Imaging alcohol cue exposure in alcohol dependence using a PET $^{15}$O-$\text{H}_2\text{O}$ paradigm: results from a pilot study

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**ABSTRACT**

Craving is a commonly used term to describe an intense desire for a substance or behaviour; however, its underlying neurobiology is not fully characterized. We have successfully used a cue exposure paradigm with functional neuroimaging ($\text{H}_2^{15}\text{O}$ PET; PET, positron emission tomography) in abstinent opiate addicts. This study showed that salient cue exposure results in activation in the left anterior cingulate/mediofrontal cortex and elicited craving correlated with activity in the left orbitofrontal cortex. We therefore aimed to replicate this study in alcohol dependence to see if a similar pattern of neural activation occurred. We recruited six abstinent alcohol-dependent and six non-dependent subjects who each underwent a 12-run PET scan using $\text{H}_2^{15}\text{O}$ to measure changes in regional blood flow during exposure to an alcoholic drink or its visually matched non-alcoholic drink. Physiological data and subjective ratings were also recorded. Statistical parametric mapping (SPM99) was used to analyse the PET images. Compared with control subjects, abstinent alcohol-dependent subjects rated their alcohol craving higher at baseline and throughout the study, but there was no significant change in the scores in response to the cues in either group. SPM analysis across all subjects showed significant activation in the occipital cortex in response to the alcohol cue as compared with the neutral one. Analysis of the same regions that were activated in the opiate study, revealed significant increases in signal activation in the left medial prefrontal area, but only in abstinent alcohol-dependent subjects. In conclusion, in abstinent alcohol dependence we suggest that a simple cue exposure paradigm is not sufficiently powerful in functional imaging studies to determine the underlying neurobiology of subjective craving. Comparisons with the finding in opiate dependence suggest a shared region, the anterior cingulate/ left medial prefrontal cortex is involved in the cue response in dependent subjects but not controls.

**Keywords** Alcohol, craving, cue-exposure, dependence, neuroimaging, PET.

**INTRODUCTION**

Craving is a term widely used by both patients and clinicians to describe a phenomenon linked to an intense desire for a drug of choice. It is complex to study and there is no one accepted research definition (Kozlowski & Wilkinson 1987). In order to understand craving more, the cue exposure paradigm has been extensively used to induce a state of conditioned craving while measuring subjective and objective responses (Drummond 2000). More recently, functional neuro-imaging approaches have increasingly been applied to characterize neural activation evoked by craving for drugs such as opiates and cocaine, and now alcohol.

Most imaging studies of cue exposure paradigms have elicted craving for cocaine and patterns of activation have been consistent, with activation generally seen in the anterior cingulate cortex, the amygdala and...
dorsolateral prefrontal cortex (Grant et al. 1996; Maas et al. 1998; Childress et al. 1999; Wang et al. 1999; Garavan et al. 2000; Kilts et al. 2001, 2004; Wexler et al. 2001; Bonson et al. 2002). In our functional neuro-imaging study of cue exposure and craving in abstinent opiate addicts, we used an individualized salient auditory cue (Daglish et al. 2001). Exposure to this cue compared with a neutral one was associated with activation in the left medial prefrontal and left anterior cingulate cortices and deactivation in the occipital cortex. In addition, craving elicited during the procedure positively correlated with activity in the left orbitofrontal cortex and later connectivity analyses showed that this was associated with changes in other drive-related brain regions (Daglish et al. 2003). Activation of the orbitofrontal cortex has been seen in some studies of cocaine craving (Grant et al. 1996; Wang et al. 1999) and also in another study of opiate craving (Sell et al. 2000). Therefore, it appears that there are many similarities in the patterns of neural activation associated with cue exposure and craving in cocaine and opiate dependence.

Early studies using neuro-imaging to determine the pattern of neural activation in alcohol dependence revealed less consistency in the patterns of activation. For instance, in alcohol-dependent individuals, increased desire to drink was shown to correlate with increased blood flow in the right caudate nucleus (Modell & Mountz 1995), or that cue exposure activated the anterior thalamus and prefrontal cortex (George et al. 2001), the right amygdala/hippocampal area and cerebellum (Schneider et al. 2001) or the ventral putamen (Braus et al. 2001).

