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Anterior Cingulate Cortex and Amygdala Dysfunction Among Patients with Alcohol Dependency During Exposure to Negative Emotional Stimuli

Mi-Sook Park*†

*Department of Rehabilitation Counseling Psychology, Seoul Hanyoung University

Abstract

This study aimed to identify specific psychological and brain activation responses relating to the processing of negative emotions in patients with alcohol dependency. The authors hypothesized that patients with alcohol dependency would demonstrate the abnormal functioning of brain regions involved in negative emotions. Eleven male patients diagnosed with alcohol dependence in an inpatient alcohol treatment facility and 13 social drinkers with similar demographics were scanned using functional magnetic resonance imaging (fMRI) as they viewed film clips that evoked negative emotions. During exposure to negative emotional stimuli, the control group evinced significantly greater activity in the right anterior cingulate cortex (ACC) in comparison to patients with alcohol dependency. Correlation analyses demonstrated a negative association in the relationship between beta values from the right ACC and amygdala in participants classified in the control group. No statistically significant relationship was observed for blood oxygenation level-dependent (BOLD) changes between the two regions in the patient group during the elicitation of negative emotions. On the other hand, patients exhibited a greater activation of the amygdala as negative emotions were induced. These results suggest that alcoholism presents pathophysiology of brain activation that is distinct from the responses of healthy individuals functioning as controls.

Key words: Alcohol Dependency, Negative Emotion, fMRI, Brain Activation

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† Corresponding Author : Mi-Sook Park (Department of Rehabilitation Counselling Psychology, Seoul Hanyoung University)
E-mail : misook_park1121@hanmail.net
TEL : 02-2669-2469
FAX : 02-2669-2209

1. Introduction

Research indicates that people consume alcohol to manage feelings of negative emotion (Sitharthan et al., 2009), and it is common for problem drinkers to report negative mood states as a major reason for relapsing (Sitharthan et al., 2009). Childress et al. (1987) observed that when negative mood states were provoked in drug addicts, two thirds of the them reported craving or withdrawal symptoms regardless of the presence of drug cues. Others (Litt et al., 1990; Stasiewicz & Maisto, 1993) have noted that negative emotional states play a significant role in the maintenance of alcohol use. The cognitive model of drug use (Tiffany, 1990) also supports the view that a person who is depressed may fail to maintain his or her motivation to resist drug use. Several investigators have tested whether negative mood states elicit arousal to drink alcohol. For example, Litt et al. (1990) tested the role of negative mood as a cue or trigger to arouse alcohol craving. They recruited inpatient alcoholics and induced a neutral mood or a negative mood by asking the participants to discuss the past specific episodes in detail and they found negative mood was associated with drinking among inpatient alcoholics.

Due to the advancement of neuroimaging techniques, the brain region associated with negative emotion has been revealed among healthy men (Freed and Mann, 2007). The brain regions implicated in negative emotions are the amygdala and related temporolimbic structures, the hypothalamus, the anterior cingulate cortex (ACC), and the prefrontal cortex (PFC; most notably the ventral PFC). It is well known that alcoholics are likely to experience negative emotions more than healthy controls (Elkins et al., 2006; Sher et al., 1999). In the study, we hypothesized that patients with alcohol dependency would show higher level of negative emotion during exposure to negative emotion-inducing stimuli in an experimental setting. Since emotional impairments among patients with alcohol dependency are associated with the alterations of brain functioning in the emotion-related regions (Salloum et al., 2007; Gilman et al., 2007; Maurage et al., 2012; Marinkovic et al., 2009), we also hypothesized that abnormal functioning of brain regions involved in negative emotion would be shown in the patients. Those regions are notably the the amygdala and related temporolimbic structures, the hypothalamus, ACC, and the prefrontal cortex. In order to remove the emotional effects, alcoholic patients who are suffered from depression or other psychiatric disorders were excluded from the study (see the method section). In the study, a mood induction task which consists of neutral and negative emotional film extracts was utilized which was adopted from the previous studies (Côte et al., 2007; Eugene et al., 2003; Lévesque et al., 2003a) to induce temporary negative emotion when the neural activation was measured.

