Alcohol & Alcoholism Vol. 42, No. 5, pp. 417–422, 2007
Advance Access publication 16 February 2007
doi:10.1093/alcalc/agl117

BRAIN SUBSTRATES OF CRAVING TO ALCOHOL CUES IN SUBJECTS WITH ALCOHOL USE DISORDER

MI-SOOK PARK[1], JIN-HUN SOHN[1,*], JI-A SUK[1], SOOK-HEE KIM[2], SUNJU SOHN[3] and RICHARD SPARACIO[2]

[1]Department of Psychology, Brain Research Institute, Chungnam National University, Daejeon, South Korea, [2]Army Substance Abuse Program, US Army, South Korea and [3]School of Social Work, University of Texas Austin, TX, USA

(*Received* 24 *November* 2006; *accepted* 6 *December* 2006; *advance access publication* 16 *February* 2007)

Abstract — Aims: This study's purpose was to identify the neural substrates and mechanisms responsible for craving among subjects with alcohol use disorders (AUDs) using functional magnetic resonance imaging (fMRI). **Methods:** Alcohol abusers with AUD ($n = 9$) and demographically similar non-abusers ($n = 9$) participated in this study. After given 5 cc of alcohol, subjects were exposed to different types of stimuli [i.e. alcohol, non-alcoholic beverage, and visual control pictures and one rest (cross-hair)]. Craving levels were rated through self-report on a Likert scale immediately after the presentation of visual cues. **Results:** Brain activations in the fusiform gyri, temporal gyri, parahipocampal gyrus, uncus, frontal gyri, and precuneus were correlated with the level of craving among subjects with AUD in response to alcohol cues. **Conclusions:** In conclusion, specific brain regions were identified that are associated with craving among subjects with AUD.

INTRODUCTION

Alcohol and other drug abuse facilitate dopamine release in the ventral striatum which includes the nucleus accumbens, a core region of the brain reward system (Heinz *et al*., 2004). Neurons located in the nucleus accumbens extend to both the amygdala and the frontal cortex areas (Anton, 1999). One of the frontal cortex areas is the dorsolateral prefrontal cortex (DLPFC) where the reward memory of alcohol use is thought to be located (Kalivas *et al*., 1998). Situations or stimuli previously associated with alcohol use may activate the reward system and induce craving (Anton, 1999). Since craving plays a role to trigger compulsive drug/substance use among active users and relapse among those in recovery there is a need for improved understanding of underlying neurobiological mechanisms (Schneider *et al*., 2001).

Neuroimaging techniques, e.g. functional magnetic resonance imaging (fMRI) and PET, have helped to identify the brain regions associated with craving. It has been known that viewing cocaine images is associated with a relative increase in regional brain activity (Grant *et al*., 1996; Breiter *et al*., 1997; Childress *et al*., 1999). Brain regions known to be involved in reward (the nucleus accumbens), arousal (the medial temporal lobes, cingulate gyrus), memory (the DLPFC), and sensory integration (thalamus) were activated during the exposure to cocaine cues.

Relatively few studies to date have identified the brain areas associated with alcohol craving. Modell and Mountz (1995) reported increased blood flow in the right caudate nucleus during a craving condition in alcoholics. George *et al*. (2001) evaluated regional brain activity in both alcoholics and social drinkers using both taste and visual cues. Alcoholics had increases in brain activation in the anterior thalamus and left DLPFC, while the social drinkers did not. Recently, Tapert *et al*. (2003) identified the relationship between a self-reported desire to drink and brain response using visual cues in adolescents with alcohol use disorder (AUD). They found a strong desire for drinking to be associated with both left temporal and right thalamic responses. Myrick *et al*. (2004) reported activation on the prefrontal cortex and anterior limbic regions in alcoholics during exposure to alcohol cues. These studies identified the differences in brain activation areas between the two groups, alcoholics and the control group. However, reported results were inconsistent. A more recent study by Myrick *et al*. (2004) reported a positive correlation between the level of craving and brain activations. Brain activations in the left nucleus accumbens, the anterior cingulate and the left orbitofrontal cortex were correlated positively with cravings in alcoholics.

Initially, we examined differences in craving and brain activations between AUDs and non-alcoholic control subjects when exposed to a variety of visual alcohol cues.

Secondly, using the methodology of the Myrick *et al*. (2004) study, this study was conducted to extend the results of these earlier researchers to include both alcoholics and alcohol abusers.

