical maps for high-risk > low-risk decisions to drink alcohol in alcohol dependents (ADs) > controls. $[(ALC^{\text{High-risk}} \text{ versus } ALC^{\text{Low-risk}}) - (FOOD^{\text{High-risk}} \text{ versus } FOOD^{\text{Low-risk}}) + (ITEM^{\text{High-risk}} \text{ versus } ITEM^{\text{Low-risk}})]$. Red arrows mark regions associated with the SN; blue arrows: CEN; orange arrows: visual processing; gray arrows: cerebellar processing. Abbreviations: AIC, anterior insular cortex; FIC, fronto-insular cortex; IFG, inferior frontal gyrus; LOC, lateral occipital cortex; FG, fusiform gyrus; cIPS, caudal inferior parietal sulcus

namely greater activation with alcohol decisions than other decisions in core regions of the DMN (posterior cingulate and vmPFC) (Fig. 5a). These were the same regions that controls activated—and the *only* regions that controls activated—for high-risk alcohol decisions. It is worth noting that, unlike controls, ADs people with AD showed no regions of significant ‘deactivation’ for alcohol decisions relative to food or item decisions (see Supporting Information Table S2.2 for list of high-risk ROIs for ADs-only).

To summarize the results of low- and high-risk decisions analyzed separately, controls activated the same network (DMN) for high- and low-risk alcohol decisions, but for high-risk alcohol decisions they also deactivated regions of the SN. ADs activated the same regions as controls for low-risk decisions; however, for high-risk decisions, ADs not only activated regions of the DMN they also activated regions of the SN and CEN, and also activated visual regions, including the LOC and FG, and cerebellar regions. Controls showed ‘deactivation’ with alcohol decisions relative to other decisions in the SMA for high-risk decisions, whereas ADs showed no significant ‘deactivation’.

Decisions-to-drink: high risk > low risk

The effects within low and high risk are important to examine; however, perhaps the most important effect is the relative difference of high- and low-risk alcohol decisions (compared with other decisions) between ADs and controls. Thus, lastly, we tested to see if there were any brain regions that were associated with a *stimulus × risk condition × group* interaction [i.e. $(ALC^{\text{High-risk}} - ALC^{\text{Low-risk}}) - (FOOD^{\text{High-risk}} - FOOD^{\text{Low-risk}}) + (ITEM^{\text{High-risk}} - ITEM^{\text{Low-risk}})$]. Consistent with a comparison of low- and high-risk maps, the regions showing the greatest difference of high and low risk between ADs and controls included the right anterior insula (BA13), right FIC (BA44/13), right IFS (BA6), inferior temporal gyrus, ventral occipitotemporal aspect (BA37), FG (BA37), LOC (BA19), caudal inferior parietal sulcus (cIPS, BA 31) and cerebellum (vermis and bilateral crus I) (Fig. 6). In all of these clusters, the three-way interaction was driven by a greater difference in activation between alcohol decisions and food and item decisions that was greater for high- than low-risk situations, and that was greater for ADs than controls (see Supporting Information

Table S3.2 for list of high-risk > low-risk ROIs for ADs > controls).

To further explain these results of the three-way interaction, we examined the two-way interactions between stimulus and risk for each group, by performing the same contrast $[(ALC^{High-risk} \text{ versus } ALC^{Low-risk}) - (FOOD^{High-risk} \text{ versus } FOOD^{Low-risk}) + (ITEM^{High-risk} \text{ versus } ITEM^{Low-risk})]$ in each group separately. This contrast showed no significant clusters of activation or 'deactivation' for controls. However, there was a significant *stimulus* \times *risk* interaction for ADs in all of the regions that showed the significant three-way interaction described earlier (*stimulus* \times *risk* \times *group*). In addition to those regions, ADs also showed a significant *stimulus* \times *risk* interaction in the supramarginal gyrus (BA40), middle frontal gyrus (BA8), IFG (BA46), frontopolar (BA10), orbital frontal cortex (BA11), precentral gyrus (BA4), postcentral gyrus (BA3), middle temporal gyrus (BA22), dACC (BA24), paracingulate gyrus (BA32) and lingual gyrus (BA18) (see Supporting Information Table S3.1 for list of high-risk > low-risk ROIs for ADs-only).