We have successfully developed a cue exposure paradigm that, under laboratory conditions, can induce craving for alcohol using visual alcohol cues or with scripts or imagery in abstinent alcohol-dependent individuals (Weinstein et al. 1998). This study suggested that we had a robust cue exposure paradigm that could be used with neuro-imaging. We therefore replicated our neuro-imaging study of opiate cue exposure to explore the pattern of neural activation to a salient cue in alcohol dependence to test the hypothesis that a similar pattern of neural activation would occur with cue exposure and craving with alcohol as with opiate dependence.

**MATERIALS AND METHODS**

**Subjects**

Six male abstinent alcohol-dependent subjects who fulfilled DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition) for alcohol dependence were recruited from local alcohol treatment services. They had to be abstinent for at least 6 weeks. A control group of six male subjects who had never fulfilled such criteria, i.e. non-dependent alcohol drinkers, were recruited through colleagues and advertisements. All subjects were right handed. They had no history of other major psychiatric illness and were taking no psychotropic medication at the time of the study (except for one alcohol-dependent subject who was taking amitriptyline). Subjects with clinical evidence of hepatic, cognitive or neurological impairment or medical disorder were excluded.

All subjects were assessed for their severity of dependency [the severity of alcohol dependency questionnaire (SADQ), Stockwell, Murphy & Hodgson 1983]. Anxiety and depression were assessed prior to the positron emission tomography (PET) scan [Beck’s depression inventory (BDI), Beck et al. 1961; Spielberger state anxiety inventory (SSAI) and Spielberger—trait anxiety inventory (STAI), Spielberger 1983]. Prior to the scan, craving for alcohol was rated using the obsessive compulsive drinking scale (OCDS, Anton, Moak & Latham 1996) and alcohol craving questionnaire (ACQ) derived from Tiffany’s craving questionnaire (see Love, James & Willner 1998). The ‘Urge to Use’ questionnaire (Bahn, Krahn & Staehe 1995) was used to assess changes in craving during the scanning procedure because this could be delivered in the short space of time available. This is an eight-item self-completion questionnaire containing items representing three domains of drinking urges, desire for a drink (four items), expectation of positive effect from drinking (two items) and inability to avoid drinking if alcohol was available (two items). Two items from the ACQ were also used to assess negative reinforcement. These were ‘Alcohol would make me feel less jittery’ and ‘If I used alcohol right now, I would feel less tense’. Subjects are asked to indicate their agreement or disagreement with each statement by stating where they felt on a Likert-type scale between strongly disagree (1) and strongly agree (7). Two items are reversed. Because of technical reasons, a small number of questionnaires were unable to be accurately scored. An independent sample t-test (two-tailed) was used to compare the two groups with the SPSS statistical package (SPSS Inc., Chicago, IL, USA).

Prior to the PET scanning session, subjects selected their preferred alcoholic drink from a list and this was used as an alcohol stimulus. From a second list of non-alcoholic drinks, they were asked to indicate if any were associated with alcohol. From the remaining list, a non-alcoholic drink, visually matched to their alcoholic drink but not associated with it, was chosen as a control stimulus (e.g. vodka: water). There was no olfactory stimulus because both stimuli were in sealed original packaging.

The study was approved by the appropriate Local Ethics and Research Committees and the Administration of Radioactive Substances Advisory Committee. After full
explanation of the study, written informed consent was obtained from all subjects.

Scanning protocol

Each subject underwent a 12-run PET scan of regional cerebral blood flow (rCBF) using the tracer \(^{15}\)O-H\(_2\)O, with a slow bolus technique. Each run lasted 8 minutes with the total scanning procedure lasting 1.5 hours. A brain dedicated ECAT EXACT 3D HR++ PET camera (CTI/Siemens, Knoxville, TN, USA) was used, operating in high-sensitivity 3D mode. Briefly, this scanner consists of six rings of standard detector blocks with \(4.39 \times 4.05 \times 30\) mm elements giving an axial field of view of \(2.3.4\) cm. Thus, data from the whole brain can be simultaneously acquired. The mean spatial resolution is \(4.8 + 0.2\) mm full width half maximum in plane and \(5.6 + 0.5\) mm axially.

