Addiction Biology

HUMAN IMAGING STUDY

doi:10.1111/j.1369-1600.2011.00383.x

The effect of intravenous alcohol on the neural correlates of risky decision making in healthy social drinkers

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ABSTRACT

Alcohol is thought to contribute to an increase in risk-taking behavior, but the neural correlates underlying this effect are not well understood. In this study, participants were given intravenous alcohol or placebo while undergoing functional magnetic resonance imaging (fMRI) and playing a risk-taking game. The game allowed us to examine the neural response to choosing a safe or risky option, anticipating outcome and receiving feedback. We found that alcohol increased risk-taking behavior, particularly among participants who experienced more stimulating effects of alcohol. fMRI scans demonstrated that alcohol increased activation in the striatum to risky compared with safe choices and dampened the neural response to notification of both winning and losing throughout the caudate, thalamus and insula. This study suggests that alcohol may increase risk-taking behavior by both activating brain regions involved in reward when a decision is made, and dampening the response to negative and positive feedback.

Keywords Alcohol, imaging, impulsivity, nucleus accumbens, reward, risk taking.

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Numerous studies have demonstrated a relationship between alcohol consumption and risky decision making (see Corte & Sommers 2005 for a review). Alcohol has been shown to increase the probability of maladaptive risk-taking behavior, including aggression, violence, risky sexual activity and unsafe driving. The effects of alcohol on neural circuitry involved in decision making, reinforcement and punishment, however, have not been well characterized.

The neural correlates of decision making have been demonstrated in a number of neuro-imaging studies. Studies have found activation in the orbitofrontal, lateral frontal and parietal regions, along with the caudate, thalamus and cerebellum, when participants make a risky versus a non-risky choice (see Krain *et al.* 2006 for a review). The neural correlates of response to outcome have also been well characterized. The nucleus accumbens (NAcc) has emerged as a key structure in representing wins (Knutson *et al.* 2001, 2005), while the anterior insula plays a role in representing loss (Mohr, Biele & Heekeren 2010). Researchers have also implicated specific neurotransmitter systems that affect decision making and other cognitive processes. Both serotonin and dopamine are critical in modulating processes such as attention and working memory (Roberts *et al.* 1994; Robbins 1997), and animal studies have shown that ascending serotoninergic systems contribute to behavioral inhibition [for example, when a rat is required to inhibit responding to provide food reinforcement (Wogar, Bradshaw & Szabadi 1992)]. Human studies also suggest that dopamine and serotonin may affect impulsivity (Rogers *et al.* 1999; Vollenweider, Liechti & Paulus 2005). To our knowledge, however, studies have not examined how acute drug administration modulates neural activation related to decision making in these regions.

There is also a paucity of behavioral studies on decision making and sensitivity to outcome under the influence of alcohol. Early animal work has shown that squirrel monkeys (Glowa & Barrett 1976) and rats (Vogel *et al.* 1980) become less sensitive to a punishing stimulus after ingesting alcohol, but few studies have examined this effect in humans. Assaad *et al.*(2006) found that participants made more commission errors during a behavioral disinhibition task when they were intoxicated

(Assaad *et al.* 2006), but researchers were unable to determine whether this was due to increased sensitivity to reward, decreased sensitivity to punishment or a general disinhibtion effect of alcohol. Other works on disinhibition using go/no-go tasks have shown that alcohol can reduce the ability to inhibit prepotent motor responses (de Wit, Crean & Richards 2000; Marczinski & Fillmore 2003; Ostling & Fillmore 2010). Studies have also investigated alcohol-induced impaired performance on working memory, response inhibition, and motor and word-completion tasks, and have found that incentives and rewards can counteract some impairment (Fillmore & Vogel-Sprott 1997, 1999; Grattan & Vogel-Sprott 2001; Fogarty & Vogel-Sprott 2002). These studies, however, have not directly investigated risky decision making. Lane *et al.* (2004) used a two-choice paradigm in which participants could choose small guaranteed wins or larger risky wins and found that alcohol increased risky response rates (Lane *et al.* 2004). This study suggests that risk taking could be a probe to explore the relationship between alcohol and decision-making circuitry.

Mechanistically, alcohol affects the brain in part by reducing the pace of information transfer through decreasing the excitatory actions of the neurotransmitter glutamate, as well as by increasing the inhibitory actions of gamma-aminobutyric acid (Diamond & Gordon 1997). Alcohol may modulate behavior by modifying the communication between neurons at the synaptic level (i.e. interfering with information transfer between neurons), the intracellular level (i.e. modulating signaling processes within neurons) and the systems level (i.e. disrupting integrated activity between brain regions)(NIAAA 2000). In this manuscript, we take a systems-level approach by investigating how alcohol affects the activity of multiple brain regions that have been implicated in decision making. In this study, we have defined risky decision making using the criterion developed by Lane *et al.* (2004), in which risk-taking behaviors have the following parameters: (1) a choice is made between two or more options; (2) one of those options has some probability > 0 of producing either a reinforcing or an aversive consequence; and (3) the probability of that aversive consequence is unknown at the time the risky option is chosen. We hypothesize that (1) alcohol will behaviorally increase risk taking and (2) alcohol will downregulate brain regions involved in decision making and feedback notification via its inhibitory effects on the brain.

METHODS

Participants

Twenty community-recruited healthy social drinkers (12 women) participated in this study. All participants underwent a complete medical and psychiatric evaluation. Participants were excluded from the study if they had a body weight > 20% of the ideal body weight, had an abnormal physical exam or had laboratory values outside of normal ranges. Participants were given a structured clinical interview for DSM-IV (First *et al.* 2002) and were excluded if they met criteria for an Axis I psychiatric disorder. In order to reduce variability in familiarity with alcohol's effects and to ensure subjects could tolerate the target level of exposure, participants were excluded if they had never consumed at least two standard drinks of alcohol within 1 hour. They were also excluded if they reported to have a 'facial flushing' response to the consumption of alcohol. They drank an average of 4.2 drinks per week (SD = 3.0) and an average of 2.4 drinks per drinking day (SD = 0.9).

Participants were all right-handed, the average age was 26.1 years (SD = 2.8) and none had ever had a head injury requiring hospitalization. They were instructed not to take any prescribed, non-prescribed or over-the-counter medications in the 14-day period prior to the study visits. Additionally, participants were asked to abstain from alcohol for at least 3 days prior to each study visit. A urine sample was obtained from each participant at the start of each study visit for a urine drug screen (testing for amphetamine, cocaine metabolites, benzodiazepines, opiates and cannabinoids) and for a pregnancy test in females.

