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PREFRONTAL CORTEX VOLUMES IN ADOLESCENTS WITH ALCOHOL USE DISORDERS: UNIQUE GENDER EFFECTS

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ABSTRACT

Background. Adolescents with alcohol use disorders (AUD) have shown smaller prefrontal cortex (PFC) volumes compared to healthy controls; however, differences may have been due to comorbid disorders. This study examined PFC volumes in male and female adolescents with AUD who did not meet criteria for comorbid mood or attention disorders.

Methods. Participants were adolescents aged 15-17 who met criteria for AUD (n=14), and demographically similar healthy controls (n=17). Exclusions included any history of a psychiatric or neurologic disorder other than AUD or conduct disorder. MRI scans occurred after at least 5 days of abstinence from alcohol or drugs. Overall PFC volumes and white matter PFC volumes were compared between groups.

Results. After controlling for conduct disorder, gender, and intracranial volume, AUD teens demonstrated marginally smaller anterior ventral PFC volumes (p=.09) than controls, and significant interactions between group and gender were observed (p<.001 to p<.03). Compared to same-gender controls, females with AUD demonstrated smaller PFC volumes, while males with AUD had larger PFC volumes. The same pattern was observed for PFC white matter volumes.

Conclusions. Consistent with adult literature, alcohol use during adolescence is associated with prefrontal volume abnormalities, including white matter differences. However, adolescents with AUD demonstrated gender-specific morphometric patterns. Thus, it is possible that gender may moderate the impact of adolescent alcohol use on prefrontal neurodevelopment, and the neurodevelopmental trajectories of heavy drinking boys and girls should be evaluated separately in longitudinal studies.

Keywords: Adolescence, Brain Imaging**,** MRI, Alcohol Abuse, White Matter, Prefrontal Cortex

1. INTRODUCTION

In the U.S., alcohol is the most widely consumed intoxicant among adolescents, with 75% of 12th graders having drank. More startling is that 30% of seniors reported getting drunk in the previous month (Johnston et al., 2005). Given the prevalence of alcohol use during adolescence, its effects on neuromaturation are of great interest.

In adults, the prefrontal cortex (PFC) appears to be particularly vulnerable to the neurotoxic effects of alcohol use (Desmond et al., 2003; George, et al. , 2004; Pfefferbaum et al., 2001; Pfefferbaum et al., 1997; Schweinsburg et al., 2001; Sullivan et al., 2003). Postmortem studies have found reduced glial and neuronal cell densities in the PFC of adults with alcohol use disorders (AUD) (Miguel-Hidalgo, et al., 2006). Morphometric studies have revealed smaller PFC total volume (Kubota et al., 2001; Liu, et al., 1998), gray matter (Chanraud et al., 2007; Liu et al., 1998; Pfefferbaum et al., 1997), and white matter volume (Kril, et al., 1997; Pfefferbaum et al., 1997) among adults with alcohol use disorders compared to controls. The more anterior portions of the PFC appear most vulnerable to alcohol-induced neurotoxic effects (Kril et al., 1997). Gender may moderate the effects of alcohol on PFC morphometry. It appears that women with AUD may be more sensitive to the neurotoxic effects of alcohol than men (Agartz, et al., 1999; Hommer, et al., 2001; Mann et al., 2005; Schweinsburg et al., 2003), although some studies have pointed to relative vulnerabilities in males (Pfefferbaum et al., 2001) and others found no evidence of brain abnormalities among alcoholic females (Kroft et al., 1991; Pfefferbaum, et al., 2002).

Because neuromaturation continues into late adolescence (Giedd et al., 1996; Lenroot & Giedd, 2006; Sowell, et al., 2004) studies based on adults cannot necessarily generalize to adolescents with AUD, particularly findings in the PFC, a late region to undergo gray matter pruning (Gogtay et al., 2004; Lenroot & Giedd, 2006; Sowell, Thompson, et al., 2004). Maturation of white matter appears to continue into the twenties, with white matter volume typically increasing (Giedd, et al, 1999; Jernigan & Gamst, 2005; Paus et al., 2001) and PFC white matter integrity improving (Ashtari et al., 2007; Barnea-Goraly et al., 2005; Watts, et al., 2003) from childhood to adulthood, although one study found decreased white matter density from ages 16-17 (Paus et al., 1999). Gender differences in neuromaturation also exist. Females' frontal gray matter volumes peaks at age 11.0 while males' peak at age 12.1 years on average, and male brains are about 9% larger than females' (Giedd, Vaituzis et al., 1996). Furthermore, in contrast with most prior studies of white matter neuromaturation (e.g., Giedd et al., 1999; Pfefferbaum et al., 1994; Reiss et al., 1996), our laboratory found that among healthy adolescent females ages 12-18, PFC white matter volume actually decreased from age 15-18, while males' PFC white matter remained relatively stable (Nagel et al., 2006). Thus, as male and female brains mature with somewhat different time courses during adolescence, neurotoxic exposures may have disparate effects.

