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Gender Effects in Alcohol Dependence: An fMRI Pilot Study Examining Affective Processing

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Abstract

Background—Alcohol dependence (AD) has global effects on brain structure and function, including frontolimbic regions regulating affective processing. Preliminary evidence suggests alcohol blunts limbic response to negative affective stimuli and increases activation to positive affective stimuli. Subtle gender differences are also evident during affective processing.

Methods—Fourteen abstinent AD individuals (8 F, 6 M) and 14 healthy controls (9 F, 5 M), ages 23 to 60, were included in this facial affective processing functional magnetic resonance imaging pilot study. Whole-brain linear regression analyses were performed, and follow-up analyses examined whether AD status significantly predicted depressive symptoms and/or coping.

Results—Fearful Condition—The AD group demonstrated reduced activation in the right medial frontal gyrus, compared with controls. Gender moderated the effects of AD in bilateral inferior frontal gyri. Happy Condition—AD individuals had increased activation in the right thalamus. Gender moderated the effects of AD in the left caudate, right middle frontal gyrus, left paracentral lobule, and right lingual gyrus. Interactive AD and gender effects for fearful and happy faces were such that AD men activated more than control men, but AD women activated less than control women. Enhanced coping was associated with greater activation in right medial frontal gyrus during fearful condition in AD individuals.

Conclusions—Abnormal affective processing in AD may be a marker of alcoholism risk or a consequence of chronic alcoholism. Subtle gender differences were observed, and gender moderated the effects of AD on neural substrates of affective processing. AD individuals with enhanced coping had brain activation patterns more similar to controls. Results help elucidate the effects of alcohol, gender, and their interaction on affective processing.

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Keywords

fMRI; Alcohol Dependence; Gender; Affective Processing; Coping

Previous studies have demonstrated affective processing deficits in the development and maintenance of alcohol dependence (AD) (Oscar-Berman and Bowirrat, 2005). AD individuals exhibit deficits in interpreting affective prosody (Uekermann et al., 2005) and have difficulties processing affective positive and negative emotions (Foisy et al., 2007). There is also the potential role for aberrant affective processing in the development of AD (Gilman et al., 2008) as abnormal affective processing may help initiate and maintain problematic drinking patterns; however, the exact role these processing deficits play in AD are not clear.

The prefrontal cortex (especially the medial and orbitofrontal regions), cingulate cortex, limbic system, and cerebellum all play important roles in affective processing (Fine et al., 2009), with the amygdala and medial prefrontal cortex (mPFC) appearing to play critical roles (Jimura et al., 2009; Pessoa, 2010). Interestingly, there is plasticity in affective processing as evidenced by enhanced coping being associated with normalization (specifically decreased amygdala and increased prefrontal cortex activation) of brain activation to negative emotional stimuli (Drabant et al., 2009).

In addition to these regional brain effects, gender differences in affective processing have been reported in healthy adults. Previous research suggests that women are more accurate at recognizing and expressing affective states than men, while men react faster during facial affective decision-making tasks (Goos and Silverman, 2002; Hall and Matsumoto, 2004). Despite these documented behavioral differences, relatively few studies have examined gender differences in neuronal correlates of processing affective stimuli. Results are mixed as to which gender has more activation to positive and negative affect, and in which regions. Some studies have found gender differences in activation in frontal as well as subcortical areas like the amygdala, without demonstrable behavioral differences (Kempton et al., 2009). Others have found that while negative faces activated the anterior cingulate in both men and women, men activated left dorsolateral and lateral orbitofrontal areas, while women activated left medial orbitofrontal cortex (Mak et al., 2009). In addition, in response to positive faces, men demonstrated greater left lateral orbitofrontal activation than women. In contrast, another study found that men had greater activation to positive affective stimuli in right anterior cingulate, superior temporal, and superior and medial frontal areas than women (Mak et al., 2009). Taken together, although results are mixed, the prefrontal cortex and limbic system seem to be consistently and critically involved in affective processing, with subtle gender differences moderating these responses.

Prolonged alcohol exposure has global effects on both brain structure and function. Chronic alcohol exposure in adults leads to widespread atrophy of the cortex, including structures associated within the frontolimbic reward network (Makris et al., 2008). Although not all studies agree (Hommer, 2003), women appear more vulnerable than men to the widespread damaging effects of alcohol on the brain, including volumetric loss in frontolimbic regions that subserve affective processing despite, on average, having fewer years of drinking and

consuming less alcohol in their lifetimes (Mann et al., 1992; Medina et al., 2008). On par, both men and women with AD demonstrate atrophy following years of chronic drinking, however, atrophy appears to develop faster in women, suggesting an increased vulnerability (Mann et al., 2005). However, Pfefferbaum and colleagues (2010) did not find a gender vulnerability to the effects of alcohol when examining white matter bundles, nor were there gender differences in gray or white matter volumes in recently detoxified individuals with AD (Demirakca et al., 2011). Therefore, results concerning the interaction between AD and gender remain inconsistent and warrant further investigation. In sum, chronic alcohol use is associated with widespread volume reductions in areas that include structures underlying the processing of affective stimuli (Fine et al., 2009), and women may be particularly vulnerable. However, the functional consequences of AD on affective processing are less well understood.

Despite the hypothesized role of poor affective processing in AD, few studies have directly studied the impact of acute or chronic alcohol use on this neural network. Preliminary evidence suggests that acute alcohol use may impair basic affective processing skills, with subtle gender differences in alcohol's acute effects. For example, acute alcohol administration, but not placebo, leads to misidentification of emotional faces, (Attwood et al., 2009a) and males had more difficulty correctly labeling a sad facial emotion compared with females following a high dose of alcohol (Attwood et al., 2009b). Gilman and colleagues (2008) reported that acute alcohol consumption increased activation to fearful stimuli in striatal regions, but attenuated activation in visual and limbic areas. Similarly, our group found that acute alcohol consumption attenuated insula activation to positive and negative facial stimuli (Padula et al., 2011), and speculated that one motivation for drinking may be to reduce negative affect and increase positive affect in response to aberrant affective processing.

The gender-specific effects of *chronic* alcohol exposure on neuronal response to affective stimuli in AD men and women remain understudied. Abstinent AD individuals demonstrated an *increase* in blood oxygen level dependent (BOLD) activation in the anterior cingulate cortex, prefrontal cortex, ventral striatum, and thalamus in response to *positive* (or appetitive) stimuli compared with controls, and this increased activation was related to reduced relapse risk at a 6-month follow-up (Heinz et al., 2007). In contrast, another sample of abstinent AD individuals demonstrated *reduced* brain response in the anterior cingulate to *negative* emotional facial stimuli compared with controls (Salloum et al., 2007). Yet, another study found that abstinent AD men had a blunted limbic response with heightened prefrontal cortex response for all types of emotional faces, although this may not generalize to women (Marinkovic et al., 2009). To summarize, AD seems to be associated with blunted brain response to fearful or negative facial affective stimuli and increased brain response to positive affective stimuli. However, these results are based on only 3 studies, only 2 of which included females.