Experimental design

Alcohol was infused as a 6% v/v solution in saline. Methods have been described previously (Gilman *et al.* 2008). Briefly, infusion rates were based on a physiologically based pharmacokinetic model for alcohol (Ramchandani *et al.* 1999), consisting of an exponentially increasing infusion rate until the target breath alcohol concentration (BrAC) of 0.08 g% was reached. This method has been used successfully in several studies of the pharmacokinetics and pharmacological effects of alcohol in humans (Kwo *et al.* 1998; Ramchandani *et al.* 1999, 2002, 2011; Ramchandani, Kwo & Li 2001; Blekher *et al.* 2002; Morzorati *et al.* 2002). The study consisted of three infusion sessions given on separate days. The typical interval between sessions was 7 days [mean (SD) interval: 12 (8.7 days)], although seven subjects had intervals ranging from 8 to 42 days between sessions. During each study session, participants reported to the NIH Clinical Center Day Hospital. An intravenous (i.v.) catheter was inserted in each forearm; one was used for the infusion of alcohol or saline and the other for the collection of blood samples for blood alcohol concentrations.

The first study session (familiarization session) took place in the Clinical Center Day Hospital. Participants

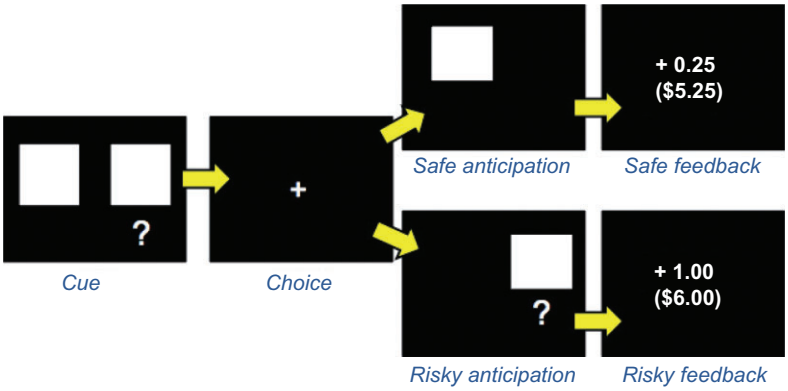

Figure 1 Risk-taking task. Each trial consisted of four events (cue, choice, anticipation and feedback). Each event was displayed for 2 seconds, and the time between events was jittered between 2 and 6 seconds to allow for separation of events in time. See methods for details

received an alcohol infusion over 45 minutes to ensure that they tolerated the alcohol infusion without experiencing nausea or marked sedation. Serial breathalyzer measurements were obtained every 3–5 minutes from the start of the infusion using the Alcotest 7410 handheld breathalyzer (Drager Safety Inc, Irving, TX, USA) to ensure that the BrACs were within 0.01 g% of the target and to enable minor adjustments to the infusion rates to overcome errors in parameter estimation (Ramchandani *et al*. 1999; O'Connor, Ramchandani & Li 2000). Subjective response to alcohol was measured using the biphasic alcohol effects scale (Martin *et al*. 1993) and the modified drug effects questionnaire (DEQ) (de Wit & McCracken 1990), which were given before the beginning of the infusion and every 10–15 minutes during the infusion. Blood samples (6 ml) were collected at three timepoints: before the start of the infusion, and at 15 and 45 minutes after the start of the infusion. After the infusion was completed, BrAC measurements were taken every 30 minutes. Participants were sent home in a taxi cab when their BrAC dropped below 0.02 g%.

On the second and third study sessions, participants received the infusions in the scanner following i.v. catheter insertion. One of these infusions was saline (placebo) and one was alcohol, given in a double-blind, randomized order. A nurse was present in the scanning room throughout the infusion.

Structural scans were acquired as the infusion began. Target BrAC was expected to be achieved at 15 minutes, and the risk-taking task was performed at 20 and 35 minutes. Blood samples (6 ml) were collected at three timepoints: before the start of the infusion, at 15 minutes after the start of the infusion and at 45 minutes when the infusion ended. The DEQ was given at baseline, and before and after the participant completed each run of the task. The total duration of the infusion was 45 minutes, after which participants were escorted from the scanner and immediately given a breathalyzer test. They were then transported to the clinical unit, where BrAC measurements were taken every 30 minutes. On the day in which they received alcohol, participants were sent home in a taxi cab when their BrAC dropped below 0.02 g%.

Risk-taking task

The task used in this study, a modified version of the Lane risk-taking task (Lane & Cherek 2000), was designed to measure brain activation associated with each aspect of the risk-taking process from selecting between safe and risky options to anticipating and receiving feedback (see Fig. 1). Each run consisted of 40 trials. At the beginning of each trial, participants were shown two white squares. One of the squares displayed a question mark beneath it. If the participant chose the square *without* the question mark (the 'safe' square), they were guaranteed to win \$0.25. If the participant chose the square *with* the question mark (the 'risky' square), they could win \$1.00 or \$5.00, but they also risked losing \$1.00 or \$5.00. Fifty percent of risky squares resulted in wins and 50% resulted in losses, but the participants had no knowledge of these probabilities. Therefore, choosing 'safe' every time yielded a net gain of \$10 (40 trials × \$0.25/trial), whereas choosing 'risk' every time yielded a net gain of \$0 but a maximum of \$35 if the participant happened to choose 'risk' only in winning trials. Wins and losses were pseudorandomized. Participants began each run with \$5.00 in order to prevent them from accruing negative earnings early in the run. Prior to scanning, participants were read an instruction script describing the task, and performed approximately 10 practice trials.

The first screen presented consisted of two white squares; when looking at this screen, participants were told to think about which square they wanted to choose. After a jittered interval, a crosshair appeared, and participants registered their choice using a Lumina LSC-400 (Cedrus Corporation, San Pedro, CA, USA) two-button fiber optic button box. After the participant made a choice, the selected square re-appeared on the screen. The participants were then given feedback for that trial, which included how much money was won or lost on that

trial as well as cumulative earnings for the run. Each stimulus was presented for 2 seconds. All trial stimuli, as well as the trials themselves, were jittered at 2-, 4-, or 6-second intervals so that the events could be separated in time (see Fig. 1). Participants played two 12-minute runs of the game while in the scanner, and the money from both runs was added together for total game earnings. Each run was independent (so that regardless of the earnings of the first run, the second run was reset to a starting point of $5.00). Participants were informed that they could keep all of the money they won.

Psychometric measures

During the screening visit, participants were given the Barratt impulsiveness scale (BIS) version 11 (Patton, Stanford & Barratt 1995). In addition, after the scanning sessions, participants were asked to rate on a 4-point scale how they felt (excited, nervous, and calm) after making either a safe or a risky choice.

