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Acute Alcohol Effects on Attentional Bias are Mediated by Subcortical Areas Associated with Arousal and Salience Attribution

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Acute alcohol ingestion increases attentional bias to alcohol-related stimuli; however, the underlying cognitive and brain mechanisms remain unknown. We combined functional magnetic resonance imaging (fMRI) with performance of a dual task that probed attentional distraction by alcohol-related stimuli during 'conflict' processing: the Concurrent Flanker/Alcohol-Attentional bias task (CFAAT). In this task, an Eriksen Flanker task is superimposed on task-unrelated background pictures with alcohol-associated or neutral content. Participants respond to the direction of a central 'target' arrow and ignore adjacent congruent (low cognitive load) or incongruent (high cognitive load) 'flanking' arrows. Using a between-subject design, 40 healthy moderate-to-heavy social drinkers received either no alcohol (placebo), 0.4 g/kg (low dose), or 0.8 g/kg (high dose) of alcohol, and underwent fMRI while performing the CFAAT. The low alcohol dose, relative to placebo, increased response latencies on trials with alcohol-associated backgrounds and, under low cognitive load, increased the activity evoked by these pictures within a medial hypothalamic region. Under high cognitive load, the low alcohol dose, relative to placebo, elicited greater activity within a more lateral hypothalamic region, and reduced activity within frontal motor areas. The high alcohol dose, relative to placebo, did not reliably affect response latencies or neural responses to background images, but reduced overall accuracy under high cognitive load. This effect correlated with changes in reactivity within medial and dorsal prefrontal cortices. These data suggest that alcohol at a low dose primes attentional bias to alcohol-associated stimuli, an effect mediated by activation of subcortical hypothalamic areas implicated in arousal and salience attribution.
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INTRODUCTION

In heavy social drinkers, alcohol-associated stimuli grab attention (Field and Cox, 2008; Townshend and Duka, 2001) and increase both the urge to drink alcohol and the amount of alcohol ingested (eg, Field and Eastwood, 2005). Alcohol ingestion increases this attentional bias to alcohol-associated stimuli (eg, Duka and Townshend, 2004). The cognitive processes and brain mechanisms involved in this effect of alcohol remain unknown.

Neurocognitive models of selective attention propose that the regulation of attentional resources is mediated by a specialized 'interference monitor', which detects and evaluates the coactivations of processing pathways associated with different inputs (Desimone and Duncan, 1995). When sensory/informational conflict is detected (eg, when one input is task relevant, while another is salient but task irrelevant), the 'interference monitor' triggers top-down cognitive control mechanisms. Top-down control resolves the interference by engaging selective attention to enhance the representation of task-relevant information (Botvinick *et al*, 2001; Egner and Hirsch, 2005; Posner and Petersen, 1990). These processes are typically revealed using paradigms in which task-irrelevant stimuli (or stimulus features) directly conflict with task-relevant information (Fan *et al*, 2003). Functional magnetic resonance imaging (fMRI) studies generally attribute conflict monitoring to engagement of medial prefrontal and dorsal anterior cingulate cortices (dACC; eg Botvinick *et al*, 2001; Kerns *et al*, 2004; Ridderinkhof *et al*, 2004a). Attentional selection is attributed more to posterior parietal regions (Wang *et al*, 2009) and cognitive control to lateral prefrontal cortex (LPFC; Egner *et al*, 2005).

Selective attention to task-relevant stimuli can be 'overturned' by incidental processing of information with strong motivational salience acting in a bottom-up manner (Anderson *et al*, 2011). Recent fMRI studies suggest that brain regions associated with cognitive control processes

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underlie attentional bias to drug-associated stimuli (Hester and Garavan, 2009; Luijten *et al*, 2011), albeit without using typical tests of cognitive control.

In this study, we modified a 'conflict' task (Flanker task; Eriksen and Schultz, 1979) to test whether task-irrelevant, but motivationally salient, alcohol-related stimuli affect cognitive control and selective attention in social drinkers: The Concurrent Flanker/Alcohol-Attentional bias task (CFAAT; Nikolaou *et al*, 2013) comprised of the Flanker task presented on backgrounds of task-unrelated alcohol-associated or neutral pictures. In the context of these salient and neutral background images, participants responded to the direction of a central arrow (target), while ignoring adjacent arrows (flankers). On different trials, these flankers pointed to the same (congruent; low cognitive load) or to the opposite (incongruent; high cognitive load) direction as the target.

We predicted a bottom-up interference effect of alcohol-associated images during both congruent and incongruent conditions. Consistent with the load theory of selective attention (Lavie *et al*, 2004), we anticipated *enhanced* activation within regions implicated in attentional bias towards alcohol-related stimuli (eg, ventral prefrontal areas; Luijten *et al*, 2011; Nestor *et al*, 2011) during the congruent condition, yet *attenuated* activation during the incongruent condition, reflecting reduced processing of background images during higher cognitive load.

