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Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics

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Objective: **Alcohol dependence may be associated with dysfunction of mesolimbic circuitry, such that anticipation of nonalcoholic reward fails to activate the ventral striatum, while alcohol-associated cues continue to activate this region. This may lead alcoholics to crave the pharmacological effects of alcohol to a greater extent than other conventional rewards. The present study investigated neural mechanisms underlying these phenomena.**
Methods: **16 detoxified male alcoholics and 16 age-matched healthy volunteers participated in two fMRI paradigms. In the first paradigm, alcohol-associated and affectively neutral pictures were presented, whereas in the second paradigm, a monetary incentive delay task (MID) was performed, in which brain activation during anticipation of monetary gain and loss was examined. For both paradigms, we assessed the association of alcohol craving with neural activation to incentive cues.**
Results: **Detoxified alcoholics showed reduced activation of the ventral striatum during anticipation of monetary gain relative to healthy controls, despite similar performance. However, alcoholics showed increased ventral striatal activation in response to alcohol-associated cues. Reduced activation in the ventral striatum during expectation of monetary reward, and increased activation during presentation of alcohol cues were correlated with alcohol craving in alcoholics, but not healthy controls.**
Conclusions: **These results suggest that mesolimbic activation in alcoholics is biased towards processing of alcohol cues. This might explain why alcoholics find it particularly difficult to focus on conventional reward cues and engage in alternative rewarding activities.**

Keywords: Ventral striatum; Reward system; fMRI; Alcoholism; Craving

Introduction

Alcohol addiction is based on well-learned behavior of alcohol consumption, which eventually becomes habitual (Everitt and Wolf, 2002; Robbins and Everitt, 2002). Stimuli associated with alcohol can serve as conditioned cues that promote alcohol consumption (O'Brien et al., 1998; Stewart et al., 1984). This process may be mediated by recruitment of circuitry innervated by midbrain dopamine neurons, since presentation of alcohol-associated stimuli elicits increased activation of the striatum, anterior cingulate cortex (ACC), amygdala, and medial prefrontal cortex (mPFC) in alcoholics, relative to healthy volunteers (Braus et al., 2001; George et al., 2001; Grusser et al., 2004; Heinz et al., 2004; Hommer, 1999; Myrick et al., 2004; Schneider et al., 2001; Tapert et al., 2004; Wrase et al., 2002).

However, associative learning alone is not sufficient to explain the compulsive behavior of alcoholics. Chronic consumption of alcohol and other drugs of abuse may additionally derange motivation, leading to pathological "wanting" of the abused substance (craving) (Berridge and Robinson, 2003), and excessive attribution of incentive salience to drug-related cues. Thus, drug-related cues may selectively and effectively trigger relapse (Robbins and Everitt, 1999; Robinson and Berridge, 2003). Changes wrought in neural circuits by years of chronic abuse may not reverse, even after extended abstinence, making addiction a chronic condition (O'Brien, 2005). These changes could affect the function of mesolimbic circuits in a number of ways. For instance, alcohol abuse may simply blunt responsiveness to conventional reward-indicating cues. On the other hand, alcohol abuse may "hijack" mesolimbic circuitry—increasing the salience of drug-associated cues at the expense of conventional reward-indicating cues (Kalivas and Volkow, 2005; Nesse and Berridge, 1997).

fMRI-studies indicate that conventional reward-indicating cues increase ventral striatal (including the nucleus accumbens) oxygenation (hereafter, "activation") in healthy volunteers (Aharon et al.,

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2001; Breiter et al., 2001; Knutson et al., 2001b; Stark et al., 2005). In detoxified alcoholics, alcohol cues can also activate the ventral striatum (Braus et al., 2001; Myrick et al., 2004; Wrase et al., 2002). However, it is not clear how detoxified alcoholics respond to conventional reward-indicating cues, and whether this reflects their neural response to alcohol cues. If alcoholics had a decreased response to conventional reward-indicating cues but an increased response to alcohol-associated cues, such an effect would be consistent with the notion that drugs of abuse can "hijack" and reorganize the priority of reward processing (Nesse and Berridge, 1997). To examine this possibility, we examined whether (1) cues that predicted potential monetary gain would elicit less activation of the ventral striatum in detoxified alcoholics than in healthy control subjects, whether (2) alcohol cues would elicit more ventral striatal activation than in healthy control subjects, and (3) the extent of these types of activations would correlate with degree of alcohol craving.

