University of Cincinnati

Date: 1/14/2011

I, Claudia B Padula, hereby submit this original work as part of the requirements for the degree of Master of Arts in Psychology.

It is entitled:
Alcohol Dependence and Gender: An fMRI Pilot Study Examining Affective Processing

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Alcohol Dependence and Gender: An fMRI Pilot Study Examining Affective Processing

A thesis submitted to the
Graduate School
of the University of Cincinnati
in partial fulfillment of the
requirements for the degree of

Master of Arts

in the Department of Psychology
of the McMicken College of Arts and Sciences

by

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Abstract

Alcohol dependence (AD) has global effects on brain structure and function, including frontolimbic regions regulating affective processing. Preliminary evidence suggests alcohol is associated with blunted limbic response to negative affective stimuli and increased activation to positive affective stimuli. Gender differences have also been found in neural correlates of facial affective processing. No studies to date have characterized the independent and interactive effects of AD and gender on the neuronal correlates of affective processing. Therefore, the current study examined whether AD group status, gender and AD*gender interaction predict brain response to happy and fearful affect during a functional magnetic resonance imaging (fMRI) task. Brain regions that differed by AD status were also examined in relation to mood symptoms and coping strategies.

Fourteen abstinent AD individuals (8F, 6M) and 14 healthy controls (9F, 5M), ages 23 to 60, were included in this IRB-approved study. Participants performed a facial affective processing fMRI task. Whole-brain linear regression analyses were performed to extract clusters that yielded significant group, gender, and group-by-gender interaction results for fearful and happy affective processing. Follow-up analyses examined whether brain activation in regions that significantly differed according to AD status or AD*gender interactions significantly predicted depressive symptoms and/or coping styles.

Results revealed that during the fearful condition, the AD group demonstrated reduced BOLD response compared with the control group in the right medial frontal gyrus. Gender analyses demonstrated that females had increased BOLD response during fearful faces in left superior temporal gyrus and right inferior frontal gyrus compared to males. Gender moderated the effects of AD in left and right inferior frontal gyri during the fearful condition. During the happy condition AD individuals had increased BOLD response in right thalamus. Also, females activated more in left hippocampus, but less in right insula and left superior temporal gyrus, as compared to males. Gender moderated the effects of AD in left caudate, right middle frontal
gyrus, left paracentral lobule, and right lingual gyrus activation during happy faces. Interactive effects for fearful and happy faces were in the same direction: AD males activated more than male controls, but AD females activated less than female controls. Follow up analysis revealed that planful problem solving coping predicted greater BOLD activation in right medial frontal gyrus during the fearful condition in the AD group.

Abnormal affective processing in AD individuals may be markers of risk for alcohol problems or consequences of prolonged alcohol exposure. Subtle gender differences were observed, and gender moderated the effects of chronic alcohol exposure on the neural substrates of affective processing. AD individuals with stronger planful problem solving skills had brain activation patterns that were more similar to controls during fearful condition. Although the current pilot study had several limitations, results help elucidate the effects of chronic alcohol exposure, gender and their interaction on facial affective processing, and how coping ability may buffer the effect of alcohol dependence, but future research is needed.
Acknowledgements

There were several individuals who contributed to the current study, including Tom Blom, M.S., Kerri Dawson, B.A., Rebecca Kramer, B.A., Eric Harper, B.A., Patrick Logan, B.A., Omid Khalili, M.S., James Eliassen, Ph.D., Erik Nelson, M.D., the BraiN Laboratory and of course my committee members. Financial support was provided by NIDA R03 DA027457 (Medina), NIAAA R01 AA013307 (Anthenelli), Department of Veterans Affairs Research Services, NIMH K23 MH67705 (Nelson), AstraZeneca IRUSQUET0456 (Nelson), and University of Cincinnati URC Interdisciplinary Grant (Medina & Anthenelli). Thank you to all who have supported this project in many ways. It would not have been possible without you.
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Introduction

Alcohol is the most commonly used drug of abuse, and alcohol dependence costs society an estimated $166.5 billion annually (Stein, 2001). In 1998, approximately 23% of individuals who had used alcohol in the past year reported at least one symptom of dependence, 13% reported at least two symptoms, and 8% reported at least three symptoms (SAMHSA, 2000). In 1997, over 18 million individuals who had used alcohol in the past year reported that they felt the need for treatment, although only 1% of those who had used alcohol had received treatment for alcohol-related problems (SAMHSA, 2000). Alcohol dependence is a chronic, relapsing condition: of 2000 alcohol dependent participants who entered a large-scale study in remission, 51% relapsed at least once over the next three years (Dawson, Goldstein, Rise & Grant, 2007). The underlying mechanisms responsible for the development and maintenance of alcohol dependence, however, remain unclear.

Alcohol Dependence and Affective Processing

Due to the societal as well as individual cost of this prevalent disorder, it is important to understand the underlying mechanisms that perpetuate alcohol dependence. Previous studies have demonstrated a role for mood, affective processing deficits and stress dysregulation in the development and maintenance of this chronic disorder (Koob, 2008; Koob & Volkow, 2010; Oscar-Berman & Bowirrat, 2005; Philippot et al., 1999). Specifically, the risk for addiction and high incidence of relapse might be explained, at least in part, by premorbid and/or alcohol-induced impairments in either positive or negative affective processing (Sinha, 2009; Oscar-Berman & Bowirrat, 2005). Furthermore, facial affective processing deficits to all emotions, positive and negative, have repeatedly been observed in alcohol dependence individuals (Philippot et al., 1999; Foisy et al., 2007). The neural mechanisms that underlie these deficits, however, remain unclear.

Abnormal affective processing has been linked in adults to increased mood irregularities, misinterpretation of environmental cues, and craving for alcohol (Gilman, Ramchandani, Davis,
Bjork & Hommer, 2008; Thorberg & Lyvers, 2006), thus increasing the risk for initiation of problematic drinking behaviors. A related finding is that AD individuals have been shown to have deficits in recognizing affective prosody, which authors speculate may contribute to the interpersonal problem solving difficulties observed in this population (Ukermann, Daum, Schlebusch & Trenckmann, 2005). There is a potential role for aberrant affective processing in the development of alcohol dependence (Gilman et al., 2008; Koob & Volkow, 2010; Thorberg & Lyvers, 2006; Philippot et al., 1999) and abnormal affective processing may also help maintain problematic drinking patterns (Thorberg, Young, Sullivan & Lyvers, 2009), however the exact role positive and negative affective processing plays in alcohol use disorders is still unknown. Therefore, understanding how chronic alcohol exposure affects the neural correlates of processing both positive and negative stimuli in AD individuals compared to controls is of great importance, as abnormal affective processing may be an underlying factor leading to the development and maintenance of alcohol dependence.