We further predicted modulation of activity supporting cognitive control (identified from the comparison of incongruent *vs* congruent trials, as the conflict elicited by incongruent flankers evokes the need for greater control) by alcohol-related background stimuli when compared with neutral stimuli.

Low doses of alcohol increase attentional bias (Adams *et al*, 2012; Duka *et al*, 2004), whereas higher doses impair cognitive control processes (Loeber and Duka, 2009). We therefore tested how a low (0.4 g/kg) and a high (0.8 g/kg) dose of alcohol would affect the CFAAT. We expected qualitatively different effects by the two alcohol doses, following previous observations of nonlinear dose effects on visual perception and memory (Bisby *et al*, 2009; Calhoun *et al*, 2004). Consequently, we undertook separate comparisons between the low alcohol dose and placebo, and between the high alcohol dose and placebo.

We predicted that alcohol at the low dose would increase the salience of alcohol-related stimuli (maximally in the congruent condition), whereas alcohol at the high dose would affect cognitive control (evident in the incongruent condition). These interactions would be expressed in neural activity within brain regions associated, respectively, with emotional reactivity (eg, amygdala) and cognitive control (eg, LPFC).

MATERIALS AND METHODS

Participants

In all, 40 healthy moderate-to-heavy social drinkers (21 male and 19 female; age 18–40 years; right-handed; English-speaking) with a weekly alcohol consumption of 10–60 units were recruited from the University of Sussex subject pool (see Supplementary Materials and methods for inclusion/exclusion criteria). The study was approved by the University of Sussex ethics committee.

Design/Procedure

Participants were randomly allocated to receive one of three flavored drinks that contained either no alcohol (placebo group) or 0.4 g/kg (low-dose group) or 0.8 g/kg (high-dose group) of bodyweight alcohol under double-blind conditions (see Supplementary Materials and methods—'Alcohol preparation/administration procedure').

After an initial task-familiarization session, participants underwent the scanning session. They drank their allotted drink over a period of 30 min, and were then placed in the 1.5 T Siemens Avanto scanner where they completed the CFAAT alongside additional tasks during acquisition of functional (fMRI) data sets (T2*-weighted images covering the whole brain). The CFAAT was always presented 15–30 min after the end of drink administration, close to when blood alcohol concentrations (BACs) reach a plateau (eg Weissenborn and Duka, 2003).

Subjective feelings associated with alcohol ingestion (Subjective Effects Visual Analog Scale; VAS; Duka *et al*, 1998), and indices of alcohol craving (Desire for Alcohol Questionnaire; DAQ; Love *et al*, 1998) were rated immediately before and 10 min after drink administration (see Supplementary Materials and methods—'State questionnaires').

Breath alcohol concentrations, transformed to BACs, were measured (see Supplementary Materials and Methods): (1) at the start of each session to ensure zero blood alcohol levels; (2) after drinking; and (3) after completion of the scanning procedure. At the end of the scanning session, participants were debriefed and remained in the laboratory until BACs had fallen below 0.4 g/l (ie, half of the legal driving limit).

Measures

Baseline measures/trait characteristics. During the baseline session, participants completed a set of tests and questionnaires to ensure that the groups were matched on baseline trait characteristics (see Supplementary Materials and methods).

Concurrent Flanker/Alcohol-Attentional bias task. The CFAAT involved performing the Eriksen Flanker task (Eriksen *et al*, 1979) in the presence of background, task-unrelated, alcohol-associated, or neutral images (see Figure 1 and Supplementary Materials and methods for task details). A row of five arrows consisting of a central 'target' and two flanking—arrows on either side, were superimposed on the center of each background image. Participants ignored the flankers, and responded by pressing one of two keys on a keypad, depending on whether the 'target' was pointing left or right. Flankers pointed either in the same direction as the 'target' (eg, $\ll\!<\!\ll$; congruent condition; low cognitive load) or in the opposite direction (eg, $\ll\!>\!\ll$; incongruent condition; high cognitive load; bold font added only for illustration).

