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Differentiating Heavy from Light Drinkers by Neural Responses to Visual Alcohol Cues and Other Motivational Stimuli

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The course to alcohol dependence often starts with a preclinical period of heavy drinking. The present article reports functional magnetic resonance imaging data showing that even this pattern of alcohol consumption is associated with maladaptive neural responses to alcohol and other stimuli. When participants were confronted with visual cues related to alcohol, heavy drinkers showed amplified blood oxygen level–dependent signal responses in specific emotional areas (insular cortex) and in parts of the brain's reward circuitry (ventral striatum). This neuronal amplification was not present in light drinkers. Crucially, at the same time heavy drinkers showed reduced responses in frontal areas to pictures related to higher order life goals and in the cingulate cortex to appetitive food stimuli, suggesting that they have difficulty finding alternative, socially desirable goals. Using discriminant function analysis, we demonstrate that the combination of alcohol-related overactivation and underactivation to alternative goals allows heavy and light drinkers to be differentiated with a high degree of precision. Our findings highlight the diagnostic value of functional brain mapping of cue reactivity. Imaging measures may help to identify addictive dispositions in preclinical stages and to clarify the mechanisms that underlie the development and maintenance of alcohol dependence.

Keywords: addiction, alcohol abuse, alcoholism, brain imaging, fMRI

Introduction

The pathway into alcohol dependence and more broadly into all kinds of substance dependence is not an abrupt one; rather, it is marked by small behavioral changes. In the case of alcohol dependence, these changes include increased tolerance to alcohol, failed efforts to control the drinking, and increased levels of alcohol consumption (Royal College of Psychiatrists 2008). In recent years, evidence has accrued that the final stage of this process—clinically diagnosed alcohol dependence—is related to significant neuroplastic changes, but changes in gene expression and modifications occur earlier in the pathway from initial alcohol exposure to alcohol dependence (Moonat et al. 2010).

When alcohol-dependent drinkers are confronted with pictures showing alcoholic beverages, they show a regionally specific increase in blood oxygen level–dependent (BOLD) responses, relative to their responses to pictures showing nonalcoholic beverages (Heinz et al. 2004). These amplification effects have been found in the anterior thalamus and dorsolateral prefrontal cortex (George et al. 2001) as well as in limbic, temporal, and occipital regions (Tapert et al. 2003) and the dopaminergic reward circuitry (ventral striatum and orbitofrontal cortex; Wrase et al. 2002).

One crucial question is whether maladaptive brain responses are confined to alcohol-dependent drinking patterns or whether we can identify a relationship between drinking behavior and increased BOLD responses to alcohol pictures even in nonclinical samples. Establishing such a relationship could be the basis for developing functional magnetic resonance imaging (fMRI)-derived markers that help to identify neuronal risk for alcohol dependence. In particular, the present study tested whether healthy, nonalcoholic heavy drinkers compared with light drinkers would show increased engagement of key structures in the brain's reward pathway (e.g., ventral striatum) in response to visual alcohol cues, as has been observed with alcohol-dependent participants (Heinz et al. 2004).

Another key question is whether the differences between heavy and light drinkers reflect differences in their sensitivity to alcohol cues, to appetitive cues, or to emotional stimuli in general. We therefore compared participants' responses to alcohol cues with those to nonspecific appetitive stimuli (food objects) and aversive cues. We also exposed participants to pictures related to higher order goals representing their current concerns. According to the motivational theory of current concerns (Klinger and Cox forthcoming), people's behavior and cognitions are forged by their pursuit of goals to obtain positive incentives or to get rid of negative ones. A current concerns is defined as a person's internal state corresponding to each goal pursuit. The inclusion of stimuli related to participants' current concerns reflected our theoretical position that alcohol abuse is characterized by a failure to find emotional satisfaction through striving for higher order, nonchemical incentives (such as those related to employment or personal relationships; Cox and Klinger 1988, forthcoming).

To summarize, we exposed heavy and light drinkers to 5 categories of stimuli whose physical and perceptual characteristics were carefully controlled: 1) alcohol-related pictures, 2) concern-related pictures, 3) positive pictures (food), 4) negative pictures (disgust-related objects), and 5) neutral pictures (household objects). We hypothesized that, compared with light drinkers, heavy drinkers would show increased reactivity to alcohol cues and that they would show the converse pattern in response to other incentives (concern-related and other positive pictures) and to negative pictures.

Materials and Methods

Participants

Participants (12 light and 11 heavy drinkers) were university students and community residents recruited from School of Psychology participant panels. Recruitment targeted participants who reported themselves as drinking either more (heavy drinkers) or less (light drinkers) than the criteria for sensible drinking set by the British

Medical Association (1995), that is, 21 units of alcohol/week or less for men, 14 units/week or less for women. One unit of alcohol is defined as 10 mL of pure ethanol and corresponds to one small glass (125 mL) of wine, half a pint (284 mL) of beer, or a pub measure (25 mL) of spirits. All participants gave informed written consent to participate in the study, which had been approved by the School of Psychology Research Ethics Committee. Group assignment was verified by assessing participants' current alcohol consumption (i.e., mean weekly consumption during the prior 3 months) immediately before the fMRI session. This led to exclusion of one participant who had incorrectly reported himself to be a light drinker.