With these gaps in mind, the purpose of this pilot study was to examine (i) differences in neuronal response to fearful and happy face processing between abstinent AD and healthy control groups, and (ii) the interactive effects of group and gender on fearful and happy facial affective processing. A secondary aim was to explore whether brain regions that

significantly differed by AD status or gender-by-AD status were associated with mood symptoms or coping strategies in the AD group, as few studies have examined brain activation in relation to behavioral or functional indices. Based on previous studies, we hypothesized the AD group would have blunted activation to fearful and increased activation to happy stimuli, and that gender would significantly moderate the effects of AD on facial affective processing. Last, we hypothesized that fewer mood symptoms and/or better coping skills would be related to normalized brain activation in regions where AD individuals differed from controls.

MATERIALS AND METHODS

Participants

Twenty-eight individuals, ages 23 to 60 years, were included in this pilot study. Fourteen abstinent AD individuals (8 women, 6 men) were recruited from a parent study that examined hormonal responses to pharmacological stressors in AD individuals (Anthenelli et al., 2009; NCT00226694). Fourteen healthy controls (9 women, 5 men) were recruited from the community as part of a parent study examining neural stress response in depression (NIMH K23 MH67705, AZ IRUSQUET0456, NCT01200901). The Institutional Review Board at the University of Cincinnati and Cincinnati Veterans Affairs Medical Center Research and Development Committee approved all aspects of the study. All participants provided written informed consent.

Alcohol-dependent participants met lifetime DSM-IV criteria for AD (American Psychiatric Association, 1994) and were in sustained or partial full remission when they enrolled in the parent study. At the time of this study, AD individuals were abstinent from all substances except tobacco for at least 1 month prior to the magnetic resonance imaging (MRI) session. Exclusionary criteria for both groups included current use of psychotropic medications, lifetime history of serious neurologic injuries or disorders or major medical illness (except hypertension and hyperlipidemia). Female participants were not using oral contraceptives and were not pregnant or lactating. No participants had MRI contraindications (e.g., metal anywhere in or on the body, >250 lbs., claustrophobia). In the AD group only, nicotine dependence, lifetime diagnoses of other substance use disorders or substance-induced mood or anxiety disorders, attention deficit/hyperactivity disorder and antisocial personality disorder were not exclusionary. Independent mood or anxiety disorders that were not secondary to substance dependence and lifetime psychotic disorders were exclusionary.

Procedures

All AD individuals had completed the parent study (which did not include an imaging component) and were rescreened for this study via phone screening conducted by trained research assistants. Healthy controls were recruited via an email flyer sent to a local hospital email list. Controls were also screened over the phone to assess basic eligibility criteria. Qualified controls were then scheduled for a detailed diagnostic interview. The Semi-Structured Assessment for the Genetics of Alcoholism (Hesselbrock et al., 1985) was used in the AD group to determine inclusion and exclusion diagnostic criteria. The Structured Clinical Interview for DSM Disorders II (First et al., 1997) was used in the control group to

assess for Axis I and Axis II disorders in this cohort. Eligible participants were scheduled for imaging. Upon arrival to the imaging session, recent abstinence was confirmed by self-report, urine drug toxicology (DrugTestStrips.com™12 Panel drug test) and cotinine levels (NicAlert; Craig Medical Distribution, Inc. Vista, CA), and breathalyzer (Intoximeter, St. Louis, MO) testing in AD individuals. Pregnancy tests were administered to all females. Following negative toxicology and pregnancy results, self-report questionnaires assessed current mood and coping in the AD group. Consistent with the parent study payment schedules, AD participants were paid $100 for study completion and control participants were paid $75. If positive on toxicology or pregnancy tests, participants were paid $5 and regarded as ineligible for the study. Participants then completed the functional MRI (fMRI) protocol described below.

Measures

In the AD participants, the Time Line Follow Back (TLFB; Sobell and Sobell, 1992) was used to confirm abstinence and measure substance use during the 3 months prior to participating in the study. Individuals with reported abstinence for longer than 3 months were coded as such. To assess current mood, the Beck Depression Inventory-2nd Edition (BDI-II; Beck et al., 1996) was administered to AD participants and total score was computed. The Ways of Coping Questionnaire (WAYS; Folkman and Lazarus, 1980) was administered to assess coping styles in AD individuals. On the WAYS, total scores were calculated to descriptively assess absolute use of individual coping styles (i.e., escape-avoidance, planful problem solving). The Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960) was administered to healthy controls to assess current mood. The total HAM-D score was used to characterize the control sample but was not used in statistical analyses.

fMRI Task Procedure

To assure task instruction comprehension, participants were administered a brief practice test before placement in the scanner. During the 14-minute, event-related, fMRI facial affective processing task, the participants were shown individual faces that displayed fearful, sad, happy, or neutral emotions for 2 seconds (see Fig. 1; Gur et al., 2002). The task was centrally presented using high-resolution video goggles (Resonance Technologies, Inc. Northridge, CA). A fixation cross was presented between stimuli for varying amounts of time (1 to 5 whole seconds). This task has been used previously in fMRI studies of emotion (Gur et al., 2002). Participants were instructed to press button 1 if the face was male and button 2 if the face was female to ensure attention to the stimuli.

Image Acquisition

Imaging was conducted at the University of Cincinnati's Center for Imaging Research, using a 4.0 Tesla Varian, Unity INOVA Whole Body MRI/MRS System (Varian, Inc., Palo Alto, CA). For anatomical reference, a T1-weighted, 3D anatomical brain scan was first obtained using a modified driven equilibrium Fourier transform sequence (T_{MD} = 1.1 seconds, TR = 13 ms, TE = 6 ms, field of view [FOV] = 25.6 × 19.2 × 19.2 cm, matrix 256 × 192 × 96 pixels, flip angle = 20°, 15 in.). Functional images were collected while participants performed the task using a T2-weighted gradient-echo echo planar imaging pulse sequence

(TR/TE = 2,000/30 ms, FOV = 25.6 × 25.6 cm, matrix 64 × 64 pixels, slice-thickness = 4 mm, flip angle = 75°) and were overlaid onto the anatomical image to provide a structural atlas.

Imaging Data Preprocessing

Imaging data were analyzed using the Analysis for Functional NeuroImages (AFNI; Cox, 1996) software. Anatomical data sets were smoothed at 1.8 times the voxel size (5.4 mm), warped into standard space (Talairach and Tournoux, 1988), and resampled into 3.0 mm^3 voxels to align with functional images acquired at the same resolution. As spatial smoothing was conducted at the preprocessing level, spatial blurring was not used in cluster determination. An experienced researcher (CBP) inspected time series data to remove repetitions on which the movement algorithm (Cox and Jesmanowicz, 1999) did not adequately adjust for motion or other artifacts. Using a deconvolution procedure (Ward, 2000), time series data were correlated with a task-specific (fearful and happy faces contrasted with neutral faces) reference function, yielding a fit coefficient that represented the fit between the observed and hypothesized signal for each of the affective faces to prepare for group-level analyses.

fMRI Data Analysis

Using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Mac, Version 22.0. Armonk, NY: IBM Corp.), demographic group differences data were examined with independent samples *t*-tests or chi-square analyses, and variables differentiating the groups were included in subsequent analyses as covariates.