Methods

Subjects and instruments

16 male alcoholics (mean age: 42.4±7.5, range: 25–57 years) and 16 male age-matched healthy control subjects (mean age: 39.9±8.6, range: 24–59 years) were included in the study. In total we scanned 22 patients, but had to exclude 6 patients due to head motion exceeding 4 mm from one scan to the next. The local ethics committee approved the study, and written informed consent was obtained from all participants after the procedures had been fully explained. All patients were diagnosed as alcohol dependent according to ICD-10 and DSM-IV criteria and had no other psychiatric axis I disorders, no past history of dependency or current abuse of other drugs as verified by random urine drug testing and SCID-interview (First et al., 2001). Patients had abstained from alcohol in an in-patient detoxification treatment program for 11.5±7.5 days (range 5–37 days) as verified by random administration of alcohol breath test. Besides medical care they had received psycho-education in group therapy. All subjects were free of benzodiazepine or chlormethiazole medication for at least 1 week. The severity of alcoholism was assessed with the Alcohol Dependence Scale (Skinner and Horn, 1984). The severity of alcohol craving during the last seven drinking days was measured with the Obsessive Compulsive Drinking Scale (OCDS) (Anton, 2000) (Table 1). Healthy control subjects had no psychiatric axis I or II disorder (SCID-interview) (First et al., 1997, 2001) and no history of psychiatric disorders (including alcohol dependence) in first-degree relatives, while 6 of the alcohol dependent subjects had a positive family history for alcohol dependence.

The Hamilton Depression Rating Scale (Hamilton, 1960) was used to quantify depressive symptoms. Before and after the fMRI-paradigm mood was rated on a visual analog scale. All participants were right-handed as confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971) (Table 1). We verified that smokers were not in a withdrawal state during acquisition of scans.

Monetary incentive delay (MID) task

We used a "monetary incentive delay" (MID) task as described previously (Knutson et al., 2001a). In brief, subjects were examined with fMRI during trials in which they anticipated potential monetary gain, loss, or no consequences. The participants' monetary gain depended on their performance in a simple reaction time task at the end of each trial, which required pressing a button during the brief presentation of a visual target. Task details are given in Fig. 1. Subjects were informed that they would receive the monetary reward they earned after the scanning session, and the money was shown in cash to them before entering the scanner. During structural scans, participants completed a short practice version of the task (in order to minimize later learning effects) for which they did not receive monetary payment. Subsequently functional scans were collected. After scanning, subjects retrospectively rated their own exertion in response to each of the seven cues on a visual analog scale (Table 1).

Table 1
Clinical data

	Alcoholics		Controls	
	Mean	SD	Mean	SD
Age in years	42.38	7.52	39.94	8.59
Obsessive Compulsive Drinking Scale	21.88	5.96	3.25	3.66
VAS effort to obtain gain (1–10)	8.76	3.51	7.88	1.70
VAS effort to avoid loss (1–10)	9.20	5.32	8.73	5.44
Mean hit rate in %	65.13	11.66	70.25	12.09
Mean reaction time in ms	275.07	94.46	247.93	76.91
Total gain in euros	17.93	6.40	23.00	8.62
Hamilton Depression Scale	3.19	3.33	1.14	1.68
Stanford Sleepiness Scale	2.27	1.19	2.29	0.83
Edinburgh Handedness Inventory	89.1	21.9	95.8	8.12
Number of cigarettes per day	24.5	12.1	7.94	8.90
Years of education	9.06	1.69	11.69	1.54
Severity of alcohol dependence	20.69	7.01		
Duration of alcohol dependence (years)	12.69	7.09		
No. of detoxifications	10.19	18.07		

Alcohol paradigm

We used affectively unpleasant, pleasant and neutral pictures from the International Affective Picture System (Center for the Study of Emotion and Attention [CSEA-NIMH], 1999) and standardized alcohol-related pictures (Wrase et al., 2002). Neutral stimuli were all inanimate and matched for complexity and colour with the alcohol pictures, which have previously been shown to elicit significant activation in mesolimbic and other regions in alcoholics (Wrase et al., 2002). Each category included 18 pictures, resulting in 72 total trials. fMRI results for the affective pictures will be reported elsewhere. Participants were instructed to passively view the stimuli, since even simple rating tasks can influence amygdala activation (Taylor et al., 2003). To control for a decrease in attention, participants had to confirm every viewed picture with a button press with the right thumb. Pictorial stimuli were presented for 2 s using an event-related design and were arranged in an individually randomised order for each subject. Intertrial interval (ITI) was randomly jittered between 2 and 4 acquisition times, which means that the duration between trial t and $t+1$ was randomly varied between 4.6 and 9.2 s in order to sample the hemodynamic response with different data points. A fixation cross was presented during each ITI.