Materials

Participants were presented with 24 images in each of the 5 categories of pictures: 1) alcohol-related pictures showed alcoholic beverages (bottles or glasses), 2) positive pictures showed appetitive food objects, 3) neutral pictures illustrated household objects, 4) negative pictures showed disgust-related objects, such as excrement, and 5) concern-related pictures depicted objects related to 3 life areas that participants in previous studies had most frequently indicated were related to their most important current concerns. Specifically, the concern-related stimuli included 8 pictures related to "relationships" (e.g., a wedding ring), 8 pictures related to "finances and employment" (e.g., a piggy bank), and 8 pictures illustrating "education and training" (e.g., a blackboard). Pictures were taken from the Normative Appetitive Picture System (Stritzke et al. 2004), the International Affective Picture System (Lang et al. 2005), and the Internet.

Picture categories were matched for brightness, contrast, and perceptual complexity. Brightness was calculated as the average of the pixels' mean RGB values. Contrast was measured by extracting the standard deviation of pixels' mean RGB values in each image column and then computing the standard deviation of these values (see Bradley et al. 2007). Statistical analyses confirmed that the categories were comparable in brightness, $F_{4,115} = 1.59$, $P = 0.18$, and contrast, $F_{4,115} < 1$, values across all stimulus sets. Picture categories were also matched for perceptual complexity (e.g., single vs. multiple objects in a scene) by using within each category semantically homogenous pictures and not including human faces. In addition, we matched the pictures' spatial frequencies, which have been considered as an objective index of perceptual complexity (Bradley et al. 2007). Using the approach and algorithms suggested by Delplanque et al. (2007), we applied discrete wavelet transformation to test for category differences in low-frequency bands (2–8 cycles per image) and high-frequency bands (>16 cycles). After stimulus selection, an analysis of variance (ANOVA) indicated no significant differences in z-transformed energy values for low frequencies, $F_{4,115} < 1$. However, there was a main effect for Picture Category in the high-frequency band, $F_{4,115} = 5.25$, $P < 0.01$. Post hoc Scheffé tests showed that positive and negative pictures had slightly higher values than alcohol pictures ($P < 0.05$). Participants viewed the pictures, which were back-projected onto a screen behind the MR scanner, through a mirror mounted on the MRI head coil. All pictures were colored and had a 1024 × 768 pixel resolution.

Procedure

After having MRI safety screening and giving informed consent, participants were familiarized with the scanning environment. The scanning session comprised 6 functional runs (each 6 min 12 s) and 1 structural run, resulting in a total scanning time of approximately 45 min. Pictures were presented in short blocks of 8 s. Picture blocks were separated by fixation intervals with a jittered duration of 6–12 s. In each picture block, we presented 4 different pictures of the same category with an interstimulus interval of 50 ms. In the concern-related condition, pictures in the same subcategory (relationships, finance, and employment, education, and training) were used in each block.

One fMRI data acquisition run comprised 20 picture-viewing blocks/trials (4 blocks per category). Accordingly, across the 6 runs, data from 24 blocks were available for each category/condition. To keep participants alert, a 1-back task was included in the scanning session. Participants were instructed to monitor the picture blocks for any occurrence of the same picture presented twice in a row. In each run, there were 2 repetitions occurring in 2 randomly interspersed task blocks, which showed different pictures than in the experimental blocks and were not used for analyses. Category of the task blocks was balanced across all runs. Apart from the task blocks, no repetition of the same picture exemplar occurred within one functional run. Accuracy in the 1-back task was generally high, indicating that participants complied with the instruction to attentively monitor the picture stream.

After scanning, participants were encouraged to rest before continuing with the behavioral assessment. It included in the following order: 1) a questionnaire to measure current urges to drink alcohol (Bohn et al. 1995), 2) ratings of the stimuli seen on hedonic valence, emotional arousal, and concern relatedness, and 3) a questionnaire to measure participants' current alcohol consumption and demographic characteristics (Fadardi, Cox, Hogan, unpublished questionnaire). In this questionnaire, participants are presented with 2 lists of different types of alcoholic beverages (e.g., beer, wine, and spirits). On the first list, participants indicate their consumption during a "typical" week, and on the second list, they indicate their consumption during an "atypical" week, that is, when they drink either more or less than during a typical week. Participants are instructed to take into account their drinking behavior during the prior 3 months. For each of the 2 lists, participants are asked to report the kind of beverage and the kind and number of servings (e.g., 2 pints and 1 can) that they drank and the percentage of alcohol per volume that each beverage contained. Emotional ratings were obtained using a computerized version of the Self-Assessment Manikin (SAM; Bradley and Lang 1994). SAM ratings indicate whether a stimulus is perceived as appetitive, neutral, or aversive (valence dimensions) and reflect the intensity of motivational activation (arousal ratings). Concern-related pictures were additionally evaluated with regard to 1) the degree to which the picture reminded the participant of one of his/her current positive goals or of something that he/she wanted to keep from happening and 2) the amount of time he/she spend thinking about this goal. After the behavioral testing, participants were debriefed, thanked, and paid £25.

MRI Data Acquisition

MRI images were acquired with a Philips 3T scanner equipped with a SENSE parallel head coil for radio frequency transmission/reception. To measure BOLD signals in the picture-viewing runs, a gradient echo planar T_2-weighted sequence was used that was synchronized to the onset of picture blocks and covered the whole cerebrum (time repetition = 2000 ms; time echo = 35 ms; matrix size = 96 × 96; field of view = 192 × 192 mm^2; voxel size = 2 × 2 × 3 mm^3; flip angle = 90°; number of slices = 30 contiguous axial slices). An anatomical high-resolution T_1-weighted volume scan (1 mm^3) was interspersed in the middle of the scanning session.