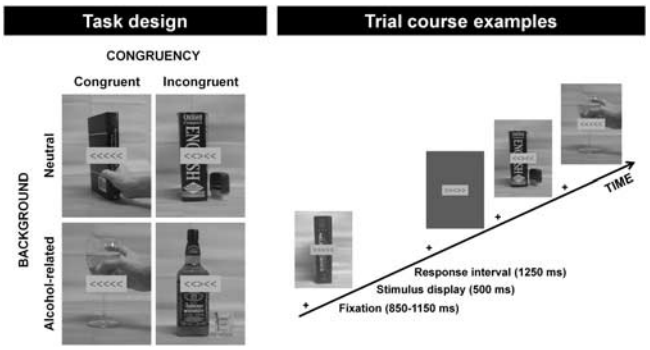

Figure 1 Concurrent Flanker/Alcohol-attentional bias task (CFAAT). Task design is depicted on the left: participants responded to the direction of a central 'target' arrow and ignored adjacent congruent or incongruent flanking arrows, in the presence of task-unrelated neutral or alcohol-associated pictures. Trial course examples are depicted on the right: each trial began with the presentation of a central fixation cross of varied duration (850–1150 ms). The fixation cross was replaced by the stimulus display, which was presented for 500 ms, and consisted of the centrally presented row of 'target' and 'flanking' arrows superimposed on the task-unrelated background displays. Each trial terminated when the response interval ended. Filler trials, in which the task was performed in the absence of the background pictures, were also included in the CFAAT to reduce habituation with the background pictures. An example of an incongruent filler trial is provided in the figure.

Dependent variables were reaction time to correct responses (latency) and accuracy of responding (% correct responses) to the direction of the 'target'.

Statistical Analysis: Baseline/Questionnaire/CFAAT: Behavioral Data

Details of the analyses performed on baseline demographic data and subjective rating scales can be found in Supplementary Materials and methods.

For the analysis of the CFAAT latency and accuracy data, mixed $2 \times 2 \times 2$ ANOVAs were undertaken comparing each alcohol dose to placebo separately. Each ANOVA included flanker congruency (congruent *vs* incongruent), background (neutral images *vs* alcohol-related images), and group (placebo *vs* low dose or placebo *vs* high dose) as factors. Significant interactions were explored with *post hoc* Bonferroni-corrected *t*-tests.

fMRI Methods and Analysis

Details of fMRI data acquisition, preprocessing and first-level modeling are given in Supplementary Materials and methods.

Following first-level specification, regionally specific condition effects were tested by linear contrasts for each subject at each task condition (ie Neutral_Congruent (NC), Neutral_Incongruent (NI), Alcohol_Congruent (AC), and Alcohol_Incongruent (AI)). The contrasts AC > NC; AI > NI; AI > AC; and NI > NC were also computed.

These contrast images were submitted to separate second-level random-effects analyses (Henson *et al*, 2005; Penny *et al*, 2003; see below).

Task-related effects. Activations arising from the interaction between each background image and cognitive load were assessed using a second-level full factorial model in the placebo group only, which included flanker congruency (congruent *vs* incongruent) and background (neutral *vs* alcohol) as factors. Individual participant's parameter estimates for each condition from each significant cluster peak were extracted and entered into SPSS 18 (SPSS) to explore the interaction using *post hoc*, Bonferroni-corrected paired-samples *t*-tests ($p < 0.0125$).

Alcohol effects on the CFAAT. Two separate second-level models were used to examine the effect of each dose of alcohol, relative to placebo, on the background × congruency interaction. Full factorial models were computed, with group (placebo *vs* low dose or placebo *vs* high dose), flanker congruency (congruent *vs* incongruent), and background (neutral *vs* alcohol-associated images) as factors.

For each model, the group × background × congruency interaction was computed and participant's parameter estimates from each significant cluster peak were entered into SPSS 18 for further analysis. For each cluster peak, four difference scores were calculated from participant's parameter estimates (AC > NC; AI > NI; AI > AC; and NI > NC). These difference scores were compared between groups using *post hoc*, Bonferroni-corrected *t*-tests ($p < 0.0125$), to explore the group × background × congruency interaction further.

Regressions: The coordinates of each significant cluster peak resulting from the factorial analyses (ie background × congruency interaction—'task-related effects'; and group × background × congruency interaction—'alcohol-related effects') were used as centers of 4 mm sphere regions of interest (ROIs), created using MarsBaR (http://marsbar.sourceforge.net/). Separate SPM regression models tested significant relationships between regional activity differences (first-level contrasts: AC > NC; AI > NI; AI > AC; and NI > NC) within these ROIs and (1) the WM capacity score and the respective latency difference scores in the placebo group, and (2) overall craving changes from baseline and the respective latency difference scores in each alcohol dose group.

Thresholding and localization. To protect against false-positive activations, factorial analyses met a threshold of $p < 0.005$ uncorrected, and a cluster volume exceeding 176 mm^3 ($k = 22$ voxels). This conjunction of specific voxel-level and cluster-extent thresholds corresponds to a whole-brain-corrected significance of $p < 0.05$. The non-arbitrary cluster-extent threshold (ie $k = 22$) was determined by Monte-Carlo simulation (1000 iterations; https://www2.bc.edu/sd-slotnick/scripts.htm; see Green *et al*, 2009; Katanoda *et al*, 2002; Ross and Slotnick, 2008) to establish an appropriate voxel contiguity threshold (Slotnick and Schacter, 2004), using the same parameters as in our study.

ROI regression analyses were thresholded at a family-wise threshold of 0.05.