Functional magnetic resonance imaging (fMRI) acquisition

Imaging was performed using a 3T General Electric MRI scanner (General Electric, Milwaukee, WI, USA) and a 16-channel head coil. Functional scans were acquired using T2*-sensitive echoplanar sequence that measures changes in blood oxygen level dependent (BOLD) contrast [371 volumes, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90, matrix = 64 × 64, field of view (FOV) = 24 cm]. We collected 30 5.0-mm thick interleaved axial slices with no gap drawn from the base of the cerebellum to the top of the brain (in plane resolution 3.75 × 3.75 mm), providing whole-brain coverage. Structural scans were acquired using a T1-weighted magnetization-prepared rapid acquisition gradient echo sequence (TR = 2000 ms, TE = 3 ms, matrix = 256 × 256, FOV = 22 cm) that facilitated the localization and coregistration of functional data.

fMRI analysis

Analyses were conducted using Analysis of Functional Neural Images (AFNI) software (Cox 1996). Echoplanar image volumes were preprocessed in AFNI. First, voxel time series was interpolated to correct for non-simultaneous slice acquisition within each volume (using sinc interpolation and the most inferior slice as a reference). Volumes were then concatenated across the two runs. Next, volumes were corrected for head motion in a three-dimensional space. A middle volume collected during the risk-taking task was used as the reference volume. Motion-correction estimates indicated that no participant's head moved > 1.0 mm in any dimension from one volume acquisition to another. Across the entire task, no participant's head moved > 3.0 mm in any dimension. We applied a 6-mm full-width, half-maximum smoothing kernel in the spatial domain. A mask was created so that all the background values outside the brain were set to 0 and all voxels inside the brain were set to 1. We then multiplied the mask by the average signal of each voxel and divided it by the whole brain mean intensity, which allowed for the calculation of percent signal change in each voxel.

The regression model featured regressors of interest and six regressors of no interest modeling residual motion after volume registration. Regressors of interest included cue presentation when the participant went on to choose the safe square, cue presentation when the participant went on to choose the risky square, motor response when the participant chose the safe square, motor response when the participant chose the risky square, safe choice anticipation, risky choice anticipation, safe (+$0.25) feedback, win $1.00 risky feedback, win $5.00 risky feedback, lose $1.00 risky feedback and lose $5.00 risky feedback. These were convolved using a gamma-variate function that modeled hemodynamic response time for each individual based on their choices. Individual signal time courses were time-locked to image onset. Statistical maps were generated for each individual separately that consisted of event-related β-coefficient and a *t*-statistic representing each of the regressors of interest across runs.

Groupwise and group-difference maps of β-coefficients and *t*-statistics were spatially normalized by warping to Talairach space (Talairach & Tournoux 1988) and were consolidated using AFNI 3dANOVA (Cox 1996) and 3dttest (Cox 1996). Alcohol and placebo runs were analyzed separately and then compared using *t*-tests. To correct for multiple comparisons, we used AFNI's 3DClustSim program, which indicated that to obtain a corrected P value < 0.05, voxels with an uncorrected P value < 0.005 must form a cluster of at least 80 voxels. All reported clusters in all tables and figures met this criterion.

T-statistics from the group maps were subsequently characterized by an assessment of actual BOLD signal changes in volumes of interest (VOIs). We chose to analyze VOIs in the NAcc (Talairach left: −9, 7, −7; right: 9, 7, −7) and the anterior insula (left: −34, 17, 11; right: 34, 17, −11) based on previous literature implicating these regions as active during notification of wins and losses (Knutson *et al.* 2001, 2005; Matthews *et al.* 2004; Bjork & Hommer 2007; Mohr *et al.* 2010). BOLD signal data were analyzed in 5-mm 3D spherical masks based on the anatomical region specified by the Talairach-Tournoux Atlas (Talairach & Tournoux 1988). Visual inspection of this mask overlaid atop Talairach-warped structural images indicating that these voxels were