Alcohol’s Effect on Frontolimbic Structure

Alcohol produces its reinforcing effects through multiple neurotransmitter systems (Koob, Sanna & Bloom, 1998). Specifically, alcohol enhances inhibitory neurotransmission of GABA, reduces excitatory glutamate neurotransmission and has direct and indirect actions on opiate and cannabinoid synapses and receptors (Stahl, 2008). Ultimately these processes increase dopamine concentrations in extracellular space, especially in the mesolimbic dopamine reward pathway (Merue & Gessa, 1985). Together with increases in serotonin, these neurotransmitter alterations, along with other factors, contribute to the reinforcing effects of alcohol (LeMarquand, Pihl & Benkelfat, 1994). Frontolimbic structures have high GABAergic, serotonergic and dopaminergic receptor densities, implicating these regions in alcohol’s rewarding as well as potentially damaging effects (McBride & Li, 1998; Koob & Volkow, 2010).

Prolonged alcohol exposure has global effects on both brain structure and function. Chronic alcohol exposure in adults leads to widespread atrophy of the cortex, subcortical
regions and cerebellum (Pfefferbaum, Sullivan, Mathalon & Lim, 1997; Schweinsburg et al., 2001; Agartz, Momenan, Rawlings, Kerich & Hommer, 1999). More specifically, chronic alcohol exposure leads to abnormalities in regions that include structures associated with affective processing, such as the frontolimbic reward network (encompassing the dorsolateral prefrontal cortex, orbitofrontal cortex, cingulate cortices, insula, amygdala, hippocampus, nucleus accumbens, and ventral tegmental area) (Krill, Halliday, Scoboda & Cartwright, 1997; Makris et al., 2008). Grey matter has been specifically affected in similar regions (Harper & Krill, 1991; Chanraud et al., 2009; Krill & Halliday, 1999; Jernigan et al., 1991; Shear et al., 1992). However, AD individuals have also demonstrated white matter abnormalities (Harper & Krill, 1988; Hommer et al., 1996; Pfefferbaum & Sullivan, 2002; Pfefferbaum, Adalsteinsson & Sullivan, 2005). Particularly, white matter tracts critical to frontal and limbic connectivity have reduced integrity in AD individuals, particularly in the right hemisphere (Harris et al., 2008), which has been shown to have greater involvement in negative affect processing than the left hemisphere (Oscar-Berman & Schendan, 2000). White and gray matter atrophy may be amenable to some recovery with prolonged abstinence from alcohol (Agartz, Shoaf, Rawlings, Momenan, & Hommer, 2003; Shear, Jernigan & Butters, 1994), and volumes may return to baseline after four years of abstinence (Gansler, Harris & Oscar-Berman, 2000).

With few exceptions (Hommer, 2003), women appear more susceptible than men to the widespread damaging effects of alcohol on the brain, 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 (Mann, Batra, Gunthner & Schroth, 1992; Schweinsburg et al., 2003; Sullivan, Marsh, Mathalon, Lim, & Pfefferbaum, 1995; Agartz et al., 2003; Medina, McQueeny, Nagel, Hanson, Schweinsburg & Tapert, 2008). In sum, chronic alcohol use is associated with widespread volume reductions in areas that include frontolimbic and cerebellar regions, structures underlying the processing of affective stimuli (Blasi, Lo Bianco, Taurisano, Gelao, Romano, Fazio, 2009; Fine, Semrud-Clikeman & Zhu, 2009;
Affective Processing

The prefrontal cortex (especially the medial and orbitofrontal regions), cingulate cortex,limbic system and cerebellum all play a role in affective processing (Blasi, et al., 2009; Fine et al., 2009; Wiethoff et al., 2009; Zald, 2003; Baeken, et al., 2009; Nielen, et al., 2009). Animal research has shown a role of the amygdala and middle prefrontal cortex in emotional learning in animals (Baxter & Murray, 2002; Rozenkranz & Grace, 2002; Rozenkranz & Grace, 2003; DeeProse, Andrade, Varma & Edwards, 2004; Wong, Bernat, Snodgrass & Shevrin, 2004; Laviolette, Lipski & Grace, 2005; Milad, Vidal-Gonzalez & Quirk, 2004; Milad & Quirk, 2002). The amygdala also plays a critical role in affective processing in humans (Pessoa, 2010), particularly during the processing of fearful stimuli. The medial prefrontal cortex has also been implicated in emotional processing, especially in negative emotions, and activation in this region was related to depressive mood in one study (Jimura, Konishi, Asari & Miyashita, 2009). The use of appropriate coping has also been implicated in normalizing brain activation to negative emotional stimuli, specifically decreased amygdala and increased prefrontal cortex activation (Drabant, McRae, Manuck, Hariri & Gross, 2009). There is also evidence for lateralization of affective processing, with the right hemisphere playing a disproportionate role (Oscar-Berman & Schendan, 2000), particularly in the lateral frontal cortex (Wager, Phan, Liberzon, & Taylor, 2003). Studies have suggested that the left hemisphere is more involved in processing of positive affective stimuli, while the right hemisphere plays a more dominant role in processing negative affective stimuli (Gur, Skolnick & Gur, 1994; Baeken et al, 2009; Nielen et al, 2009; Maxwell & Davidson, 2007; Davidson, Shackman & Maxwell, 2004). Authors hypothesize that positive affective stimuli might be better handled by the left hemisphere because language is
more likely to be involved in approaching and engaging in social communication (Oscar-Berman & Bowirrat, 2005; Maxwell & Davidson, 2007).

Gender differences in affective processing have also been reported in healthy adults. Previous research suggests that females are more accurate at recognizing and expressing affective states than males, while men provide faster reaction times during facial affective decision making tasks (Goos & Silverman, 2002; Hall & Matsumoto, 2004). Despite documented behavioral differences, few studies have examined gender differences in neuronal correlates of processing affective stimuli, however of the studies conducted, results seem mixed as to which gender activates more to positive and negative affect, and in which regions. Some studies have not found gender differences in behavioral task performance but rather differences in the underlying neural networks, with activation differences identified in frontal as well as subcortical areas such as the amygdala (Kempton et al., 2004). One study found that negative faces activated the anterior cingulate in both men and women, but males activated left dorsolateral and lateral orbitofrontal areas, while females activated left medial orbitofrontal cortex (Mak, Hu, Zhang, Xiao & Lee, 2009). This same study found that for positive faces, males had greater left lateral orbitofrontal activation than females. However, another study found no gender differences in the neural correlates of negative affective processing, but men had more activation to positive affective stimuli in anterior cingulate, superior temporal, and superior and medial frontal areas, all on the right side. In general, greater laterality is suggested in brain activation among men during affective processing tasks (Harrison, Gorelczenko & Cook, 1990) than women. Therefore, although results have been mixed, the prefrontal cortex and limbic system seem to be consistently and critically involved in affective processing, with some subtle gender differences.