MRI Data Preprocessing and Analysis

Functional data were preprocessed and analyzed using the BrainVoyager QX software. Raw images were submitted to slice scan time correction, 3D motion correction using trilinear interpolation, and a temporal high pass filter (0.006 Hz). Functional images were realigned and coregistered with participants' structural scans and then spatially normalized by warping to Talairach space. The resulting volume time courses were further preprocessed using spatial smoothing (4-mm Gaussian kernel), temporal filtering (2.8 s), and z-value based normalization. Image time series were then analyzed with a whole-brain general linear model approach. We created 5 regressors corresponding to the 5 picture categories. The regressors were convolved with a canonical hemodynamic response function locked to the onset of each picture block. The resulting beta values were then entered into a second-level, 2-factorial random effect ANOVA. The goal of this analysis was to identify brain regions showing a statistically significant interaction between Group and Picture Category ($P < 0.05$). Contrasts were specified that measured a potential group difference between the neutral pictures and the other 4 picture categories. Comparing the other categories with the neutral pictures was essential for controlling for nonspecific group differences, such as in sustained attention or fatigue. Specifically, the data were tested for increased

BOLD responses to alcohol versus neutral pictures in the heavy drinkers, but this difference was not expected to occur in the light drinkers. Furthermore, we hypothesized that light drinkers would show larger BOLD responses to concern versus neutral, positive versus neutral, and negative versus neutral pictures, whereas heavy drinkers would show reduced or no differences for these contrasts. Finally, we examined which brain regions showed an interaction between group and the contrast alcohol versus concern-related pictures. Specifically, we aimed at identifying areas where heavy drinkers showed larger responses to alcohol versus concern and, at the same time, light drinkers showed larger responses to concern versus alcohol pictures.

It should be noted that only significant interactions in the hypothesized direction are described below. Nonetheless, for all contrasts, only one area showed significant effects in the opposite direction: In the right superior temporal gyrus, the contrasts concern–neutral and negative–neutral yielded larger values for heavy drinkers, relative to light drinkers.

To control for multiple comparisons in voxel-based whole-brain analyses, we took a cluster-level statistical thresholding approach, which calculates for a given P value and volumetric activation map a minimum cluster size using iterative Montecarlo simulations (Forman et al. 1995). For the current data set, the algorithm determined a cluster threshold of 837 voxels (1 × 1 × 1 mm). The beta values in the identified regions of interest (ROIs) were further analyzed by planned comparisons (F-tests), in which each group was tested separately for the expected category differences. Effect sizes (partial η^2) for significant differences are reported where appropriate.

To evaluate the "relative" diagnostic utility of the identified ROI activation patterns in differentiating the 2 groups, we conducted a stepwise discriminant function analysis (F_{enter}: $P < 0.01$). The beta differences between the target categories (alcohol, concern, positive, and negative) and the neutral category in the respective 9 identified ROIs were entered as independent variables, using group as dependent measure.

Results

Behavioral Assessment and Subjective Ratings

Statistical analysis confirmed a clear group difference in drinking levels as assessed by the Drinking Record Questionnaire (Fadardi, Cox, Hogan, unpublished questionnaire), F_{20} = 10.11, $P < 0.01$ (for mean values and demographic characteristics, see Table 1). All light drinkers reported alcohol consumption within the range of sensible drinking (<21 units/week for men, <14 units/week for women; British Medical Association 1995). Seven of the heavy drinkers were in the range of hazardous drinking (22–50 units/week for men, 15–35 units/week for women; British Medical Association 1995) and 3 fell in the harmful range (above 50 units/week). One heavy drinker reported current consumption at the threshold for heavy drinking but was retained in the sample because in previous studies this participant had consistently indicated consumption levels in the heavy range. Furthermore, omitting this participant's data from the BOLD analyses did not change the pattern of significant results. Critically, all heavy drinkers showed normal psychosocial functioning during all stages of the study, indicating no signs of alcohol dependence. The 2 groups did not differ in age, F_{20} = 3.17, P = 0.09, years of education, $F_{10} < 0.5$, or their subjectively rated urge to drink alcohol, which was measured after the scan, $F_{20} < 0.5$.

Table 1

Sample properties (SD, standard deviation; group difference significance: *$P < 0.01$, n.s, not significant)

	Heavy drinkers (n = 11)	Light drinkers (n = 11)
Mean weekly drinking in units (SD)*	58.56 (54.76)	4.53 (4.45)
Drinking urges (maximal 56) after experiment (SD)$^{n.s}$	17.91 (2.21)	16.64 (2.52)
Gender	10 males, 1 female	8 males, 3 females
Mean age (SD)$^{n.s}$	26.91 (6.28)	22.82 (4.31)
Mean years of education (SD)$^{n.s}$	16.20 (5.90)	15.45 (1.97)
Mean rated valence alcohol pictures (SD)$^{n.s}$	5.80 (0.73)	5.65 (0.67)
Mean rated valence concern-related pictures (SD)$^{n.s}$	6.55 (0.62)	6.39 (0.57)
Mean rated valence positive pictures (SD)$^{n.s}$	6.98 (0.78)	7.30 (0.86)
Mean rated valence negative pictures (SD)$^{n.s}$	2.32 (0.85)	2.04 (0.55)
Mean rated valence neutral pictures (SD)$^{n.s}$	4.95 (0.72)	5.11 (1.33)
Mean rated arousal alcohol pictures (SD)$^{n.s}$	5.20 (1.31)	3.98 (1.74)
Mean rated arousal concern-related pictures (SD)$^{n.s}$	5.63 (1.40)	4.63 (1.88)
Mean rated arousal positive pictures (SD)$^{n.s}$	6.17 (0.98)	5.42 (1.81)
Mean rated arousal negative pictures (SD)$^{n.s}$	5.74 (2.12)	6.07 (1.73)
Mean rated arousal neutral pictures (SD)$^{n.s}$	3.20 (1.60)	2.49 (1.32)