Anatomical localization of significant activations was assessed by superimposition of the SPM maps on the single-subject T1-weighted MNI standard brain supplied by SPM5 and MRIcro (http://www.mccauslandcenter.sc.edu/mricro/index.html). Anatomical localization of subcortical

regions was assessed using Duvernoy's anatomical atlas (Duvernoy, 1999).

RESULTS

Demographic Information, Trait Characteristics, and BAC

The three groups were matched on all demographic information and trait characteristics (see Table 1 and Supplementary Results).

BACs measured post-drinking and post-scanning did not differ with regard to gender in either alcohol group (no main effects of gender, or gender × time interactions; $F<2.9$, NS, in all cases). Before scanning, BACs ranged between 0.35 and 0.75 g/l in the low-dose group and between 0.80 and 2.19 g/l in the high-dose group (means presented in Table 1).

State Characteristics

Supplementary Tables S1 and S2 present mean DAQ and VAS scores for each group pre- and post-drinking. Details of alcohol effects on the DAQ and the VAS are presented in Supplementary Results.

CFAAT: Behavioral Results

Mean latency and accuracy scores on the CFAAT for each group under each condition, as well as details of all CFAAT behavioral effects are presented in Supplementary Table S3 and Supplementary Results, respectively.

Behaviorally, ingestion of the low alcohol dose, compared with placebo, resulted in significantly slower responding in the presence of the alcohol-associated, relative to the neutral, pictures (group × background interaction: $F(1,24)=5.19$, $p=0.05$); and in slower responding in the congruent compared with the incongruent condition (group × congruency interaction: $F(1,24)=4.78$, $p=0.05$).

The high dose, compared with placebo, did not significantly affect latencies ($F<3.06$, NS, in all cases).

The low dose, compared with placebo, did not affect accuracy ($Fs<1.7$, NS, in all cases).

The high dose, relative to placebo, resulted in more errors in the incongruent, relative to the congruent, condition (group × congruency interaction: $F(1,25)=4.63$, $p<0.05$).

Table 1 Demographic Information (age, gender, and weight), Trait Characteristics (AUQ, AEQ, and word recall), and BAC Measurements (post-drinking and post-scanning) Presented Separately for the Placebo and the Low- (0.4 g/kg) and High-dose (0.8 g/kg) Alcohol Groups

Variable	Placebo	0.4 g/kg Alcohol	0.8 g/kg Alcohol
Age (years)	22.92 (±5.07)	24.23 (±7.31)	21.07 (±2.40)
Gender	7M, 6F	8M, 5F	6M, 8F
Weight (kg)	71.63 (±11.14)	70.48 (±13.18)	70.56 (±9.22)
AUQ—weekly units	26.42 (±13.76)	26.33 (±11.51)	26.86 (±9.37)
AUQ—total score	47.08 (±24.88)	53.41 (±37.34)	51.46 (±24.75)
Word recall (RAVLT score)	8.92 (±2.22)	8.31 (±1.93)	7.93 (±1.49)
AEQ—positive	13.23 (±2.01)	13.02 (±2.25)	14.05 (±2.07)
AEQ—negative	12.97 (±2.54)	13.54 (±1.93)	15.36 (±2.06)
BAC (g/l)—10 min post-drink	0	0.58 (±0.12)	1.15 (±0.33)
BAC (g/l)—45 min post-drink (post-scanning)	0	0.36 (±0.11)	0.94 (±0.20)

Abbreviations: AEQ, Alcohol Expectancy Questionnaire; AUQ, Alcohol Use Questionnaire; BAC, blood alcohol concentration; RAVLT, Rey auditory verbal learning test.
Data are presented in mean (±SD).

CFAAT: fMRI Results

Task-related effects. The background × congruency interaction was associated with suprathreshold activations in ventrolateral prefrontal (PFC) areas (right inferior frontal gyrus pars opercularis (BA48); left inferior frontal gyrus pars triangularis (BA45); Figure 2a and b, respectively). A more dorsal region within right inferior frontal gyrus (BA44) and a region within precentral gyrus (BA6) were also activated (Figure 2c and d, respectively). Cerebellum, inferior temporal cortex, and post-central gyrus (BA1/2) were also activated (see Supplementary Table S4 and Supplementary Results).

Regressions: WM capacity scores correlated negatively with activation within right inferior frontal gyrus pars opercularis (BA48; MNI: 50, 4, 10; contrast value = 0.14; $p_{FWEcor}=0.04$), when the contrast AC > NC was regressed with WM capacity in the placebo group. No other ROI regression analysis was significant.