A black box was mounted above the scanner, in the centre of the field of view of the subjects, at a distance of approximately 60 cm. Prior to each scan run, one of the preselected drinks (alcoholic or non-alcoholic) was concealed within the box. Immediately prior to the uptake of tracer into the brain, the door of the box was drawn back to reveal the drink. Image acquisition began 15 seconds after the presentation of the stimulus to allow craving to be induced in response to the stimulus. Images were acquired in a single 90 seconds frame during which the drink remained in view. Each stimulus was presented six times in random order. Actual bottles or cans were used as the stimuli and when seen, subjects were asked to imagine drinking it.

The modified ‘Urge to Use’ questionnaire (Bohn et al. 1995) was administered 1 minute before and 2 minutes after stimulus presentation. During the scanning session, physiological data were collected using a Finapres® Ohmeda which non-invasively measures pulse and blood pressure continuously from a finger probe.

Image analysis

The PET images of rCBF were analysed using the statistical parametric mapping (SPM99) software package (Welcome Department of Cognitive Neurology, London, UK). The 12 images for each subject were realigned to a mean image for that subject. This partially corrects for motion of the subject between the 12 scans. Realigned images were normalized to a standardized template \(^{13}\)O-H\(_2\)O PET image in Montreal Neurological Institute space. The resultant realigned normalized images were then smoothed with a Gaussian function at \(12\) mm full width half maximum.

For the statistical analysis using SPM, the images were analysed using a cognitive subtraction and a correlational analysis. A condition comparison was carried out with the stimulus type (alcoholic or non-alcoholic) determining the conditions. For the correlational analysis, all the subjective scores derived from modified ‘Urge to Use’ questionnaire (Bohn et al. 1995) were averaged to produce a composite ‘craving’ score. This composite ‘craving’ score was then used as a covariate of interest to examine areas of rCBF that covaried with subjective craving. These analyses were performed on all the subjects together and within each group. In addition, a comparison between the control and alcohol-dependent groups was performed using a mean image for each subject of all 12 scans and covarying for ACQ score, OCDS score, STAI, STAI and BDI score individually.

In these SPM analyses, time from the start of the first scan was entered as a covariate of no interest to take account of any rCBF changes that were related to time-related factors. All covariates were centred around subject means, and entered with a subject-specific fit. Global cerebral blood flow effects were removed by ANCOVA model allowing a subject-specific fit. As commonly performed for SPM analyses, where no a priori hypothesis exists, the threshold for statistical significance for all analyses was set at \(P < 0.05\) after correction for multiple comparisons for either peak change in rCBF or the size of the activated cluster (Friston et al. 1995).

To explore whether there was any activation in response to the alcohol cue in order to determine whether this protocol was worthy of further development, we also performed a hypothesis-led SPM analysis using results from our previous opiate-led SPM analysis using results from our previous opiate study (Daglish et al. 2001). In this study, we found that cue exposure was associated with increased rCBF in the left anterior cingulate/medial prefrontal cortex and craving with increased rCBF in the left orbitofrontal cortex. Therefore, in these regions, a sphere of \(12\) mm radius was specified, at the following Talairach coordinates \(±10, 46, 20\) mm (left anterior cingulate gyrus) and \(±26, 42, ±14\) mm (left orbitofrontal region). A sphere of \(12\) mm was chosen because this was the size of the smoothing kernel in both the opiate and present study. This reduces the level of correction for multiple comparisons to include only the specified regions as opposed to the whole brain volume. This increases the sensitivity of the analyses in these regions (Friston 1997).

RESULTS

Clinical and demographic details

The clinical and demographic details are described in Table 1. There was no significant difference in the age of the non-dependent and abstinent dependent alcohol drinkers. The length of abstinence ranged from 7 weeks to 1.5 years (mean ± SD: 27.33 ± 27.32; median: 12.5 weeks). As expected, SADQ scores were significantly...

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higher in the alcohol-dependent than non-dependent group (see Table 1, \( p < 0.01 \)) where a score of over 31 indicates severe dependency. The scores on two measures of craving for alcohol, the OCDS and ACQ, were also significantly higher in abstinent alcohol-dependent drinkers than non-dependent drinkers (see Table 1, \( p < 0.05 \)). While the level of anxiety prior to the scanning procedure was no different between the groups, the trait anxiety levels in the abstinent alcohol-dependent group were higher (see Table 1, \( p < 0.05 \)). Lastly, the abstinent alcohol-dependent group showed significantly higher depression scores (see Table 1, \( p < 0.05 \)); however, none met diagnostic criteria for major depression.