Acute Effects of Alcohol on Affective Processing

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, Ataya, Benton, Penton-Voak & Munafo, 2009). Acute alcohol administration has also been shown to blunt brain response to negative facial stimuli in electroencephalography (EEG) studies (Franken, Nijs, Muris & Van Strien, 2007). Most relevant to the current study due to similar methodologies, Gilman and colleagues (2008) examined neural correlates of fearful facial affective processing during acute alcohol administration using a functional magnetic resonance imaging (fMRI) task. They found that acute alcohol consumption increased activation to fearful stimuli in striatal regions but attenuated activation in visual and limbic areas. Authors speculated that one motivation for drinking may be to reduce negative affect and increase positive affect in response to aberrant affective processing.

Few studies have examined whether gender moderates the acute effects of alcohol on affective processing. One study found that males had more difficulty correctly labeling a sad facial emotion compared to females following a high dose of alcohol (Attwood, Ohlson, Benton, Penton-Voak & Munafo, 2009), although another study reported no gender differences (Craig, Attwood, Benton, Penton-Voak & Munafo, 2009). In summary, acute administration of alcohol seems to blunt neuronal activity in limbic regions during negative affective processing, but it remains relatively unclear whether gender differences exist. To date, no study has reported on the acute effects of alcohol on the neural correlates of processing positive affective stimuli in healthy adults.

Chronic Effects of Alcohol on Affective Processing

The effects of chronic alcohol exposure on neuronal response to affective stimuli remain relatively unknown. AD individuals have been shown to have affective processing deficits (Ukermann et al., 2005), specifically for facial affective stimuli and particularly for happy faces (Philippot et al., 1999). In one of only three fMRI studies, 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 to controls, and this increased activation was related to reduced relapse risk at a six-
month follow up (Heinz et al., 2007); this study did not use facial stimuli consistently throughout
the task, but rather positively valenced imagery. Nonetheless, the authors suggested that the
ability to activate these reward-related regions during the presentation of positive or appetitive
affective stimuli might act as a protective factor against risk for relapse (i.e., patients with this
response on imaging tasks may respond more to natural positive rewards after treatment). 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). A recent 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, alcohol dependence is
associated with blunted brain response to fearful or negative facial affective stimuli and
increased brain response to positive affective picture stimuli. However, these results are based
on only three studies, only two of which included females. Therefore, there is a need to study
the interactive and independent effects of chronic alcohol use and gender on the neural
substrates underlying the processing of both positive and negative facial affective stimuli given
the potential role it plays in alcohol dependence and the relatively sparse research.

Study Aims

The primary aim of the current study was to examine (1) differences in neuronal
response to fearful and happy face processing between abstinent AD and healthy control
groups, (2) gender differences in fearful and happy faces, and (3) 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, since few studies have
examined brain activation in relation to behavioral or functional indices such as subclinical mood
symptoms and/or coping. Based on previous studies (Heinz et al., 2007; Salloum et al., 2007;
Marinkovic et al., 2009), we hypothesized that the AD group would have blunted functional brain response to fearful (Salloum et al., 2007; Marinkovic et al., 2009) and increased response to happy or appetitive cues (Heinz et al., 2007) and that gender would significantly moderate the effects of alcohol dependence on facial affective processing given gender differences in the effects of alcohol on the brain regions underlying affective processing. Lastly, due to the potential relationship affective processing has with mood and affect (Gilman et al., 2008; Thorberg & Lyvers, 2006), we hypothesized that fewer mood symptoms and better coping styles would be related to more normalized brain activation in the regions where AD individuals differed from controls.

Methods

Participants

A total of 29 individuals, ages 23 to 60, were included in the study. Fifteen abstinent individuals with alcohol dependence (9 females, 6 males) were recruited from a parent study that examined hormonal changes with stress (Anthenelli, Blom, Johnson, Heffner & Wand, under review; Anthenelli & Maxwell, 2002; NCT00226694, PI: Anthenelli). Fourteen healthy controls (9 females, 5 males) were recruited from the community as part of a larger study examining stress and brain response in depression (NIMH K23 MH67705, AZ IRUSQUET0456, PI: Nelson). The Institutional Review Boards at the University of Cincinnati and Cincinnati Veterans Administration Medical Center approved all aspects of the study, and all participants provided written informed consent.

AD participants met DSM-IV criteria for AD in sustained, partial, or full remission and were seeking treatment when they enrolled in the parent grant study (NIAAA R01 AA013307 PI: Anthenelli). At the time of the current study, AD individuals were abstinent from all substances for at least one month prior to the MRI session and continued to meet DSM-IV criteria for AD in sustained, partial, or full remission. Controls had no history of any Axis I or Axis II disorders, including substance use disorders (SUD). Recent abstinence from drugs and alcohol were
confirmed by drug toxicology (DrugTestStrips.com™12 Panel drug test), cotinine levels (NicAlert) and breathalyzer (FC10 Breath Alcohol Tester® to verify .000 breath alcohol concentration) testing in AD individuals. Exclusionary criteria for both groups included current use of psychotropic medication, lifetime history of serious neurologic injuries or disorders, major medical illness (except hypertension and high cholesterol), known diagnosis of an Axis I psychiatric disorder or Axis II personality disorder in the control group, use of oral contraceptives, current pregnancy or lactation in women, or MRI contraindications (e.g., metal anywhere in or on the body, greater than 250 lbs., claustrophobia). In the AD group only, nicotine dependence, substance use disorders in early or sustained full remission, a lifetime or current diagnosis of substance-induced mood disorder, attention deficit/hyperactivity disorder and antisocial personality disorder were not exclusionary. Current mood or anxiety disorders that were not secondary to substance use or lifetime psychotic disorders were exclusionary.

 Procedures

All AD individuals had previously participated in the parent grant (PI: Anthenelli). Current eligibility criteria and recent drug use were examined via phone screening by trained research assistants. Healthy controls were recruited via an email flyer sent to a local hospital list serve (PI: Nelson). Interested healthy controls were screened over the phone to assess basic eligibility criteria. Qualified controls were then scheduled for a detailed diagnostic interview. The Semi-Structured Assessment of the Genetics of Alcoholism (SSAGA; Hesselbrock, Meyer & Keener, 1985) was used in the AD group to assess for Axis I disorders that met exclusionary criteria. The Structured Clinical Interview for DSM Disorders II (SCID-II; First, Gibbon, Spitzer, Williams & Benjamin, 1997) was used in the healthy control group also to assess for Axis I and Axis II disorders. If eligible, participants were scheduled for imaging. Upon arrival to the imaging study session, trained researchers collected bioassays in the AD group (not controls) to assess recent drug use (urine toxicology screen, cotinine test, breathalyzer), and pregnancy tests were administered to all (AD and control) females. After participants demonstrated negative results
on toxicology and pregnancy tests, self-report questionnaires (described below) were administered to assess current mood and coping strategies 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 participants tested positive on toxicology or pregnancy tests, they were paid $5 and regarded as ineligible for the study. Participants then completed the fMRI protocol described below.