Alcohol effects

Low alcohol dose: Following alcohol ingestion, alcohol-associated background pictures in the incongruent condition led to an increased activation within lateral hypothalamus, whereas in the congruent condition to an increased activation within a medial hypothalamic cluster (Figure 3a and b, respectively; see also Supplementary Table S5 for details) similar to one previously labeled as 'BNST/hypothalamus' (O'Daly *et al*, 2012; see Supplementary Material and Methods, and Supplementary Figure S1 for further discussion). Alcohol ingestion generally decreased activation within supplementary motor area (SMA), in particular in the presence of neutral background pictures in the incongruent condition (Figure 3c). Activations in the putamen (see Supplementary Table S5 for further details) and the pons were also observed. Post-hoc *t*-tests for this pontine cluster did not survive Bonferonni corrections. Therefore, the effects in this region are not discussed further.

Regressions: The latency difference score AI > NI correlated positively with activation within lateral hypothalamus (MNI: −8, −4, −4; contrast value = 0.14; $p_{FWEcor}=0.05$), when the contrast AI > NI was regressed with this performance determinant in the low-dose group. No other ROI regression analysis was significant.

High alcohol dose. The separate full factorial model comparing the high-dose and placebo groups did not reveal

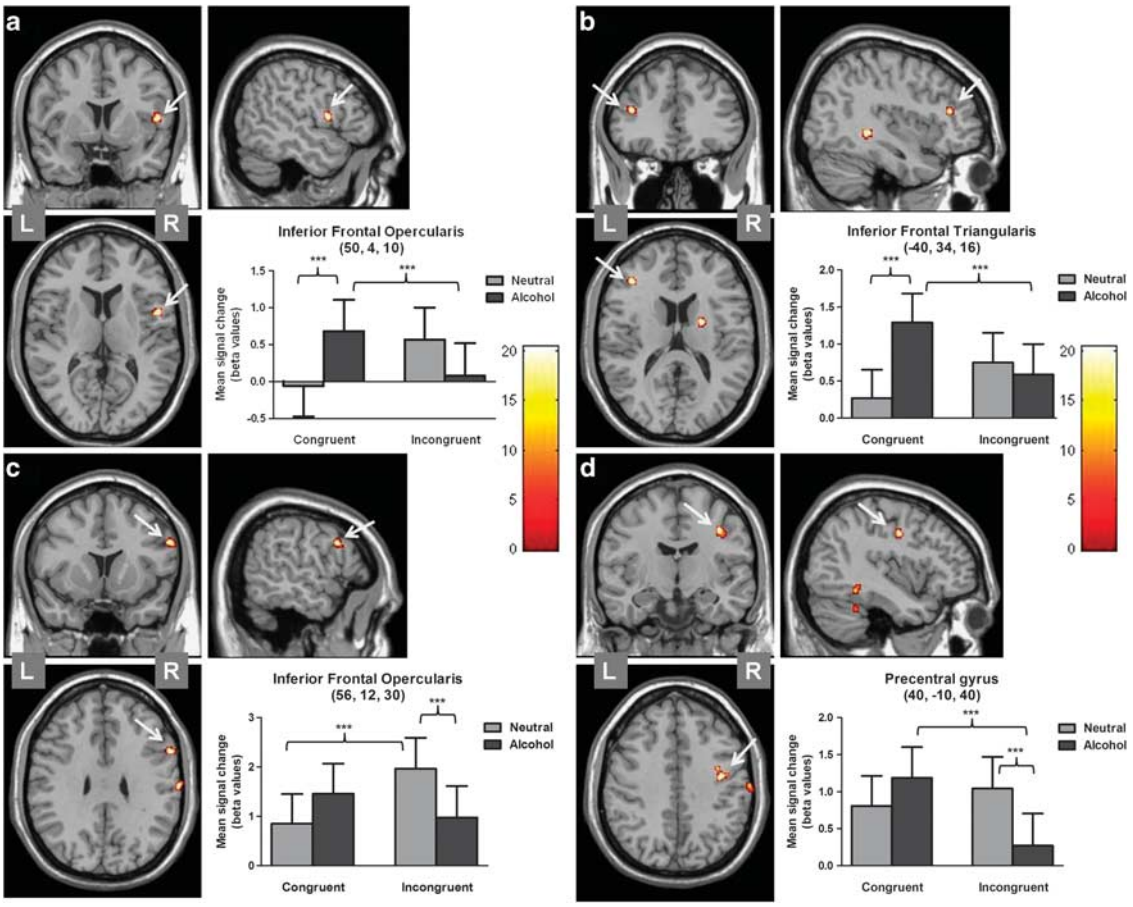

Figure 2 Activations reflecting the background × congruency interaction in the placebo group only (thresholded at $p<0.005$, $k=22$; scale represents F-statistic; ***: significantly different; L: left; R: right). When the alcohol-associated background pictures, relative to the neutral background pictures, were presented in the *congruent condition*, there was an increased activation within ventrolateral prefrontal areas, including right inferior frontal gyrus pars opercularis (BA48; (a)) and left inferior frontal gyrus pars triangularis (BA45; (b)). This selective responsiveness to the presence of the alcohol-associated pictures significantly decreased in the incongruent condition (a and b). By contrast, when the alcohol-associated, relative to the neutral, background pictures were presented in the *incongruent condition*, there was a significant decrease in activation in the right inferior frontal gyrus pars opercularis (BA44; (c)). The same area showed increased responsiveness in the incongruent relative to the congruent condition in the *absence* of the alcohol-associated pictures (c). The precentral gyrus (BA6; (d)) also showed reduced activation in the incongruent condition and in the presence of the alcohol-associated relative to the neutral background pictures. However, it displayed *decreased* responsiveness in the incongruent relative to the congruent condition in the *presence* of the alcohol-associated pictures (d).