Animal models indicate that adolescence is a period of particular vulnerability to the neurotoxic effects of alcohol (Barron et al., 2005; Carpenter-Hyland, 2007; Crews, et al., 2000; Spear, 2000). Compared to adults, adolescent animals exposed to alcohol are more likely to demonstrate cognitive, social, and neuronal damage (Crews, et al., 2000; Little et al., 1996; Pyapali, et al., 1999; Silveri & Spear, 1998; Swartzwelder, et al., 1995; Swartzwelder, et al., 1998; Varlinskaya & Spear, 2006; White et al., 2002; Yttri, Burk & Hunt, 2004). Despite that many of these abnormalities are subserved by frontal systems, few studies have examined the PFC morphometric consequences of heavy alcohol use during adolescence in humans.

Thus far, human adolescent studies examining the neural effects of heavy drinking have suggested alcohol-related structural (De Bellis et al., 2000; De Bellis et al., 2005, Medina et al., 2007; Nagel et al., 2005), and functional (Tapert et al., 2004) abnormalities. Specifically,

despite similar performance during a spatial working memory task, adolescents with AUD showed less PFC and cerebellar activation to complete the task as compared to controls (Tapert et al., 2004), with a greater degree of abnormality linked to lifetime alcohol withdrawal symptoms. These results may indicate that the brain compensates for subtle alcohol-induced neuronal insult by relying on other areas (e.g., parietal cortex). A follow-up study revealed that gender moderated the relationship between alcohol use and brain response to this spatial working memory task (Caldwell et al., 2005). That is, after controlling for typical blood alcohol concentrations, girls with AUD demonstrated less frontal cortex response than female controls, while the males showed the opposite pattern. Overall, females demonstrated more alcohol-related abnormalities than males.

The only study to date examining PFC morphometry (defined as anterior to the genu) in adolescents with AUD compared a treatment sample of 13- to 21-year-olds with AUD and other Axis I disorders (including conduct, depressive, attention deficit hyperactivity, post-traumatic stress, generalized anxiety, bipolar, and cannabis and hallucinogen use disorders) to controls without a history of AUD (De Bellis et al., 2005). Even after controlling for comorbid disorders, males and females with AUD demonstrated smaller PFC total and white matter volumes than controls, although psychiatric contributions cannot entirely be ruled out, and gender-by-group interactions were not found.

Therefore, no studies to date have examined PFC volume among adolescents with AUD without comorbid psychiatric disorders. As comorbid psychiatric and other premorbid risk factors for substance use disorders (e.g., familial AUD) are also linked to neurocognitive abnormalities (Kamarajan et al., 2006; Kim, et al., 2001; Kruesi et al., 2004; Meyerhoff et al., 2004; Tapert & Brown, 2000), the current study examined the relationship between AUD and PFC structure among adolescents without comorbid mood, attention, or anxiety disorders. Conduct disorder, which is highly prevalent among adolescents with AUD, was statistically controlled for, and family history of substance use disorders was equivalent between the groups. A secondary goal of the study was to examine whether gender moderated the relationship between alcohol use and PFC morphometry.

METHODS

Participants

Adolescent participants ages 15 – 17 were recruited from San Diego area high schools (Medina et al., 2007; Tapert et al., 2004; Tapert et al., 2003). Written informed consent and assent were obtained from each participant and parent in accordance with the University of California San Diego Human Research Protections Program. Participants and their parents were screened for eligibility with telephone interviews. Exclusion criteria included history of head injury with loss of consciousness >2 minutes, neurological or medical problems, learning disabilities, DSM-IV psychiatric disorder other than conduct disorder as ascertained by the Computerized Diagnostic Interview Schedule for Children 4.0 (Shaffer, et al., 2000) parent and youth versions, current psychotropic medication use, significant maternal drinking (≥4 drinks per occasion or ≥7 drinks per week) or drug use during pregnancy, family history of bipolar I or psychotic disorder as assessed by the Family History Assessment Module screener (Rice et al., 1995), left handedness, and MRI contraindications. Teens meeting criteria for mild or moderate conduct disorder (n = 5) were not excluded due to high comorbidity with substance use disorders (Button et al., 2006). Eligible participants in the current study were 14 teens (9 male) who met current criteria for DSM-IV alcohol use disorders (AUD) and 17 (10 male) demographically similar non-abusing controls with limited alcohol experience.