Functional magnetic resonance imaging

fMRI was performed on a 1.5 T scanner (Magnetom VISION Siemens®) equipped with a standard circularly polarized head coil

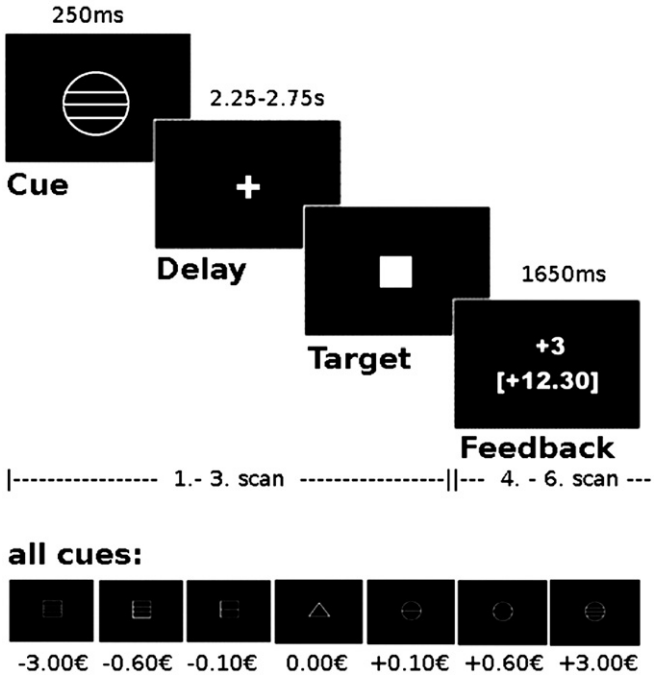

Fig. 1. Task structure for a representative trial. In each trial, volunteers saw one of seven shapes ("cue"; 250 ms), which indicated that they would, in a few moments, be able to respond and either win or avoid losing different amounts of money (3.00 euros, 0.60 euros, or 0.10 euros) or that they should respond for no monetary outcome. The different cues are shown at the bottom of the figure. Cues signaling potential gain were denoted by circles, potential loss was denoted by squares, and no monetary outcome was denoted by triangles; the possible amount of money that subjects were able to win was indicated by one horizontal line for 0.10 euro, two horizontal lines for 0.60 euro and three horizontal lines for 3.00 euro. Similarly, loss cues signaled the possibility of losing the same amounts of money. After the cue, volunteers waited a variable interval (delay: 2250, 2500 or 2750 ms) and then responded to a white target square that appeared for a variable length of time (target) by pressing a button. To succeed in a given trial, volunteers had to press the button while the target was visible. Immediately after target presentation, feedback appeared ("feedback"; 1.650 ms), notifying volunteers that they had won or lost money and indicating their cumulative total at that point. Through an adaptive algorithm for the time of the target presentation, subjects succeeded on average in 67% of the trials. The inter-trial interval was 4000 ms. Trial types were randomly ordered within each session.

(CP-Headcoil) using gradient echo–echo planar imaging. For both fMRI-paradigms the following parameters were used: GE-EPI, TE = 40 ms, flip angle = 90 degrees, matrix = 64 × 64, voxel size = 4 × 4 × 3.3 mm. For the MID-paradigm 18 slices were collected every 1.8 sec approximately parallel to the bicommissural plane (ac–pc-plane), covering the inferior part of the frontal lobe (superior border above the caudate nucleus), the whole temporal lobe and large parts of the occipital region. fMRI volume acquisitions were time-locked to the offset of each cue and thus were acquired during anticipatory delay periods. Six fMRI volumes were acquired per trial, resulting in 450 total volumes.

For the alcohol-cue paradigm, 24 slices covering the whole head parallel to ac–pc plane were collected every 2.3 s. Five fMRI volumes were acquired per trial, resulting in 380 total volumes. For anatomical reference a 3D MPRAGE (*M*agnetization *P*repared *R*apid *G*radient *E*cho, TR = 9.7 ms; TE = 4 ms; flip angle 12 degrees; matrix = 256 × 256, voxel size 1 × 1 × 1 mm) image data set was acquired. Head movement was minimized using a vacuum pad.