In summary, consistent across all regions, the three-way *stimulus* \times *risk* \times *group* interaction was driven by ADs' over-activation during high-risk alcohol decisions compared to high- and low-risk decisions with both appetitive and neutral control stimuli and compared to controls. The three-way interaction was seen in regions that are components of the SN (right anterior insula) and CEN (right IFG), as well as visual processing regions, and the cerebellum.

DISCUSSION

The critical question addressed in this study is whether high-risk decisions-to-drink alcohol in ADs is more associated with a hypersensitive reward response or deficits in prefrontal cortical cognitive control circuits. The results suggest that a main factor driving excessive drinking behavior in ADs is heightened reward sensitivity compared to controls in high-risk scenarios that is specific to alcohol decisions. ADs showed greater activation for alcohol decisions than other decisions in regions of the SN, including the substantia nigra and anterior insula. Regions of the PFC implicated in cognitive control were also involved in ADs' high-risk decisions-to-drink, but not in the manner hypothesized. Importantly, ADs showed *greater* activation in regions of the CEN, including the IFS/IFG and FIC. Based on previous reports of the function of the CEN, this finding suggests that ADs were exerting *more* effort at cognitive control than control participants, perhaps in an attempt to override their reward hypersensitivity. One of the clearest findings was that control participants recruited very similar networks for low- and high-risk decisions, whereas ADs recruited

the same network as controls for low-risk decisions (DMN), but recruited different networks than controls for high-risk decisions (SN, CEN and DMN). We suggest that part of the problem with high-risk decisions-to-drink in ADs is related to poor regulation of—or more specifically difficulty switching between—different brain networks and that the key site of this impairment may be the anterior insula.

Anatomical (Stevens, Hurley & Taber 2011) and functional (Sridharan, Levitin & Menon 2008; Menon & Uddin 2010) evidence suggests that the anterior insula is a network 'hub' and that it plays a causal role (Sridharan *et al.* 2008) in switching between the CEN and DMN, which are normally negatively correlated (Fox *et al.* 2005). Our results show that for high-risk decisions-to-drink, controls 'deactivated' the SN, including the anterior insula, pre-SMA and dACC, and activated the DMN. On the contrary, ADs activated regions from the DMN, CEN, and SN (including the anterior insula). First, the fact that controls 'deactivated' the anterior insula for alcohol decisions relative to other decisions and ADs *activated* the same region suggests a crucial role for the anterior insula in explaining the differences in decision making between groups. Second, like healthy controls in previous studies, the controls in this study did not recruit both the DMN and the CEN simultaneously. This is in stark contrast to ADs who activated the CEN and DMN together. Together, these findings suggest that the problem with alcohol decisions in ADs may not be a deficit in either the DMN or CEN per se, but instead may be a deficit in the regulation of those networks. We speculate that the site of the deficit may be the anterior insula and that the specific problem may involve effective switching between recruitment of the DMN and CEN.

Other regions associated more with high- compared to low-risk decisions-to-drink in ADs included the high-order visual regions LOC and FG. Because the same stimulus cues were used for high- and low-risk conditions and for ADs and controls, it is difficult to explain activation in these regions as an artifact of stimulus characteristics. Serences (2008) showed that activation in visual regions as early as V1 is influenced by learned reward histories with objects. The LOC and FG are also highly sensitive to affective or motivational arousal associated with stimulus cues (Lang *et al.* 1998; Hendler, Rotshtein & Hadar 2001; Schupp *et al.* 2003). It is possible that activation in the LOC and FG in our data is associated with the motivational reward aspect of the alcohol cues. For this to be the case, we would need to assume that the risk information provided in the high-risk condition not only increased the perceived risk of the decision but also increased the perceived reward. This premise, and how it limits the interpretation of the findings, is discussed further below. There is also research showing that the

dorsal visual system has direct anatomical projections to the anterior insula (Uddin *et al.* 2010). It is plausible that the activation observed in the LOC and FG is a part of the salience detection network for high-risk decisions-to-drink in AD. It is also possible that the LOC and FG receive recurrent feedback from regions of the SN and/or CEN, and that activation in these regions in ADs reflects an inability to control visual engagement with a salient or rewarding stimulus.