2. Method

2.1. Participants

Eleven male patients with alcohol dependency (mean age: 48.91 years, age range = 39 ~ 56 years) in a local inpatient alcohol treatment facility voluntarily took part in this study. Literate individuals who had an alcohol dependency diagnosis were identified by a psychiatrist based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria (American Psychiatric Association, 1994) and included in this study. These individuals completed detoxification, had no history of or concurrent psychiatric disorder(s), and were maintaining sobriety. Patients with a current or a history of mental disorders were excluded from the study due to complications with alcohol use. Fourteen days before scanning, patients on prescribed medication (i.e., sleeping pills or anti-craving medication, not psychotropic drugs) were asked to abstain from such

medicines in agreement with their primary physician.

The Korean version of the Alcohol Use Disorders Identification Test (AUDIT) (Kim, 1998) was administered to both groups to assess the level of alcohol use; individuals who scored 15 points or higher are considered to meet the DSM-IV alcohol-use disorder criteria (Park et al., 2000). AUDIT is composed of three questionnaires about quantity of alcohol use, three items about alcohol using behaviours, and four items on psychosocial problems with drinking. The Korean version of the Alcohol Dependence Scale (ADS) (Lee et al., 2000) was also administered to determine the level of alcohol dependency in terms of impaired control over alcohol use, salience of drink-seeking behaviour, tolerance, impulse control, and withdrawal symptoms. The time frame of reporting any alcohol-related issues were 12 months prior to their hospitalization.

The control group consisted of 13 non-alcoholic male volunteers who are demographically similar to the alcoholic group (mean age: 49.77 years, age range = 31~61 years). These individuals were recruited randomly through advertisements and flyers. Upon recruiting the control group, researchers excluded anyone reporting a current or a history of mental disorder for its complication with alcohol use and ambiguity interpreting the research outcomes. These volunteers did not report any history or impairment in their central nervous systems or any psychiatric disorder (s). The controls stayed abstinent from alcohol for at least 48 hours prior to the scanning. In the case of the patients, they were abstained from alcohol since they were hospitalized for alcoholism. Demographics and alcohol use of both patient and control groups are shown in Table 1.

Prior to the beginning of the experiment, a full introduction to research, instructions, as well as the voluntary nature of participation were delivered to the group. Among those who agreed verbally to voluntarily participate in our study, we obtained a written informed consent form prior to beginning the study. This study obtained approval from the Institutional Review Board of the University (IRB no. 4-2014- 0988). Upon completion of all tasks, all participants were debriefed and then remunerated of $70 for their time and voluntary participation.

Table 1. Demographics and alcohol use of the participants

Characteristics	Control group (n=13)	Patient group (n=11)
Age (years)	49.77(5.34)	48.91(8.14)
Education level	12.08(3.48)	11.36(3.96)
Family history of alcoholism (%)	0	44.4**
Number of drinks (days per week)	0.71(0.89)	4.02(2.46)***
Amounts of drinks (drinks per drinking day)	2.87(2.27)	15.33(13.41)**
Maximum number of drinks in a lifetime	9.45(12.20)	32.54(26.37)**
AUDIT-K	6.23(5.76)	26.64(10.28)***
ADS-K	28.23(5.94)	51.55(12.83)***

***p < .001, **p < .01. Note. Means (standard deviations) are represented. One drink = 14 g ethanol. AUDIT-K Korean version of the Alcohol Use Disorders Identification Test, ADS-K Korean version of the Alcohol Dependence Scale.

2.2. Stimuli and Procedure

The emotional clips were excerpted from a Korean television program, “Exclamation Point (Ahn and Park, 2007).” The clips were to evoke negative emotion, video clips showing a mother and a son crying over their painful experiences caused by extreme poverty. The purpose of presenting this particular film clip was to help the study participants become deeply empathetic with the circumstances that the characters were experiencing in order to provoke negative feelings similar to those of the characters. Accurately identifying what others are feeling makes us share in their similar

experiences (Batson et al., 1995). Neutral scenes were also presented, which were designed to not evoke any emotions in participants. These clips were chosen from the same audio-visual clip to match the contents, colour, and hue with the emotional condition. More specifically, these neutral scenes comprised of a mother and son talking with an interviewer. For the fMRI paradigm for stimuli presentation, participants watched five 30-s blocks of emotionally neutral film excerpts followed by five 30-s blocks of negative film excerpts while they underwent a functional scan. Film clips were developed and validated in our pilot study (Sohn et al., 2005).