### Physiological

No differences were seen between the groups in baseline measures of the parameters measured (pulse rate, systolic and diastolic blood pressure, interbeat interval, beat-to-beat variability; see Table 2).

#### Changes during scanning procedure

**Subjective**

Scores derived from the modified Bohn et al. (1995) ‘Urge to Use’ questionnaire, reflecting craving, were significantly higher in the alcohol-dependent group compared with the non-dependent group throughout the study (\( p < 0.05 \), one-tailed \( t \)-test). For example, the mean ± SD of alcohol urge questionnaire (AUQ) score prior to either stimulus in the alcohol-dependent group was 32.15 ± 13.2 and in the non-dependent group 17.6 ± 10.4. This is comparable to a mean AUQ score of 28 reported by a community alcohol-dependent population (Drummond & Phillips 2002). Figure 1 shows the mean scores in alcohol-dependent and control groups for each repetition of each stimulus condition before and after the stimulus exposure. However, exposure to the salient alcohol cue did not result in significantly increased craving scores in either group. There was a visible trend for the alcohol-dependent group to show a small increase in subjective craving following the alcohol stimulus and a small decrease following the neutral stimulus. This distinction was not seen in the control group.

**Physiological**

No changes were seen in any of the parameters measured (pulse rate, systolic and diastolic blood pressure, interbeat interval, beat-to-beat variability) in either group during the procedure. As an example, data from the second presentation of the stimulus, over 45 seconds, were described in Table 2. Data from other stimulus presentations were similar.

#### Image analysis

The first analysis compared rCBF in response to the alcohol stimuli with response to the non-alcoholic stimuli in

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**Table 1** Patient demographic details.

<table>
<thead>
<tr>
<th></th>
<th>Non-dependent alcohol drinkers</th>
<th>Abstinent alcohol-dependent drinkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.3±7.7</td>
<td>41.3±7.6</td>
</tr>
<tr>
<td>SADQ (N: 6, AD: 5)</td>
<td>2.25±1.9</td>
<td>31.8±12*</td>
</tr>
<tr>
<td>OCDS (N: 6, AD: 6)</td>
<td>4.8±2.2</td>
<td>16.67±3.2*</td>
</tr>
<tr>
<td>ACQ (N: 5, AD: 5)</td>
<td>68.6±29</td>
<td>144±46*</td>
</tr>
<tr>
<td>BDI (N: 5, AD: 5)</td>
<td>2.0±3.1</td>
<td>17.5±7.5*</td>
</tr>
<tr>
<td>STAI (N: 6, AD: 4)</td>
<td>39.3±5.4</td>
<td>55.8±11*</td>
</tr>
<tr>
<td>SSAI (N: 5, AD: 5)</td>
<td>33±7.2</td>
<td>39.5±9.4</td>
</tr>
</tbody>
</table>

*Significantly different (\( p < 0.05 \)) comparison between non-dependent and dependent alcohol drinkers. Demographic details of subjects. The results are mean ± SD. Two-tailed \( t \)-tests were used. N = number of non-dependent; AD = number of alcohol-dependent questionnaires available for analysis; SADQ = severity of alcohol dependency questionnaire; OCDS = obsessive compulsive drinking scale (Anton et al. 1996); ACQ = alcohol craving questionnaire (in Love et al. 1998); BDI = Beck’s depression inventory; STAI = Spielberger trait anxiety inventory; SSAI = Spielberger state anxiety inventory.

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**Table 2** Mean autonomic responses recorded beat-by-beat monitoring throughout the study.