ANOVAs conducted on picture ratings showed a main effect for Picture Category (alcohol, concern, positive, negative, neutral) for both the valence, $F_{4,80}$ = 186.69, $P < 0.001$, and arousal dimensions, $F_{4,80}$ = 33.72, $P < 0.001$. Neither the main effect for Group (light vs. heavy drinkers) nor the Group × Picture Category interaction reached significance, all Fs < 2.0, all Ps > 0.10. Similarly, paired group comparisons (t-tests) of valence and arousal ratings for the different picture categories showed no significant differences between heavy and light drinkers, all Ps > 0.05. However, paired comparisons across groups revealed increasing pleasantness ratings from negative to neutral, from neutral to alcohol, from alcohol to concern-related, and from concern-related to positive pictures, all Ps (bonferroni-corrected) < 0.05. With regard to the arousal dimension, alcohol, positive, negative, and concern pictures were perceived as more arousing than the neutral stimuli, all Ps (bonferroni-corrected) < 0.05. Furthermore, alcohol pictures had arousal ratings comparable with concern-related pictures but were rated as less arousing than positive or negative pictures, all Ps (bonferroni-corrected) < 0.05. Ratings on the 3 dimensions of concern-relatedness (see Methods section) did not differ between the heavy and light drinkers, all ts < 1.0.

Brain Imaging Data

Alcohol-Related Pictures

Whole-brain ANOVA revealed 3 areas for which the contrast alcohol–neutral pictures significantly interacted with group: left ventral striatum, left insula, and right insula (see Fig. 1 for a transversal view of the identified areas and Table 2 for center of gravity Talairach coordinates and ROI sizes). Planned comparisons confirmed that for heavy drinkers, alcohol pictures elicited stronger BOLD activity than neutral pictures in the left ventral striatum, F_{10} = 44.91, $P < 0.001$, partial η^2 = 0.82, and in the left insula, F_{10} = 8.04, $P < 0.05$, partial η^2 = 0.45 (see Fig. 2). In the right insula, the difference between alcohol and neutral pictures did not reach significance, F_{10} = 3.58, P = 0.088. Interestingly, light drinkers showed a reversed pattern of BOLD responses in all 3 areas, with alcohol pictures eliciting less activation than neutral pictures, ventral striatum: F_{10} = 7.10, $P < 0.05$, partial η^2 = 0.42; left insula: F_{10} = 9.24, $P < 0.05$, partial η^2 = 0.48; right insula: F_{10} = 13.16, $P < 0.01$, partial η^2 = 0.57.

Concern-Related Pictures

For the contrast, concern related–neutral pictures, whole-brain analyses identified 2 right-hemispheric frontal clusters that dissociated the 2 groups in the expected direction: The transversal views of Figure 3 show significant effects in a region

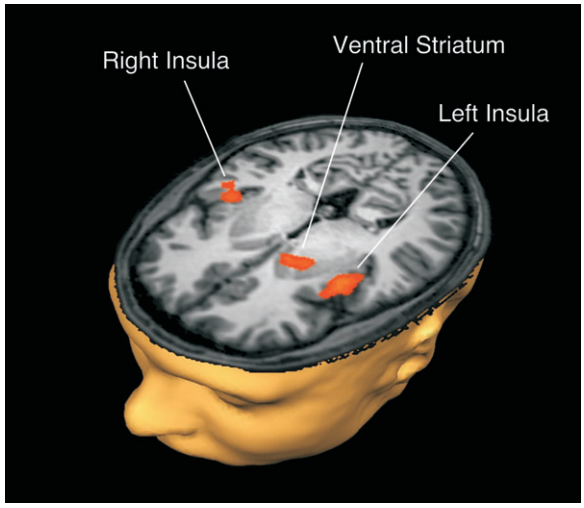

Figure 1. Results of the whole-brain analysis identifying regions that exhibit a significant interaction between group and the contrast alcohol pictures–neutral pictures. The overlaid statistical map shows positive *t*-values larger than 1.99 ($P < 0.05$) in red reflecting increased contrast differences in the heavy drinker group. The map is overlaid on a transversal cut of a 3D brain mesh derived from Talairach-transformed structural MRI images of a representative participant.