In the emotion assessment, participants were asked to label the emotion whether it was no emotion, positive, or negative. Then, they were required to rate how intense the emotion was during exposure to the emotional stimuli and neutral stimuli separately on a seven-point Likert scale ranging from 1 (least intense) to 7 (most intense).

2.3. 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. Parameters for the fMRI were as follows: repetition time/echo time (TR/TE) were 3000/30 ms, respectively, flip angle 80, field of view (FOV) 240 mm, matrix size 64×64, slice thickness 4 mm, and in-plane resolution 3.75 mm. Three dummy scans were erased from the beginning of the run to decrease the effect of non- steady state longitudinal magnetization. T1-weighted anatomical images were obtained with a 3-D FLAIR sequence (TR/TE = 280/14 ms, flip angle = 60, FOV = 240 mm, matrix size = 256×256, slice thickness = 4 mm).

2.4. Data Analysis

The fMRI data were analysed with SPM8 (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 SPM8. The realigned scans were normalized to SPM8's template image that uses the space defined by the Montreal Neurologic Institute, which is very similar to the Talairach and Tournoux's (1988) stereotaxic atlas. Motion correction was done using sinc interpolation. Time series data were filtered with a 240-s high-pass filter, to remove artefacts due to cardio-respiration and other cyclical influences. The functional map was smoothened with an 8-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 SPM8. Using the subtraction method, activated areas in the brain during the negative emotion condition were compared to the neutral condition, and were color-coded by t-score. The double subtraction method was used to test the effect of group difference. The statistical significance for the activated areas was determined as uncorrected $p < .001$ and extent threshold $k > 20$. Among the regions that showed group-effects, we found temporolimbic structures, i.e., ACC and amygdala and extracted beta values from two regions through xjView (http://www.alivelearn.net/xjview8/).

In SPM, we created a beta extraction batch file and loaded the ROI image and assigned directories where the locations of beta value files of individual subjects were stored. In this way, beta values for both negative emotion and neutral conditions in both control and patient groups were calculated. Lastly, correlation analyses between beta values from ROIs were conducted in each group to explore a notable relationship between the ACC and amygdala activity.

3. Results

3.1. Behavioral Results

For the emotional condition, all of the participants in both control and patient groups experienced negative emotion. The mean (SD) of the intensity scores of negative emotion experience for control and patient groups were 5.46 (1.33) and 6.45 (0.69), respectively. The independent *t*-test showed that the alcoholic patients experience higher level of negative emotion compared to the controls to the negative emotion-inducing stimuli (t (22) = 2.23, $p < .05$). In the neutral condition, both control and patient groups did not experience any emotion.

3.2. fMRI Results

As for the control group, brain activation was observed during the negative emotion condition in the left inferior temporal gyrus (BA 37), left fusiform gyrus, right middle occipital gyrus, bilateral lingual gyrus (BA 18), left declive, left middle frontal gyrus (BA 6), left superior temporal gyrus (BA 38), bilateral medial frontal gyrus (BA 6), bilateral middle temporal gyrus (BA 21), right cerebellar tonsil, left culmen, left inferior frontal gyrus (BA 45), left putamen, right insula, left superior frontal gyrus (BA 9), right thalamus, right parahippocampal gyrus, right anterior cingulate. A stark contrast was observed in the results of patient group. That is, activated brain regions were the right middle temporal gyrus, left thalamus, left amygdala, right ACC, right middle frontal gyrus (BA 46), right inferior frontal gyrus (BA 47), right postcentral gyrus, right parahippocampal gyrus, left superior frontal gyrus (BA 10), left superior temporal gyrus, and right cingulate gyrus (BA 24). Measures of between group differences provided clarification on the atypical negative emotion processing pattern seen in patient group. When the brain activation observed between the negative emotion and neutral conditions of both groups were compared, the control group exhibited significantly greater activation in the right ACC (BA 32) and left middle frontal gyrus compared to the patient group. On the other hand, the patient group exhibited significantly greater activity in the right amygdala, left cingulate gyrus, and right cuneus when compared to the control group. Talairach coordinates and *t*-scores of each activated area are shown in Table 2.