Using AFNI, a whole-brain voxel-wise linear regression analysis was performed to identify clusters that yielded significant group, and group × gender interaction effects for fearful and happy affective faces relative to neutral faces. A Monte Carlo simulation was performed using AFNI's AlphaSim with α of 0.025 for activation intensity threshold and $p = 0.1$ cluster size threshold to control for family-wise error, yielding a cluster size of 1,350 μl to be included in the current analyses (Ward, 2000). Mean activation for each functional region of interest that significantly differed by group, or group × gender interaction was extracted for each participant. These values were then imported into SPSS to confirm statistical significance after controlling for handedness and age (due to the inclusion of left-handed individuals and the large age span encompassed by the sample; Hasan et al., 2007; Szaflarski et al., 2002). Finally, a series of regressions were run in the AD sample to examine whether brain activation in regions that significantly differed according to group and/or group × gender interactions was significantly predicted by depressive symptoms and coping strategies (escape-avoidance, planful problem solving coping scales). Statistical significance decisions were made at $p < 0.05$.

RESULTS

Sample Characteristics

Table 1 depicts descriptive demographic information of the sample. Groups were not significantly different in age, $t(26) = -1.39$, $p = 0.18$, gender, $\chi^2(1) = 0.15$, $p = 0.70$, or

ethnicity, $\chi^2(1) = 1.47$, $p = 0.23$. Rates of left-handedness significantly differed by group, $\chi^2(1) = 4.67$, $p = 0.03$, with all of the left-handed participants falling into the AD group. Healthy controls received scores ranging from 0 to 2 on the HAM-D, well within the normal range. Most (86%) AD individuals reported minimal depressive symptoms. One reported depressive symptoms totaling a score of 15, which is in the mild clinical range (BDI-II Total = 14 to 19), and another reported depressive symptoms totaling a score of 22, which is in the moderate range (BDI-II Total = 20 to 28). TLFB assessment revealed 3 individuals who had consumed alcohol in the 3 months prior to participating, while 9 individuals with AD had maintained abstinence during the prior 3 months. Individuals with AD had comorbid disorders including nicotine dependence ($n = 8$), cocaine or stimulant abuse or dependence ($n = 9$), cannabis abuse or dependence ($n = 9$), other drug abuse or dependence ($n = 9$), substance-induced mood disorder ($n = 6$), posttraumatic stress disorder ($n = 2$), conduct disorder ($n = 4$), and antisocial personality disorder ($n = 2$).

Behavioral Task Results

The affective processing task (see Fig. 1) required participants to identify the gender of facial stimuli throughout the task. Results revealed a difference, $t(25) = 2.53$, $p = 0.02$, in accuracy of identifying gender between AD ($M = 84.1\%$, SD = 5.4%) and control ($M = 89.1\%$, SD = 4.8%) participants.

Primary Results

Whole-Brain Analysis—After controlling for family-wise error, linear regression analyses in AFNI revealed that group, gender, and group × gender interactions significantly predicted brain activation in response to fearful and happy affective faces relative to neutral faces (see Table 2). Activation clusters reported as having differences between group, gender, and group × gender interactions were regions that also elicited activation to the condition contrasts across the entire sample (see Fig S1 and S2). Therefore, it can be can inferred that these are regions related to affective processing. Follow-up linear regression analyses for each significant cluster were conducted in SPSS to control for age and handedness, and results were unchanged. Reported statistics include covariates.

Fearful Faces—*Group*—During the fearful faces condition, the AD group demonstrated reduced BOLD response in comparison to the control group in the right medial frontal gyrus ($t = -3.43$, $B = -0.61$, $p = 0.002$; see Fig. 2).

Fearful Faces—*Group × Gender Interaction*—The interaction of group and gender significantly predicted BOLD response in the left inferior frontal gyrus (IFG) ($t = -4.70$, $B = -0.72$, $p < 0.001$) and the right IFG ($t = -4.43$, $B = -0.73$, $p < 0.001$) during the fearful condition (see Fig. 3). Specifically, male AD individuals showed greater activation than male controls, but female AD individuals showed less activation than female controls.

Happy Faces—*Group*—The AD group demonstrated *increased* BOLD response in the right thalamus during the happy condition compared with controls ($t = 4.46$, $B = 0.73$, $p < 0.001$) (see Fig. 4).

Happy Faces—*Group × Gender Interaction*—During the happy condition, the group × gender interaction predicted left caudate ($t = -3.84$, $B = -0.68$, $p = 0.001$), right middle frontal gyrus ($t = -3.26$, $B = -0.59$, $p = 0.004$), left paracentral lobule ($t = -3.70$, $B = -0.67$, $p = 0.001$), and right lingual gyrus ($t = -4.40$, $B = -0.73$, $p < 0.001$) activation (see Fig. 5). All interactive effects were in the same direction. Specifically, male AD individuals activated more than male controls, but female AD individuals activated less than female controls.

Secondary Results

Mood and Coping in AD Individuals—Within the AD group, greater BOLD activation in the right medial frontal gyrus during the fearful condition significantly predicted increased planful problem solving coping skills ($t = 2.73$, $B = 0.76$, $p = 0.023$; see Fig. 6) after controlling for gender, age, and handedness. Other mood and coping measures were not related to activation patterns in the AD group.

DISCUSSION

The current study demonstrated independent and interactive effects of AD and gender on the neural mechanisms underlying negative and positive facial affective processing. In addition, these regions were also activated across the entire sample during the specific contrasts examined (see Fig S1 and S2). During fearful faces, AD status was related to *decreased* activation in right medial frontal regions relative to healthy individuals. These findings are consistent with previous results that reported reduced activation to negative emotional stimuli in AD individuals compared with controls (Marinkovic et al., 2009; Salloum et al., 2007). This finding has potential relevance because the mPFC has been implicated in drug-seeking behaviors as well as the extinction of fear. Thus, decreased ability to inhibit conditioned responses, such as fear and drug-seeking behaviors, may increase risk for addiction (Peters et al., 2009).