**Measures**

In the AD participants, the *Time Line Follow Back* (TLFB; Sobell & Sobell, 1992) was used to confirm abstinence and measure substance use during the three months prior to participating in the study. The TLFB utilizes memory cues of common holidays and personal events to measure frequency of alcohol and drug use (assessed month-by-month). To assess current mood disturbance, the *Beck Depression Inventory- 2nd Edition* (BDI-II; Beck, Steer, Ball & Ranieri, 1996) was administered to AD participants. This task is a 21-item self-report questionnaire that was designed to elicit respondents’ descriptions of their depressive symptoms over the past two weeks. The BDI-II has been shown to be reliable, internally consistent and valid in a sample of adults (Arnau, Meagher, Norris & Bramson, 2001). The BDI-II total score was used in the current study. The *Ways of Coping Questionnaire* (Folkman & Lazarus, 1980) was administered to assess coping styles. This measure has been found to be reliable and valid in identifying the thoughts and actions an individual has used to cope with stressful encounters (Folkman, Lazarus, Gruen & DeLongis, 1986). On the WAYS, total scores for each of the eight scales were calculated to descriptively assess absolute use of the coping style instead of relative use compared to other coping styles. Higher scores indicated more frequent use of the coping subtype. Each scale is comprised of four to eight questions, where higher scores indicate the person uses those behaviors often when coping with a stressful event. For example, planful problem solving skills involve abilities such as focusing on the situation at hand and drawing from previous experience to create adaptive solutions to a
problem (Folkman & Lazarus, 1980). Problem focused types of coping are more often used when the situation at hand is deemed to be changeable than in situations that must be accepted (Folkman & Lazarus, 1985). Calculating total scores for each scale yielded eight independence coping scales and did not provide relative coping use compared to other coping styles. Therefore, the raw total score for each individual coping scale was used in the current study to assess the absolute use of the coping style, not relative to other coping styles. The Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960) was administered to healthy controls to assess current mood; this examiner-administered measure has been shown to be valid and reliable for assessing the severity of depressive symptoms (Hedlung & Veiweg, 1979). The total HAM-D score was used to characterize the control sample in the current study but was not used in statistical analyses. Different mood measures were available in the two groups because participants were from different parent studies. The HAM-D was used to rule out depressive symptoms in the controls, along with the SCID-II. Coping style was only assessed in AD individuals.

**fMRI Task Procedure**

Participants were administered a brief practice task before placement in the scanner to assure comprehension of task instructions. 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 two seconds (see Figure 1; Gur et al., 2002a; Gur et al., 2002b). The task was centrally presented using high-resolution video goggles (Resonance Technologies, Inc. Northridge, CA). Note that the sad faces were included in the larger protocol but were not analyzed in the present study because they do not relate to the present hypotheses. A fixation cross was presented between stimuli for varying amounts of time (1-5 whole seconds). The stimuli were color photographs of actors and actresses who were coached by theater directors to express different emotions, a subset of which were selected for the fMRI task based on a high degree (>80%) of identification accuracy by raters. This task has been
used previously in fMRI studies of emotion (Gur et al., 1994; Gur et al., 2007; Gur et al., 2002). The actors were Caucasian, African American, Asian or Hispanic. Thirty faces were presented for each facial expression, generating a total of 120 images. The emotional valences were presented in a semi-randomized order; although two faces showing the same emotion could consecutively appear in the task, no emotion was displayed three or more times in a row. Participants were instructed to press button one if the face was male and button two if the face was female. This condition ensured attention to the stimuli and cooperation throughout the task, which was assessed by researcher monitoring of continuous responding as stimuli were presented.

**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). To provide an anatomical reference for the fMRI data, a T1-weighted, 3-D anatomical brain scan was first obtained using a modified driven equilibrium Fourier transform sequence \( T_{MD} = 1.1 \text{ s}, \text{TR} = 13 \text{ ms}, \text{TE} = 6 \text{ ms}, \text{FOV} = 25.6 \times 19.2 \times 19.2 \text{ cm}, \text{matrix} 256 \times 192 \times 96 \text{ pixels}, \text{flip angle} = 20 \text{ degrees, } 15^{\circ} \). Functional images were collected while participants performed the task using a T2-weighted gradient-echo echo planar imaging pulse sequence \( \text{TR/TE} = 2000/30 \text{ ms}, \text{FOV} = 25.6 \times 25.6 \text{ cm}, \text{matrix} 64 \times 64 \text{ pixels, slice-thickness} = 4 \text{ mm}, \text{flip angle} = 75 \text{ degrees} \) and were overlaid onto the anatomical image to provide a structural atlas.

**Imaging Data Preprocessing**

The imaging data were analyzed using the Analysis for Functional NeuroImages (AFNI; Cox, 1996) software. Anatomical datasets were warped into standard space (Talairach & Tournoux, 1988), and functional data were resampled into 3.0 mm\(^3\) voxels and smoothed at 1.8 times the voxel size (5.4mm). An experienced researcher inspected the time series data to remove any repetitions on which the movement algorithm (Cox & Jesmanowicz, 1999) did not adequately adjust for motion or other artifacts. Using a deconvolution procedure (Ward, 2000),
the time series data were correlated with a task-specific (fearful and happy faces contrasted with neutral faces) reference function. This multiple linear regression yielded 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, group differences in demographic data were examined with independent samples t tests or chi-square analyses, and variables that differentiated 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, gender, and group-by-gender interaction effects for fearful and happy affective faces relative to neutral faces. A Monte Carlo simulation was performed using AFNI’s AlphaSim program with alpha set at 0.025 for activation intensity threshold and $p = 0.1$ cluster size threshold to control for family-wise error, which required a cluster size of $1350\mu l$ to be included in the current analyses (Ward, 2000). Mean activation for each functional region of interest that significantly differed by group, gender, or the 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; Szaflarski, Binder, Possing, McKiernan, Ward & Hammeke, 2002; Hasan et al., 2007)]. Finally, a series of regressions was run in the AD sample to examine whether brain activation in regions that significantly differed according to group status and/or that showed group-by-gender interactions was significantly predicted by depressive symptoms (BDI-II) and coping strategies (WAYS escape-avoidance, planful problem solving coping scales). All decisions about statistical significance were made at $p < 0.05$. 
Results

Sample Characteristics

Table 1 includes descriptive demographic information for AD and control groups. Groups were not significantly different in age [$t(26)=-1.39$, $p=0.18$], gender [$x^2(1)=0.15$, $p=0.70$], or ethnicity [$x^2(1)=1.47$, $p=0.23$]. Rates of left-handedness significantly differed by group [$x^2(1)=4.67$, $p=0.03$], with all of the left-handed participants falling into the AD group. Healthy controls received scores ranging from 0-2 on the Hamilton Depression Rating Scale, which was well within the normal range. Of the AD individuals, most (86%) reported minimal depressive symptoms. One AD individual reported depressive symptoms totaling a score of 15, which is in the mild clinical range (BDI Total = 14-19), and another reported depressive symptoms totaling a score of 22, which is in the moderate range (BDI Total = 20-28).