METHODS

Participants

Eighteen right-handed never married male and female college students participated in the study: nine were diagnosed with AUD [i.e. DSM-IV (American Psychiatric Association, 1994) criteria for alcohol abuse or dependence]. The Korean version of Alcohol Use Disorders Identification Test (AUDIT-K) (Lee, 2000), National Alcoholism Screening Test (NAST) (Kim *et al*., 1991), and a Structured Clinical Interview based on the DSM-IV (Hahn *et al*., 2000) were administered to evaluate substance use among alcoholic subjects. Based on AUDIT-K and NAST results, all alcoholic subjects met the DSM-IV criteria for AUDs. A score >15 points on the AUDIT-K is considered sufficient to meet the DSM-IV criteria for AUDs (Park *et al*., 2000). A positive response to more than one item on the NAST is considered sufficient to meet DSM-IV criteria for AUDs (Park *et al*., 2000). The control group was composed of nine subjects who were

*Author to whom correspondence should be addressed at: Jin-Hun Sohn, Department of Psychology, Chungnam National University, Daejeon, 305-764, South Korea, Tel: +82 42 821 6369; Fax: +82 42 821 8875; E-mail: jhsohn@cnu.ac.kr

demographically similar, having no previous history of substance use disorder (Table 1).

All the participants were screened to rule out other psychiatric or co-occurring mental disorders using self-report and mental health history. The exclusion criteria incorporated any history of a serious head injury, serious medical problems, neurological disorders, Axis I psychiatric disorders other than AUD, and the current use of psychotropic medication. The complete procedure was explained to all subjects prior to execution. All subjects signed the participation consent forms and were required to be alcohol-free 24 h prior to fMRI scanning. The experimental procedure was comprehensively reviewed and conducted in strict compliance with the Institutional Review Committee.

Stimuli

Alcoholic picture cues were selected from the Normative Appetitive Picture System (NAPS; Breiner *et al*., 1995). To avoid the duplication of visual cues, 12 additional pictures were needed to supplement the original 11 pictures. Additional images were selected and downloaded from website advertisements. Those images consisted of Korean beer and mild liquor. These additional images were then pre-tested to assure a craving response could be produced. Pictures with non-alcoholic theme were selected from the NAPS. Control pictures were duplications of liquor pictures with blurred distortions for the subjects not to perceive any objects in the pictures but gaze at the picture stimuli. These distortions were made to match the alcohol picture cues in both colour and hue with non-recognizable alcohol cues. This was done in order to identify continued brain activity based solely on alcohol-associated cues by ruling out the activity resulting from visual effects, e.g. colour or hue.

Table 1. Subject demographics

	AUD (n = 9)	Control (n = 9)	Statistics
Age (years)	23.22 ± 2.48	23.00 ± 2.64	Non-significant
Educational level	14.00 ± 1.25	13.50 ± 2.23	Non-significant
Gender (% male–female)	88.89 – 11.11%	77.78 – 22.22%	Non-significant
Number of cigarettes smoked	3.33 ± 7.07	2.72 ± 6.56	Non-significant
Number of days drinking per month	9.166 ± 2.50	1.27 ± 1.00	t = 8.785, df = 16, P < 0.001
Number of drinks per drinking day	9.77 ± 0.66	2.33 ± 2.25	t = 9.517, df = 16, P < 0.001
Number of blackouts in a month	0.78 ± 0.26	0	t = 8.854, df = 16, P < 0.001
AUDIT-K	22.88 ± 3.37	2.11 ± 1.83	Significant
NAST	5.00 ± 0.50	0	Significant

Procedures

Once subjects arrived, they were individually instructed on the experimental procedure they would be expected to follow. Prior to cue exposure, they were asked to rate their craving level using the Obsessive Compulsive Drinking Scale (OCDS) (Choi *et al*., 2002) and a one-item Likert scale (range from 1 to 7 points). Prior to entering the scanner room, subjects practiced the procedure exactly in the same manner as was expected while in the scanner. Then, they were given 5 cc of alcohol (negligible blood alcohol levels) and were asked again to rate their level of craving using only the Likert scale.

The stimulus period was 9 min long and consisted of six separate runs through the cue sequence as shown in Figure 1. Four blocks of visual cues were contained in a single run. The four blocks of visual cues in a run were associated with alcohol, non-alcoholic beverage, and visual control pictures and one rest (cross-hair). One block had four individual pictures, with a visual exposure period of 18 s for each block presentation. Blocks were counterbalanced to control time and order effects across subjects. Subjects were again given 6 s to rate their craving levels after each block.