Extracted beta values for the two brain regions

Table 2. Talairach coordinates and *t*-scores of activated brain areas

Region	Side	X	Y	Z	Brodmann's areas (BA)	*t* value
Negative emotion condition-neutral condition comparison						
Control group						
Inferior temporal gyrus	left	-62	-58	-4	BA 37	6.66
Fusiform gyrus	left	-46	-54	-16	BA 37	1.94
Middle occipital gyrus	right	40	-76	4	BA 19	5.63
Lingual gyrus	right	10	-80	-8	BA 18	5.00
Declive	left	-24	-78	-20		3.96
Lingual gyrus	left	-18	-92	-4	BA 19	3.75
Middle frontal gyrus	left	-48	8	52	BA 6	2.74
		-34	-6	44	BA 6	2.45
Superior temporal gyrus	left	-52	10	-20	BA 38	2.67
Medial frontal gyrus	right	6	-24	64	BA 6	2.67

Table 2. (Continued)

Region	Side	X	Y	Z	Brodmann's areas (BA)	*t* value
Middle temporal gyrus	left	-64	-6	-14	BA 21	2.30
		-50	-34	-6	BA 21	2.29
Cerebellar tonsil	right	44	-46	-36		2.26
Culmen	left	-46	-52	-28		2.26
Inferior frontal gyrus	left	-48	16	14	BA 45	2.24
Putamen	left	-24	6	8		2.06
Medial frontal gyrus	left	-12	-6	60		2.20
		-10	-6	48	BA 24	1.89
Insula	right	44	-18	14	BA 13	2.19
Middle temporal gyrus	right	54	-68	22	BA 39	2.08
Superior frontal gyrus	left	-6	54	30	BA 9	2.01
Thalamus	right	20	-26	14		1.96
Parahippocampal gyrus	right	22	-16	-18	BA 28	1.88
anterior cingulate gyrus	right	10	46	-2	BA 32	1.78
Patient group						
Middle temporal gyrus	right	46	-54	4	BA 37	9.30
		38	4	-34	BA 21	1.88
Thalamus	left	-20	-18	6		3.23
Amygdala	left	-26	-2	-14		2.08
Anterior cingulate gyrus	right	8	12	22	BA 33	2.78
		26	4	-16	BA 34	
Middle frontal gyrus	right	54	32	14	BA 46	2.57
Inferior frontal gyrus	right	36	30	-4	BA 47	2.44
		46	36	0	BA 46	1.62
Postcentral gyrus	right	56	-20	16	BA 40	2.23
Parahippocampal gyrus	right	28	-24	-8		2.10
Superior frontal gyrus	left	-12	62	18	BA 10	2.10
Superior temporal gyrus	left	-36	8	-28	BA 38	1.63
Cingulate gyrus	right	8	-12	40	BA 24	1.59
Control group > Patient group						
Anterior cingulate gyrus	right	16	44	-2	BA 32	3.29
Middle frontal gyrus	left	-14	-6	60	BA 6	2.93
Patient group > Control group						
Amygdala	left	-16	-4	-16	BA 34	3.82
Cingulate gyrus	left	-14	-16	32		3.29
Cuneus	right	16	-102	6	BA 18	2.67

Brain activation comparisons between negative emotion and neutral conditions in each group and contrasting effects between the patient group and control group (uncorrected $p < .001$, k=20).

shown in the group difference (i.e., AUD and control groups) for each experimental condition (i.e., negative emotion and neutral conditions) are shown in Fig. 1. blood oxygenation level-dependent (BOLD) signals were significantly different between the two groups in the right ACC and left amygdala (Fig. 1). Correlation analyses were performed on signal changes from the ACC and amygdala in each group. Results showed that the greater the ACC activated, the less signal changes were in the amygdala in control participants (r=-0.54, p=.056; Fig. 2 left). However, this correlation was not found in patients with alcohol dependency (r=-0.026, p=.939; Fig. 2 right).