Behavioral Task Results

The affective processing task 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 in identifying gender between AD ($M=84.11\%, SD=5.45\%$) and control ($M=89.12\%, SD=4.79\%$) participants.

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Insert Table 1 here
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Primary Results

Whole Brain Analysis. After controlling for family-wise-error, linear regression analyses in AFNI revealed that group, gender and group by gender interactions significantly predicted brain activation in response to fearful and happy affective faces, after subtracting out neutral face activation (see Table 2). Follow-up linear regression analyses for each of these significant clusters were conducted in SPSS to control for age and handedness, and results were
unchanged. Reported statistics from the SPSS analysis, which are in parenthesis after each cluster, include the covariates in the model.

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Fearful Faces. Group. During the fearful faces condition, the AD group demonstrated a 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 Figure 2).

Gender. Females demonstrated increased BOLD response during fearful faces in the left superior temporal gyrus ($t = 4.20$, $B = 0.70$, $p < 0.001$, see Figure 3) and right inferior frontal gyrus ($t = 3.77$, $B = 0.62$, $p = 0.001$, see Figure 3) compared to males.

Group by Gender Interaction. The interaction of group and gender significantly predicted BOLD response in the left inferior frontal gyrus ($t = -4.70$, $B = -0.72$, $p < 0.001$) and the right inferior frontal gyrus ($t = -4.43$, $B = -0.73$, $p < 0.001$) during the fearful condition (see Figure 4). Specifically, male AD individuals showed greater activation than male controls, but female AD individuals showed less activation than female controls.

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Happy Faces. Group. In contrast to the fearful results, the AD group demonstrated increased BOLD response in the right thalamus during the happy condition compared to the controls ($t = 4.46$, $B = 0.73$, $p < 0.001$). (See Figure 5).

Gender. During the happy faces condition, females activated more in the left hippocampus ($t = 3.64$, $B = 0.55$, $p = 0.001$) but less in the right insula ($t = -3.88$, $B = -0.66$, $p = 0.001$) and the left superior temporal gyrus ($t = -3.45$, $B = -0.59$, $p = 0.002$) as compared to males (see Figure 6).
Group by Gender Interaction. During the happy condition, the group by 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 Figure 7). 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

Follow Up Analyses: 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 ($t = 4.01, B = 0.79, p = 0.003$, see Figure 8). Other mood (BDI-II) and coping (escape – avoidance) measures were not related to activation patterns in the AD group.

Discussion

Fearful Affective Processing in AD Individuals: Overview of Findings

The current study demonstrated independent and interactive effects of alcohol dependence and gender on the neural mechanisms underlying negative and positive facial affective processing. In terms of response to fearful faces, alcohol dependence was related to decreased activation in right medial frontal regions relative to activation patterns in healthy individuals. The medial prefrontal cortex has been implicated in drug-seeking behaviors as well as in the extinction of fear, meaning decreased ability to inhibit conditioned responses, such as
fear and drug-seeking behaviors, which may increase risk for addiction (Peters, Kalivas & Quirk, 2009). This relationship between the medial prefrontal cortex and decreased ability to inhibit fear might partly be explained by the overlap in brain regions responsible for identifying fear in others and the ability to feel the emotional state of fear (Derntl et al., 2010). On the other hand, the medial prefrontal cortex may be related to addiction more generally (Peters et al., 2009).

In general, females viewing fearful faces had increased activation in inferior frontal and superior temporal areas relative to males; however, AD females actually had *blunted* bilateral responses in this region compared with female controls, while AD males had increased activation compared with male controls. These findings are consistent with previous reports that inferior frontal regions are associated with threat detection, such as recognizing fearful faces, as well as gender differences in fearful affective processing (Fine et al., 2009). Inferior frontal regions have also been linked to stress-induced craving in cocaine dependent individuals, with gender differences in the neuronal pattern exhibited during stress (Li, Kosten & Sinha, 2005), suggesting that this region may be generally related to addiction. It is possible that gender may moderate the function of inferior frontal regions in processing negative affective stimuli, which may result in craving in addiction-prone individuals, as reported in cocaine addiction (Li, Kosten & Sinha, 2005); however the current study did not examine this relationship, so this hypothesis is more speculative. The group findings in the current study were generally consistent with results by Salloum and colleagues (2007), who reported blunted fearful affective 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 an average of 28-days of abstinence. The current study examined formerly problematic drinking in successfully treated AD individuals after at least one month of abstinence, with some individuals maintaining abstinence for years, compared to normal social drinkers, not AD individuals compared with non-drinkers. This may partially explain why our results are more subtle than those in previous reports.
Follow up analyses revealed that increased planful problem solving in the AD group was significantly predictive of greater right medial frontal gyrus activation during processing of fearful faces. In other words, individuals using more planful problem solving skills as a coping strategy had brain activation patterns to negative stimuli that were more similar to those of the healthy controls. Planful problem solving skills involve abilities such as focusing on the situation at hand and drawing from previous experience to create adaptive solutions to a problem (WAYS, Folkman & Lazarus, 1980). Problem focused types of coping are more often used when the situation at hand is deemed to be changeable than in situations that must be accepted (Folkman & Lazarus, 1985), and the medial prefrontal cortex has been implicated in planning emotional decisions (Ardila, 2008). Thus, it is possible that AD participants who employ more planful problem solving utilize the medial frontal gyrus more often when appraising negative affective stimuli, which may translate into deeming the situation as controllable or changeable rather than something that must be accepted. 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 planful problem solving coping style; however these findings need to be verified with additional research. Activation in regions that differed by group or group by gender was not related to mood or other coping skills.

Self-report research on the acute effects of alcohol in non-substance-dependent, social drinkers suggests that alcohol is used to enhance positive affect and reduce negative affect (Cooper, Frone, Russel & Mudar, 1995; Kassel, Jackson & Unrod, 2000). A complementary finding is that AD individuals report that a primary reason for alcohol consumption is to reduce negative affect (Woody, Urshel & Alterman, 1992). However, there was no direct relationship observed in the current study with respect to internal mood state. Perhaps mood and more negative coping styles (i.e., escape-avoidant) are related to processing of different affective stimuli, such as sad facial affective, and we therefore did not find a relationship since we did not
examine other facial affective processing. Alternatively, mood and other coping abilities may only be related to internal affect and not the processing of affect in external stimuli.