Additionally, there was a significant interaction between AD status and gender in predicting IFG activation: AD females had *decreased* activation compared with female controls, while AD males had *increased* activation compared with male controls. These findings are consistent with previous reports that the IFG is associated with threat detection, such as recognizing fearful faces, as well as gender differences in fearful affective processing (Fine et al., 2009). It is possible that gender may moderate the function of the IFG in processing negative affective stimuli, which may result in craving in addiction-prone individuals (Li et al., 2005). However, these gender effects may also be uncovering important frontal decision-making mechanisms important for processes that lead individuals to drink. The group findings in the current study were generally consistent with results by Salloum and colleagues (2007), who reported blunted fearful face activation in the medial frontal gyrus, but within the context of reduced activation in the anterior cingulate, insula, hypothalamus, caudate, putamen, and superior parietal lobule activation in AD individuals after 28 days of abstinence. The current study examined AD in successfully treated individuals after at least 1 month of abstinence, with some maintaining abstinence for several years, compared to normal social drinkers. This may partially explain why our results are subtler.

Follow-up analyses of regions where group differences were observed revealed increased planful problem solving in the AD group was significantly predictive of greater right mPFC activation during processing of fearful faces. The right mPFC activation region demonstrated decreased activation in individuals with AD compared with controls. In other words, individuals reporting more planful problem solving skills to cope had activation patterns to negative stimuli that were more similar to healthy controls. Problem focused types of coping are more often used when a stressor is deemed to be changeable (Folkman et al., 1986), and the mPFC has been implicated in planning emotional decisions (Ardila, 2008). Thus, it is possible that AD participants who employ more planful problem solving utilize the mPFC more often when appraising negative affective stimuli, which may translate into deeming the situation as controllable or changeable. Alternatively, it may be that AD individuals who utilize this brain region more are better able to planfully problem solve. In sum, the present study is the first to link neural processing of negative affective stimuli to coping style; however, these findings must be verified with additional research.

In contrast to fearful processing, *increased* left thalamus activation was associated with processing happy affective facial stimuli in AD individuals compared with controls. Current results are consistent with those of Heinz and colleagues (2007), who found increased thalamic activation for positive affective images in abstinent AD individuals; however, they also found increased cingulate and striatum activation. The difference between previous reports and our results could be due to our sample being *successfully* treated AD individuals, the wide age range of our sample, inclusion of left-handed individuals, or task design which focused on *facial* affective processing in the current study, whereas Heinz and colleagues (2007) used positively valenced affective images. The thalamus seems to play a role in impulsivity (Bengal et al., 2007), and anticipation of gained rewards (Bjork et al., 2004) particularly in substance-dependent individuals; therefore, aberrant thalamic functioning may be related to increased impulsive drinking or the ability to refuse drinking despite rewarding effects.

Gender moderated the effects of AD on happy facial processing in left middle frontal, paracentral gyrus and caudate areas, and right lingual gyrus. AD females demonstrated reduced brain response compared to control females, while AD males had the opposite pattern. With the exception of the middle frontal gyrus, these subcortical regions are more primitive and have been implicated in promoting positive social interactions (Oscar-Berman and Bowirrat, 2005). The middle frontal gyrus seems to be important in affective decision making (Phan et al., 2002), while the caudate, paracentral gyrus, and lingual gyrus are involved in emotional awareness, emotional feedback, and emotion perception, respectively (Kim et al., 2007; Lovero et al., 2009; Sung et al., 2007). The directions of these interactions were in the same direction as fearful affective processing, and may also be related to frontal lobe functioning critical in decision making.

To our knowledge, this is the first study to examine the interactive effects of AD and gender on neuronal response to affective processing. One possible explanation for these results is differential gender effects of alcohol exposure on morphometic changes in regions underlying affective processing in men and women (Makris et al., 2008; Mann et al., 1992). Women are known to be more susceptible to the brain damaging effects of alcohol, including

volumetric loss in frontolimbic regions involved in affective processing, despite on average having fewer years of drinking and consuming less alcohol in their lifetimes than men (Hommer, 2003; Mann et al., 1992; Medina et al., 2008). However, results are mixed, as other studies have not observed gender differences in the effects of prolonged alcohol exposure (Demirakca et al., 2011; Hommer, 2003; Pfefferbaum et al., 2010). The mechanisms of potential gender differences remain unclear.

Our study has several limitations. First, this was a pilot study and had a small sample size. Gender distributions are not equal between the groups and future studies should have 50% women and men as well as equal proportions in each group. In addition, the inclusion of left-handed individuals, which all fell into the AD group, may have impacted our results despite trying to control for handedness effects statistically. In an attempt to increase our likelihood of detecting activation differences in smaller brain regions (i.e., amygdala, hippocampus), we set activation thresholds at $p = 0.025$ with a cluster size threshold of $p = 0.10$. Therefore, it is possible that our Type I error was inflated, although it is noteworthy that the brain activation pattern differences were consistent with prior studies (Heinz et al., 2007; Li et al., 2005; Salloum et al., 2007) and our resulting volume (1,350 μl) is on par with other imaging studies examining affective processing as well as AD effects (Gilman et al., 2008; Simmons et al., 2008). Second, the current AD sample included individuals who met criteria for other substance use disorders in early or sustained full remission, a lifetime or current diagnosis of substance-induced mood disorder, and antisocial personality disorder, and this heterogeneity may have affected results. Although generalizable to clinical populations with AD, future studies are needed to disentangle the specific influences of each. Alcohol was the primary drug of choice for these individuals, and AD was the motivation for enrollment in the parent study. Third, groups differed in accuracy of identifying gender while viewing the affective facial stimuli, with the AD group being less accurate than controls. Therefore, it is possible that activation patterns observed may be attributable, in part, to differences in basic facial processing ability. Another possible contribution to observed findings are subclinical anxiety and mood symptoms given their effects on the neural mechanisms underlying affective processing (Ball et al., 2012). In addition, we did not find group or gender differences in affective processing in regions previously associated with such a task, such as the amygdala. Despite utilizing a smaller cluster threshold, it is likely that performing a whole-brain analysis decreased the probability of finding activation differences in this region due to the small structure and high likelihood of fMRI signal dropout (Krasnow et al., 2003). An amygdala region of interest analysis may reveal more subtle differences. Given these potential limitations, additional research with larger sample sizes balanced for gender is necessary to examine the impact of AD on affective processing across developmental stages.