any reliably significant activations arising from the group × background × congruency interaction (ie, $P<0.005$, $k=22$).

On the basis of our *a priori* predictions of an effect of the high dose on cognitive control processes (supported by the effect of the high dose on accuracy), we ran a regression model to examine the effect of the high alcohol dose on conflict processing brain activations. This model regressed accuracy (accuracy_incongruent–accuracy_congruent) against the average conflict contrast image (incongruent > congruent) within the high-dose group.

Applying the voxel-level corrected threshold ($p<0.005$, $k=22$) to the regression data revealed a significant positive correlation between behavioral accuracy difference scores and activation within both anterior cingulate (BA32; MNI: 8, 28, 34; $F=32.96$; $Z=3.65$) and right dorsal inferior frontal gyrus pars opercularis (BA44; MNI: 8, 28, 34; $F=23.8$; $Z=3.3$; see Supplementary Table S6). The larger the impairment in accuracy in the incongruent condition, relative to the congruent condition, the greater the activation within these regions.

DISCUSSION

This study assessed brain mechanisms through which alcohol engenders attentional biases to alcohol-associated stimuli. In accordance with previous reports (Adams *et al*, 2012; Duka *et al*, 2004), attentional bias to alcohol-associated stimuli was reliably observed at the low, but not the high alcohol dose when compared with placebo. Correspondingly, neural activity changes occurred within cortical and subcortical regions that reflected the interaction between the attentional capture of these stimuli and levels of cognitive demand. In addition, as reported previously (Loeber *et al*, 2009), the high alcohol dose compared with placebo impaired cognitive control processes, apparent as increased errors in the incongruent trials of the foreground task, but did not reliably modulate the degree of distraction by background alcohol-associated stimuli.

The CFAAT task provided further insight into brain substrates supporting selective attention and cognitive