<table>
<thead>
<tr>
<th></th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
<th>Heart rate (b.p.m.)</th>
<th>Heart rate variability (SD of heart rate)</th>
<th>Beat-to-beat variability (mean of interbeat differences)</th>
<th>Beat-to-beat variability (SD of interbeat differences)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-dependent subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol cue</td>
<td>121.7±13.1</td>
<td>76.5±9.5</td>
<td>63.4±1.8</td>
<td>2.5±0.3</td>
<td>33.3±4.5</td>
<td>25.8±3.2</td>
</tr>
<tr>
<td>Non-alcohol cue</td>
<td>131.1±14.2</td>
<td>78.9±11.6</td>
<td>62.6±2.8</td>
<td>2.6±0.3</td>
<td>32.2±3.7</td>
<td>26.1±3.2</td>
</tr>
<tr>
<td><strong>Alcohol-dependent subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol cue</td>
<td>131.2±12.5</td>
<td>76.0±8.8</td>
<td>73.6±5.5</td>
<td>4.7±1.1</td>
<td>46.9±12.3</td>
<td>55.3±20.5</td>
</tr>
<tr>
<td>Non-alcohol cue</td>
<td>127.2±12.9</td>
<td>73.7±9.0</td>
<td>72.7±4.6</td>
<td>4.9±1.0</td>
<td>50.0±12.3</td>
<td>51.4±19.5</td>
</tr>
</tbody>
</table>

Second presentation of cue, values for 0–45 seconds after presentation. Results are presented as mean±SD. *Corrected to heart rate of 60 b.p.m. BP = blood pressure. b.p.m. = beats per minute.
all subjects. This showed a significant increase in rCBF in the fusiform gyrus of the visual cortex bilaterally. This effect was only statistically significant when all the subjects were analysed together but not separately, although the direction of the response appeared consistent across both the alcohol-dependent and control groups. This increase was statistically significant on the left side (Talairach coordinates $-20, -92, -7$ mm, $t = 3.81$, number of voxels $= 208$, cluster-level $P < 0.05$). A trend towards significance was seen on the right side (Talairach coordinates $24, -88, -2$ mm, $t = 3.96$, number of voxels $= 168$, cluster-level $P = 0.09$). There were no significant differences when the two groups were compared.

No correlational analysis was undertaken because no changes in craving, derived from the modified ‘Urge to Use’ questionnaire, were reported.

In our final hypothesis-led analysis, changes in rCBF were investigated within 12-mm-radius spheres centred on the regions that showed significant activation following cue exposure in our previous opiate craving study (Daglish et al. 2001). In the sphere centred on the left anterior cingulate cortex, the comparison of rCBF responses to the alcohol and non-alcohol stimuli showed a significant increase in rCBF in the alcohol-dependent group only. This increase was located in the left medial prefrontal region (Brodmann area 9) (Talairach coordinates $-18, 50, 25$ mm, $t = 3.23$, voxel-level $P = 0.038$, corrected for multiple comparisons within the 12-mm-radius sphere). There was no significant difference between the control and abstinent alcohol-dependent groups when activation effects in this region of interest were compared. Figure 2 shows the relative changes in rCBF in the left mediofrontal region for each individual participant. The change in rCBF in response to the alcohol stimuli was consistent in five of the six alcohol-dependent subjects, with a relative increase in rCBF in response to the alcohol stimuli. Less relative activation to the alcohol stimuli was seen in the control subjects with two subjects showing the reverse (see Fig. 2). No such pattern of activation was seen in the sphere centred on the left orbitofrontal cortex.

None of the reported significant activations above were related to depression or anxiety because where we found significant rCBF changes, no activation was seen here that correlated with scores from the BDI, STAI or SSAI. In addition, no significant effect of the BDI score was found when comparing the control and alcohol-dependent groups using a mean image for each subject of all 12 scans.

**DISCUSSION**

We have shown in this study that exposure to a salient visual alcohol cue is associated with increased regional blood flow (rCBF) in the visual cortex in both alcohol-dependent and non-dependent subjects. Restricting analysis to areas where we had an a priori hypothesis from our opiate craving study (the left anterior cingulate/mediofrontal cortex and orbitofrontal cortex) revealed increased rCBF in the left medial prefrontal cortex in abstinent alcohol-dependent subjects only. No such activation was seen in the social alcohol drinkers nor in the orbitofrontal cortex in either group. No cardiovascular changes were seen either. Despite using a cue exposure protocol that had successfully induced cardiovascular and subjective changes, including craving, outside the scanner, the same paradigm failed to generate similar responses during the neuro-imaging procedure.