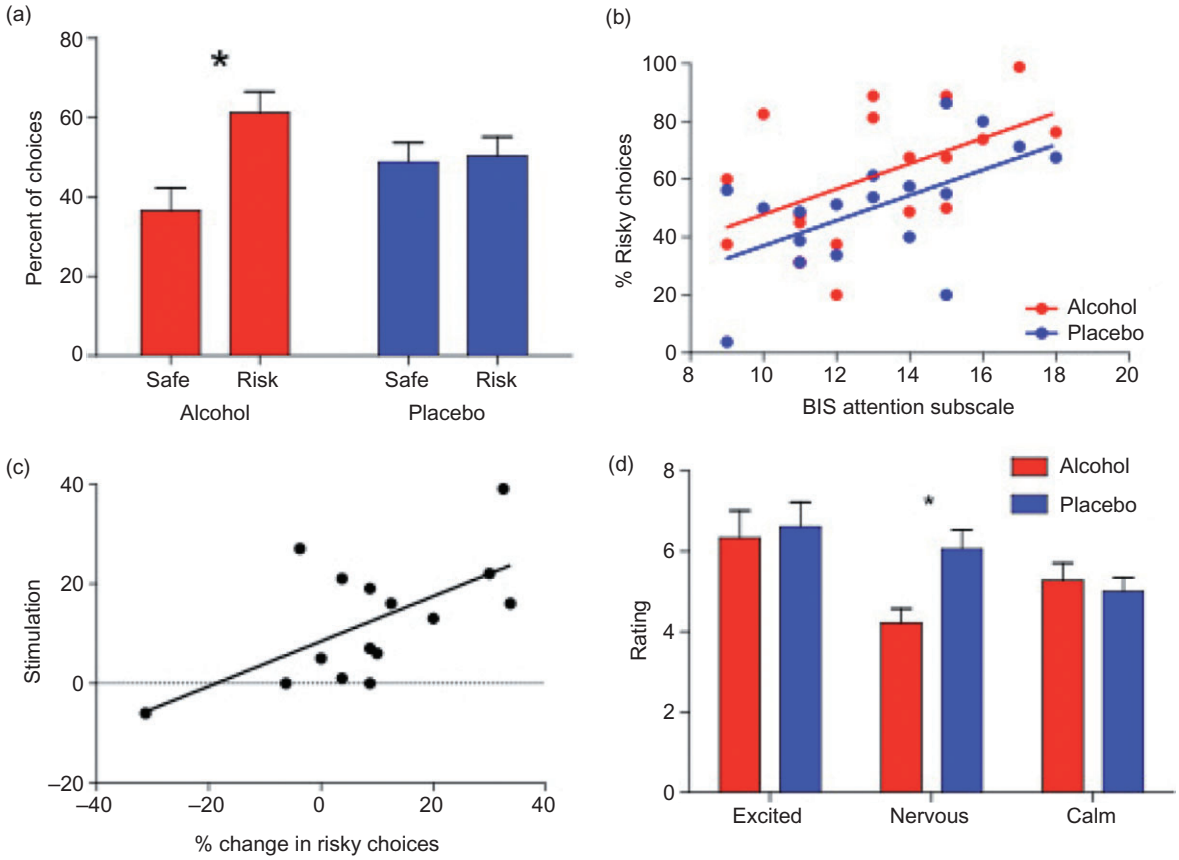

Figure 2 Behavioral data. (a) Percentage of risky choices during the alcohol and placebo sessions. An asterisk indicates a significant difference. (b) Association between participants' scores on the Barratt impulsiveness scale (BIS) attention subscale and the percentage of risky choices during the task. (c) Association between self-reported stimulation and the change in the number of risky choices from the alcohol to the placebo session. (d) Self-reported mood ratings indicating how participants felt after making a risky choice. An asterisk indicates a significant difference

localized almost entirely or entirely in striatal gray matter. Signal data were extracted from the time series as follows: (1) signal at each voxel was converted to a (percentage) deviation from the mean for that voxel across the entire time series; (2) signal was averaged by stimulus type and spatially translated into Talairach space; and (3) a mask was created consisting of the VOI through which each individual participant's data was extracted.

RESULTS

Self-reported alcohol effects

All participants tolerated the infusions without complications. The average blood alcohol concentration was 0.0 g% on the placebo day and 0.070 g% (SD, 0.012) at the end of the infusion on the alcohol day. All participants reported expected subjective effects of alcohol on the DEQ, with significant increases in high, intoxication, 'feeling effects', 'liking' the drug and 'wanting more' of the drug, compared with baseline. None of the participants reported feeling any alcohol effects during the placebo infusion.

Behavioral results

There was a significant interaction between alcohol and choice type (risky versus safe) ($F = 5.0$, $P = 0.029$) (Fig. 2a). *Post hoc* tests indicated that participants chose a higher percentage of risky than safe options during the alcohol session ($F = 6.44$, $P = 0.01$) but not during the placebo session. Participants won an average of $23.95 during the placebo session and $21.36 during the alcohol session (P = NS). There were no significant differences in reaction time by treatment (alcohol versus placebo) or choice type (risky versus safe), and there was no interaction. There was a significant association between the Barratt impulsiveness scale (BIS) attention subscale and the percentage of risky choices during both the alcohol day ($F = 5.74$, $r^2 = 0.27$, $P = 0.029$, d.f. = 1, 16) and the placebo day ($F = 7.50$, $r^2 = 0.32$, $P = 0.015$, d.f. = 1, 16); slopes were not significantly different

(Fig. 2b), indicating that alcohol did not modulate the relationship between the BIS attention subscale and percentage of risky choices. We did not find significant correlations with the motor or non-planning subscales or with the total BIS score. (All non-significant results yielded P values > 0.05.)

As a measure of behavior change, we subtracted the number of risky choices during the placebo session from the number of risky choices during the alcohol session. We found a significant association between the change in the number of risky choices and self-reported stimulation during the familiarization session ($F = 7.90$, $r^2 = 0.39$, $P = 0.013$, d.f. = 1, 16) (Fig. 2c), and a negative association between change in risky choice and self-reported sedative effects ($F = 11.36$, $r^2 = 0.43$, $P = 0.004$, d.f. = 1, 16). The change in the number of risky choices did not correlate with drinking behavior or self-reported intoxication measures on the DEQ.

After the scan, participants were asked to rate their feeling of 'excited', 'nervous' and 'calm' after choosing either a risky or safe option. During both alcohol and placebo sessions, participants reported feeling more excited and nervous, and less calm when they chose the risky compared with the safe option ($P < 0.01$). A two-way ANOVA [2 (alcohol, placebo) × 3 (excited, nervous, calm)] found a significant interaction between alcohol and mood rating ($F = 5.34$, $P = 0.0078$, d.f. = 2, 51), and a significant effect of alcohol was found ($F = 5.0$, $P = 0.029$, d.f. = 1, 51) when participants made a risky choice (Fig. 2d). *Post hoc* tests indicated that participants reported feeling significantly more nervous on the placebo than on the alcohol day when making a risky choice ($P = 0.003$). There were no differences in excitement or calmness between the alcohol and placebo sessions. An ANOVA showed no significant differences between alcohol and placebo when participants chose a safe option.

Neuro-imaging results

The jittered risk-taking task allowed us to isolate neural activation during the cue, choice, anticipation and feedback phase of each trial. Alcohol and placebo scans were analyzed separately in order to reveal brain activation under both conditions; they were then contrasted using t-tests of the β-coefficients of the regressors of interest, as well as tested for condition by task interactions.

Activation to cue phase

During the cue phase, we observed activation in lingual, frontal and cingulate cortices in both alcohol and placebo conditions. We analyzed the cue phase separately when the participants went on to choose risky and when they went on to choose safe, in order to isolate this part of the decision-making process. There were no significant interactions between condition (alcohol versus placebo) and cue type (cue followed by a risky choice versus cue followed by a safe choice).

Activation to choice phase

During the choice phase (when the participants pressed the button to indicate a safe or risky option), there were significant interactions between condition (alcohol versus placebo) and choice type (risky versus safe) in the bilateral anterior cingulate extending to the caudate, as well as in the precuneus and the right middle temporal gyrus (Table 1). When we compared activation with making risky versus safe choices during placebo, there were no significant differences. During the alcohol infusion, there was more activation to risky than safe choices bilaterally in the caudate as well as in the left cingulate gyrus.

Activation to anticipation phase

During the anticipation phase, we observed a significant interaction between condition (alcohol versus placebo) and anticipation (risky versus safe) in the left middle temporal gyrus. During the placebo condition, there was significantly more activation to safe than risky anticipation in the inferior parietal lobule and in the bilateral middle frontal gyrus. During the alcohol infusion, there was greater activation following safe choice than risky choice in the right middle temporal gyrus and right precuneus (Table 1).

Activation to feedback phase

We analyzed feedback by comparing activation in response to safe feedback (when the participant received $0.25), with feedback to notification of winning ($1.00 or $5.00) and feedback to notification of losing (–$1.00 or –$5.00).