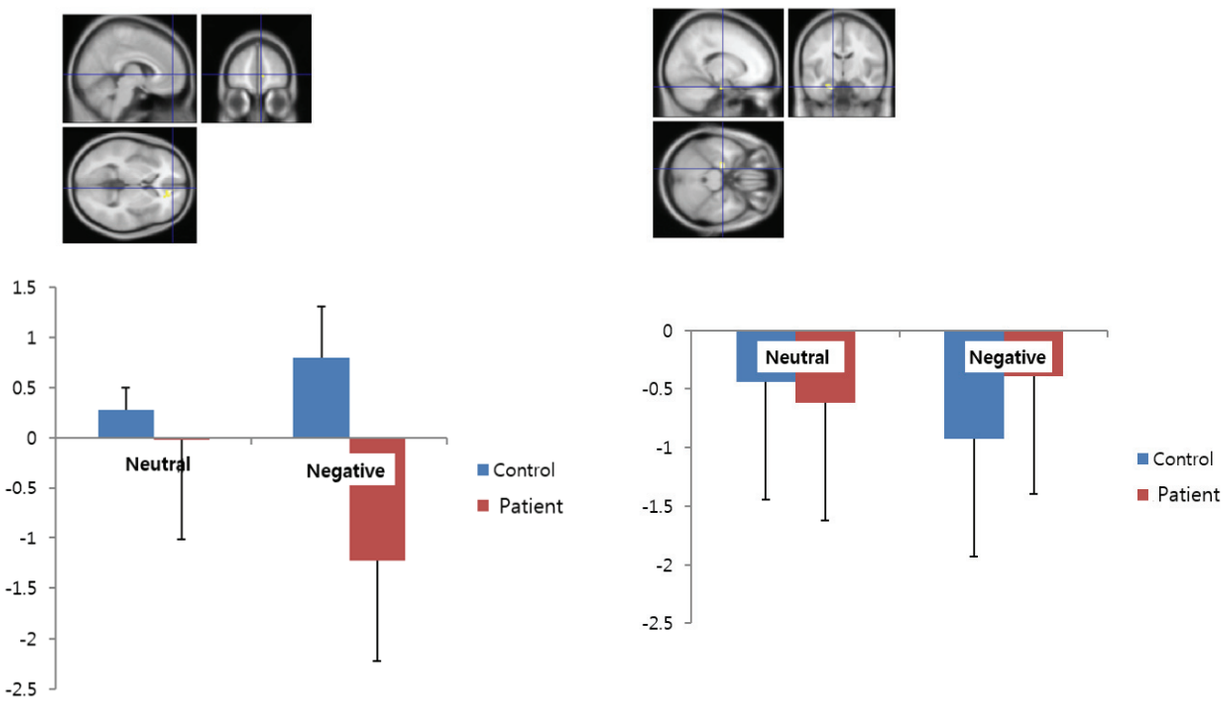

Fig. 1. The extracted beta values for the right ACC (left) and left amygdala (right) (average beta value ± SEM) in the control group and patient group for each experimental condition

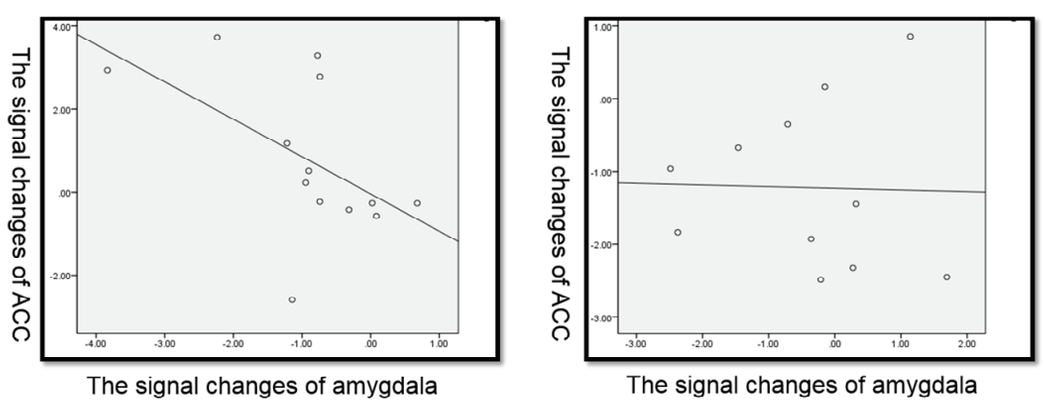

Fig. 2. The correlation between beta values from the right ACC (BA 32) and the left amygdala in the control group (left) and patient group (right). X-axis represents the signal changes of amygdala and y-axis represents the signal changes of ACC