The changes in blood flow seen occurred in regions of the brain consistent with a visual cue exposure paradigm. The increased blood flow in the occipital cortex (primary visual and visual association areas) in both the control and alcohol-dependent groups is likely to represent perception of the alcohol cue and also maintenance
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of selective or sustained attention to it (Cabeza & Nyberg 2000; Kastner & Ungerleider 2000). The activation in the left mediofrontal cortex (Brodmann area 9) found only in abstinent alcohol-dependent subjects is consistent with our previous findings in opiate dependence and others in cocaine cue exposure (e.g. Childress et al. 1999; Daglish et al. 2001; Wexler et al. 2001). Brodmann area 9 has also been described to correspond to the dorsolateral prefrontal cortex (Fletcher & Henson 2001). This is interesting because this area has been reported to be activated by cocaine cues in addicts in some but not all studies (Grant et al. 1996; Maas et al. 1998; Childress et al. 1999; Wexler et al. 2001). However, where activation was reported, the area appeared more lateral than that reported here. The medial prefrontal area plays a role in processing positive or negative emotions (Lane et al. 1997; Reiman et al. 1997) and is also a brain region whose metabolism is altered by drugs of abuse, e.g. opiates (Schlaepfer et al. 1998), cocaine (Breiter et al. 1997) and also alcohol (Schreckenberger et al. 2004). This area of the brain has been shown to be activated in patients with 'working memory', particularly when reflective demands of the memory task are relatively complex (Nolde, Johnson & Raye 1998; Cabeza & Nyberg 2000; Fletcher & Henson 2001). Therefore, it is not unexpected that a region involved in attention, memory and emotion is activated in alcohol-dependent subjects exposed to a salient alcohol cue.

Comparing our pilot study with other similar neuroimaging studies using alcohol-related cues reveals both similarities and differences in brain regions activated. The first study found increased activation in the head of the right caudate in abstinent (1–6 weeks) alcohol-dependent subjects that correlated with elicited craving induced by sips of alcohol and imagery (Modell & Mountz 1995). Using alcohol pictures with sips of alcohol, George et al. (2001) reported increased activation in the anterior thalamus and prefrontal cortex in non-treatment-seeking alcohol-dependent subjects to these alcohol cues. In a follow-up study, activation in the nucleus accumbens, ventral tegmental area, insula and anterior cingulate cortex was reported to the alcohol cues and craving correlated with activity in the nucleus accumbens, anterior cingulate and orbitofrontal cortices (Myrick et al. 2004). Using alcohol odour as their cue to study craving for alcohol in recently abstinent patients, Schneider et al. (2001) described increased activity in the right amygdala/hippocampal area and cerebellum which was no longer present after 3 weeks of treatment with cognitive-behavioural therapy and a tricyclic antidepressant, doxepin. Another series of studies using pictures showed activation in areas including the visual

Figure 2. Graph showing the direction and relative change in rCBF in the left medial prefrontal cortex (Brodmann area BA9, Talairach coordinates: −18, 48, 23) in response to the alcohol or control stimulus for each individual subject. The direction and relative change in rCBF in the left medial prefrontal cortex in each individual subject in response to a salient alcohol stimulus (light grey bars + standard error for the 6 repetitions) in contrast to a neutral stimulus (dark grey bars + standard error for the 6 repetitions) within the 12-mm-radius sphere placed as described in the paper. In all alcohol-dependent subjects, except subject 6, relative increases in rCBF were seen in response to the alcohol cue. By contrast, in the non-dependent subjects, less relative activation is present and in subjects (9 & 11) a decrease is seen in response to the alcohol cue. rCBF = regional cerebral blood flow.
system, orbitofrontal cortex, anterior cingulate/medial prefrontal cortex and ventral striatum to alcohol cues in abstinent alcohol-dependent patients (Braus et al. 2001; Wrase et al. 2002; Grüsser et al. 2004). Activation of the anterior cingulate and left prefrontal cortices was also seen in alcohol-dependent women in response to alcohol-related words (Tapert et al. 2004).

Therefore, common areas activated by salient alcohol visual cues in abstinent alcohol-dependent subjects in our study and others include the anterior cingulate/medial prefrontal cortex and visual cortex. While not seen in our study, other groups have reported activation of the ventral striatum, a region implicated in drug dependence in both animals and humans (see Koob, Sanna & Bloom 1998).