Activation to notification of wins

Several regions showed a significant interaction between condition and winning feedback, most prominently in the bilateral thalamus extending to the caudate, as well as in the left NAcc and right middle frontal gyrus (Table 1). During the placebo session, winning versus safe feedback yielded widespread and robust activation bilaterally throughout the entire caudate, putamen and thalamus, as well as in the insula and frontal brain regions (Fig. 3, top panel). During the alcohol infusion, there were no brain regions that showed a significant difference between activation to winning versus safe feedback. When we compared activation to winning during the placebo versus the alcohol day, we saw significantly more

Table 1 Linear contrasts between event types for the placebo and the alcohol sessions.

Comparison	*Treatment*	*Cluster size*	*x*	*y*	*z*	t-*score*	*Brain region*
Choice:							
Risky > safe	Placebo	No clusters detected					
	Alcohol	295	−9	−57	42	4.55	L. cingulate/precuneus
		156	19	33	2	6.17	R. caudate/anterior cingulate
		91	−7	15	8	5.13	L. caudate
	Interaction	339	19	−33	4	6.37	R. anterior cingulate/caudate
		265	−17	27	12	4.66	L. anterior cingulate/caudate
		208	−1	−79	40	5.51	L. precuneus
		140	7	−59	48	4.16	R. precuneus
		109	37	−53	6	4.3	R. middle temporal gyrus
Anticipation:							
Risky > safe	Placebo	297	−43	−45	38	−5.71	L. inferior parietal
		265	39	33	34	−6.86	R. middle frontal gyrus
		234	−35	33	24	−5.59	L. middle frontal gyrus
	Alcohol	158	41	−73	20	−7.38	R. middle temporal gyrus
		80	27	−43	42	−5.36	R. precuneus
	Interaction	83	−31	−57	30	4.78	L. middle temporal gyrus
Feedback:							
Win > safe	Placebo	4150	−25	25	2	12.02	Caudate/putamen/thalamus
		2768	−35	−53	44	7.28	L. inferior parietal/ precuneus
		394	3	−67	−14	9.18	R. lingual gyrs
		239	−43	7	18	5.09	L. insula
		163	−39	23	34	5.55	L. precuneus
		133	−25	−5	48	5.6	L. middle frontal gyrus
		99	27	−5	48	4.95	R. middle frontal gyrus
	Alcohol	No clusters detected					
	Interaction	3612	−1	−27	8	9.71	Bilateral thalamus/ caudate
		156	−13	9	−10	5.64	L. nucleus accumbens
		106	23	55	18	4.43	R. middle frontal gyrus
		91	−59	−39	38	4.6	L. inferior parietal lobule
Loss > safe	Placebo	1292	11	31	30	9.49	R. medial frontal/ cingulate
		1051	31	23	6	8.88	R. insula
		679	−29	19	6	8.79	L. insula
		334	19	5	36	−7.07	R. cingulate
		121	−3	−15	−8	5.20	L. thalamus
	Alcohol	No clusters detected					
	Interaction	346	29	15	−8	5.29	R. insula
Win > loss	Placebo	3510	33	−49	16	5.14	R. superior temporal gyrus
		794	17	−11	44	5.64	R. cingulate
		639	−31	−31	46	5.73	L. postcentral gyrus
		567	−41	47	10	5.17	L. middle frontal gyrus
		381	−7	33	28	4.35	L. cingulate
		247	−11	7	−12	5.65	L. nucleus accumbens
		191	11	13	−14	5.80	R. nucleus accumbens
		186	−49	−49	−14	4.78	L. fusiform gyrus
		145	−13	41	−14	3.90	L. medial frontal gyrus
	Alcohol	No clusters detected					
	Interaction	No clusters detected					

Activations thresholded at $P < 0.005$, uncorrected with a cluster size k ≥ 80 voxels, yielding a corrected value of $P < 0.05$. Coordinates refer to the Talairach system.

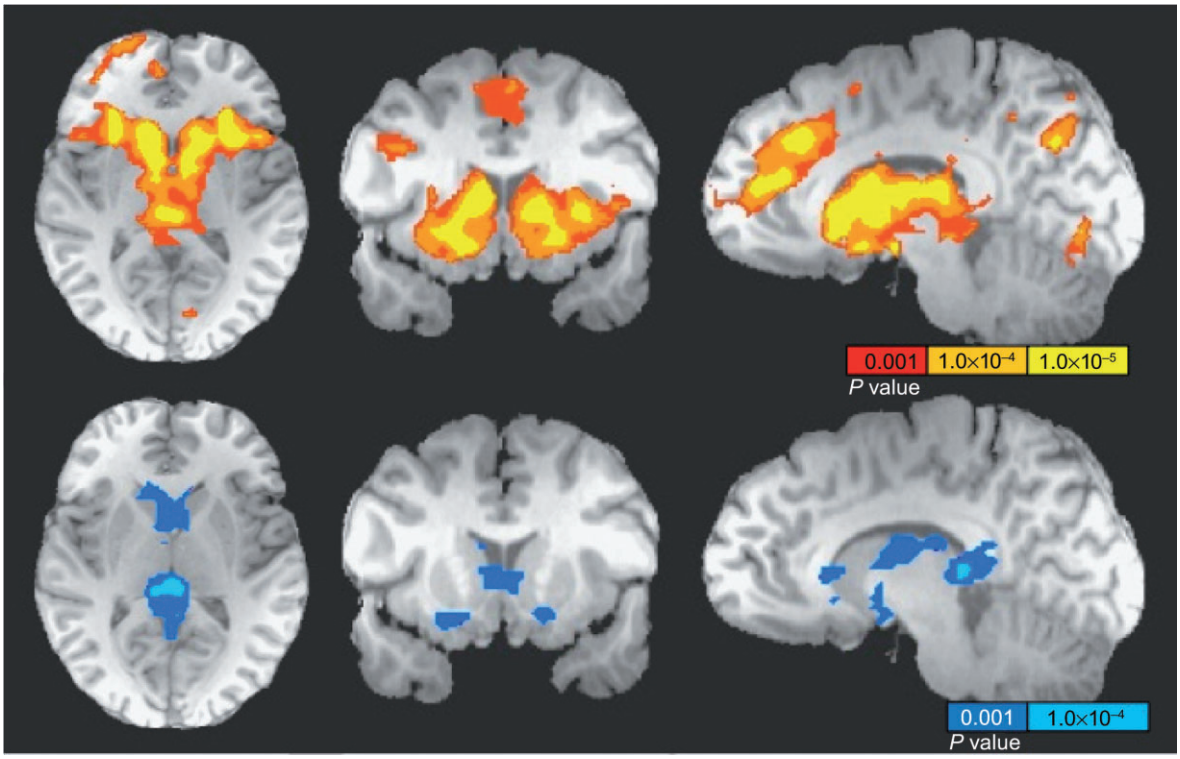

Figure 3 During the placebo session (top row), the comparison of win versus safe elicited widespread activation throughout the caudate, putamen, thalamus and insula. During the alcohol session (not shown), there were no significant differences between activation to winning versus safe feedback. When comparing winning under placebo versus alcohol condition (bottom row), there was significantly more activation during the placebo session. *P* values are uncorrected

activation to winning throughout the caudate on the placebo session (Fig. 3, bottom panel).