4. Discussion

The present fMRI study of patients with alcohol dependency and their responses to negative emotion yields several important findings. First, this study replicated findings from others that have investigated the involvement of the anterior paralimbic structures during negative emotion induction in healthy individuals (Freed and Mann, 2007). Second, control subjects demonstrated significantly greater right ACC increases than patients with alcohol dependency during the condition that evoked negative emotions when compared to the neutral condition. Third, in the control subjects, interregional correlation analyses found an inverse correlation between right ACC changes and left amygdala changes during negative emotion provocations. However, the patient group demonstrated no correlation in BOLD changes in the right ACC and the left amygdala, suggesting an altered functional relationship between these brain

regions in patients with alcohol dependency.

Functional neuroimaging studies have used emotion induction paradigms to investigate the neural basis of negative emotion in control subjects. Although these studies used different techniques to induce negative emotion, all of them demonstrated the involvement of common anterior paralimbic structures during negative emotion-evoking states such that activity in the cingulate, basal ganglia, thalamus, and parahippocampal gyrus (Freed and Mann, 2007). Regarding the group difference, the dACC (BA32) was greater in the control group than in the patient group. It is known that the ACC is prominently involved in negative emotion (Drevets et al., 1997, Drevets et al., 2002, Mayberg et al., 2014). These structures are known to play a critical role in emotion regulation (Ochsner and Gross, 2005, Phillips et al., 2008). Particularly, recent theoretical models suggest an association between emotion regulation and top‐down processes regarding the ACC. It is likely that the ACC (BA 32) plays a significant role in processing negative emotion, as this region has been shown to be activated during visually elicited grief in bereaved women (Gündel et al., 2014) and externally triggered sad moods by using film clips, which relate to the subjective experience of negative emotion (Lévesque et al., 2003a). This indicates an emotion-specific regulatory function in this region; that is, emotional evaluation and control (Hariri et al., 2003, Phan et al., 2002, Stuhrmann et al., 2011). A functional neuroimaging study of individuals with a predisposition toward negative emotion found that these individuals (i.e. those with depression) exhibit decreased activity in the ACC compared with control subjects (Stuhrmann et al., 2011). Taken together, these studies provide strong evidence that dysfunction of the ACC is common in the pathophysiology of negative emotion or depression in psychiatric populations including patients with alcohol dependency.

Consistent with our hypothesis, correlational analyses examining the relationship between beta values from the right ACC and amygdala in controls demonstrated a negative correlation. It is suggested that psychiatric disorder may be associated with “dual brain pathology” in which abnormalities in the amygdala result in dysfunctional arousal states and those in the frontal regions result in uncontrolled states (van Elst et al., 2001). There are known bilateral directional connections between the ACC and the amygdala, and there is evidence that in control subjects these two structures are mutually regulatory in that increased activity in one structure elicits decreased activity in the other structure (Fava et al., 1990). Because the controls in the present study showed an inverse relationship between BOLD signals in the right ACC and left amygdala during the negative emotion vs neutral comparison, we examined this relationship in the patient group. We did not demonstrate any statistically significant relationship for BOLD changes during negative emotion induction between the two regions in the patient group. Regarding the emotional responses to negative stimuli in other psychiatric population, individuals with major depressive disorders showed dysfunctional prefrontal‐subcortical circuitry in response to viewing images of negative facial expression (Lee et al., 2008). This suggests that, at least in the context of negative emotion induction, the normal (inverse) functional relationship between the ACC and the amygdala is absent in the patient group. Therefore, this profile of ACC and amygdala activity and their interactions may be responsible for the unique clinical presentation of abnormal emotional functioning during induction of transient negative emotion among patients with alcohol dependency.

Despite aforementioned important findings in understanding how alcoholics respond abnormally to negative emotion, there are some limitations of this study that require consideration in future studies. The first was sample size; although efforts were made to match the two groups by important demographic variables that included gender, age, education level, and handedness for comparison purposes, the sample

size remained relatively small. A second limitation was the race composition of the subjects selected in that all subjects were Asian. Taken together, these two factors (sample size and race composition) limit the ability of this study to generalize to broader populations. Finally, we could not investigate the relationship between functional connectivity parameters and emotion experience in both group together. Nonetheless, this is the first study to reveal altered brain functions associated with the processing of negative emotion among patients with alcohol dependency.

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