Measures

Demographic and Behavioral Assessment. Screening interviews were conducted separately with each teen and their parent to obtain information on personal and family background. Adolescents and parents were administered parallel versions of the Computerized NIMH Diagnostic Interview Schedule for Children 4.0 (Shaffer et al., 2000) to ascertain current and past psychiatric disorders for adolescent participants, the Family History Assessment Module screener (Rice et al., 1995) to determine family history of substance use and other psychiatric disorders, and a structured clinical interview (Brown, et al., 1989) to collect information on demographic characteristics, medical and developmental history, and social and academic functioning.

Substance Involvement. Substance involvement was determined with the Customary Drinking and Drug Use Record (Brown et al., 1998), which collects lifetime and past 3-month information on alcohol, nicotine, and other drug use, and assesses DSM-IV abuse and dependence criteria, withdrawal symptoms, and other consequences of substance use. Good internal consistency, test-retest, and inter-rater reliability have been demonstrated with adolescents (Brown et al., 1998, Stewart & Brown, 1995). The Timeline Followback (Sobell & Sobell, 1992) obtained substance use patterns for the 30 days prior to scanning. Participants provided samples for Breathalyzer (Intoximeter, St. Louis) and urine drug toxicology on the day of scanning.

Procedures

Participants were asked to abstain from alcohol and other drugs for at least 48 hours before scanning. Imaging sessions were held on Thursday evenings to maximize recovery from weekend drinking and to minimize possible circadian influences. All participants submitted samples for Breathalyzer and urine drug toxicology analyses prior to scanning.

Anatomical imaging was acquired on a 1.5 Tesla General Electric Signa LX system. The high-resolution imaging protocol used a sagittally acquired inversion recovery prepared T1-weighted 3D spiral fast spin echo sequence (TR = 2000 ms, TE = 16 ms, FOV = 240 mm, voxel dimensions = 0.9375 x 0.9375 x 1.328 mm, 128 continuous slices, acquisition time = 8:36) (Wong, 2000).

Image Processing

Each participant's high resolution anatomical image was AC-PC aligned and skull-stripped using a combination of a hybrid watershed and deformable surface semi-automated skull-stripping program (Segonne et al., 2004) and manual editing. Intracranial volume (ICV) was determined from the skull-stripped brain. PFC regions of interest (ROI) were defined manually in AFNI (Cox, 1996) by raters blind to participant characteristics who attained high levels of inter-rater reliability (intraclass correlation coefficients >.90) prior to data collection.

All ROIs were manually delineated on coronal 3D images (perpendicular to the AC-PC plane). The PFC ROI was defined based on Nagel and colleagues (2006). The posterior PFC ROI included all cortical area anterior to the anterior commissure and posterior to the anterior edge of the genu. This ROI excluded the corpus callosum, subcortical regions (caudate, putamen, globus palladus, internal capsule), optic tracts, insula, and lateral ventricles. The anterior PFC ROIs (dorsal and ventral) included all cortical areas anterior to the anterior edge of the genu. The anterior dorsal PFC ROI included all cortex superior to the midline of the most anterior portion of the genu, while the anterior ventral PFC ROI included cortex inferior to the midline of the genu. Tracing continued until the most anterior slice on which cortex was still visible. These ROIs excluded the lateral ventricles and the corpus callosum. The corpus callosum was excluded from the mid-sagittal slice and then from each left and right lateral slice until the edge could no longer be detected (using AFNI's *edge detection* and *sharpen* features).

Insert Figure 1 About Here

White matter was segmented from gray and CSF compartments by processing skull-stripped T1 images with the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain's FAST automated segmentation tool (Zhang, et al., 2001). This process uses a hidden Markov random field model and an associated expectation-maximization algorithm that corrects for spatial intensity variations. The segmentation process did not reliably separate gray matter from CSF, but reliably identified white matter. Each PFC ROI mask was applied to the white matter compartment to calculate the white matter volume for each region. All total volume and white matter ROIs were analyzed as a ratio to overall ICV to control for individual variability in brain size (Giedd et al., 1996).