Activation to notification of loss

When comparing loss to safe feedback, there was an interaction between condition and feedback (loss versus safe) in the right insula (Table 1). During the placebo session, we observed activation in the bilateral insula, right cingulate and left thalamus during loss notification (Fig. 4, top panel). There were no differences during the alcohol infusion to loss versus safe outcome. When we directly compared notifications of losses during the placebo versus the alcohol session, we found significantly more activation to loss on the placebo day (Fig. 4, bottom panel).

Comparison of win versus loss

When we compared wins with losses, during the placebo infusion, we observed activation in several frontal and temporal regions, as well as bilaterally in the NAcc. During the alcohol infusion, there were no significant differences between notification of wins and notification of losses. We did not see an interaction between condition and outcome (win versus loss).

VOI analysis

In order to clarify the directionality of significant differences and to further examine how activation is related to subjective alcohol effects, we conducted a VOI analysis in the NAcc and the insula. We examined BOLD data collected during the choice and feedback phase of the experiment because these phases showed significant differences in the voxel-wise BOLD analysis; we did not extract VOIs during the cue or anticipation phase because there were no differences between alcohol and placebo scans in these regions.

NAcc VOI

In the NAcc VOI, we examined BOLD data collected during the choice phase and the feedback phase of the experiment. During the choice phase, there was a significant interaction between condition (alcohol or placebo) and choice type (risky or safe) ($P = 0.029$, $F = 3.23$) (Fig. 5a). *Post hoc* tests indicated that there was a significant difference between activation to risky versus safe choices during the alcohol condition ($t = 2.96$, $P < 0.05$) but no significant difference during the placebo condition. There was a significant association between NAcc activation during risky choice and the percentage of risky

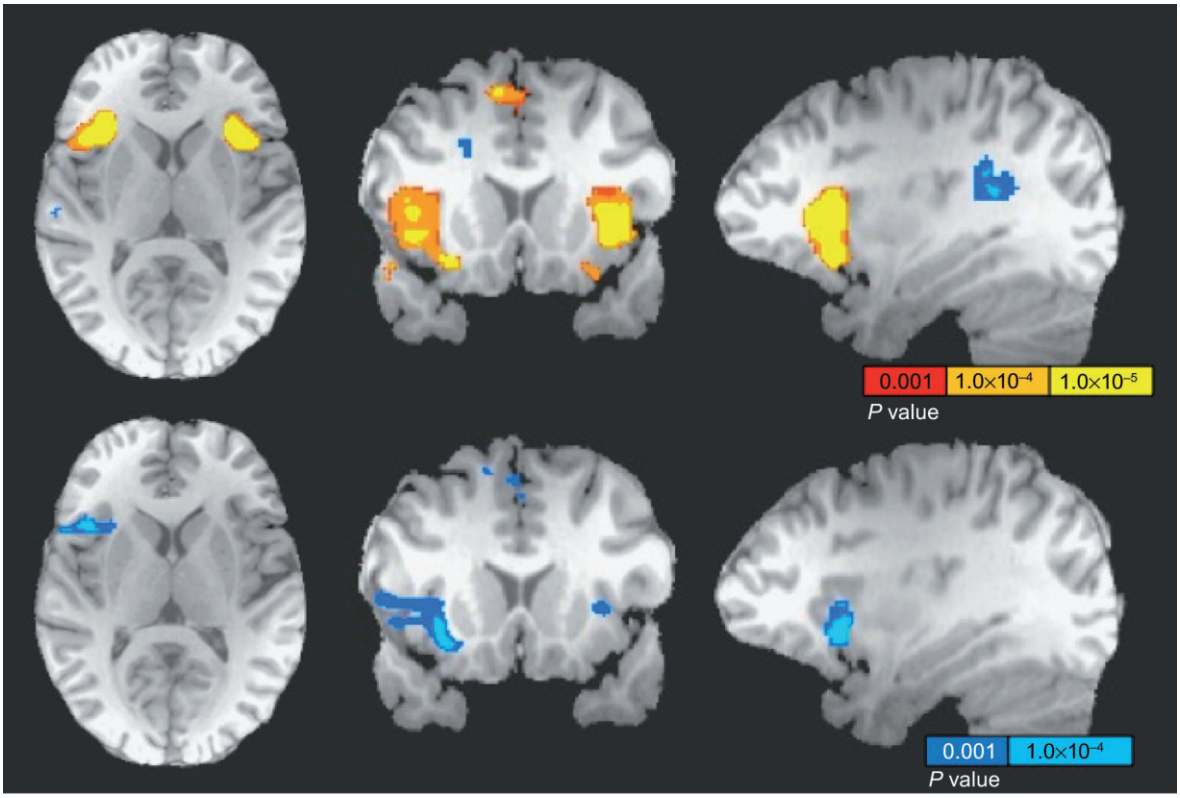

Figure 4 During the placebo session (top row), the comparison of loss versus safe elicited activation primarily in the bilateral insula. During the alcohol session (not shown), there were no significant differences between activation to losing versus safe feedback. When comparing losing under placebo versus alcohol condition (bottom row), there was significantly more activation during the placebo session. *P* values are uncorrected

choices selected during the alcohol condition ($F = 6.84$, $r^2 = 0.31$, $P = 0.019$, d.f. = 1, 16) (Fig. 5b); this association was not significant during the placebo session. We did not find a significant association between NAcc activation and measures of the DEQ activation or subjective measures of stimulation or sedation during choice.

During the feedback phase, we found a significant interaction in the NAcc between condition and feedback type ($P < 0.001$, $F = 6.18$) (Fig. 5c). There was a significant difference during the placebo session between activation to win versus safe ($t = 4.34$, $P < 0.05$) and win versus loss ($t = 4.28$, $P < 0.05$) but no differences during the alcohol session. During notification of feedback, we did not find an association between activation in the NAcc and percentage of risky choices.

Insula VOI

In the insula VOI, we examined BOLD data collected during the feedback phase of the experiment and found a significant interaction between condition and feedback ($P < 0.001$, $F = 5.01$) (Fig. 5d). During the placebo session, there was a significant difference between win versus safe ($t = 4.10$, $P < 0.05$) and between loss versus safe ($t = 3.55$, $P < 0.05$) but no differences during the alcohol session. There was no association between activation in the insula and percentage of risky choices.