Table 2

Center of gravity Talairach coordinates and cluster size (in 1 × 1 × 1 mm voxel) of areas showing group effects for different statistical contrasts

Statistical contrast	Region (L/R)	Center of gravity (*x*, *y*, *z*)	Cluster size (voxel)
Alcohol–neutral	Ventral striatum (L)	−18, 7, −3	1594
Alcohol–neutral	Insula (L)	−39, 2, 3	1740
Alcohol–neutral	Insula (R)	45, −6, 2	955
Concern–neutral	Inferior frontal gyrus (R)	45, 15, 20	1307
Concern–neutral	Precentral gyrus (R)	31, −3, 34	1355
Alcohol–concern	Insula (L)	−39, −6, 8	841
Alcohol–concern	Inferior frontal gyrus (R)	44, 6, 24	1495
Positive–neutral	Inferior parietal lobe (R)	51, −31, 33	1270
Positive–neutral	Cingulate cortex (R)	8, −17, 38	1174
Negative–neutral	Cerebellum (R)	9, −52, −18	984
Negative–neutral	Cerebellum (L)	−8, −31, −17	1011
Negative–neutral	Corpus callosum (R)	11, −36, 14	954
Negative–neutral	Subgyral white matter frontal lobe (L)	26, 27, 19	1111

of the prefrontal cortex (inferior frontal gyrus, BA 9) and in a second cluster more dorsally and posterior in the precentral gyrus. Figure 4 illustrates the groups' BOLD response profiles underlying this interaction: Light drinkers showed a substantial amplification of BOLD activation in response to concern versus neutral pictures, inferior frontal gyrus: $F_{10} = 20.90$, $P < 0.01$, partial $\eta^2 = 0.68$; precentral gyrus: $F_{10} = 27.56$, $P < 0.001$, partial $\eta^2 = 0.73$. In contrast, there were no frontal differences between the 2 picture categories for the heavy drinker group, Fs < 0.5.

For the contrast, alcohol concern–related pictures, ANOVA revealed 2 significant clusters showing the predicted group × category interactions. These clusters overlapped with 2 regions that had been identified in the comparisons between alcohol/concern and neutral pictures, namely the left insula and right inferior frontal gyrus. The left insula was more strongly activated to alcohol versus concern-related pictures in heavy drinkers, $F_{10} = 6.50$, $P < 0.05$, partial $\eta^2 = 0.39$, while it showed the opposite pattern in light drinkers (stronger activation to concern-related vs. alcohol pictures), $F_{10} = 7.64$, $P < 0.05$, partial $\eta^2 = 0.43$. Similarly, light drinkers showed stronger activation to concern-related versus alcohol pictures in the inferior frontal gyrus, $F_{10} = 12.00$, $P < 0.01$, partial $\eta^2 = 0.55$. In heavy drinkers, the difference between those categories missed significance in the inferior frontal gyrus, $F_{10} = 2.11$, $P > 0.10$.

Positive Pictures

We found 2 areas showing the hypothesized group differences in response to positive versus neutral pictures, which were again confined to the right hemisphere: a region in the inferior parietal lobe (supramarginal gyrus, BA 40) and a cluster in the cingulate cortex (see Fig. 5). In the light drinkers, planned comparisons verified stronger responses to positive than to neutral pictures (see Fig. 6) but only for the parietal region, $F_{10} = 5.11$, $P < 0.05$, partial $\eta^2 = 0.34$ and not for the cingulate, $F_{10} = 1.90$, $P = 0.20$. Heavy drinkers also showed a differential response pattern but in the opposite direction, with positive pictures producing less BOLD activation than neutral pictures, inferior parietal cortex: $F_{10} = 4.44$, $P = 0.061$, partial $\eta^2 = 0.31$; cingulate: $F_{10} = 5.61$, $P < 0.05$, partial $\eta^2 = 0.36$.

Negative Pictures

ANOVAs indicated 2 clusters in the left and right cerebellum exhibiting Group × Category interactions. Light drinkers showed stronger cerebellar responses to negative pictures than to neutral pictures, left: $F_{10} = 12.28$, $P < 0.01$, partial $\eta^2 = 0.55$; right: $F_{10} = 5.24$, $P < 0.05$, partial $\eta^2 = 0.34$, but these areas failed to show category differences in the heavy drinkers group, left: $F_{10} < 0.5$; right: $F_{10} = 2.88$, $P = 0.12$. Because these effects occurred in anatomically unpredicted (noncortical and nonlimbic) regions, we are cautious about interpreting these results.

ANOVAs also revealed 2 other significant areas covering white matter in the frontal cortex and in the corpus callosum. Light drinkers showed stronger BOLD responses to negative than to neutral pictures in the right frontal region, $F_{19} = 25.58$, $P < 0.001$, partial $\eta^2 = 0.72$, whereas there was no significant difference in heavy drinkers, $F_{10} = 2.95$, $P = 0.12$. In the corpus callosum, the BOLD response difference did not reach significance in the light drinker group, $F_{10} = 3.22$, $P = 0.10$, whereas in heavy drinkers, this region was significantly less activated in response to negative relative to neutral pictures, $F_{10} = 31.90$, $P < 0.001$, partial $\eta^2 = 0.76$. Because the BOLD signal is usually difficult to detect in white matter (Logothetis and Wandell 2004), future work will need to test the replicability of these effects before firm conclusions can be drawn. Alternative accounts of the results are that they were caused by vascular or motion artifacts or that they reflect differences in nearby gray matter areas, such as the thalamus (corpus callosum effect) or the insula (frontal effect), which were displaced during coregistration of the functional and anatomical data or through spatial smoothing.