Only one study to date has examined whether brain activation patterns in response to affective stimuli are related to functional outcomes. Heinz and colleagues (2007) found that increased activation to positive stimuli was related to reduced risk of relapse in AD individuals at a six-month follow-up. The authors suggest that the ability of AD individuals to respond to pleasant stimuli may be a protective factor that contributes to a positive treatment outcome. We observed a more normalized activation pattern AD individuals with stronger planful problem solving abilities, although the current study was not designed to test the link between brain activation patterns and functional outcomes like relapse. Nonetheless, planful problem solving may also be a contributing, protective factor for AD individuals by engaging the medial prefrontal cortex, a region known to be involved in emotional decision making (Ardila, 2008). If, in fact, individuals with beneficial coping skills exhibit neural patterns more similar to healthy controls as the current data suggest, then resiliency to relapse could potentially improve with the successful implementation of coping skills training in a treatment setting. Taken together, these two studies suggest that neuronal activation patterns during affective processing and coping ability need to be examined in future research. More adaptive coping styles may be related to normalized brain response to affective stimuli (Drabant et al., 2009), and could aid in normalizing function in treatment settings, which could be related to functional outcomes. For example, coping ability has been linked to reduced risk for relapse (Hasking & Oei, 2008), but the underlying mechanism for this relationship has not been explored. In summary, successfully increasing planful problem solving coping might help alleviate some of the aberrant affective processing demonstrated by male and female AD individuals. However, as stated above future studies are critically needed to examine if increasing coping ability can normalize neuronal response to affective processing and whether this intervention is linked to decreased relapse rates.
Happy Affective Processing in AD Individuals: Overview of Findings

In contrast to fearful processing, increased left thalamus activation was associated with processing happy affective facial stimuli in AD individuals compared with controls. These group 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 increases in activation in the anterior cingulate and striatum, which we did not. 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 used positively valenced affective images. The thalamus seems to play a role in impulsivity (Bengal, Antony, Venkatasubramanian & Jayakumar, 2007), and anticipation of gained rewards (Bjork, Knutson, Fong, Caggiano, Bennett & Hommer, 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 differences were observed such that females activated more in the left hippocampus, but less in the right insula and the left superior temporal gyrus. Gender also moderated the effects of AD on happy facial processing in left middle frontal, paracentral gyrus and caudate areas and the right lingual gyrus. Similar interaction patterns were observed as with fearful face processing in that 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 & Bowirrat, 2005). The middle frontal gyrus seems to be important in the interpretation of affective stimuli or affective decision-making (Pan, Wager, Taylor & Liberzon, 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, Simmons, Aron & Paulus, 2009; Sung, Yoo, Yoon, Oh, Han & Park, 2007).
Most regions found to have independent and interactive effects of group and gender in the present study were in the left hemisphere. In general, our results are consistent with the large body of literature suggests that the left hemisphere is more involved in processing positive affect while the right hemisphere plays a more dominant role in processing negative affect (Gur et al., 1994; Baeken et al, 2009; Nielen et al, 2009, Maxwell & Davidson, 2007). Authors of previous research suggest that this asymmetry might be explained by assuming that positive affect might be better handled by the left hemisphere, as this function is used to inform behaviors that involve approaching and engaging in social communication (Oscar-Berman & Bowirrat, 2005), although this hypothesis was not directly tested in the current study.

**Aberrant Affective Processing in AD Individuals**

Abnormal affective processing in AD males and females may be a marker of risk for alcohol problems or consequences of prolonged alcohol exposure. Regarding the former, animal studies have revealed that reduced limbic function causes decreases in alcohol consumption (Moller, Wiklunch, Sommer, Thorsell & Heilig, 1997), suggesting an important role of the limbic system in alcohol seeking behaviors. If decreased limbic function is related to decreased alcohol consumption, perhaps premorbid increases in limbic functioning to appetitive cues could lead to increased alcohol seeking behaviors. This hypothesis needs further examination in human longitudinal studies. In addition, children of alcoholics demonstrate altered emotional reactivity to environmental cues and affective recognition abnormalities before any exposure to alcohol (Monnot, Nixon, Lovallo & Ross, 2001; Miranda, Meyerson, Buchanan & Lovallo, 2002), suggesting a premorbid genetic or familial environmental influence. Therefore, although the neural mechanisms underlying the interaction between affective processing and alcohol consumption are not fully understood, there is some evidence to suggest that abnormal affective processing could predate and put individuals at risk for alcohol use disorders.

On the other hand, affective processing deficits are also observed after acute alcohol exposure, and so in addition to any affective vulnerabilities in individuals who go on to develop
AD, those who drink may also show diminished performance on affective tasks because of the direct role that alcohol plays in affective processing (Attwood et al., 2009; Attwood et al., 2009; Craig et al., 2009; Franken et al., 2007; Gilman et al., 2008). Chronic alcohol exposure, which is more characteristic of the participants in the present study, has been associated with white matter abnormalities (Harper & Kril, 1988; Hommer et al., 1996; Pfefferbaum & Sullivan, 2002; Pfefferbaum et al., 2005) and grey matter volume reductions in both cortical and subcortical areas, particularly in frontal, temporal, hippocampal, caudate, and cerebellar regions (Chanraud et al., 2009; Harper & Kril, 1991; Kril & Halliday, 1999; Jernigan et al., 1991; Shear et al., 1992). Specifically, white matter tracts critical to frontal and limbic connectivity have reduced integrity in AD individuals, particularly in the right hemisphere, which has been demonstrated to have greater involvement in negative emotional processing than the left hemisphere (Harris et al., 2008; Oscar-Berman & Schendan, 2000). Thus, these structural changes may underlie some of the cognitive and emotional abnormalities (Sullivan & Pfefferbaum, 2005) as well as the affect misidentification (Uekermann et al., 2005; Philippot et al., 1999) observed in AD individuals. Functional connectivity studies in conjunction with white matter track analysis are needed to further understand the relationship between structure and function in this population. Although these deficits are consistent across studies, cortical white matter volume changes and overall shrinkage may be amenable to some recovery with prolonged abstinence from alcohol (Shear et al., 1994), and it is suggested that recovery of these morphologic brain changes may return to baseline levels after four years of abstinence (Gansler et al., 2000). Our group findings were subtle, and involved fewer regional differences than previous studies on affective processing in AD individuals (Heinz et al., 2007; Salloum et al., 2007; Marinkovic et al., 2009); however, our sample may have had a longer recovery period, with 86% of AD individuals abstinent for more than three months. Further, with continued abstinence it is possible that the subtle differences observed in the current study may no longer be significant.
Additional research is needed to understand the independent and interactive effects of risk for developing alcohol dependence and the effects of chronic alcohol exposure. Subtle affective processing abnormalities may put individuals at risk for developing alcohol dependence (Monnot et al., 2001; Miranda et al., 2002) and alcohol consumption to compensate for these abnormalities may exacerbate the deficits (Attwood et al., 2009; Attwood et al., 2009; Craig et al., 2009; Franken et al., 2007; Gilman et al., 2008). Longitudinal studies in high and low risk individuals are needed to disentangle the chronological emergence of these abnormalities.