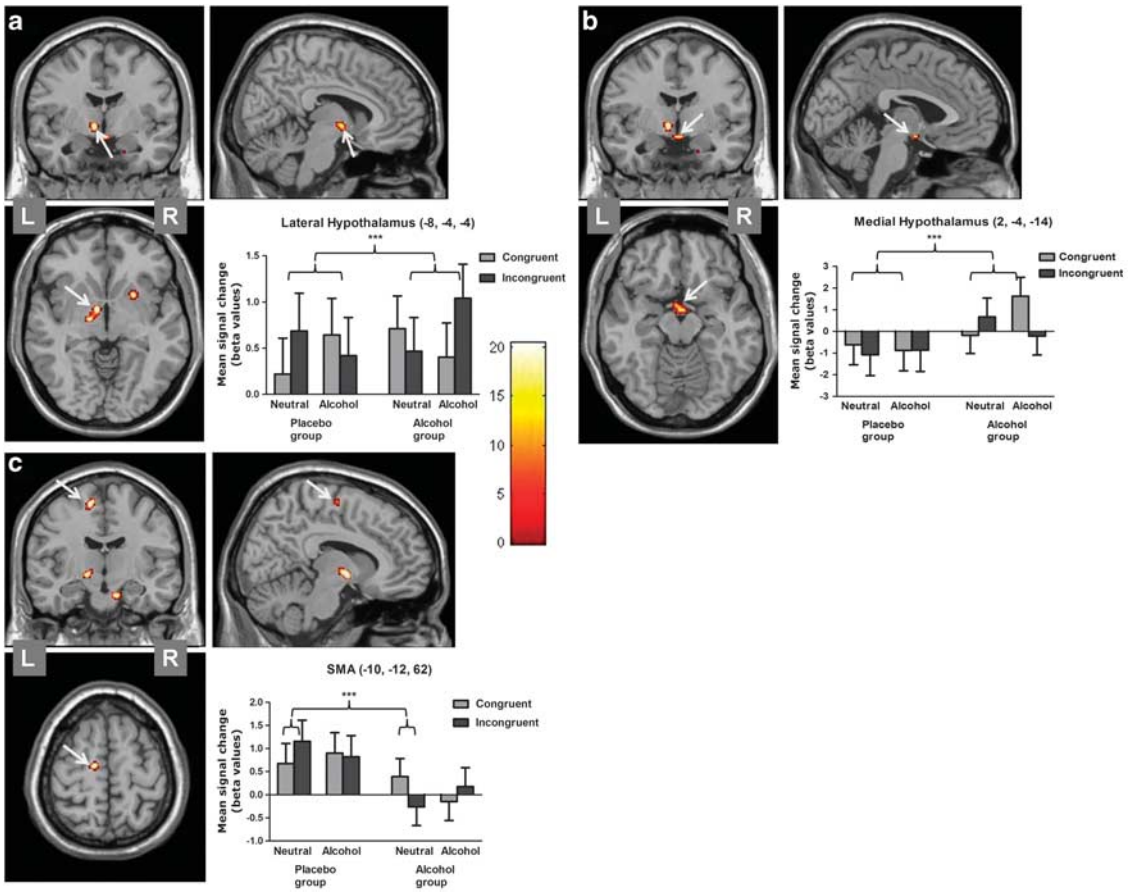

Figure 3 Activations associated with the group × background × congruency interaction in the second-level model that included the placebo and low-dose groups (thresholded at $p < 0.005$, $k = 22$; scale represents F-statistic; ***: significantly different; L: left; R: right). Following ingestion of the low alcohol dose, the presence of alcohol-associated background pictures in the incongruent condition was coupled to an increased activation within a lateral hypothalamic cluster (a); Conversely, the presence of the alcohol-associated background pictures in the congruent condition was linked to increased activation under alcohol within a more medial hypothalamic region (encompassing the bed nucleus of the stria terminalis (BNST); (b)). Decreased activation within SMA was seen following alcohol ingestion in the incongruent condition when exposed to neutral background pictures (c).

control (Ridderinkhof *et al*, 2004b). The high cognitive load condition, in the absence of alcohol-associated images, engaged regions associated with the exertion of control (ie, BA44; Compton *et al*, 2003). In the presence of alcohol-associated images, these same regions showed reduced activation. Thus, a competitive attenuation of cognitive control processes by the attentional capture of background alcohol-associated stimuli may occur. During the *low-demand* congruent condition, in the presence of alcohol-associated images, there was *enhanced* engagement of more ventrolateral parts of the prefrontal cortex, associated with managing the interference from emotional stimuli (Browning *et al*, 2010). Interestingly, BOLD changes within right inferior opercularis correlated negatively with WM capacity. This observation extends (Hester and Garavans's, 2009) finding with cocaine-related stimuli. Regions implicated in the general orientation of attention (posterior parietal and inferior temporal cortices) also showed significantly increased activation under low load in the presence of the alcohol-associated, relative to the neutral, stimuli.

Previous studies highlight involvement of dACC in attentional bias in cocaine and nicotine users (Goldstein *et al*, 2007; Luijten *et al*, 2011) or in models of interference monitoring (dACC; eg, Botvinick *et al*, 2001). Engagement of dACC was not observed in this study: our small sample size meant the study was not powered to detect differential dACC representation of levels of interference by task-relevant (arrows) and task-irrelevant (images) distracters.

Alcohol ingestion at moderate levels (BACs between 0.035 and 0.075%) evoked activity increases under specific task conditions within two hypothalamic clusters, a lateral one, and a second more medial cluster, but was associated with reduced activation within the SMA. Previous studies of alcohol intoxication have reported decreased activation of prefrontal and related cortices during cognitive performance. For example, alcohol ingestion reduced dACC activation during incongruent (conflict) trials of the color–word Stroop task (Marinkovic *et al*, 2012). Similarly, alcohol attenuated activation in dACC and cerebellum during a working memory task (Gundersen *et al*, 2008), yet a slightly lower alcohol dose (during a different working memory task) increased activation in LPFC (Paulus *et al*, 2006).

In our study, cognitive control during flanker task performance was challenged by the processing of alcohol-associated background stimuli. This allowed us to probe the central effects of alcohol on behavior arising from both increased emotional reactivity or weakened prefrontal functions. Thus an acute low dose of alcohol, compared

with placebo, enhanced the activation of subcortical areas, with little impact on other prefrontal cortices. Under the low alcohol dose, those areas of PFC activated during the placebo condition did not show additional changes. This suggests that this low dose of alcohol did not compromise the function of these regions. However, it is worth noting that with the sample size used in this study it is hard to interpret negative results confidently.

Similarly, the absence of an effect of the high dose, relative to placebo, on the interaction between congruency and background stimuli cannot be easily interpreted given the sample size used in this study. Speculatively, it is possible that under the high alcohol dose the background stimuli lose their salience over the neutral stimuli. Alternatively, a differential response across participants to the high alcohol dose that depended on the degree of alcohol use could have hidden such an effect. Attentional bias to alcohol-associated stimuli can be differentially affected by alcohol depending on the level of participant's alcohol use (eg, Adams *et al*, 2012). Future studies could examine the acute effects of alcohol within groups of participants of varying alcohol use to address this question directly. The high alcohol dose, relative to placebo modulated activity within rostral cortices implicated in conflict control (dACC and frontal gyrus pars opercularis), and impaired cognitive control (reduced accuracy in the incongruent condition) as shown in regression analyses. These findings extend observations from previous studies that tested effects of alcohol on cognitive tasks (Marinkovic *et al*, 2012). Interestingly, additional brain areas, associated with attention and motor performance, also showed greater activation in association with impaired performance accuracy.