Statistical Analysis

Sample Characterization. ANOVAs and chi-square tests compared groups on the potentially confounding variables of gender, ethnic category, family history of substance use disorders, conduct disorder, age, parental socioeconomic status (SES), verbal intellect, and reading ability. Differences between groups in frequency, duration, and severity of substance use and ICV were also analyzed. A post-hoc analysis (due to the significant gender-by-group interactions on PFC morphometry) examined whether group and gender differences (utilizing ANOVAs) existed in the aforementioned demographic variables. If necessary, post-hoc Tukey's HSD tests were conducted. Interpretations about statistical significance were made if $p < .05$.

Prefrontal Cortex (PFC) Volume. To examine the whether group status or group-by-gender interactions predicted PFC volume after controlling for potentially confounding variables that significantly differentiated the groups (conduct disorder), univariate ANOVAs were run ($N = 31$) with each of the eight PFC volume/ICV measures (total volume, posterior, anterior dorsal, and anterior ventral; white matter volume: total, posterior, anterior dorsal, and anterior ventral) as dependent variables. Factors included group status (AUD vs. control), conduct disorder status, and gender. An interaction between group and gender was also examined. To ensure family history of substance use disorders did not influence results, the ANOVAs were re-examined with family history status included. Interpretations of statistical significance were made if $p < .05$. No correction for multiple tests was made to manage low power due to small sample size (Jennions & Møller, 2003; Nakagawa, 2004). To help interpret the magnitude of findings, partial eta squares (η_p^2) are reported.

RESULTS

Group Characterization

Demographics/Intracranial Volume. The teens with AUD did not significantly differ from controls on age [$F(1,30)=.42$, $p<.52$], ethnic category [$x^2(2)=2.74$, $p<.26$], gender composition [$x^2(1)=.09$, $p<.76$], family history of substance use disorders (negative versus positive) [$x^2(1)=1.1$, $p<.74$], parental SES (based on Hollingshead) [$F(1,31)=.02$, $p<.89$], reading ability [$F(1,30)=.02$, $p<.88$], verbal intellectual functioning [$F(1,30)=.09$, $p<.77$], or intracranial volume [$F(1,30)=.04$, $p<.85$] (See Tables 1 & 2). Male adolescents with AUD were more likely than control males to meet criteria for conduct disorder [$x^2(1)=7.24$, $p<.01$].

Substance Use. All participants were abstinent from alcohol and drugs for at least 5 days before scanning. As shown in Table 1, user groups reported more recent alcohol use than controls, as well as more lifetime alcohol use, drinks per month, alcohol abuse/dependence symptoms, lifetime marijuana use, and cigarettes smoked per day (*p*s <.05). Teens with AUD

did not differ from controls in lifetime use of other drugs, recent marijuana use, or marijuana abuse/dependence criteria.

Gender x Group Interactions. When groups were examined by gender, males with AUD were more likely to be diagnosed with conduct disorder than other groups, and females with AUD smoked more cigarettes than other groups. Otherwise, males and females with AUD had similar substance use patterns (see Table 1).

Insert Tables 1 & 2 About Here

Primary Results: PFC Volumes

All PCF volumes were analyzed as ratios to ICV to control for individual differences (see Table 2 for means and SD).

Group Status. After controlling for ICV, conduct disorder status, and gender, AUD teens demonstrated marginally smaller anterior dorsal PFC volumes [$F(4,31)=2.97$, $p<.09$, $\eta_p^2 = .10$], but no differences in other PFC volumes.

Conduct Disorder Status. Controlling for ICV, group, and gender, youths with conduct disorder had significantly smaller total PFC volumes than participants without conduct disorder [$F(4,31)=5.67$, $p<.03$, $\eta_p^2 = .18$] [conduct disorder PFC volume mean=.224 (±.005); no conduct disorder PFC volume mean=.225 (± .017)]. This difference was driven primarily by smaller anterior dorsal [$F(4,31)=7.10$, $p<.01$, $\eta_p^2 = .22$] and anterior ventral [$F(4,31)=5.41$, $p<.03$, $\eta_p^2 = .17$] regions of the PFC. Conduct disorder was also associated with significantly smaller volume of the anterior dorsal PFC white matter volume [$F(4,31)=5.71$, $p<.03$, $\eta_p^2 = .18$].