BOLD Response-Based Group Discrimination

The stepwise discriminant function analysis selected 3 out of the 9 regional activation patterns that best differentiated heavy from light drinkers (Wilks λ for discriminant function: 0.11, $\chi^2 = 40.69$; $P < 0.001$; 100% of cases correctly classified): 1) The beta difference between alcohol and neutral pictures in the left ventral striatum (standardized discriminant function coeffecient: 0.85), 2) the difference between alcohol and neutral

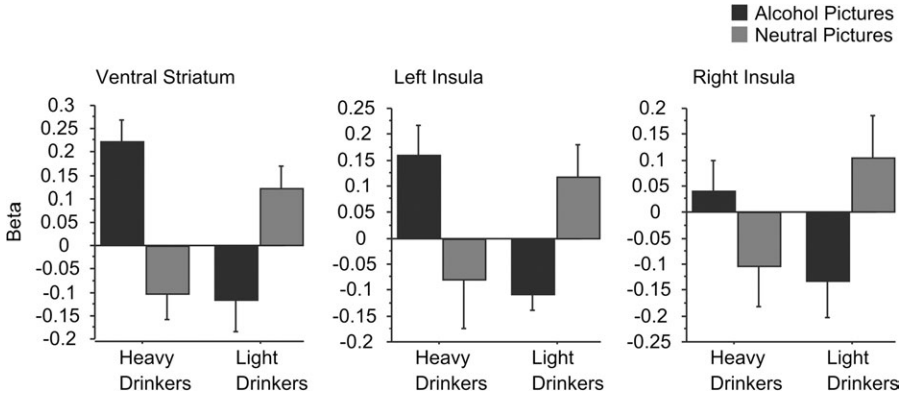

Figure 2. Heavy and light drinkers' mean beta values (general linear model parameter estimates) for alcohol and neutral pictures in the ventral striatum and left and right insula.

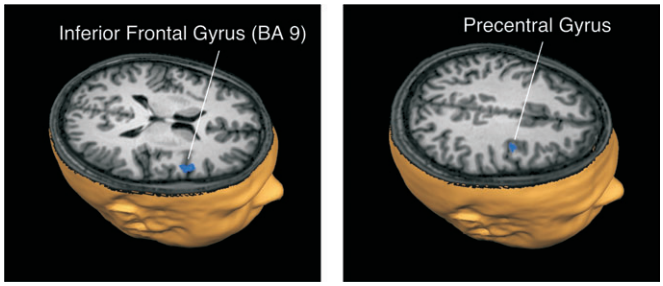

Figure 3. Transversal view of regions showing a significant interaction between group and the contrast concern–neutral pictures. Blue colors indicate negative *t*-values ($P < 0.05$) reflecting reduced contrast differences for heavy drinkers.

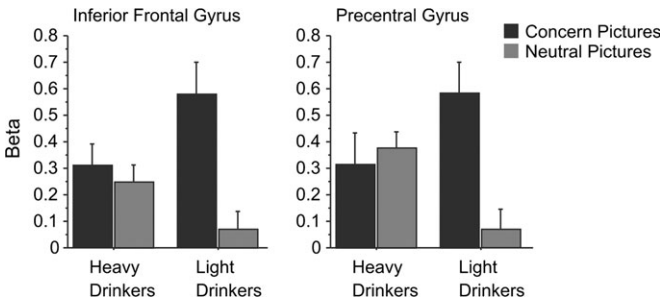

Figure 4. Mean beta values for concern and neutral pictures in the inferior frontal gyrus and precentral gyrus.

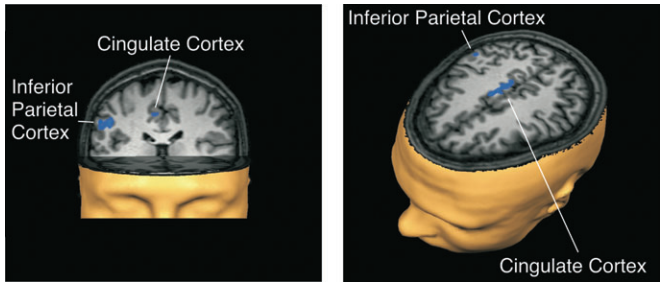

Figure 5. Coronal (left) and transversal (right) views of areas exhibiting a significant interaction between group and the contrast positive (food)–neutral pictures. Negative *t*-values ($P < 0.05$) are plotted in blue and indicate that heavy drinkers show reversed contrast differences.

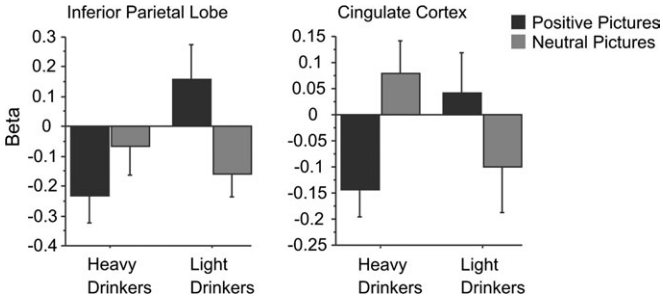

Figure 6. Mean beta values for positive and neutral pictures in statistically significant regions (inferior parietal cortex, cingulate cortex).

pictures in the left insula (coefficient: 0.93), and 3) and the beta difference between concern-related and neutral pictures in the right inferior frontal gyrus (coefficient: −1.30). Figure 7 illustrates single participants' scores for the identified discriminative contrasts (upper panel), which—when combined—allow for a perfect group separation within a 2D "motivational space" (lower panel).