Ingestion of the low alcohol dose increased activity within the hypothalamus (a lateral cluster), an area mediating physiological arousal to natural rewards (Brunetti *et al*, 2008), in the presence of alcohol-associated stimuli and under high cognitive load. Regression analyses revealed a positive relationship between response latency and hypothalamic activation during this condition. These observations suggest that central arousal, evoked during effortful cognitive processing, may amplify the sensitivity of hypothalamus to motivationally salient stimuli, perhaps via (low-level) physiological arousal.

On the other hand, alcohol ingestion enhanced activation within another more medial region of the hypothalamus, in the presence of alcohol-associated background stimuli when interference by the primary task was low (congruent condition), and hence the rewarding significance of alcohol cues was more pronounced. This latter hypothalamic area is found within a cluster encompassing regions previously labeled as BNST, a part of extended amygdala (eg, O'Daly *et al*, 2012; Somerville *et al*, 2010). The extended amygdala is involved in the processing of salience of aversive (Somerville *et al*, 2010) and also appetitive stimuli (Liberzon *et al*, 2003). Alcohol ingestion enhanced activation in this region possibly by increasing the salience of the alcohol-associated background stimuli. A recent study observed increased functional neural connectivity between a neighboring hypothalamic region (labeled BNST/hypothalamus) and amygdala in alcoholic patients compared with controls when processing emotional signals (O'Daly *et al*, 2012). Thus, BNST/hypothalamus alongside other hypothalamic areas may be important in mediating both acute and chronic alcohol effects on emotional regulation. We note that the identification of human BNST is difficult, constrained by the spatial resolution of human neuroimaging methods that hinder the exact anatomical segregation of this structure in the anatomical scans (see also Supplementary Material and Methods and Supplementary Figure S1). Alcohol decreased activation in SMA during incongruent trials in the absence of alcohol-associated background stimuli, indicating that mobilization of cortical resources, including motor response planning, might be weakened following alcohol ingestion.

This study was not designed to compare the two doses of alcohol. Nevertheless, taken together, our data are consistent with the prediction that alcohol cues have a biasing impact at low alcohol doses, whereas high alcohol doses influence cognitive control more generally. Such predictions, if formally validated, have important implications for understanding disinhibitory behavior under the influence of alcohol. The effects of the high alcohol dose may also be relevant for the long-term consequences of alcohol abuse. Further studies should explore dose-dependent effects of alcohol on brain function, and test for linear and nonlinear performance effects on distinct cognitive processes.

We observed bidirectional patterns of task-related activity increases and decreases associated with alcohol ingestion at different doses. This suggests an absence of a global confounding effect of alcohol. Nevertheless, alcohol ingestion, relative to placebo, can increase regional cerebral blood flow within lateral medial frontal cortices (eg, Sano *et al*, 1993; Volkow *et al*, 1988), and may therefore impact on apparent brain activation patterns through direct vascular effects. In our fMRI study, we used a hemodynamic measure that integrates changes in oxygenated blood flow and volume (Buxton *et al*, 2004) from which short-term changes in local neural activity are inferred. It is therefore possible that alcohol's vasoactive effects may confound the interpretation of regional neural activity changes. Nevertheless, the absence of global, and the emphasis on short-term, signal changes (apparent after high-pass temporal filtering), and the focus of our analyses on interactions (within the factorial experimental design) mitigate the potential confounding impact of alcohol-induced vasoactive-related changes on our findings. Arterial spin labeling, a direct measure of cerebral perfusion, may prove a useful tool to quantify nonspecific cerebrovascular consequences of acute alcohol ingestion in relation to task-evoked activity changes.

Our data highlight the impact of alcohol on brain mechanisms underlying attentional bias to alcohol-associated stimuli, which represent salient stimuli for moderate alcohol drinkers. Alcohol, under certain conditions, reduced activation in cortical areas supporting motor planning, but activated areas involved in emotional reactivity and processing of salient drug-associated rewarding stimuli. It remains to be clarified whether acute alcohol also generally influences attentional processing of positively and/or negatively valenced emotional stimuli. This would allow evaluation of whether the mechanisms involved in alcohol's effects are similar across classes of emotional stimuli or are specific to alcohol-associated stimuli. It would also allow assessment of the degree to which alcohol's

effects on the processing of emotional valence overall exhibit context dependence.

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DISCLOSURE

The authors declare no conflict of interest.

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