Although not hypothesized, there was robust and widespread activation of the cerebellum that was associated more with high- compared to low-risk decisions-to-drink in ADs. Other research has suggested that activation of the cerebellum is associated with automatic motor responses for addictive cues, such as alcohol for people with AD (Yalachkov, Kaiser & Naumer 2010). There is also evidence that the vermis of the cerebellum plays a significant role in the storage and recall of automatic, emotional memories conditioned by drug cues (Miquel *et al.* 2009). Additionally, the vermis has connections to the ventral tegmental area (VTA) and substantia nigra. In our results, we observed that AD activated the substantia nigra during high-risk decisions-to-drink, and we also observed activation in the ventral thalamus, dorsal striatum, and sensorimotor cortex. These regions are all part of the 'sensorimotor network' described by Yin & Knowlton (2006) that is the major network underlying habit formation. Thus, ADs choosing to endorse high-risk alcohol may also be in part due to the initiation of automatic approach motor responses upon seeing alcohol cues, and changes to the cerebellum related to AD may be an important contributor to this hypothesized mechanism.

Previous work also shows that the cerebellum contributes to activation in the CEN, SN and DMN (Habas *et al.* 2009), all of the networks that were active in ADs during high-risk decisions-to-drink. Habas *et al.* (2009) found that crus I and II of both cerebellar hemispheres were especially involved in contributing to activation in the left and right CENs. In our results, we not only observed activation of the cerebellar vermis but also activation in crus I, specifically during high-risk decisions-to-drink in ADs. Activation of both the vermis and crus I may be a contributing factor to ADs activation of the CEN, SN and DMN during high-risk alcohol decisions. Alternatively, it may be that fronto-cerebellar circuits represent a secondary 'route'—and perhaps a less adaptive route—for decision making that is recruited by ADs in high-risk situations, but not by controls, again possibly due to problems with switching between recruitment of different decision making networks.

Thus far, we have discussed regions of activation specific to high-risk decisions-to-drink for ADs greater than controls that are associated more with cue saliency;

however, we also observed activation in the right FIC (BA 44/13) and mid-vlPFC (IFS, BA9), which are regions mainly associated with the CEN. A large body of research has suggested that the right inferior frontal gyrus (mid-vlPFC) has a specialized role in inhibiting motor responses (Aron, Robbins & Poldrack 2004). However, other research has found that the mid-vlPFC is also active in situations where increased attentional control is needed regardless of the motor response associated with the task (Hampshire *et al.* 2010; Dodds, Morein-Zamir & Robbins 2011). For example, Dodds *et al.* (2011) showed that the FIC and mid-vlPFC (referred to in their paper as right inferior frontal cortex) increase in responsiveness when there was an increase in cognitive demand, regardless of whether or not the motor response was to be inhibited. Hampshire *et al.* (2010) showed a relation between activation in the mid-vlPFC and attentional demands in the absence of a motor response, even though activation in the mid-vlPFC was maximized if a motor response was required. Furthermore, in a recent meta-analysis, Nee *et al.* (2013) found that the IFS, insula and frontal operculum are active during tasks where it is necessary to filter out memories or information that are not aligned with the goal or aim of the task (intrusion resistance). Taken together, these previous studies suggest that activation in the FIC and the mid-vlPFC is driven by efforts at cognitive control, whether or not that control is effective at inhibiting a response. Our behavioral data show that ADs were unable to inhibit their responses relative to controls with high-risk decisions-to-drink. However, activation in the FIC and mid-vlPFC may still be due to the increased effort expended on attentional control needed by ADs to decide whether or not to drink in high-risk contexts. This activation may be further exaggerated due to heightened levels of input from overactive reward regions or from automatic sensorimotor processes.

Other regions that were activated more for high-risk alcohol decisions compared to food and item decisions were regions of the DMN. Both ADs and controls activated mainly regions of the DMN during low-risk decisions. The DMN has been primarily associated with the 'resting-state' or 'task-negative' network. However, researchers are now demonstrating that tasks involving self-referential mental simulations (e.g. imagining yourself in particular scenarios) and prospective, goal-directed mental stimulations (Gerlach *et al.* 2011; Menon 2011) primarily activate regions of the DMN. These previous results and our own results support the idea that the DMN is not solely a 'resting-state' or 'task-negative' network (Spreng 2012). For high-risk decisions-to-drink, controls only activated core regions of the DMN (posterior cingulate and vmPFC) and deactivated core regions of the SN (AI and dACC), illustrating the potential importance of the DMN in prospective, risky decision making.