The variation in the brain regions seen gives us the opportunity to learn more about neural responsivity associated with cue reactivity in alcohol dependence. In the present study, the length of abstinence ranged from 7 weeks to 1.5 years, while in the other studies it ranged from 1 day (George et al. 2001; Myrick et al. 2004) to around 1 week (Braus et al. 2001; Schneider et al. 2001) to around 7 weeks (Grüsser et al. 2004). Grüsser et al. (2004) reported no association between the degree of activation and length of abstinence, whereas in our opiate study, longer periods of abstinence were associated with greater activation in the anterior cingulate cortex (Daglish et al. 2001). It is also noteworthy that although other studies (Braus et al. 2001; Schneider et al. 2001) have described reduced cue-induced brain activation with increasing abstinence, these studies did not explicitly recruit patients reporting problems with craving as we did, but rather followed up patients after detoxification and in treatment. Nevertheless, it may be that using individuals with the longest period of abstinence compared with the other studies may have reduced their cue reactivity. To address this potential confound, we had selected patients who described problems with craving and also those with high SADQ and OCDS scores which are associated with greater levels of craving (Drummond 2000). Indeed, the mean score derived from the OCDS was higher in the present study than that reported by George et al. (2001) or Myrick et al. (2004).

An important issue relates to the lack of provoked craving in our study. One reason may be that our subjects were in an abstinence-focused programme and this may have reduced the likelihood of their responding to the cue exposure (though they still had higher levels of baseline craving). It may also have prevented them from acknowledging such a response to the alcohol cue and caused dissociation between their subjective experience and objective responses. However, most other neuro-imaging studies have similarly used individuals in inpatient and outpatient treatment facilities, although George et al. (2001) and Myrick et al. (2004) used non-treatment-seeking alcohol-dependent individuals in their studies. Recently, Wilson, Sayette & Fiez et al (2004) reviewed neuro-imaging studies of cue-elicited craving, including the protocols used in the studies described here, and emphasized the influence of treatment-seeking status on regions activated. In particular, activation of the dorsal-lateral prefrontal and orbitofrontal cortices were seen in studies of active drug users compared with those in treatment. Of note, a study in cocaine dependence reported that methylphenidate induced activation of the orbitofrontal cortex only occurred in some individuals and was associated with craving (Volkow et al. 1999). Therefore, activation of the orbitofrontal cortex appears to be directly linked to the subjective experience of craving.

It has been recognized that cue-specific craving effects for alcohol are less robust than craving effects for other drugs (Tiffany, Carter & Singleton 2000) and even in studies of opiate and cocaine craving using neuro-imaging, only two-thirds reported craving (Daglish et al. 2001; Wexler et al. 2001). It is noteworthy that the other neuro-imaging studies reporting activation associated with craving, used sips of alcohol or alcohol odour in patients just detoxified from alcohol or sips of alcohol in non-treatment-seeking alcohol-dependent patients (Modell & Mountz 1995; George et al. 2001; Schneider et al. 2001; Myrick et al. 2004). Similarly to the present study, Heinz’s group used pictures as cues (Braus et al. 2001; Wrase et al. 2002; Grüsser et al. 2004). They focused on the relationship between activation and relapse, but noted that baseline craving prior to the scan did not correlate with degree of activation nor did the subjective ratings of arousal or valence in response to the cue. Consequently, it appears that cue exposure paradigms using ‘simple’ cues such as pictures or the actual preferred drink, even if they are salient and individualized, may not be sufficiently strong enough to elicit ‘craving’ in abstinent alcohol-dependent subjects in the scanning situation especially in patients currently receiving treatment for their dependence.

In conclusion, we evaluated whether a ‘simple’ cue exposure paradigm of seeing their favourite alcoholic drink could be used with functional neuro-imaging to determine neural activation associated with cue exposure and craving in abstinent alcohol-dependent patients. We found that cue exposure elicited changes in brain activation but, unlike our study in opiate addiction, it did not generate craving in an ‘on-off’ manner, rather craving was consistently higher throughout. We suggest that neuro-imaging studies to investigate craving for alcohol in abstinent dependent patients attending an outpatient abstinence-focused treatment programme may require more robust procedures than simple cue exposure to induce changes in craving. In addition, understanding...
the influence of variables such as treatment status, context, involvement of affective or cognitive processes will not only help to optimize suitable protocols but also inform us about what contributes to experiencing craving.

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