**Gender Differences in Affective Processing**

In the current study, gender differences were seen in brain activation, with females demonstrating greater BOLD response in left temporal and right frontal regions to fearful faces compared to males. However, when processing happy faces, females exhibited greater activation patterns in the left hippocampal, but less activation in the right insular and left temporal areas compared with males. Estrogen’s effect on neurotransmitters that are prolific in neural structures related to affective processing (McBride & Li, 1998; Koob & Volkow, 2010) may explain some of the neurocognitive gender differences observed. Specifically, estrogen exerts profound effects on serotonin and dopamine release, particularly in frontal and limbic regions, therefore indirectly affecting mood, craving and emotion processing (Fink, Sumner, Rosie, Grace & Quinn, 1996). Previous research by Mak and colleagues (2009) found gender differences in affective processing such that viewing negative faces was associated with activation in the anterior cingulate in both genders, but males activated left dorsolateral and lateral orbitofrontal areas, while females activated left medial orbitofrontal cortex. For positive faces, males had greater left lateral orbitofrontal activation than females (Mak et al., 2009), which are different regions than the ones found in this study. One potential reason for these contrasting results is the age range of participants. Previous studies examining gender differences in affective processing focused primarily on young adults (Mak et al., 2009; Baeken
et al, 2009; Nielen et al, 2009). The current study included a wider age range (29-58 in the AD group and 23-60 in controls), which encompassed pre- and post-menopausal women and, thus, greater variations in sex hormone levels (Phillips & Sherwin, 1992) were possible. However, the hormonal status of women in the study was not assessed during the imaging session, and therefore this relationship cannot be directly examined in the current study. Regardless, gender differences observed in the current study may not be consistent with previous research because of hormonal variations throughout development. Additional research including teens, young adults, middle adults and older adults are needed to examine the impact of gender on affective processing across the lifespan.

**Gender Moderates the Effects of AD on Affective Processing**

To our knowledge, this is the first study to examine the interactive effects of alcohol dependence and gender on neuronal response to affective processing. Sex steroids may interact with chronic alcohol exposure through various neurotransmitters (LeMarquand et al., 1994) resulting in these gender-moderating effects on affective processing. For example, sex hormones in healthy individuals have been found to have opposing effects on brain activation to fearful faces; oxytocin seems to attenuate amygdala activation in men but enhance activation in women (Domes et al., 2010). While a similar pattern of attenuated activation in men but increased activation in women was true for the healthy control group in the current study, the AD group demonstrated the opposite pattern. Therefore, additional research is needed to examine the impact of hormones on brain response in AD male and females.

Another possible explanation for these results is differential gender effects of alcohol exposure on morphometric changes in regions underlying affective processing in men and women (Kril et al., 1997; Makris et al., 2008; Pfefferbaum et al., 1997; Schweinsburg et al., 2001; Mann et al., 1992; Schweinsburg et al., 2003; Sullivan et al., 1995; Agartz et al., 2003). Women are known to be more susceptible to the widespread damaging effects of alcohol on the brain, 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 (Mann et al., 1992; Schweinsburg et al., 2003; Sullivan et al., 1995; Agartz et al., 2003; Medina et al., 2008, Hommer, 2008), however the mechanisms of these gender differences remains unclear (Thomasson, 1995; Greenfield, 2002). In sum, gender moderated the functional differences observed in alcohol dependence in the current study, and this may be due to gender moderated structural abnormalities in regions associated with affective processing.

The interactive effects of alcohol dependence and gender during affective processing observed in the current study might help explain different rates of comorbid mood and externalizing behavior problems in men and women with alcohol dependence. Specifically, in clinical settings AD women are more likely to have depressive symptoms or comorbid depressive disorders than AD men (Boykoff et al., 2010; Landheim, Bakken & Vaglum, 2003), however this was not observed in the current study. Similarly, AD men are more likely to display aggressive and externalizing behaviors than AD women (Landheim et al., 2003), however this was also not measured in the current study. Previous research has found that mood disorders are associated with blunted emotional processing activation (Ritchey, Dolcos, Eddington, Strauman & Cabeza, 2010) and individuals with aggressive behavior problems demonstrate neural hyperresponsivity (Lee, Chan & Raine, 2009). Specifically, aggressive behaviors were associated with hyperactivation to threatening stimuli in the hippocampus, fusiform gyrus, posterior cingulate, thalamus and occipital cortex (Lee et al., 2009). With respect to mood, depressed individuals had overall reduced brain activity in the ventromedial prefrontal cortex compared to health controls (Ritchey et al., 2010). Speculatively, these studies may partly explain the attenuated activation of AD women compared to AD men and control women, and the hyper activation of AD men compared to AD women and control men observed in the current study. Although studies on mood and aggression examined only fearful or threat processing, the patterns and regions are similar during both fearful and happy affective processing in the current study. Future studies examining the impact of mood and aggression
symptoms on affective processing in males and females with AD could help explain why these behavioral differences are observed clinically (Landheim et al., 2003).

Limitations

There were several limitations to the current study that should be noted. This was a pilot study and had a limited sample size. 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 (Salloum et al., 2007; Li et al., 2005; Heinz et al., 2007) and our resulting volume (1350 µl) is on par with other imaging studies examining affective processing as well as alcohol dependence effects (Simmons, Matthews, Feinstein, Hitchcock, Paulus & Stein, 2008; Gilman et al., 2008). Secondly, our study aimed to characterize affective processing differences between AD individuals and healthy controls that did not meet criteria for substance use disorders, although social drinking in our controls was possible. Our study did not examine dose-dependent effects of recent alcohol use on affective processing, but rather the effects of problematic drinking behavior. On balance, the AD group included a treatment-seeking community sample that was able to successfully maintained abstinence for an extended period of time. Therefore, the ability for the brain to recover with prolonged abstinence from alcohol (Shear et al., 1994) may explain why our results were, in general, more subtle than prior affective processing studies (Salloum et al., 2007; Heinz et al., 2007) that included participants who had shorter periods of abstinence. Furthermore, the current AD sample included individuals who met criteria for nicotine dependence, substance use disorders in early or sustained full remission, a lifetime or current diagnosis of substance-induced mood disorder and antisocial personality disorder. However, alcohol was the primary drug of choice for these individuals, and alcohol dependence was the motivation for enrollment in the parent study. The inclusion of left handed individuals and the wide age range included in this study may also have unforeseen
influence on the results despite controlling for these variables statistically (Szafarzski et al., 2002; Hasan et al., 2007). Participants were asked to identify gender and were not required to label or match emotion directly, which made the task more passive in relation to facial affective processing. 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. 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.