fMRI data analysis

Three alcoholic subjects only participated in one paradigm (MID), resulting in a total of 16 subjects for MID paradigm and a total of 13 subjects in the alcohol cue paradigm. Functional MRI data were analyzed using SPM2 (http://www.fil.ion.ucl.ac.uk/spm). The first three volumes of each functional time series were discarded in order to avoid non steady-state effects caused by T1 saturation. Sinc interpolation was used to realign all volumes to the middle volume to correct for between-scan movements and to remove signals correlated with head motion. All six movement parameters (translation; *x*, *y*, *z* and rotation; pitch, roll, yaw) were included in the statistical model. The structural 3D data set was co-registered with the first T2* image. The coregistered structural image was spatially normalized to the standard template provided by the Montreal Neurological Institute (MNI-Template) using an automated spatial transformation (12-parameter affine transformation followed by non-linear iterations using 7 × 8 × 7 basis functions), resulting in an isometric voxel size of 4 × 4 × 4 mm^3. The normalized images were smoothed with a Gaussian kernel designed to optimize the signal-to-noise ratio in small subcortical structures of interest (e.g., the nucleus accumbens) (full width at half maximum = 4 mm).

Functional MRI data were then analyzed in the context of the general linear model (GLM) approach. Changes in the BOLD response can be assessed by linear combinations of the estimated GLM parameters (beta values) and are contained in the individual contrast images (equivalent to percent signal change or effect size). For the MID task, this analysis was performed by modelling the different conditions ("anticipation of gain", "anticipation of loss" and "anticipation of no outcome") as explanatory variables

convolved with the gamma variate function described by Cohen (1997) and similar to the method of Knutson et al. (2001b) and Breiter et al. (2001). For the alcohol paradigm we used the hemodynamic response function (HRF) provided by SPM2 with time deviation, that contrasts the BOLD response during alcohol-related vs. neutral pictures.

To detect group differences between alcohol dependent patients and healthy controls, individual contrast images (i.e. the BOLD response differences) of all subjects in each group were included in a second level random effects analysis, comparing within-group activation with a one-sample t test and between-group differences with a two-sample t test. For this exploratory analysis we used a significance level of $p<0.001$ uncorrected and a cluster threshold of $k>1$. To test the hypothesis of activation in the ventral striatum elicited by both paradigms, SPM's small volume correction (S.V.C.) was performed using binary masks from the publication-based probabilistic MNI-atlas (Fox and Lancaster, 2002) at the threshold of 0.5 probability (please refer to http://hendrix.imm.dtu.dk/services/jerne/ninf/voi/index-alphabetic.html, access date 19.06.2006) and a significance level of $p<0.05$ FWE-corrected for the volume of interest (VOI, left and right ventral striatum).

Correlation analysis between ventral striatal activation and alcohol craving

In the confirmatory analysis, we tested the hypothesis that the severity of alcohol craving (1) is *negatively* correlated with ventral striatal activation during anticipation of monetary reward versus nonreward but (2) is *positively* correlated with ventral striatal activation during viewing of alcohol versus neutral pictures. These contrasts within the ventral striatal VOI were defined by a probabilistic map (see above) and were correlated with the craving score of the obsessive compulsive drinking scale (OCDS (Anton, 2000)) using SPM2 simple regression analysis with a significance level of $p<0.05$ FWE-corrected for the VOI.

We also explored correlations between alcohol craving and functional activations outside of the ventral striatum as indicated in the group contrast (alcoholics vs. controls) for both paradigms. In the exploratory analysis, we further assessed correlations between the activation contrasts for the MID task and the alcohol paradigm described above and potentially confounding variables (age, severity of alcohol dependence (Skinner and Horn, 1984), duration of alcohol dependence, number of detoxifications, duration of abstinence before scanning, number of cigarettes smoked per day, and severity of depression (Hamilton, 1960) using SPM2 simple regression analysis and a significance level of $p<0.001$, uncorrected.

Results

Behavioral data

Alcoholics reported stronger alcohol craving than healthy controls ($t=10.65$, $p<0.001$). No significant group difference was observed in the Hamilton Depression Rating Scale ($t=1.53$, $p=0.142$) (Hamilton, 1960). Performing the MID task, there was also no significant difference between alcoholics and controls in mean hit rate ($t=1.20$, $p=0.240$), the mean reaction time ($t=0.01$, $p=0.996$), the amount of money that was gained ($t=1.89$, $p=0.068$), self-reported alertness during the task assessed with the Stanford Sleepiness Scale (Hoddes et al., 1973) ($t=-0.36$, $p=0.720$), or self-reported effort to achieve monetary gains ($t=0.91$, $p=0.371$) or to prevent losses as assessed with visual analog scales (VAS) ($t=0.24$, $p=0.810$) (Table 1). For the mood ratings: there were no main effects of diagnosis ($F(1,42)=0.013$, $p=0.910$) and time ($F(1,42)=0.229$, $p=0.634$) nor an interaction diagnosis × time ($F(1,42)=1.33$, $p=0.245$). This shows that the stimulus materials did not elicit significant changes in mood ratings.