Discussion

Alcohol Cue Reactivity

Consistent with our hypotheses, heavy drinkers showed amplified BOLD responses when they were exposed to pictures related to alcohol, relative to emotionally neutral stimuli, such as household objects. These amplification effects occurred in circumscribed brain areas that constitute key parts of basic motivational circuits, namely the ventral striatum and the insular cortex. The effects reached strong effect size estimates (e.g., 0.82 for the effect in the ventral striatum), underscoring the robustness of our results even though group sample sizes were limited to 11 participants. Crucially, in the light drinkers, the alcohol cues did not activate these areas more strongly than the neutral pictures. These findings are consistent with work linking these regions to drug craving (insula) and reward (ventral striatum, see Camara et al. 2008). The role of the ventral striatum in ethanol reinforcement is well established. For example, local injections of opioid antagonists into the nucleus accumbens decrease ethanol self-administration in rats (Le Merrer et al. 2009). The role of the insula in drug craving has been highlighted in both animal research (Contreras et al. 2007) and in studies with humans

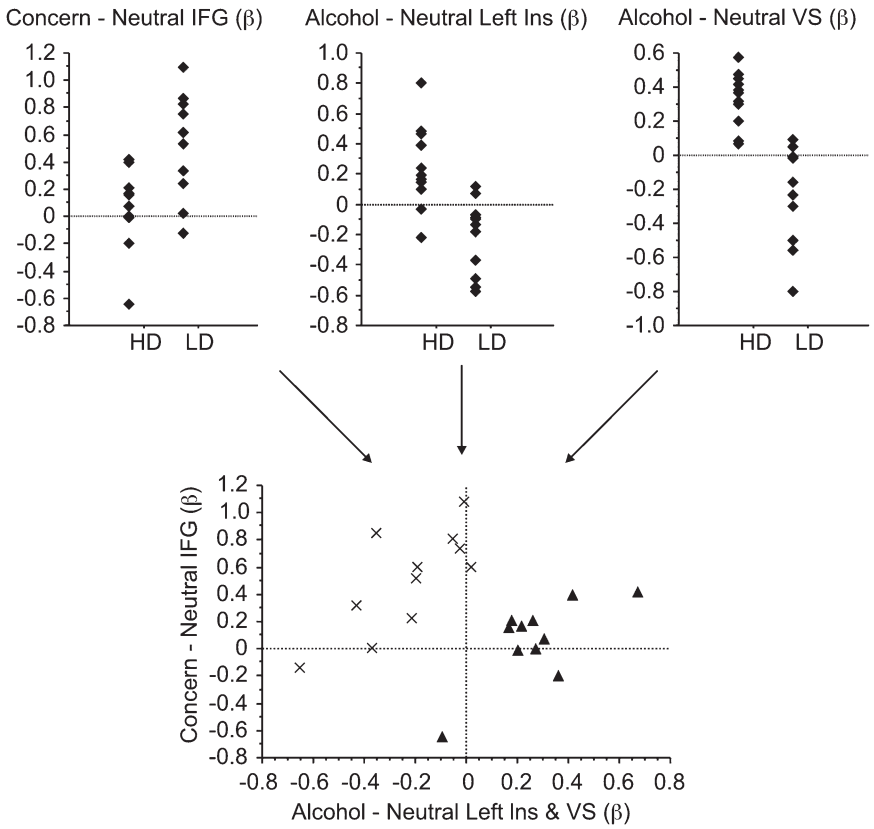

Figure 7. Top panel: Participants' (HD, heavy drinkers; LD, light drinkers) beta difference values for those contrasts and activated clusters that linear discriminant function analysis identified as being most predictive of group status (IFG, right inferior frontal gyrus; left Ins, left insula; VS, left ventral striatum). Bottom panel: When the 3 activation patterns are combined into a 2D motivational space, the 2 groups (crosses, light drinkers; triangles, heavy drinkers) can be perfectly separated. *x*-axis: mean beta difference for alcohol minus neutral cues averaged across left ventral striatum and left insula, *y*-axis: beta difference for concern-related minus neutral pictures in the right inferior frontal gyrus.

(Filbey et al. 2009). Contreras et al. (2007) showed that inactivation of the insular cortex in rats eliminates amphetamine-related place preference. Furthermore, the lesioned rats did not exhibit signs of behavioral disturbance when injected with a malaise-inducing drug. These 2 findings corroborate the idea that the insular cortex plays an important role in the interoceptive system that monitors bodily and homeostatic changes. These changes may become specifically salient during emotional states but also during drug intake or when craving arises from drug abstinence. Interestingly, functional connectivity analysis has revealed a neuronal circuit between the insula and the ventral striatum, which is activated during the processing of both gains and losses (Camara et al. 2008). Moreover, successful self-regulation of insula activity by fMRI neurofeedback is accompanied by increased striatal activity (Johnston et al. 2010). Our findings inform the debate on the functional significance of these circuits because they show that insula and ventral striatum activation in response to visual alcohol cues can distinguish people with different levels of alcohol consumption even in a nonclinical setting. This heightened responsivity to alcohol cues would be compatible with neurobiological models of addiction that posit remodeling of basal ganglia and limbic circuits for motivation and learning during the acquisition phase of drug-seeking behavior (Moonat et al. 2010).

The question arises as to why light drinkers showed reduced BOLD responses to alcohol pictures, relative to neutral stimuli. One interpretation is that alcohol-associated deactivation in the light drinker group indicated inhibition of motivational or craving-related brain areas, which may serve a protective function. Alternatively, these brain circuits may be recruited to process higher order goals and incentives rather than alcohol cues. This idea is supported by our finding that in light drinkers low activation of the left insula to alcohol cues was accompanied by increased activation to concern-related cues.