**Conclusion & Future Directions**

In conclusion, this pilot study demonstrated effects of alcohol dependence, gender, and their interactions on neural processing of fearful and happy faces. Specifically, alcohol dependence was related to decreased activation in right medial frontal regions when processing fearful faces, whereas increased left thalamus activation was associated with happy faces in AD individuals. Gender moderated the effects of AD on brain response in several task-related regions. Specifically, during fearful faces, AD females activated less than female controls in left and right inferior frontal areas, while AD males demonstrated the opposite pattern. For happy facial processing, the left middle frontal, paracentral gyrus and caudate areas and the right lingual gyrus showed that AD females demonstrated reduced brain response while AD males had the opposite pattern. These subtle differences in affective processing were seen despite a minimum of one month of abstinence in treatment seeking AD individuals. Perhaps most
notably, follow up analyses revealed that in the 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 healthy controls. This suggests the possibility that coping skills training may help normalize neuronal response to negative affective stimuli in individuals recovering from alcohol dependence, or those that already possess these skills may have reduced risk of relapse.
References


Table 1. Characteristics of Alcohol Dependent \((n = 14)\) and Healthy Control Individuals \((n = 14)\).

<table>
<thead>
<tr>
<th></th>
<th>Alcohol Dependent</th>
<th>Healthy Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% or (M (SD), \text{Range})</td>
<td>% or (M (SD), \text{Range})</td>
</tr>
<tr>
<td>Age</td>
<td>43.21 (9.13), 29-58</td>
<td>37.57 (12.08), 23-60</td>
</tr>
<tr>
<td>% Female</td>
<td>57%</td>
<td>64%</td>
</tr>
<tr>
<td>% Caucasian</td>
<td>79%</td>
<td>57%</td>
</tr>
<tr>
<td>% Right handed*</td>
<td>71%</td>
<td>100%</td>
</tr>
<tr>
<td>Education (in years)</td>
<td>13.36 (1.91), 10-17</td>
<td>15 (1.85), 12-18</td>
</tr>
<tr>
<td>Household Income (% below poverty)</td>
<td>57%</td>
<td>29%</td>
</tr>
<tr>
<td>% Nicotine Smokers</td>
<td>57%</td>
<td>-</td>
</tr>
<tr>
<td>Recent Alcohol Use in Past 3 Months</td>
<td>14%</td>
<td>-</td>
</tr>
<tr>
<td># Drinks if Drank in Past 3 Months ((n=3))</td>
<td>91.33 (139.43), 2-252</td>
<td>-</td>
</tr>
<tr>
<td>Alcohol Dependence Scale ((n=8))</td>
<td>16.88 (9.67), 6-37</td>
<td>-</td>
</tr>
<tr>
<td>Days Abstinent Parent Study</td>
<td>941.57 (1744.60), 27-5515</td>
<td>-</td>
</tr>
<tr>
<td>Days Abstinent Current Study ((n=8))</td>
<td>1003.14 (1696.70), 29-4759</td>
<td>-</td>
</tr>
<tr>
<td>Beck Depression Inventory Total Score</td>
<td>6.36 (6.40), 0-22</td>
<td>-</td>
</tr>
<tr>
<td>Hamilton Depression Scale</td>
<td>-</td>
<td>0.38 (0.77), 0-2</td>
</tr>
<tr>
<td>WAYS Planful Problem Solving Scores</td>
<td>9.93 (4.38), 3-17</td>
<td>-</td>
</tr>
<tr>
<td>WAYS Escape-Avoidance Scores</td>
<td>6.43 (3.37), 1-12</td>
<td>-</td>
</tr>
</tbody>
</table>

Notes: *significant difference between groups \((p < 0.05)\)
Table 2. Brain activation clusters that significantly predicted group or gender differences or group by gender interactions by facial affect.

<table>
<thead>
<tr>
<th>Region</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Volume (µl)</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
</table>

**Fearful vs. Neutral Results**

**Group**

- Right medial frontal gyrus (AD<HC)  
  -17.4  -3.2  52.5  1593  -3.43  0.002

**Gender**

- Left superior temporal gyrus (F>M)  
  43.7  52.4  14.9  1566  4.20  <0.001

- Right inferior frontal gyrus (F>M)  
  -47.8  -3.0  24.2  1350  3.77  0.001

**Group* Gender Interaction**

- Left inferior frontal gyrus (FAD<FHC; MAD>MHC)  
  24.9  -35.8  -17.0  1350  -4.70  <0.001

- Right inferior frontal gyrus (FAD<FHC; MAD>MHC)  
  -31.0  -39.3  -7.0  1350  -4.43  <0.001

**Happy vs. Neutral Results**

**Group**

- Left thalamus (AD>HC)  
  7.0  23.2  -3.4  1431  4.46  <0.001

**Gender**

- Left hippocampus (F>M)  
  -48.6  25.6  31.5  7722  3.64  0.001

- Right insula (F<M)  
  27.7  43.3  5.9  1539  -3.88  0.001

- Left superior temporal gyrus (F<M)  
  41.2  20.2  19.4  1485  -3.45  0.002

**Group* Gender Interaction**

- Left caudate (FAD<FHC; MAD>MHC)  
  28.0  43.6  23.5  2322  -3.84  0.001
| Left middle frontal gyrus (FAD<FHC; MAD>MHC) | 24.6 | -49.6 | -4.1 | 1917 | -3.26 | 0.004 |
| Left paracentral lobule (FAD<FHC; MAD>MHC) | 16.7 | 36.7  | 51.2 | 1566 | -3.70 | 0.001 |
| Right lingual gyrus (FAD<FHC; MAD>MHC) | -9.9  | 90.2  | 4.2  | 1458 | -4.40 | <0.001 |

Notes: AD = alcohol dependent group; HC = healthy control group; F = female; M = male
Figure 1. Facial affective processing task administered during fMRI data collection.
Figure 2. Group differences in right medial frontal BOLD activation to fearful vs. neutral faces.
Figure 3. Gender differences in left superior temporal and right inferior frontal BOLD activation during fearful vs. neutral faces.
Figure 4. Interactive effects of group and gender on left and right inferior frontal BOLD activation to fearful vs. neutral faces.
Figure 5. Group differences in left thalamus BOLD activation for happy vs. neutral faces.
Figure 6. Gender differences in right insula, left superior temporal and hippocampal BOLD activation during happy vs. neutral faces.
Figure 7. Interactive effects of group and gender on left middle frontal, paracentral, caudate and right lingual BOLD activation during happy vs. neutral faces.
Figure 8. Increased planful problem solving is related to greater BOLD activation in the right medial frontal gyrus in AD individuals during processing of fearful vs. neutral faces.