One limitation of this study is that it was likely that the high-risk context not only increased the perceived risk of negative outcomes but also increased the perceived level of reward, compared with the low-risk context. For example, endorsing a drink with 6 units compared to 2 units increases the chances of a negative outcome, but it may also increase the potential 'high'; the increase in caloric food content may be an indicator that the food will taste better, and the increase in item cost may be an indicator that the item is of better quality. This leads to the possibility that high-risk consequences and high-risk rewards may have been perceived differently by controls and ADs. Realistically, 6 units of alcohol in one drink may differentially affect controls compared to ADs, who usually have developed a tolerance to alcohol. In fact, controls may consider the high-risk alcohol condition aversive (~6 units per drink), making it easier for controls to deactivate approach regions in the high-risk alcohol condition compared to ADs. On the contrary, ADs may consider the low-risk alcohol condition not very desirable (~2 units per drink). The high-risk alcohol condition may have produced more conflict or uncertainty for ADs compared to controls and compared to food and item decisions, eliciting stronger responses from both reward and control networks. In future work, the level of conflict or uncertainty could be controlled for, either at the group level or at the subject level. However, for this study, the goal was to produce low- and high-risk conditions that would influence the endorsement of cues by both groups. In that sense, the manipulation of 'risk' was successful because both groups endorsed all high-risk situations significantly less than low-risk situations. Nevertheless, in future work, it would be desirable to disentangle conceptions of risk (and reward) information conveyed by the text and the reward (and risk) information conveyed by stimulus cue and attempt to equate their perceived value across groups or across subjects.

Another limitation is that we only tested alcohol-dependent and control women. As such, our results may only be generalizable to women. In the future, male participants should be tested to determine if the effects we have found in the current study also exist in alcohol-dependent men compared to controls.

In conclusion, our results suggest that ADs' decision making is most impaired in situations where there is a rewarding alcohol cue and an indication of a high risk of negative consequences, as these high-risk decisions produce the strongest differences in recruitment of brain networks between ADs and controls. It is worth noting that high-risk alcohol decisions were the only situations that produced these dramatic differences; impairment did not generalize to other appetitive or neutral decisions or to any of the low-risk conditions, including low-risk alcohol decisions. For low-risk alcohol decisions, ADs and

controls did not significantly differ in their patterns of neural activation, and both groups activated regions highly consistent with the core regions of the DMN (Laird *et al.* 2009). ADs and controls also activated the DMN during high-risk decisions-to-drink, but in addition, ADs also activated regions of the SN and CEN. The simultaneous activation of these networks during high-risk decisions-to-drink in ADs may underlie a state of conflict or uncertainty where automatic or past histories of actions in these contexts primarily drive behavior. It may also be the case that the impairment in ADs is primarily one of switching between recruitment of different networks involved in decision making and that the site of the switching impairment may be the anterior insula. Our findings underscore the importance of further investigating the role of the right anterior insula in network switching, the role of visual and cerebellar regions in salience detection and automatic behavioral responses, the role of the FIC and mid-vIPFC in attentional control and intrusion resistance, and how all of these regions are particularly affected in alcohol dependence.

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Authors Contributions

TWJ and PRF were responsible for the study concept and design. LRA performed all statistical and fMRI analyses. LRA, PRF and TWJ assisted with the interpretation of findings. LRA drafted the manuscript. LRA, TWJ and PRF provided critical revision of the manuscript. All authors critically reviewed content and approved final version for publication.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 List of low-risk ROIs for ADs and controls

Table S2.1 List of high-risk ROIs for controls-only

Table S2.2 List of high-risk ROIs for ADs-only

Table S2.3 List of high-risk ROIs for ADs > controls

Table S3.1 List of high-risk > low-risk ROIs for ADs-only

Table S3.2 List of high-risk > low-risk ROIs for ADs > controls