Anticipation of gain

During anticipation of monetary gain versus no outcome, healthy control subjects showed significant bilateral activation of the ventral striatum including the nucleus accumbens (Table 2). In detoxified alcoholics, reward anticipation did not produce significant activations in the ventral striatum. Instead, alcoholics showed activations in the thalamus and in the lateral orbital frontal cortex (Table 2). Activation in the ventral striatum was only visible in the alcoholic group at a more liberal threshold on the right side ($p<0.01$; $t=3.23$; $(x\ y\ z)=(12\ 15\ -4)$).

When controls were directly compared with detoxified alcoholics, they showed significantly stronger activations in the left ventral striatum, in the right posterior putamen and in the right head of the caudate nucleus during gain versus nongain anticipation (Table 2, Fig. 2). This difference was not due to alterations in the time course of the BOLD response (see Supplementary Fig. S1 for the ventral striatum $(x\ y\ z)=(-16\ 12\ -4)$). Compared with healthy controls, alcoholics showed no stronger activations for this contrast. In alcoholics but not controls, the severity of alcohol craving correlated significantly and inversely only with the activation in the bilateral ventral striatum during the anticipation of monetary gain versus no outcome (left: $t=3.61$, $p=0.014$; $(x\ y\ z)=(-8\ 15\ -4)$; right: $t=3.49$, $p=0.024$; $(x\ y\ z)=(12\ 12\ -4)$). The higher the craving, the less the ventral striatum activated in response to the presentation of monetary reward cues (Fig. 3).

To confirm that this correlation is selective to the ventral striatum and not to the significant activations in the posterior putamen or caudate nucleus (see controls vs. alcoholics, Table 2), we also correlated these activations with alcohol craving. Both correlations were not significant (Supplementary Fig. S2). Furthermore, the correlations between alcohol craving and both the activations in the putamen and caudate were significantly smaller than the correlation

Table 2
Brain activation elicited by the anticipation of potential gain compared with the anticipation of no outcome (CON=controls, ALC=alcohol-dependent patients)

	Region	Talairach coordinates				
		left/right	x	y	z	t-value
Controls	Ventral striatum	left	−16	11	−7	6.95
		right	12	8	−4	4.86
Alcoholics	Inferior frontal gyrus, BA 47	left	−40	20	−4	4.62
	Thalamus	right	4	−15	4	5.64
CON>ALC	Ventral striatum	left	−16	12	−4	4.23
	Posterior putamen	right	32	−23	−2	4.34
	Caudate nucleus head	right	4	23	2	3.94
ALC>CON	–	–	–	–	–	–

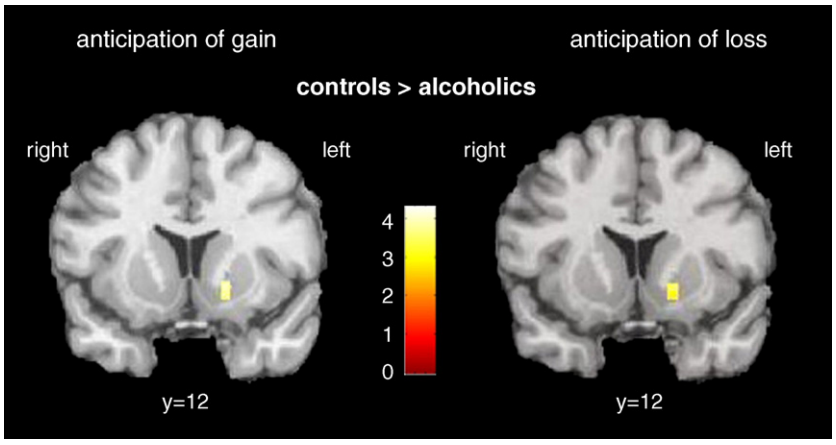

Fig. 2. Brain activation in the ventral striatum elicited by visual stimuli that indicate potential gain versus no outcome (left) or potential loss versus no outcome (right).

between craving and the activation in the left ventral striatum ($z=2.79$, $p=0.0026$ and $z=3.25$, $p=0.00058$, respectively).