DISCUSSION

Despite a long-standing view that alcohol increases risky decision making, studies have not systematically examined the effect of acute alcohol on brain function during risk-taking behavior. By using a physiologically based pharmacokinetic model for alcohol in combination with a jittered two-choice risk-taking task, we examined the neural correlates in each phase of decision making under alcohol and placebo conditions. We found that alcohol increased risky decision making, especially among participants who experienced greater stimulatory and less sedative effects of alcohol. During the alcohol infusion, participants had significantly more activation in the striatum to making a risky compared with a safe choice, and the activation during risky decision making was associated with the percentage of risky decisions. In addition, alcohol drastically reduced the neural response to

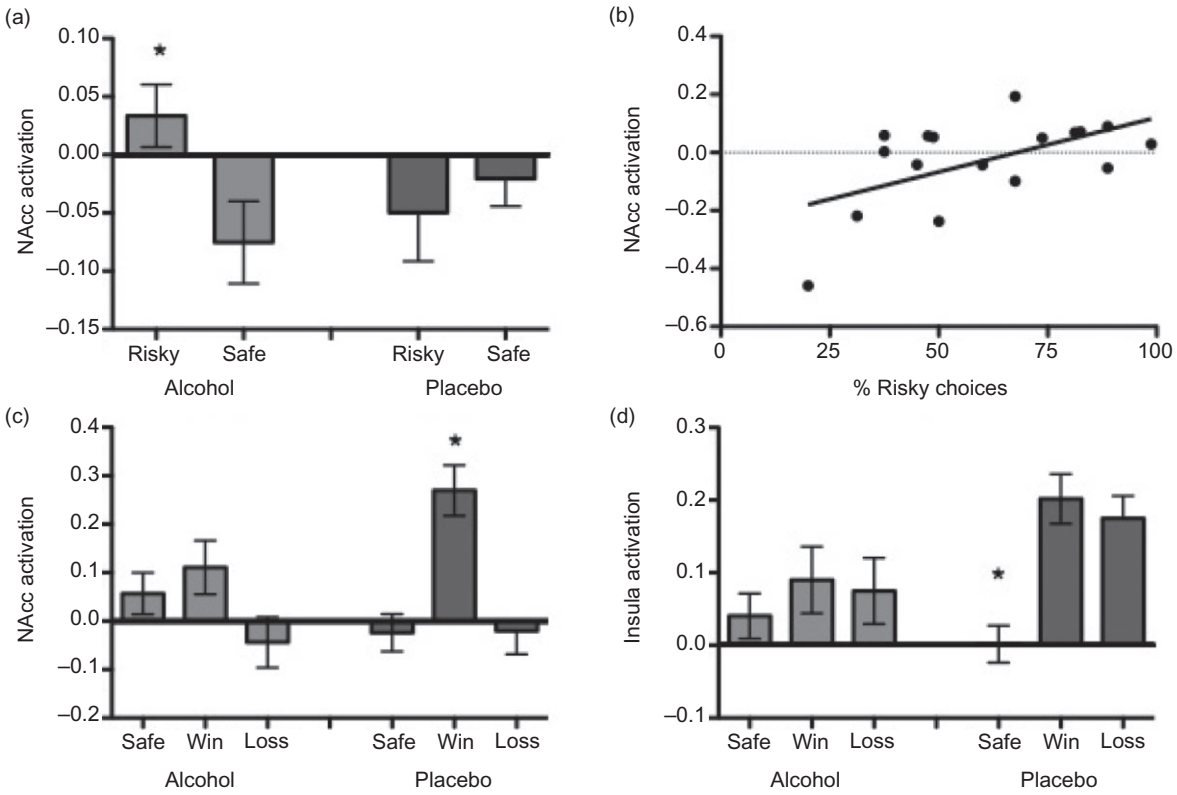

Figure 5 Volume-of-interest data. (a) Interaction in the nucleus accumbens (NAcc) between condition and choice type during the choice phase. (b) Association between activation in the NAcc and percentage of risky choices during the alcohol session. (c) Interaction in the NAcc between condition and feedback type during the feedback phase. (d) Interaction in the insula between condition and feedback type during the feedback phase. Asterisks indicate significant differences

notification of outcome, regardless of winning or losing money.

Alcohol increases risk-taking behavior, particularly in individuals who experience its stimulatory, but not sedative, effects

While some studies have shown that alcohol increases risk-taking behavior in laboratory tasks (Teger, Katkin & Pruitt 1969; Dougherty *et al.* 1999; Lane *et al.* 2004; George, Rogers & Duka 2005), others have yielded inconsistent or negative results (Meier *et al.* 1996; Breslin *et al.* 1999; Richards *et al.* 1999; Ortner, MacDonald & Olmstead 2003; Dougherty *et al.* 2008). This inconsistency could in part be due to inter-individual variability in blood alcohol concentrations, particularly following oral administration (Ramchandani *et al.* 2009), highlighting the importance of precisely controlling alcohol exposure. Inconclusive results could also be a consequence of differences in tasks, differences in personality traits or alcohol expectancies, or differences in an individual's subjective response to alcohol.

We found a significant relationship between increased risk-taking behavior and self-reported stimulatory effects of alcohol, and a negative relationship between risk taking and self-reported sedative effects. This suggests that greater sensitivity to the stimulating properties of alcohol may be a marker for increased likelihood of risk taking following alcohol consumption. In a study using a go/no-go task, individuals who exhibited increased heart rate during intoxication committed more commission errors (a measure of impulsivity) than those who did not experience increases in heart rate (Assaad *et al.* 2006). Increased heart rate response to intoxication is associated with an increase in alcohol-induced dopamine release in the NAcc (Boileau *et al.* 2003), suggesting that an elevated heart rate may be related to sensitivity to the stimulating properties of alcohol. Furthermore, heavy drinkers are more likely to report stimulation than sedation effects (King *et al.* 2002) and are more likely to take risks after drinking (Goudriaan, Grekin & Sher 2007; Yan & Li 2009; Huang, Jacobs & Derevensky 2010). This may have implications for binge drinking. It has been shown that people who binge-drink report greater stimulation from alcohol and are less likely to perceive risk when in

dangerous situations (i.e. drunk driving) (Marczinski *et al*. 2008). A recent study also showed that greater positive effects and lower sedative effects after alcohol consumption predicted increased binge-drinking frequency during follow-up in a sample of social drinkers (King *et al*. 2011). These converging lines of research suggest that stimulation from alcohol may lead to an increase in alcohol-induced impulsivity and risk taking, and this increased risk taking may be intensified in binge drinkers. However, the association between stimulation and risky decision making should be interpreted cautiously; with our small sample size, the data are not normally distributed, and it is possible that effects may be driven by outliers.