In conclusion, this pilot study demonstrated effects of AD, gender, and their interactions on neural processing of fearful and happy faces. These subtle differences in affective processing were seen despite a minimum of 1 month of abstinence in treatment-seeking AD individuals. Follow-up analyses revealed that in AD individuals, increased planful problem solving was predictive of greater right medial frontal gyrus activation during fearful facial processing, which was more similar to activation patterns of controls. This may suggest coping skills training may help normalize neuronal response to negative affective stimuli in individuals

recovering from AD, or those that already possess these skills may have reduced risk of relapse. However, it is important to note that this was a cross-sectional study, so causal inferences cannot be made. Longitudinal studies are critical to tease apart preexisting differences versus those that are a result of chronic alcohol exposure and interventions that may alter these differences in brain activation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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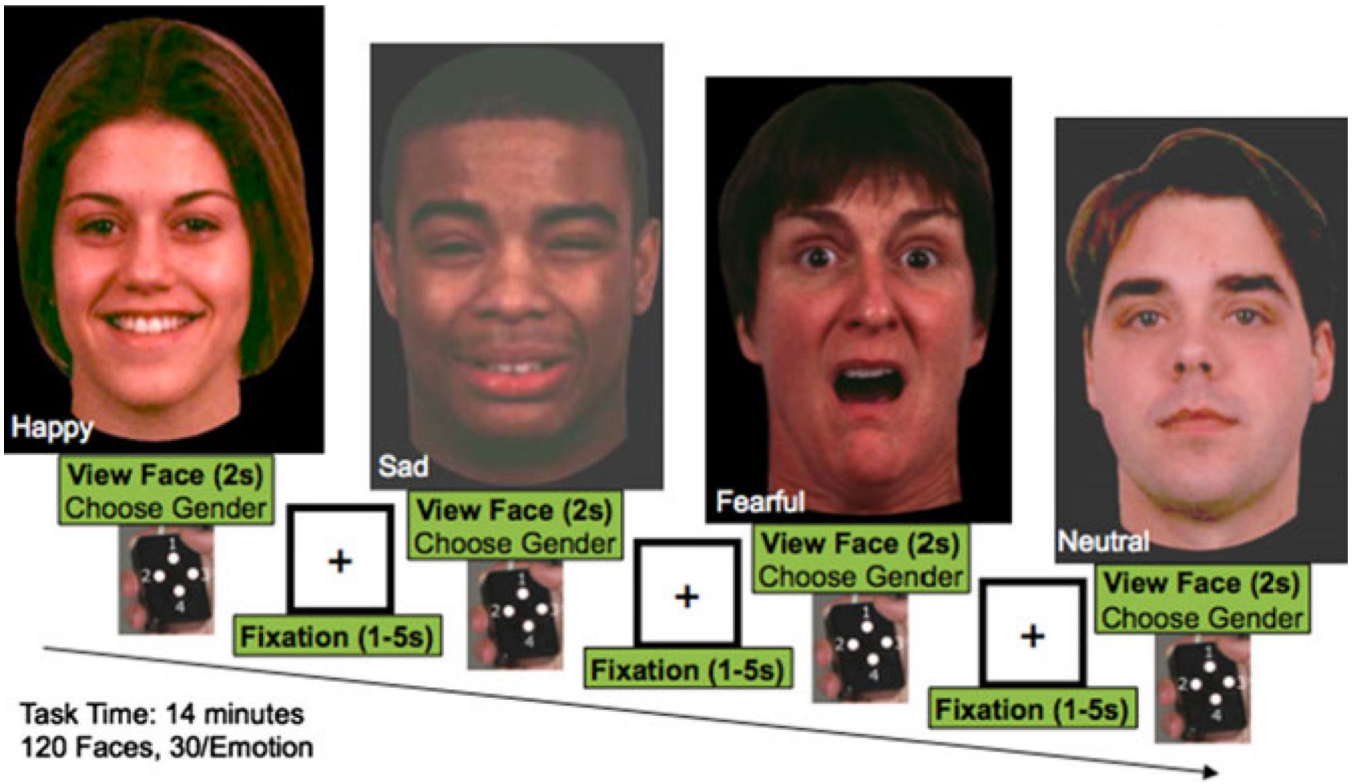

Fig. 1.
Facial affective processing task administered during functional magnetic resonance imaging data collection.

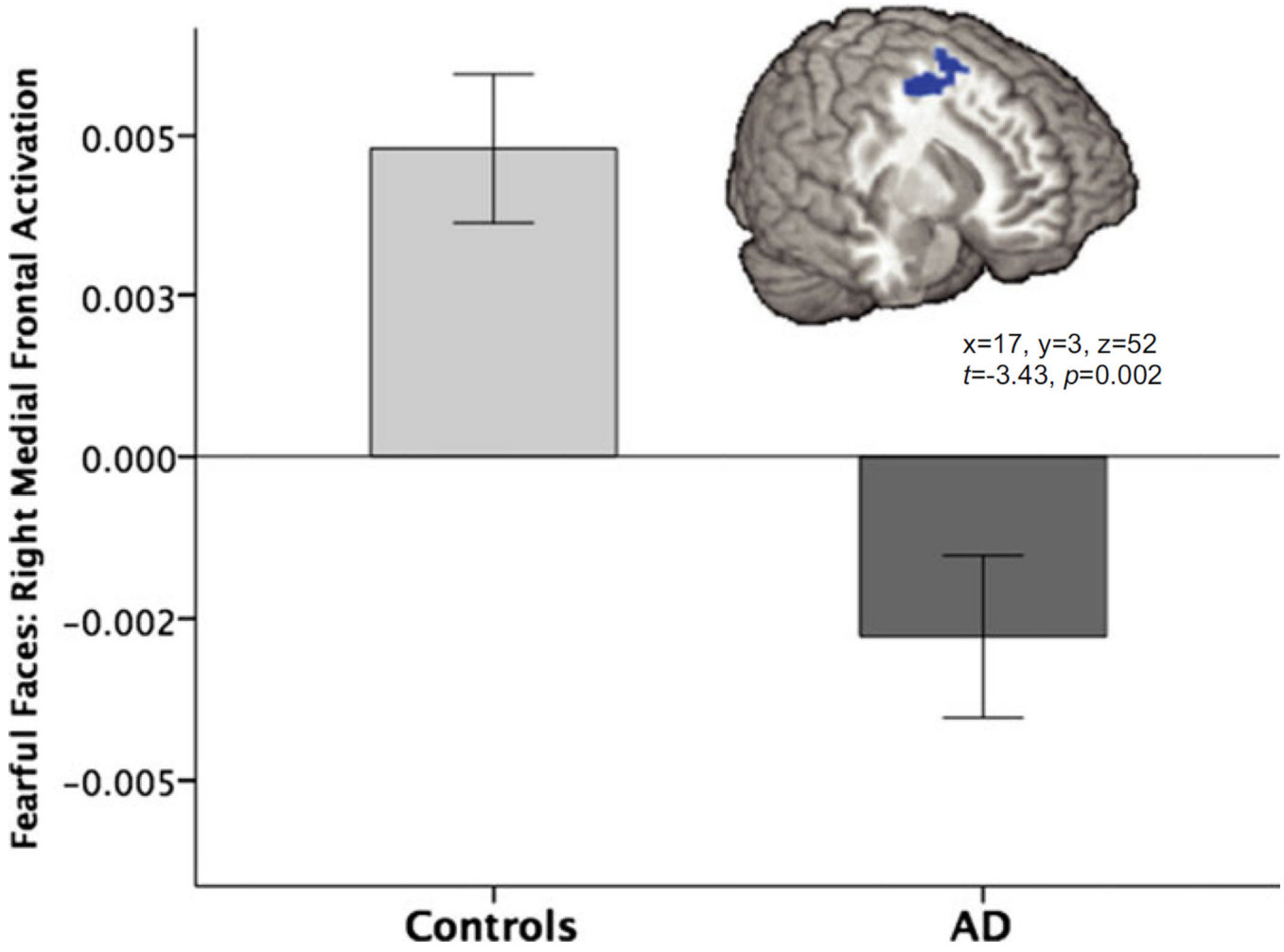

Fig. 2.