The stimulus was created in the Streamdx 1.0 (KAIST, Korea) and then projected onto a screen using a mirror. After each block, subjects were instructed to rate their level of craving in real time during visual exposure. Subjects did this by indicating the appropriate point on the 1–7 scale with a computer mouse.

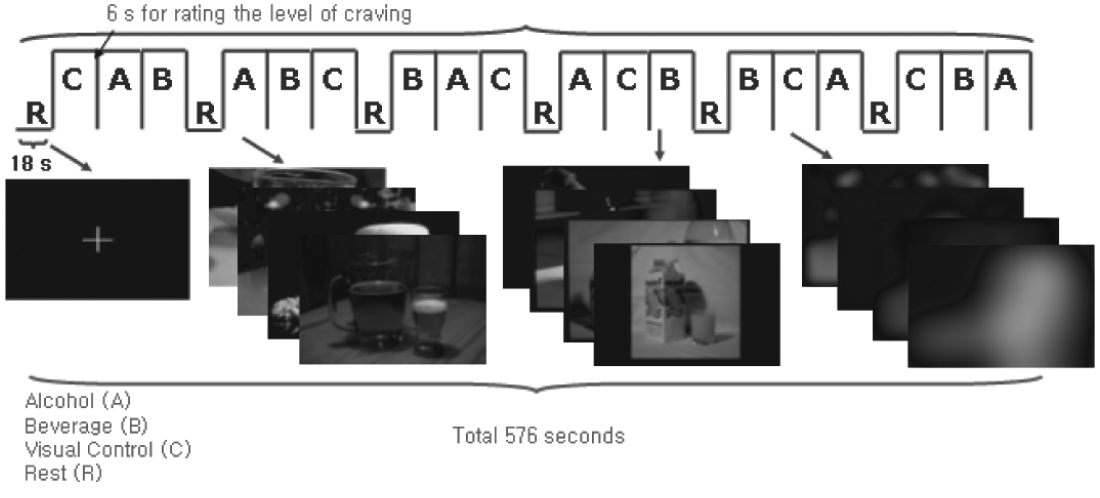


Fig. 1. The block-designed fMRI paradigm.

Imaging parameters

Imaging was conducted on a 3.0 T whole-body ISOL Technology FORTE scanner (ISOL Technology, Korea) equipped with whole-body gradients and a quadrature head coil. Single-shot echo-planar fMRI scans were acquired in 35 continuous slices, parallel to the anterior commissure–posterior commissure line. The parameters for fMRI include the following: the repetition time/echo time [TR/TE] were 3000/30 ms, respectively, flip angle 80, field of view 240 mm, matrix 64 × 64, slice thickness 4 mm, and in-plane resolution 3.75 mm. Three dummy scans from the beginning of the run were excluded to decrease the effect of non-steady state longitudinal magnetization. T1-weighted anatomic images were obtained with a 3-D FLAIR sequence (TR/TE = 280/14 ms, flip angle = 60, FOV = 240 mm, matrix = 256 × 256, slice thickness = 4 mm).

Data analysis

The fMRI data were analysed with SPM99 (Wellcome Department of Cognitive Neurology, London, UK). All functional images were realigned with the image taken proximate to the anatomical study by using affine transformation routines built into SPM99. The realigned scans were co-registered to the participant's anatomical images obtained within each session, and normalized to SPM99's template image that uses the space defined by the Montreal Neurologic Institute, which is very similar to the Talairach and Tournoux's (1988) atlas. Motion correction was done using Sinc interpolation. Time series data were filtered with 240 s high-pass filter, to remove artefacts due to cardio-respiratory and other cyclical influences. The functional map was smoothened with a 7 mm isotropic Gaussian kernel prior to statistical analysis. Statistical analysis was done individually and as a group using the general linear model and the theory of Gaussian random fields implemented in SPM99. Using the subtraction procedure, activated areas in the brain during alcoholic beverage pictures compared to non-alcoholic beverage pictures were colour-coded by *t*-score. The double subtraction method was used to test the effect of difference between two groups (i.e. the AUD group vs control group).

Finally, regression between craving scores and brain activity measured during the alcohol pictures in the AUD group was performed to investigate if brain activity significantly correlated with the levels of craving. Finally, regression analysis between craving scores and brain activity in response to alcohol-related visual cues in the AUD group was performed to investigate a possible correlation with craving levels.