Anticipation of loss

When healthy control subjects anticipated potential monetary loss, they also showed significant activation of the bilateral ventral striatum, including the nucleus accumbens. Exploratory analysis additionally revealed activation in the left lateral globus pallidus (Table 3). In detoxified alcoholics, no significant activation was found in the ventral striatum during anticipation of potential loss. Instead, alcoholics activated the left lateral orbital frontal cortex, and left thalamus (Table 3).

When controls were directly compared with detoxified alcoholics, they showed a significantly stronger activation in the left ventral striatum during loss anticipation (Fig. 2). Compared with healthy controls, alcoholics displayed a stronger activation in the left middle frontal gyrus (Table 3).

Comparison of gain versus loss anticipation in alcoholics and controls

Even though we observed significant activation in the ventral striatum during both gain and loss anticipation in healthy control subjects, the increase was much stronger during gain compared to loss anticipation (left: $t=5.06$, $p=0.002$; (x y z)=(−12 12 −4)). However, there was no significant difference between anticipated gain and loss in alcoholics.

Alcohol cues compared to neutral control cues

Pictures of alcohol-associated versus neutral cues elicited significant activation in alcoholics in the right ventral striatum, but not in healthy control subjects (Table 4). In the exploratory analysis alcoholics showed also activation in the thalamus, middle occipital gyrus, posterior cingulate and middle and superior temporal gyrus (Table 4). In the direct comparison between alcohol dependent patients and healthy controls, alcoholics exposed a stronger activation in the thalamus, precuneus and middle temporal and occipital gyrus. The ventral striatum was only observable as a trend ($t=3.20$, $p=0.102$; (x y z)=(−20 4 0); $t=3.14$, $p=0.083$; (x y z)=(16 0 0)).

The severity of alcohol craving correlated significantly and positively only with the activation elicited by alcohol versus neutral pictures in the right ventral striatum ($t=4.50$, $p=0.016$; (x y z)=(20 4 −4)) in alcohol dependent subjects. Higher craving was associated with a stronger activation. This association was not observed in healthy volunteers.

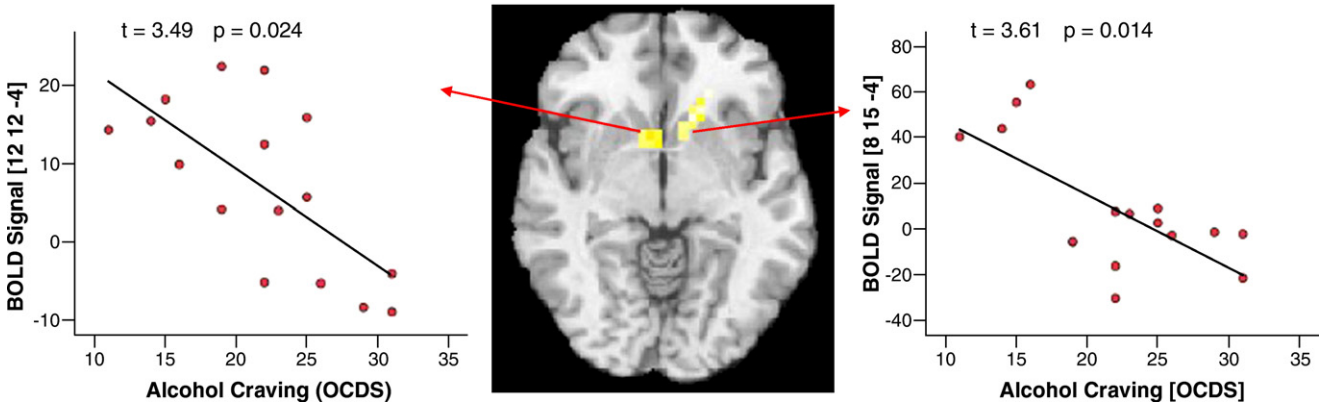

Fig. 3. Negative correlation between the severity of alcohol craving measured with the Obsessive–Compulsive Drinking Scale and brain activation in the ventral striatum elicited by the contrast anticipation of monetary gain versus no outcome.