Group differences in right medial frontal blood oxygen level dependent activation to fearful versus neutral faces. AD, alcohol-dependent individuals.

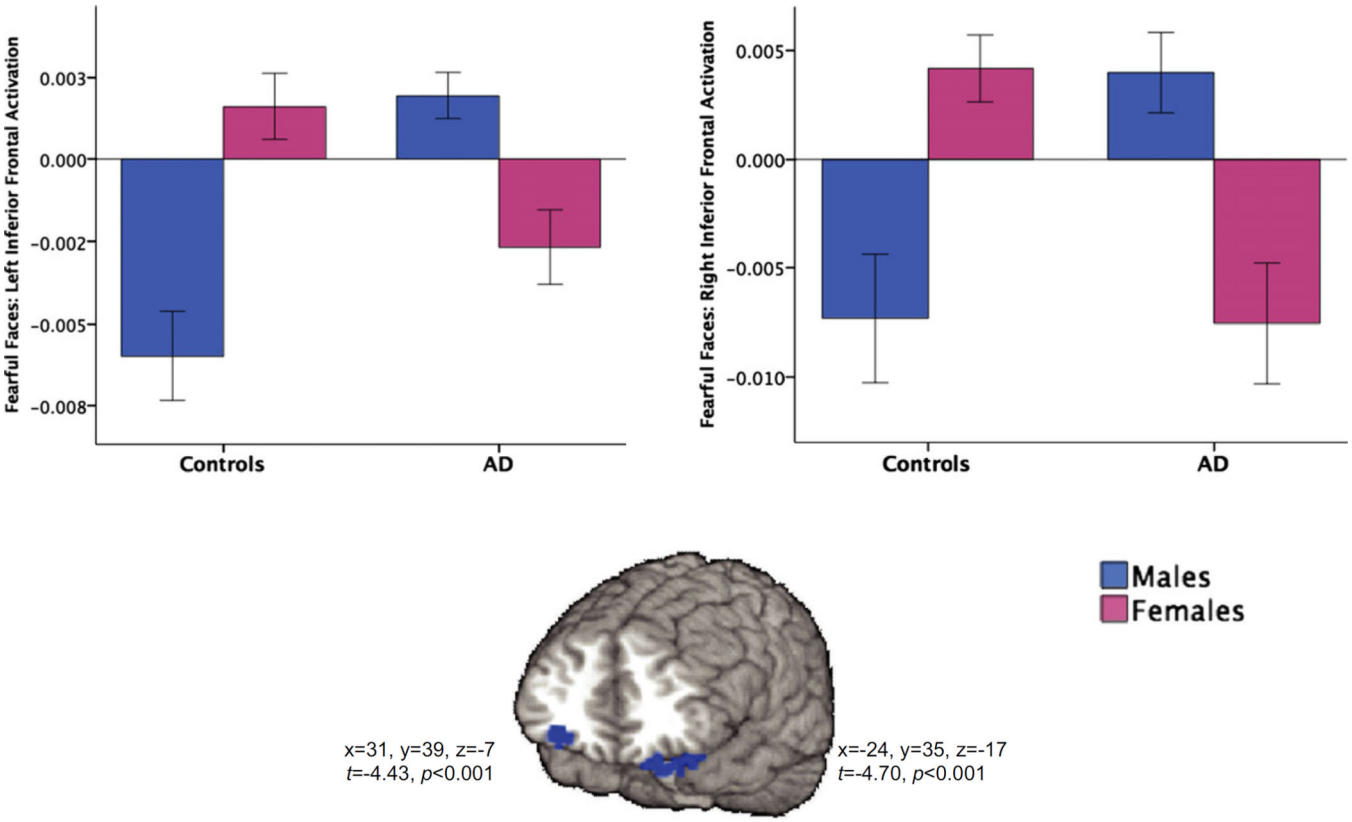

Fig. 3.

Interactive effects of group and gender on left and right inferior frontal blood oxygen level dependent activation to fearful versus neutral faces. AD, alcohol dependent.