RESULTS

Behavioural results

Table 2 shows the OCDS score and the mean levels of pre-and post-sip alcohol craving in each group. The independent *t*-test showed a statistically significant difference between two groups in the OCDS scores, pre-sip and post-sip alcohol craving. Figure 2 illustrates the levels of craving while in the scanner when the AUD and control subjects were exposed to alcoholic beverage pictures, non-alcoholic beverage pictures, visual control pictures, and cross-hair. The AUD group showed significantly higher levels of craving during visual cues.

Table 2. OCDS scores and the mean levels of craving

	AUD (n = 9)	Control (n = 9)	Statistics
ODCS	27.55 ± 4.33	14.00 ± 2.00	t = 8.521, df = 16, $P < 0.001$
Pre-sip alcohol craving	4.44 ± 0.88	1.11 ± 0.33	t = 10.607, df = 16, $P < 0.001$
Post-sip alcohol craving	4.77 ± 0.83	1.11 ± 0.33	t = 12.256, df = 16, $P < 0.001$

$P < 0.001$ AUD higher than controls.

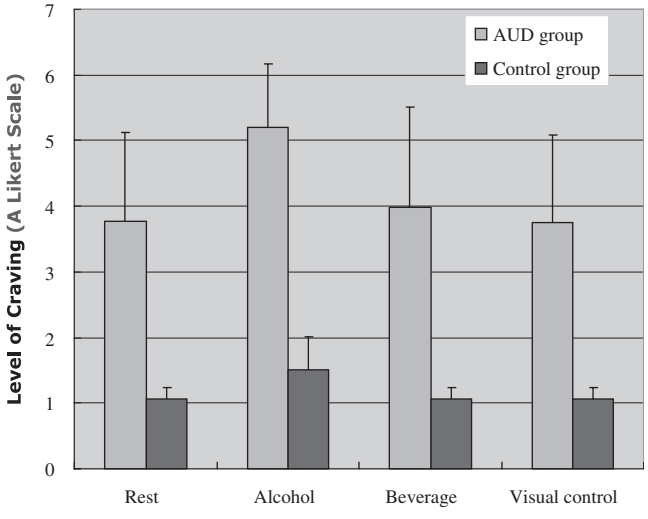
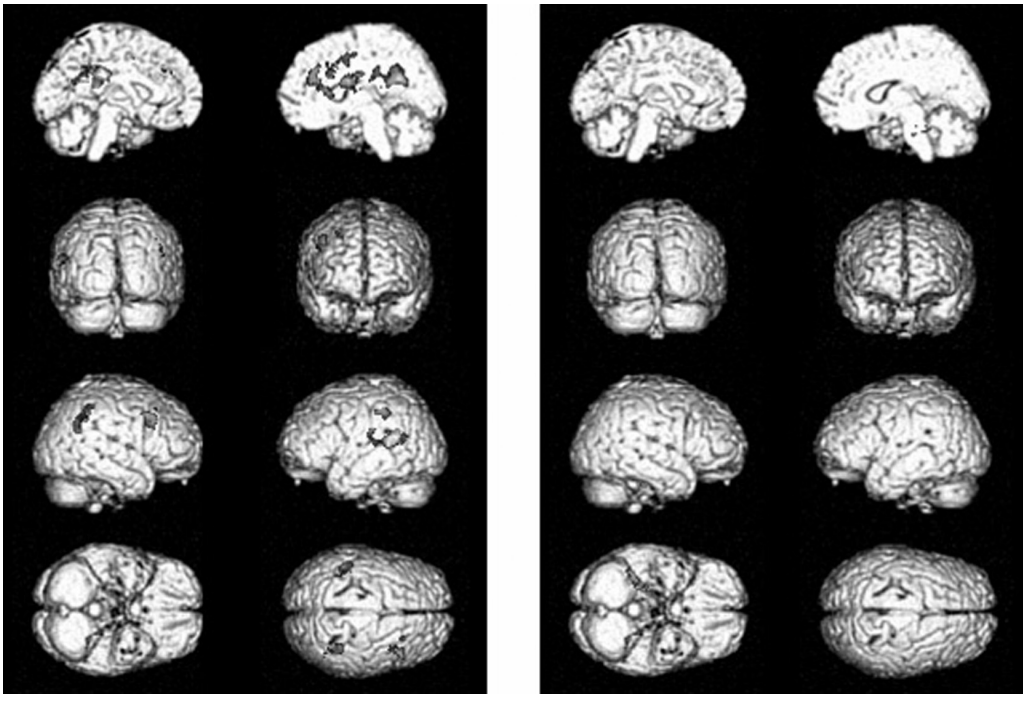


Fig. 2. The mean level of craving by different visual cues. Craving level was rated on a Likert scale (range from 1 to 7) after each block.