Table 3
Brain activation elicited by the anticipation of potential loss compared with the anticipation of no outcome (CON=controls, ALC=alcohol-dependent patients)

Sample	Region	Talairach coordinates				
		left/right	*x*	*y*	*z*	*t*-value
Controls	Ventral striatum	left	−20	15	−7	4.46
		right	20	11	−7	4.12
	Lateral globus pallidus	left	−12	4	0	5.39
Alcoholics	Inferior frontal gyrus, BA 47	left	−40	19	−4	4.69
	Thalamus	left	−4	−15	5	4.40
CON>ALC	Ventral striatum	left	−16	12	−4	3.40
ALC>CON	Middle frontal gyrus, BA 10	left	−36	51	1	4.46

To confirm that this correlation is selective to the ventral striatum and not to the significant activations in the group comparison in the thalamus, middle occipital gyrus or precuneus (see controls vs. alcoholics, Table 4), we also correlated these activations with alcohol craving but found no significant associations (Supplementary Fig. S3). Furthermore, these correlations were significantly smaller than the correlation between craving and the activation in the ventral striatum ($z=2.81$, $p=0.0025$, $z=2.61$, $p=0.0045$, $z=3.56$, $p=0.00019$, respectively).

There were no significant associations between potentially confounding variables such as the duration of abstinence before scanning, severity of alcohol dependence, number of detoxifications, duration of dependence, number of cigarettes smoked per day, severity of clinical depression, age, and the activation elicited by alcohol vs. neutral pictures or anticipation of gain vs. no outcome in the ventral striatum.

Discussion

To the best of our knowledge, these findings demonstrate for the first time that abstinent alcoholics show reduced activation of the ventral striatum including the nucleus accumbens during anticipation of conventional (i.e. monetary) rewards, and that this reduction is correlated with increased alcohol craving. However, alcoholic patients displayed increased activation in the ventral striatum when confronted with alcohol cues, which was associated with increased alcohol craving. These findings are not consistent with a global deficit of brain activation in alcoholics (e.g., due to hypoperfusion), or a selective blunting account of ventral striatal activation, but instead with the notion that alcoholism selectively diverts motivational resources away from conventional rewards towards drug rewards (Garavan et al., 2000; Nesse and Berridge, 1997). Furthermore, explorative analysis showed that alcoholics also invoked the orbitofrontal cortex to process anticipation of monetary gain and loss, while controls used more subcortical systems to do the same.

In healthy control subjects, activation of the ventral striatum was elicited by both monetary reward and loss cues, which might be interpreted as consistent with a "salience" interpretation of ventral striatal activation (Zink et al., 2004). In healthy controls, direct comparison of gain and loss anticipation revealed significantly greater ventral striatal activation during gain anticipation, which is consistent with earlier reports, and a predominant reward anticipation account of ventral striatal activation (Knutson et al., 2001a). Ikemoto and Panksepp (1999) have suggested that in the nucleus accumbens, stressful situations can also induce phasic dopamine release if an unpleasant outcome can be avoided by a motor response. A similar situation is found in this study, where subjects were able to avoid monetary loss with a fast motor response. Such an activation of the ventral striatum was not found in detoxified alcoholics. The lack of differential ventral striatal activation during anticipation of gain versus loss in alcoholics may be due to the low levels of activation shown during anticipation of all monetary incentives by this group. Failure to activate brain circuitry associated with anticipation of new, reward-indicating stimuli may thus contribute to craving for long established, well-known effects of alcohol.

While drug and drug-associated stimuli can elicit dopamine release in the ventral striatum and thus reinforce drug intake during the *acquisition* of dependent behavior, *chronic* drug intake is associated with neuroadaptation of glutamatergic neurotransmission in the ventral striatum and limbic cortex (McFarland et al., 2003; Vorel et al., 2001). After alcohol withdrawal, cue exposure may stimulate an attentional response towards cues regularly associated with drug intake via glutamatergic neurotransmission in the prefrontal cortex and ventral striatum (Kalivas and Volkow, 2005) and NMDA receptor antagonist may therefore play an important role in the treatment of alcoholism (Krystal et al., 2003).

Low presynaptic dopamine production and release and down-regulated D2 receptors in the ventral striatum (Heinz et al., 2004, 2005; Martinez et al., 2005) may interfere with the ability of detoxified alcoholics to adequately respond to new, reward-associated stimuli. Therefore, alcoholics may suffer from a deficit in the anticipation of non-alcohol associated reward and instead may crave alcohol-associated effects during exposure to alcohol cues. However, this does not mean that activation in the ventral striatum is the sole or at least primary source of craving. In cocaine addicts, PET studies have shown that decreased dopamine release in the striatum results in *reduced* baseline activation in the orbitofrontal cortex and the cingulate gyrus but *enhanced* activation in these same regions in response to drug-related cues, which was correlated with drug

Table 4
Brain activation elicited by alcohol pictures>neutral pictures (CON=controls, ALC=alcohol-dependent patients)