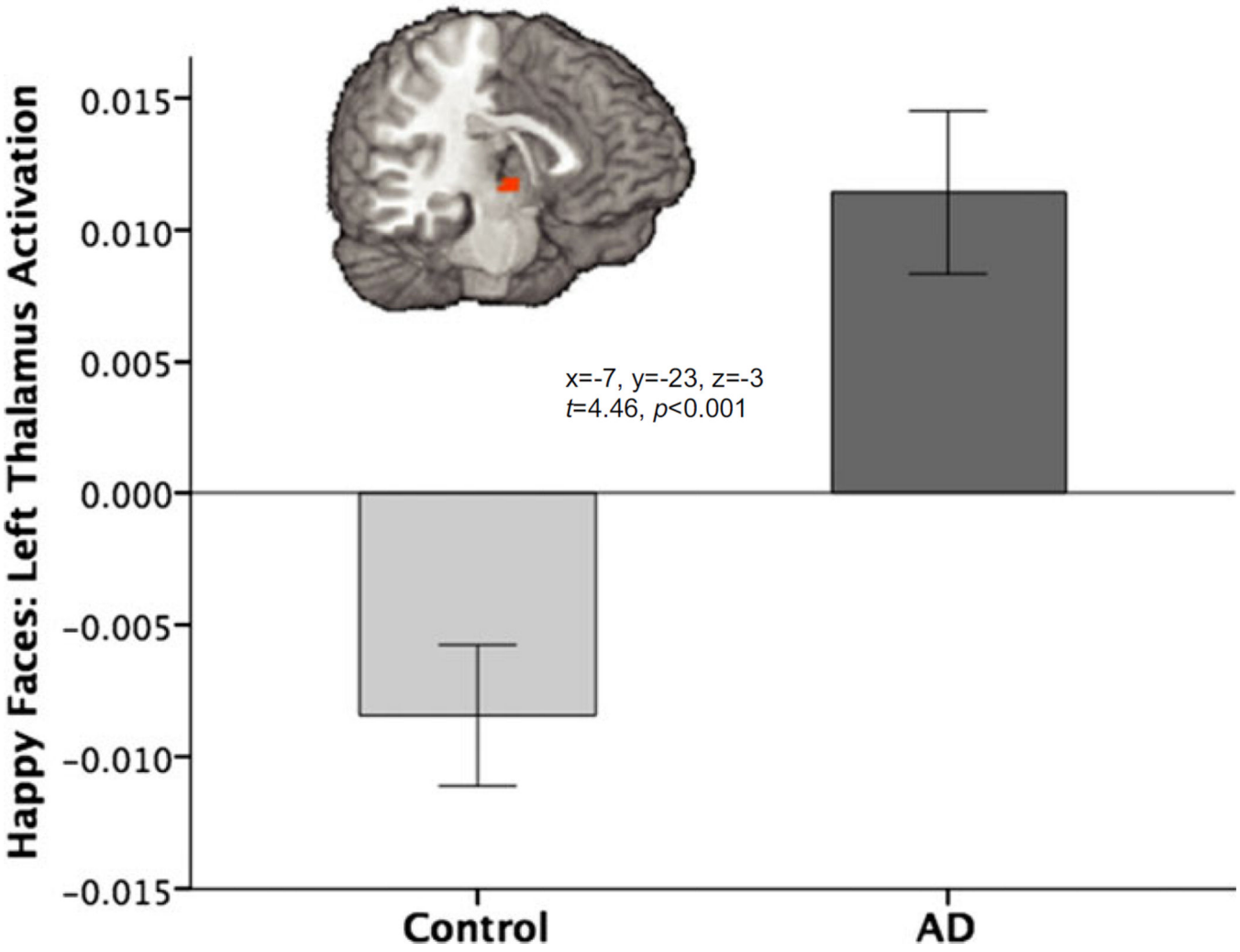

Fig. 4.

Group differences in left thalamus blood oxygen level dependent activation for happy versus neutral faces. AD, alcohol-dependent individuals.

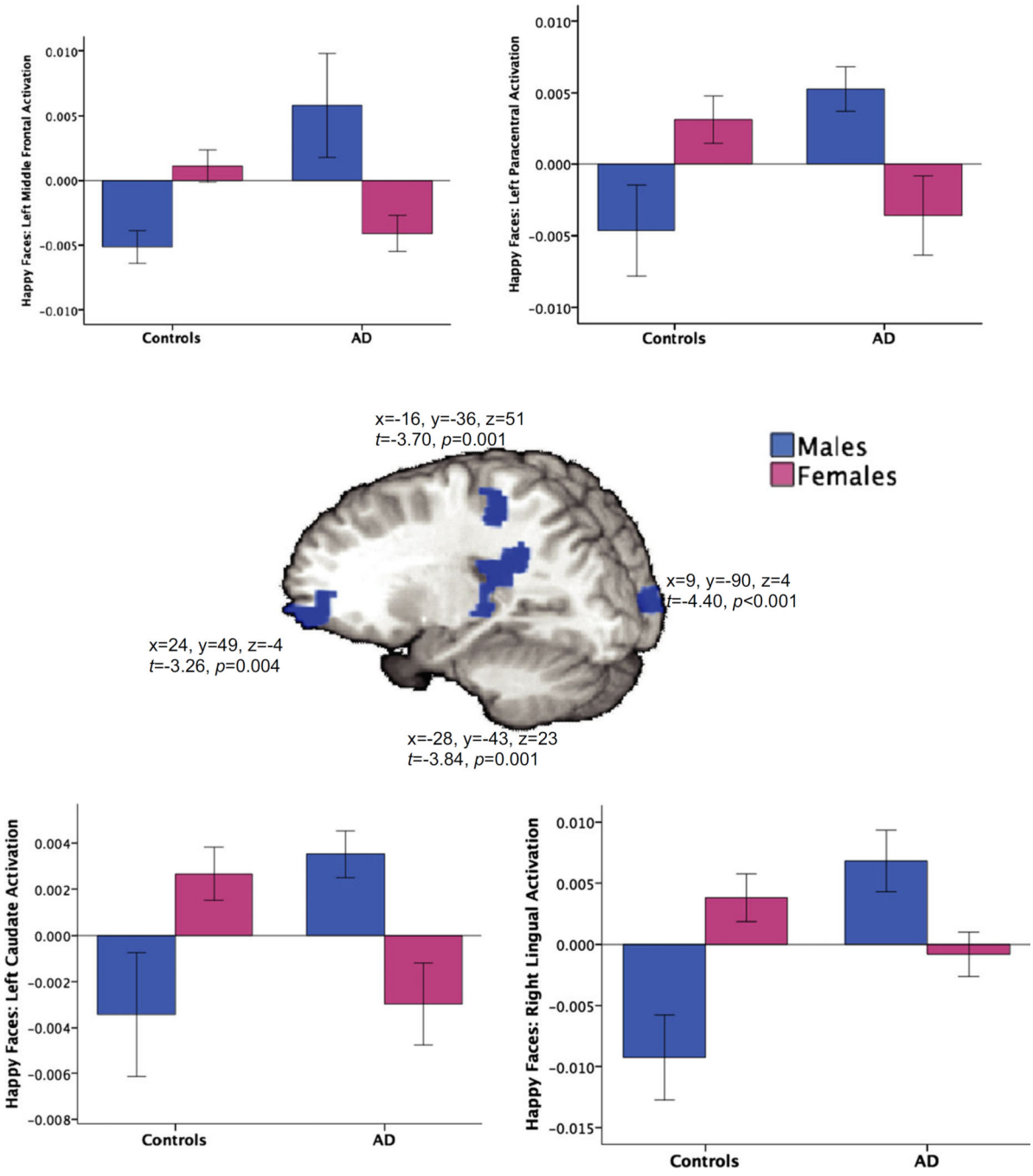

Fig. 5.

Interactive effects of group and gender on left middle frontal, paracentral, caudate, and right lingual blood oxygen level dependent activation during happy versus neutral faces. AD, alcohol dependent.