fMRI results

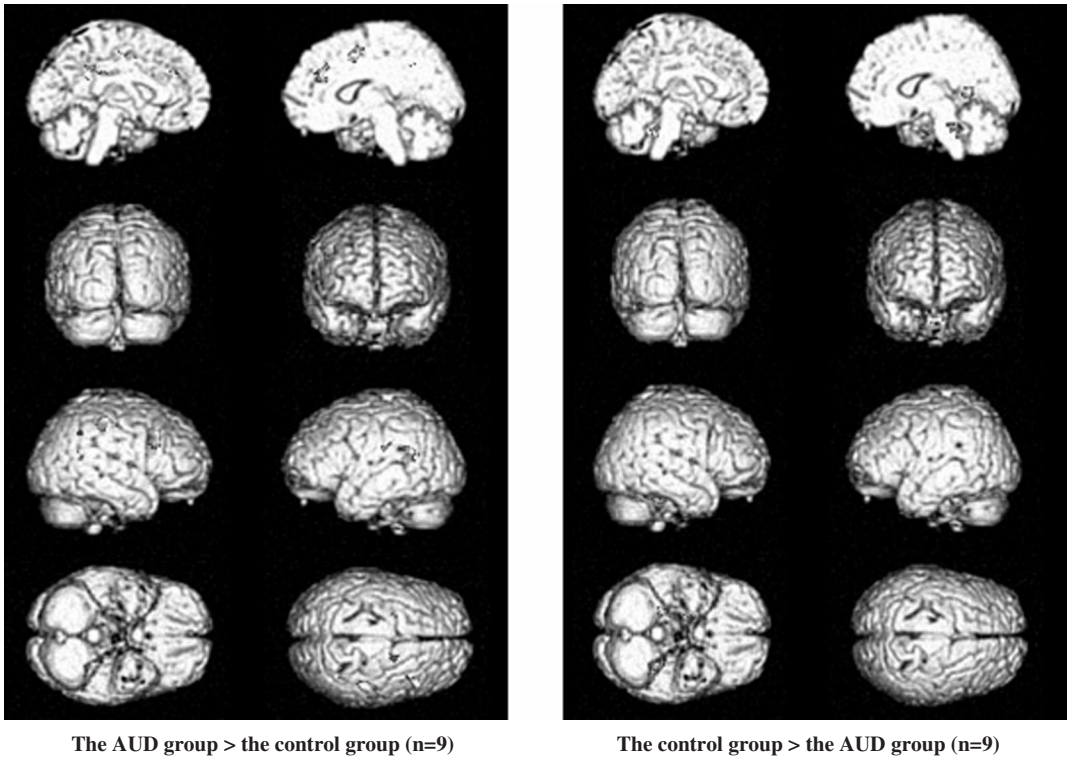
To identify brain areas generated by alcohol cues, we directly compared brain activation during exposure to alcohol cues to that of beverage cues. In this comparison, we were able to subtract brain activation generated by the neutral (control) beverage cues from brain activation generated by the alcohol cues. Theoretically, the remaining brain activation areas are considered to be related to the alcohol-specific content of the pictures (George *et al*., 2001). Figure 3 illustrates brain areas significantly activated in the AUD group and control group during exposure to alcohol cues compared to beverage cues. In the AUD group, significant activation was observed in the left cingulate gyrus, bilateral inferior parietal lobe, left superior temporal gyrus, right middle frontal gyrus, right fusiform gyrus, right medial frontal gyrus, right posterior cingulate, and left insula. In the control group, only the right culmen in the cerebellum was significantly activated (corrected $P < 0.05$).

Figure 4 reveals the contrasting effects between the AUD and control groups using the double subtraction method. These areas include the right medial frontal gyrus and right inferior parietal lobe in the AUD group compared to the control group. Significant activation was observed in the right posterior cingulate and right culmen in the control group when compared with that of the AUD group (corrected $P < 0.05$).