	Region	Talairach coordinates				
		left/right	*x*	*y*	*z*	*t*-value
Controls	–	–	–	–	–	–
Alcoholics	Ventral striatum	right	20	4	0	4.17
	Thalamus	left	−4	−19	1	5.08
	Middle occipital gyrus, BA 19	right	32	−77	22	5.00
	Posterior cingulate, BA 29	right	8	−50	10	4.99
	Middle temporal gyrus, BA 21	left	−63	−31	−5	4.64
	Superior temporal gyrus, BA 22	right	63	−38	13	4.47
CON>ALC	–	–	–	–	–	–
ALC>CON	Thalamus	right	4	−27	5	4.83
	Middle occipital gyrus, BA 19	left	−36	−85	8	4.77
	Precuneus, BA 31	left	−21	−69	22	4.18
	Middle temporal gyrus, BA 39	left	−36	−65	22	3.98

craving (Volkow et al., 2004). A comparable pattern was observed in this study, but in the ventral striatum. While fMRI cannot address potential monoaminergic correlates of the observed alterations in the cue-elicited BOLD response, future multimodal studies that combine functional brain activation and neuroreceptor imaging may help to elucidate the neurotransmitter correlates of altered reward system activation in alcoholics.

Exploratory analysis revealed that alcohol cues in alcoholics also elicited increased activation in the thalamus, posterior cingulate cortex, temporal cortex, and in areas associated with visual processing such as the middle occipital gyrus. It has previously been shown that emotionally salient stimuli, in contrast to neutral ones, strongly activate areas associated with visual processing (Lang et al., 1998). As in the present study, these brain areas were also activated by alcohol cues in previous studies (Grusser et al., 2004; Tapert et al., 2004; Braus et al., 2001). In alcoholics, increased brain activation elicited by alcohol pictures was observed in the thalamus, which conveys sensory input to the frontal cortex (George et al., 2001; Wrase et al., 2002), and this activation was reduced by a single dose of the dopamine D2 receptor antagonist amisulpride (Hermann et al., 2006). The posterior cingulate has previously been implicated in processing of alcohol- and drug-related stimuli (Garavan et al., 2000; Kosten et al., 2006; Tapert et al., 2003) and is thought to function as a rapid relay for incentive valuation and episodic memories (Kosten et al., 2006). Altogether, these additional brain areas may participate in incentive salience attribution to visual cues associated with alcohol.

Exploratory analyses also revealed greater activation in healthy controls than in alcoholics in posterior putamen and caudate head during the anticipation of monetary gain. In alcoholics, reduced activation of these brain areas was not correlated with the severity of alcohol craving, while the failure to activate the ventral striatum was associated with stronger alcohol urges. The caudate has been implicated in linking reward to behavior (Knutson and Cooper, 2005) and could be associated with greater learning benefit from reward in healthy controls. Interestingly, anticipation of both gain and loss elicited stronger activation of the orbitofrontal cortex and thalamus in alcoholics. These hyperactivations may compensate for dysfunction of the ventral striatum. Altered connectivity between the OFC and limbic brain areas has been described in opiate addicts (Daglish et al., 2003). Further studies should assess the connectivity between frontal and subcortical brain areas in alcoholism and its possible contribution to alcohol craving.

A potential limitation of the study is a difference in cigarettes smoked per day between alcoholics and controls. However, in this sample, cigarettes smoked per day did not correlate significantly with activation observed in the ventral striatum. Previous fMRI studies showed that patients and control subjects have to be matched for task performance, because the task-dependent BOLD response can be modulated by this parameter (Callicott et al., 2003). Therefore we matched controls and alcohol-dependent patients for hit rate and amount of money gained and for their effort to achieve monetary gains and to avoid loss. Since money is a secondary reinforcer, it would be interesting to assess whether alcoholics also show alterations in brain activation elicited by primary reinforcers.

Taken together, these findings suggest that detoxified alcoholics failed to activate the ventral striatum during the anticipation of conventional monetary rewards, and this decreased activation was associated with alcohol craving. On the other hand, alcoholics displayed increased activation of the ventral striatum when confronted with alcohol cues, and this increased activation was associated with alcohol craving. Since alcoholics' ventral striatal recruitment appears to be biased towards processing of alcohol cues, alcoholics may find it particularly difficult to focus on conventional rewards, and thus may find it difficult to seek and enjoy alcohol-free situations. Further studies will have to examine the role of this reprioritization of ventral striatal recruitment on the risk for relapse in detoxified alcoholics, and whether long-term abstinence or therapy can facilitate a normalization of reward processing.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2006.11.043.

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