The anxiolytic effects of alcohol have been well documented in animal and human studies, and reduced anxiety may play a role in increased risk taking during intoxication. We attempted to probe alcohol's anxiolytic effects with self-reported ratings of how the participants felt after making a risky or safe choice. There was no difference in self-reported excitement, but participants reported feeling less nervous after they made a risky choice during the alcohol condition. This decreased anxiety may contribute to an increased tendency to take risks.

We also collected data to examine how other subjective alcohol effects might be related to risky decision-making behavior. We found that self-reported feelings of 'intoxicated', 'high', 'wanting more', and 'liking' alcohol were not associated with risk-taking behavior, suggesting that risk taking may be specific to the stimulation or sedation effects of alcohol. We did find an association between the percentage of risky choices and the attention subscale on the BIS, but not the motor or non-planning subscales. Cognitive-intensive processes that require conscious thought and deliberation, particularly effortful processes (Steele *et al*. 1990) like attention, may be affected by alcohol to a greater extent than impulsive motor tasks. These results highlight the differences between various types of impulsivity and emphasize the necessity of collecting multiple measures of impulsivity in studies examining risk-taking behavior.

fMRI data suggest a heightening of activation to risk taking and a dampening of activation to risky feedback during alcohol intoxication

We saw expected activation in the cue phase in the lingual, frontal and cingulate cortices, which have been implicated in the decision-making phase in other studies (Knutson *et al*. 2005; Engelmann & Tamir 2009). During the alcohol but not the placebo session, we observed activation in the caudate when participants went on to make risky choices. In the choice phase, we saw a similar pattern; only in the alcohol session was there more activation to a risky than to a safe choice in the bilateral caudate. We tested for interactions to investigate if differences were due to a change in the hemodynamic response function caused by alcohol's effects on blood flow in general and found a significant interaction between condition and choice in the bilateral caudate, indicating that alcohol specifically affected activation in response to a risky but not a safe choice. A VOI analysis of the NAcc confirmed this interaction. The association between NAcc activation and the percentage of risky choices during the alcohol session suggests that NAcc activation during the alcohol intoxication may be a possible mechanism underlying risky decision making.

The most dramatic difference we observed between the alcohol and placebo conditions was the dampened response to notification of outcome, both winning and losing, during the alcohol condition. During the placebo condition, there was an extremely robust activation ($P < 1.0 \times 10^{-4}$) throughout the caudate, NAcc, thalamus and frontal regions during notification of wins, while in the alcohol condition, we saw no differences in winning compared with safe feedback. We found significant interactions between alcohol and winning feedback in the caudate and the left NAcc, again confirming that alcohol did not cause a general shift in hemodynamic response function but instead specifically affected the activation to notification of winning. We saw a similar dampening of response to negative feedback in the alcohol compared with the placebo condition in the anterior insula, a region that has been implicated in many studies as playing a role in loss (Mohr *et al*. 2010). This striking result suggests that reward circuitry in the brain is fundamentally altered during intoxication, particularly during notification of outcome of goal-directed behavior.

It is possible that once the reward circuitry of the brain is activated, additional non-drug rewards would not result in further BOLD-detected activation. However, if alcohol's effect on the striatum was a direct pharmacological action on brain vasculature, it is difficult to understand why alcohol increases striatal activation during choice but blunts activation during feedback. We suggest that alcohol's effect on the striatum is not a simple, direct pharmacological effect but rather the result of a more complex interaction between alcoholic's action to release dopamine combined with a depressant effect in many cortical regions that monitor outcome and project to the striatum.

The lack of activation to feedback following risky choices provides support to some classic psychological theories of alcohol's effects. Hull's (1981) model of self-awareness states that alcohol impairs the cognitive processing of self-relevant information, so therefore, if that information is unpleasant or uncomfortable, then

alcohol will attenuate that discomfort. Steele and Josephs' (1986) attention-allocation model is conceptually similar and states that alcohol decreases anxiety by impairing all cognitive activity that requires effortful processing. Insensitivity to outcome may be a factor related to an inability to process such cognitive information. In this task, participants do not consciously report feeling less excited during the alcohol infusion, but the dramatic decrease in neural activation to wins and losses suggests that the brain's ability to respond appropriately to feedback is impaired. This may have further implications for related anxiolytic effects of alcohol. For example, it is possible that neural activation to outcome is reduced not only *after* making a risky choice but also before the choice is made (i.e. imagining or anticipating the risky choice). This suggests that alcohol may modulate one's perception of a risky behavior (i.e. approaching an unknown person), and this modulation may be associated with the likelihood that one would engage in such behavior.

Limitations and future directions

This study has several limitations that suggest that the results should be interpreted cautiously. Though the neuro-imaging design allowed for the temporal separation of cue, choice, anticipation and outcome, our TR of 2 seconds may have not have sampled the hemodynamic response function optimally; this sampling can lead to incomplete characterization of the shape and magnitude of the hemodynamic response function. The shape and timing of the hemodynamic response function could have varied between the alcohol and saline conditions in ways that were undetected by our analysis methods; this is a concern when comparing two pharmacological conditions using fMRI. It is possible that subtle differences may have contributed to measurement errors across events of the decision-making task. Additionally, although we tested for interactions between the conditions and the trial events, this test does not exclude the possibility of alcohol-induced changes in cerebral blood flow. A more direct way to measure changes in absolute blood flow would be to conduct an arterial spin labeling study that provides quantitative measures of cerebral blood flow. Furthermore, while i.v. alcohol administration has advantages in its ability to precisely control blood alcohol concentration and brain alcohol exposure, this method does not mimic the time course of an actual drinking episode. The rise in BAC is faster with i.v. than with oral alcohol, and therefore, there may be a lag between BAC and brain function.

An additional limitation of this study is that we were only able to give one level of alcohol exposure to all participants. Future studies could vary blood alcohol levels to investigate if larger exposures have a greater effect on risky behavior. Future studies could also recruit individuals with different drinking patterns, especially binge drinkers, and examine the relationship between high-risk drinking behavior and risky decision making during intoxication. An interesting direction for this research would be to investigate how neural activation is related to real-life risk taking. Finally, future studies could examine how factors such as gender, age and family history of alcoholism may mediate the relationship between alcohol and risky decision making. These studies may help both researchers and clinicians better understand risk factors of impaired decision making under the influence of alcohol.

Authors Contribution

JG, AS, VR, RM, and DW were responsible for the study concept and design. RM contributed to the development and programming of the task. JG drafted the manuscript. AS, VR, RM, and DW provided critical revision of the manuscript for intellectual content. All authors critically reviewed content and approved final version for publication.

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