The AUD group (n=9) **The control group (n=9)**

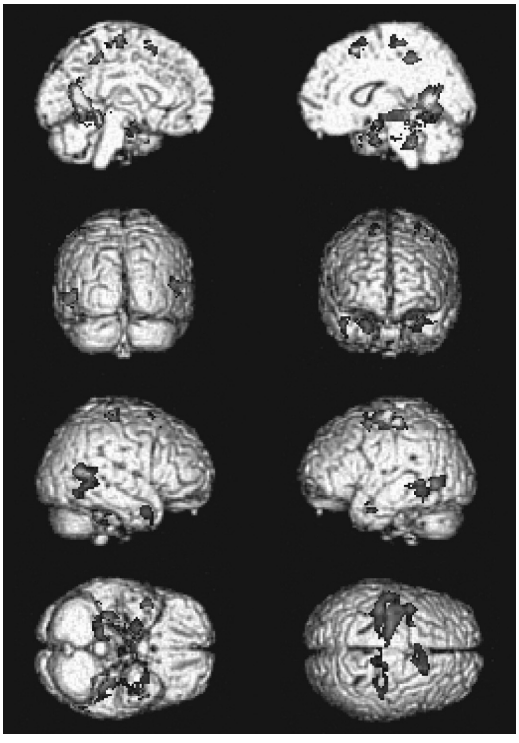
Fig. 3. Brain activation areas in each group during alcohol cues compared to beverage cues.



The AUD group > the control group (n=9) **The control group > the AUD group (n=9)**

Fig. 4. Contrasted brain activation areas.

Figure 5 shows brain areas correlated with the level of craving among AUD subjects in response to the alcohol cues. Significant activation was shown in the bilateral fusiform gyri, bilateral lingual gyri, right middle temporal gyrus, left inferior temporal gyrus, left parahippocampal gyrus, left postcentral gyrus, left precentral gyrus, right uncus, right paracentral, right superior frontal gyrus, bilateral middle frontal gyri, bilateral superior temporal gyri, and left precuneus



The AUD group (n=9)

Fig. 5. Brain areas correlated with level of craving in the AUD group.

(corrected $P < 0.05$). The Talairach coordinates and *t*-scores of each activated area are shown in Table 3.

Table 3. Talairach coordinates and *t*-scores of activated brain areas

Region	Side	*X*	*Y*	*Z*	MaxZ
Alcohol–beverage comparison					
The AUD group					
Cingulate	Left	–16	–32	30	4.21
Inferior parietal	Left	–46	–26	26	3.78
Inferior parietal	Right	38	–46	46	3.57
Superior temporal	Left	–54	–44	10	3.26
Middle frontal	Right	40	16	38	3.15
Fusiform	Right	38	–32	–16	3.15
Medial frontal	Right	18	36	20	3.14
Posterior cingulate	Right	10	–50	24	3.13
Insula	Left	–30	–20	16	3.12
The control group					
Culmen	Right	36	–40	–30	3.14
Contrasted brain activation areas					
The AUD group > the control group					
Medial frontal	Right	20	2	50	4.43
Inferior parietal	Right	38	–50	42	3.66
The control group > the AUD group					
Posterior cingulate	Right	16	–50	6	3.84
Culmen	Right	24	–34	–26	3.43
Brain areas correlated with craving level					
Fusiform	Right	26	–40	–14	4.76
Lingual	Right	16	–56	4	4.68
Middle temporal	Right	50	–62	10	4.54
Inferior temporal	Left	–50	–62	–2	4.67
Parahippocampal	Left	–24	–46	–10	4.56
Lingual	Left	–10	–54	4	4.45
Postcentral	Left	–38	–26	58	3.81
Precentral	Left	–22	–16	66	3.83
Uncus	Right	22	–4	–28	3.80
Paracentral	Right	16	–40	48	3.74
Fusiform	Left	–42	–4	–26	3.13
Superior frontal	Right	10	16	54	3.48
Middle frontal	Left	–40	4	56	3.47
Middle frontal	Right	28	–8	62	3.19
Superior temporal	Left	–22	8	–32	3.18
Precuneus	Left	–14	–38	50	3.16
Superior temporal	Right	58	4	–8	3.09

Alcohol–beverage comparison in each group, contrasting effects between two groups using double subtraction method, brain areas correlated with self-reported craving levels. The cluster statistical weight is corrected $P < 0.05$.

DISCUSSION

The purpose of the study was to find the brain substrates associated with craving in subjects with AUD. After exposure to alcohol cues, brain activations were examined in both AUD and control subjects via fMRI. Also after exposure, craving responses of both AUD and control subjects were compared.

Analysis of the behavioural data showed comparisons between the mean level of craving reported by AUD subjects to be significantly higher than that reported by control subjects after exposure to alcohol cues. These results support the concept that exposure to environmental stimuli associated with drinking (such as pictures, smells, and places of ingestion) can strongly stimulate the urge or desire to consume alcohol in alcohol-dependent individuals (Myrick *et al*., 2004).