We did not find a difference between heavy and light drinkers in visual cortex activity in response to alcohol versus neutral cues. Picture categories were carefully controlled for physical and perceptual parameters (brightness, contrast, and perceptual complexity). One limitation of previous work on the processing of pictorial alcohol cues has been the absence of such procedures. It is thus possible that the previously reported enhancement of visual processing of alcohol versus neutral cues in alcoholics (e.g., Wrase et al. 2002; Heinz et al. 2007) is partly caused by perceptual category differences. According to this view, perceptual differences may become particularly evident in participants who are highly familiar with visual alcohol cues, such as alcoholics, and are less pronounced in nonalcoholic participants.

Interestingly, we did not find clear-cut group differences in the rating data. A similar divergence of brain and behavioral responses in alcoholics has been reported by Wrase et al. (2002). These results may be attributed to social desirability biases in questionnaire data, with heavy drinker or alcoholics being particularly prone to such biases. An alternative explanation is that motivational processes as evoked by the

present stimuli are not necessarily reflected in cognitive appraisal of these stimuli but rather guide action at a subconscious level. Imaging measures may thus be more sensitive to addictive dispositions than self-report measures. However, we are aware that caution is warranted in interpreting null effects with a group size (and corresponding low power of the statistical test) as reported here, and future work is required to test these ideas.

Reactivity to Other Incentives

In addition to the group differences in BOLD responses to alcohol cues, heavy and light drinkers' brain activation patterns were also dissociable when they viewed other incentives: First, light but not heavy drinkers showed heightened sensitivity to concern-related pictures. Consistent with the assumption that scenes depicting higher order personal goals elicit complex cognitive and action-related processes, these effects were specifically prominent in frontal areas, including the right inferior frontal gyrus and the precentral gyrus. Both regions are often linked to the mirror neuron system (Rizzolatti and Craighero 2004), that is, they become active during observation of another person's actions. With regard to the processing of current concerns, it is interesting to note that observing action goals in still images—rather than observing the action itself—is sufficient to engage the inferior frontal and precentral mirror system (Johnson-Frey et al. 2003). Our data thus support the idea that these areas not only contribute to the understanding of action but also to process "action intentions/goals" (Iacoboni et al. 2005). The group difference in the recruitment of the mirror system may then correspond to the different position of higher order goals compared with the satisfaction of immediate needs (in this case: to drink alcohol) in the motivational hierarchies of heavy and light drinkers. Supporting the idea of altered motivational hierarchies, our analyses revealed that in heavy drinkers the inferior frontal gyrus was more strongly activated to alcohol cues, relative to concern-related pictures.

Second, light drinkers displayed stronger activation of the cingulate and parietal cortex in response to food stimuli. This effect was absent in heavy drinkers, indicating that they are less responsive not only to higher order cognitive goals but also to primary reinforcers. Our results are thus the first ones from a visual cue paradigm to suggest that heavy drinkers might "devalue" stimuli representing incentives other than alcohol (for a discussion of the devaluation hypothesis, see Heinz et al. 2007). Our finding is consistent with a study by Wrase et al. (2007), who reported that detoxified alcoholics showed less activation in the ventral striatum than healthy controls when waiting for a reward in a monetary incentive delay task. Interestingly, group differences in responses to other incentives (concern-related and food pictures) showed a right-hemispheric focus. This finding is consistent with previous studies reporting larger right-hemispheric activation during perception of motivationally relevant pictures (Lane et al. 1999) and during higher order emotional/motivational processes, such as emotional self-regulation (Beauregard et al. 2001).

To our knowledge, only one visual cue reactivity study (Heinz et al. 2007) has included appetitive and aversive stimuli in their experimental design, and these authors obtained mixed results. Contrary to expectations, relative to healthy controls alcoholics showed increased BOLD responses to all picture categories (alcohol, positive, and negative). Two factors may have contributed to this divergence in findings: First, participants in Heinz et al.'s study were detoxified alcoholics. Unlike heavy drinkers, in alcoholics, an increase of brain responses to positive stimuli may indeed—as the authors argue—serve a protective function. This idea is supported by the finding that increased brain activation during presentation of positive stimuli was inversely related to later risk of relapse (see also Heinz et al. 2009). Second, in contrast to the emotional picture categories used in the present study, the study by Heinz et al. (2007) use semantically heterogeneous groups of pictures, making the results more difficult to interpret.

Bivariate Differentation

Linear discriminant function analysis using responsiveness of the ventral striatum and the left insula to alcohol cues and sensitivity of the inferior frontal gyrus to goal-related stimuli allowed for a complete separation of the heavy and light drinkers (Fig. 7). The analysis suggests that the interplay between these mechanisms, rather than ventral striatum or insula alcohol cue-reactivity alone, predisposes people to potentially harmful alcohol use. It is encouraging that functional imaging can attain such diagnostic accuracy, which needs to be replicated in further studies before its clinical use can be contemplated and highlights its role in identifying potential biomarkers for the effectiveness of psychological or pharmacological interventions (Linden 2006).

To conclude, brain activation measures of cue reactivity may provide a sensitive diagnostic tool for detecting preclinical symptoms of alcohol abuse. We have identified specific brain mechanisms underlying preference for alcohol use over alternative, socially desirable goals, in heavy drinkers. Our findings highlight the importance of focusing on maladaptive brain responses during early stages of alcohol abuse in order to better understand and prevent it.

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