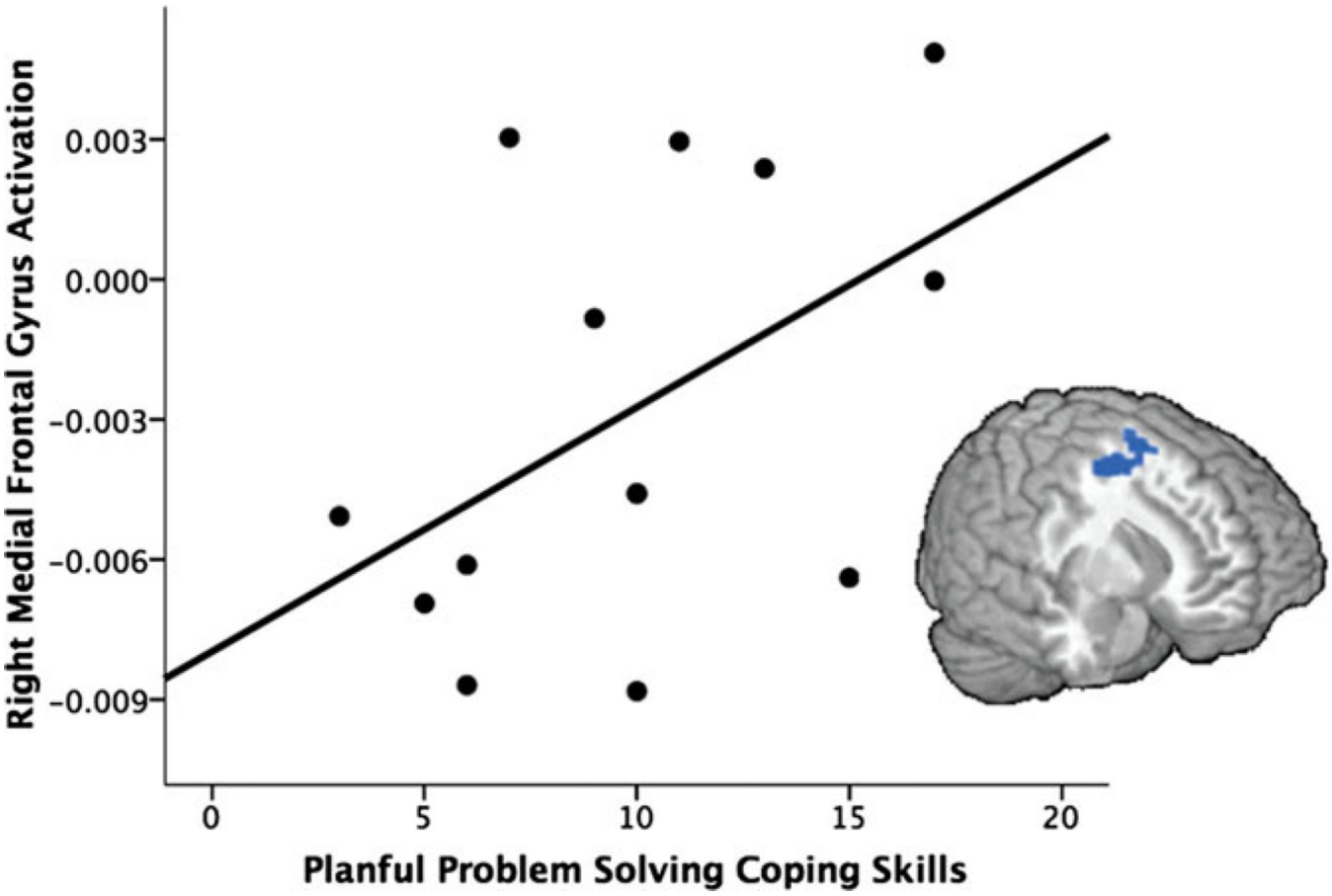

Fig. 6.

Increased planful problem solving is related to greater blood oxygen level dependent activation in the right medial frontal gyrus in AD individuals during processing of fearful versus neutral faces. AD, alcohol-dependent individuals.

Table 1

Characteristics of Alcohol-Dependent (n = 14) and Healthy Control Individuals (n = 14) by Gender

	Alcohol dependent			Healthy controls		
	M (SD)			*M* (SD)		
	Females	**Males**	**Total**	**Females**	**Males**	**Total**
N	8	6	14	9	5	14
Age	37.12 (6.22)	51.33 (4.93)	43.21 (9.13)	37.78 (13.49)	37.20 (10.50)	37.57 (12.08)
% Caucasian	75% (n = 6)	83% (n = 5)	79% (n = 11)	67% (n = 6)	40% (n = 2)	57% (n = 8)
% Right handed[a]	63% (n = 5)	83% (n = 5)	71% (n = 10)	100% (n = 9)	100% (n = 5)	100% (n = 14)
Education (in years)	13.13 (2.17)	13.67 (1.63)	13.36 (1.91)	14.00 (1.41)	16.67 (1.16)	15 (1.85)
% Below poverty	63% (n = 5)	50% (n = 3)	57% (n = 8)	44% (n = 4)	0% (n = 0)	29% (n = 4)
Current nicotine smokers	50% (n = 4)	67% (n = 4)	57% (n = 8)	–	–	–
Recent alcohol use (3 months)	0% (n = 0)	33% (n = 2)	14% (n = 2)	–	–	–
# Drinks if drank in past 3 months	0	91.33 (139.43)	91.33 (139.43)	–	–	–
Alcohol Dependence (AD) Scale total	21.67 (15.50)	14.00 (4.00)	16.88 (9.67)	–	–	–
Days abstinence for parent study	1,385 (1,918)	970 (2,227)	941.57 (1,744.60)	–	–	–
Days abstinent for current study past year (n = 3, all others >1 year)	54.00 (n = 1)	48.5 (n = 2)	50.33 (n = 3)	–	–	–
Beck Depression Inventory-II total	5.13 (7.10)	8 (5.51)	6.36 (6.40)	–	–	–
Hamilton Depression Scale total	–	–	–	0.33 (0.71)	0.40 (0.89)	0.38 (0.77)
Profile of Mood States Tension–Anxiety	6.00 (4.44)	2.83 (3.19)	4.64 (4.14)	–	–	–
State Trait Anxiety Index—State	43.88 (4.58)	43.83 (11.79)	43.86 (8.05)	–	–	–
State Trait Anxiety Index—Trait	43.63 (5.42)	42.50 (11.36)	43.14 (8.11)	–	–	–
PANAS Fear Score	–	–	–	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)
Planful Problem Solving Coping Score	9.88 (4.88)	10 (4.05)	9.93 (4.38)	–	–	–
Escape-Avoidance Coping Score	5.86 (4.12)	7.17 (2.14)	6.43 (3.37)	–	–	–
Task Accuracy[a]	81.25% (0.04)	87.92% (0.05)	84.11% (0.05)	88.78% (0.06)	89.67% (0.03)	89.12% (0.05)

[a]Significant difference between AD and control groups ($p < 0.05$).

Table 2

Whole-Brain Analysis Activation Clusters that Significantly Predicted Group Differences or Group × Gender Interactions by Facial Affect

	Talairach coordinates					
Region	***x***	***y***	***z***	**Volume (μl)**	***t*-value**	***p*-value**
Fearful vs. ne utral results						
Group						
Right medial frontal gyrus (AD < HC)	17	3	52	1,593	−3.43	0.002
Group × gender interaction						
Left inferior frontal gyrus (IFG) (FAD < FHC; MAD > MHC)	−24	35	−17	1,350	−4.70	<0.001
Right IFG (FAD < FHC; MAD > MHC)	31	39	−7	1,350	−4.43	<0.001
Happy vs. neutral results						
Group						
Left thalamus (AD > HC)	−7	−23	−3	1,431	4.46	<0.001
Group × gender interaction						
Left caudate (FAD < FHC; MAD > MHC)	−28	−43	23	2,322	−3.84	0.001
Left middle frontal gyrus (FAD < FHC; MAD > MHC)	24	49	−4	1,917	−3.26	0.004
Left paracentral lobule (FAD < FHC; MAD > MHC)	−16	−36	51	1,566	−3.70	0.001
Right lingual gyrus (FAD < FHC; MAD > MHC)	9	−90	4	1,458	−4.40	<0.001

AD, alcohol-dependent group; HC, healthy control group; F, female; M, male