Activation was significantly greater in AUD subjects than control subjects in the frontal cortex, limbic regions, and other brain areas during exposure to alcohol cues in comparison to beverage cues. Consistent with this study, a number of previous neuroimaging studies using cue stimulation identified the areas of brain activation. The brain areas known to be activated when exposed to cue stimulation of cocaine, opiates, nicotine, or alcohol include the cingulate gyrus (Breiter *et al*., 1997; Myrick *et al*., 2004), parietal lobe (Grant *et al*., 1996; Breiter *et al*., 1997; Garavan *et al*., 2000), temporal gyrus (Grant *et al*., 1996; Breiter *et al*., 1997; Garavan *et al*., 2000; Schneider *et al*., 2001), frontal gyrus (Grant *et al*., 1996; Breiter *et al*., 1997; Garavan *et al*., 2000; George *et al*., 2001), fusiform gyrus (Braus *et al*., 2001), posterior cingulate (Garavan *et al*., 2000), and insula (Breiter *et al*., 1997; Wang *et al*., 1999; Garavan *et al*., 2000; Myrick *et al*., 2004).

In this study, the brain areas directly associated with the level of craving in the AUD subjects include the fusiform gyri, temporal gyri, parahipocampal gyrus, uncus, frontal gyri, and precuneus. Our result support the contention that limbic activation is one component of cue-induced craving and thus it may be involved in appetitive craving for addictive drugs or for natural rewards (Childress *et al*., 1999). The parahippocampal gyrus, which has efferent fibres to the nucleus accumbens and amygdala, is a primary input source for the hippocampus (Breiter *et al*., 1997). Sell *et al*. (2000) found that the hippocampal activity was correlated with self-reports of feeling high, i.e. with euphoric effects of heroin in opiate addicts. They further suggested that the hippocampus has a significant role in learning and memory that may contribute to drug addiction. The hippocampus is implicated in learning about the relationship between the external cues and internal states (White, 1996). Therefore, activation of the hippocampus might be anticipated when AUD subjects

connected the environmental cues to the internal states associated with alcohol use.

Our result confirms frontal involvement in alcohol craving on cue-induced drug craving (George *et al*., 2001; Grant *et al*., 1996; Maas *et al*., 1998; Volkow *et al*., 1999; Garavan *et al*., 2000). Garavan *et al*. (2000) suggested the participation of a working memory circuit while in the craving state. It is possible to assume that the engagement of alcohol abuser's attention and his or her subsequent alcohol-related ruminations associated with alcohol cues are mediated within a working memory system (Garavan *et al*., 2000) when the AUD subjects experienced craving for alcohol.

Activation of the right precuneus was also correlated with levels of self-reported craving in this study. The right precuneus is strongly implicated in episodic memory retrieval (i.e. conscious recall of past experiences) (Shallice *et al*., 1994). When AUD subjects experienced alcohol craving, it has been assumed that visual memories associated with the alcohol use are reprocessed in this region and serve as conditioned stimuli that provoke conditioned responses (Sell *et al*., 2000).

The study had a number of limitations. The first was sample size. Although efforts were made to match the two groups by important demographic variables; age, education level, and handedness for comparison purposes, the sample size remained relatively small. A second limitation was the race composition of subjects selected. All subjects were Asian. These two factors (sample size and race composition) taken together limit the generalizability of study results to the broader universal population.

In conclusion, specific brain regions were found to be directly associated with craving. The present findings indicated that brain activation regions implicated in several forms of memory (working, episodic, emotional) are directly related to craving.

Acknowledgements — This research was supported as a Brain Neuroinformatics Research Program sponsored by Ministry of Commerce, Industry and Energy.

REFERENCES

Anton, R. F. (1999) What is craving? *Alcohol Research and Health* **23**, 165–173.

Braus, D. F., Wrase, J., Grüsser, S. *et al*. (2001) Alcohol-associated stimuli activate the ventral striatum in abstinent alcoholics. *Journal of Neural Transmission* **108**, 887–894.

Breiner, M. J., Stritzke, W. G. K., Lang, A. R. (1995) *The Normative Appetitive Picture System (Photographic Slides)*. Florida State University, Tallahassee, FL.

Breiter, H. C., Gollub, R. L., Weisskoff, R. M. *et al*. (1997) Acute effects of cocaine on human brain activity and emotion. *Neuron* **19**, 591–611.

Childress, A. R., Mozley, P. D., McElgin, W. *et al*. (1999) Limbic activation during cue-induced cocaine craving. *The American Journal of Psychiatry* **156**, 11–18.

Choi, M. J., Lee, E., Lee, B. O. *et al*. (2002) The study on reliability and validity of Korean versions of obsessive compulsive drinking scale for outpatient of alcohol dependence. *Journal of Korean Neuropsychiatry Association* **41**, 98–109.

Garavan, H., Pankiewicz, J., Bloom, A. *et al*. (2000) Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. *The American Journal of Psychiatry* **157**, 1789–1798.

George, M. S., Anton, R. F., Bloomer, C. *et al*. (2001) Activation of prefrontal cortex and anterior thalamus in alcoholic subjects on exposure to alcohol specific cues. *Archives of General Psychiatry* **58**, 345–352.

Grant, S., London, E. D., Newlin, D. B. *et al*. (1996) Activation of memory circuits during cue-elicited cocaine craving. *Proceedings of the National Academy of Sciences of the United States of America* **93**, 12040–12045.

Hahn, O. S., Ahn, J. H., Song, S. H. *et al*. (2000) Development of the Korean version of structured clinical interview schedule for DSM-IV Axis I Disorder: Interrater reliability. *Journal of Korean Neuropsychiatry Association* **39**, 362–372.

Heinz, A., Siessmeier, T., Wrase, J. *et al*. (2004) Correlation between dopamine D2 receptors in the ventral striatum and central processing of alcohol cues and craving. *The American Journal of Psychiatry* **161**, 1783–1789.

Kalivas, P. W., Cornish, J., Ghasemzadeh, M. B. (1998) Cocaine craving and paranoia: a combination of pharmacology and learning. *Psychiatric Annals* **28**, 562–574.

Kim, G. B., Han, K. S., Lee, J. K. *et al*. (1991) The preliminary study of the Korean alcoholism screening test (III)-Alcoholism Screening Test of Seoul National Mental Hospital (I): NAST (I). *Journal of Korean Neuropsychiatry Association* **30**, 569–581.

Lee, B. W. (2000) Development of the Korean version of Alcohol Use Disorders Identification Test (AUDIT-K). *Korean Academy of Addiction Psychiatry* **4**, 83–92.

Mass, L. C., Lukas, S. E., Kaufman, M. J. *et al*. (1998) Functional magnetic resonance imaging of human brain activation during cue-induced cocaine craving. *The American Journal of Psychiatry* **155**, 124–126.

Modell, J. G. and Mountz, J. M. (1995) Focal cerebral blood flow change during craving for alcohol measured by SPECT. *Journal of Neuropsychiatry* **7**, 15–22.

Myrick, H., Anton, R. F., Li, X. *et al*. (2004) Differential brain activity in alcoholics and social drinkers to alcohol cues: relationship to craving. *Neuropsychopharmacology* **29**, 393–402.

Park, B. K., Kim, J. S., Lee, D. B. (2000) Comparison of four alcoholism screening tools based on sensitivity and specificity for DSM-IV criteria. *Journal of the Korean Academy of Family Medicine* **21**, 1427–1435.

Schneider, F., Habel, U., Wagner, M. *et al*. (2001) Subcortical correlates of craving in recently abstinent alcoholic patients. *The American Journal of Psychiatry* **158**, 1075–1083.

Sell, L. A., Morris, J. S., Bearn, J. *et al*. (2000) Neural response associated with cue evoked emotional states and heroin in opiate addicts. *Drug Alcohol Dependence* **60**, 207–216.

Shallice, T., Fletcher, P., Frith, C. D. *et al*. (1994) Brain regions associated with acquisition and retrieval of verbal episodic memory. *Nature* **368**, 633–635.

Talairach, J. and Tournoux, P. (1988) *Coplanar Stereotaxic Atlas of the Human Brain. Three-Dimensional Proportional System: An Approach to Cerebral Imaging*. Thieme, New York.

Tapert, S. F., Cheung, E. H., Brown, G. G. *et al*. (2003) Neural response to alcohol stimuli in adolescents with alcohol use disorder. *Archives of General Psychiatry* **60**, 727–735.

Volkow, N. D., Wang, G. J., Fowler, J. S. (1999) Association of methylphenidate-induced craving with changes in right striato-orbitofrontal metabolism in cocaine abusers: implications in addiction. *The American Journal of Psychiatry* **156**, 19–26.

Wang, G. J., Volkow, N. D., Fowler, J. S. *et al*. (1999) Regional brain metabolic activation during craving elicited by recall of previous drug experiences. *Life Science* **64**, 775–784.

White, N. M. (1996) Addictive drugs as reinforcers: multiple partial actions on memory systems. *Addiction* **91**, 921–950.