Gender. Controlling for ICV, group, and conduct disorder, females demonstrated significantly smaller total PFC volume than males [$F(4,31)=6.32$, $p<.02$, $\eta_p^2 = .20$], due primarily to smaller anterior ventral [$F(4,31)=8.35$, $p<.008$, $\eta_p^2 = .24$] and dorsal [$F(4,31)=4.57$, $p<.04$, $\eta_p^2 = .15$] PFC volumes. Females also had smaller total PFC white matter size [$F(4,31)=7.40$, $p<.01$, $\eta_p^2 = .22$], driven by smaller anterior ventral [$F(4,31)=10.09$, $p<.004$, $\eta_p^2 = .28$] and dorsal [$F(4,31)=6.08$, $p<.02$, $\eta_p^2 = .19$] PFC white matter volumes.

Gender-by-Group Interaction. Controlling for ICV and conduct disorder, significant group-by-gender interactions were observed in total PFC volume [$F(4,31)=10.63$, $p<.003$, $\eta_p^2 = .29$], due to differences in both anterior ventral [$F(4,31)=14.71$, $p<.001$, $\eta_p^2 = .36$; see Figure 2] and dorsal [$F(4,31)=5.58$, $p<.03$, $\eta_p^2 = .18$] regions. Compared to female controls, females with AUD demonstrated smaller PFC volumes, while males with AUD had larger PFC volumes than male controls. Group-by-gender interactions were again observed in total white matter PFC volume [$F(4,31)=5.64$, $p<.03$, $\eta_p^2 = .10$], specifically in anterior ventral [$F(4,31)=11.28$, $p<.002$, $\eta_p^2 = .30$] and dorsal [$F(4,31)=5.37$, $p<.03$, $\eta_p^2 = .17$] PFC white matter volumes. As with total PCF volumes (Figure 2), AUD females demonstrated smaller PFC white matter volumes compared to female controls, while males with AUD had larger PFC white matter volumes than male controls.

Insert Figure 2 About Here

Family History of Substance Use Disorders, Alcohol Use, & PFC Volumes

To determine if family history of substance use disorders might account for the primary results, the aforementioned ANOVAs were re- run with family history included. Family history

was not associated with PFC volume (*p*'s > .10), and the relationships between alcohol use group and PFC volumes remained significant.

To examine the relationship between alcohol use indicators and PFC volumes, correlations were run among the males and females with AUD separately. No significant correlations between lifetime alcohol use, age of onset of regular alcohol use, alcohol withdrawal symptoms, or alcohol dependence symptoms and PFC volume variables were found (*p*'s > .10).

DISCUSSION

Alcohol use is highly prevalent during adolescence (Johnston et al., 2005), and adolescence is a period of increased risk for neurocognitive consequences of alcohol use (Spear, 2000). Further, adult neuroimaging data suggest that the prefrontal cortex (PFC) is particularly sensitive to alcohol neurotoxicity (Desmond et al., 2003; Harper 1987; Kril & Halliday, 1999; Oscar-Berman & Hutner, 1993; Pfefferbaum et al., 1997; Schweinsburg et al., 2001). The present study was designed to examine PFC morphometry among adolescents with AUD. The primary finding was that even after controlling for conduct disorder and family history, gender significantly moderated the relationship between alcohol use and PFC morphometry. Despite similar alcohol use patterns, the males and females with AUD demonstrated opposite PFC morphometry patterns: girls with AUD showed smaller volumes while boys had larger volumes compared to same-gender controls. These findings parallel functional neuroimaging findings, which reported that males with AUD had increased frontal activation while female drinkers had limited frontal activation in response to a spatial working memory task (Caldwell et al., 2005).

This gender by drinking status interaction is interesting to consider in the context of adolescent neurodevelopment. Boys with AUD had significantly larger PFC anterior (including the dorsolateral and orbitofrontal regions), total, and PFC white matter volumes compared to control boys. As compared to girls, boys generally demonstrate pruning later in adolescence (Lenroot & Giedd, 2006), and the introduction of heavy drinking early in adolescence may inhibit healthy pruning. However, because the CSF and gray matter could not be reliably parsed, this hypothesis could not be tested. Alternatively, differences in overall PFC volume may have been primarily driven by white matter, as the boys with AUD demonstrated larger overall white matter volumes than controls. One possible explanation of these findings is that males are less sensitive than females to the neurotoxic effects of alcohol, so the PFC continues to myelinate normally. Studies examining the functional relationships between white matter integrity (measured by diffusion tensor imaging) and neuropsychological functioning are needed to help clarify PFC white matter functioning among boys with AUD.

These findings partially conflict with De Bellis and colleagues (2005), who reported *smaller* PFC total and white matter volumes among *both* males and females with AUD. However, compared to the current study, their sample was older (ages 13-21; so pruning may have occurred already in some males) and had a greater prevalence of comorbid Axis I disorders among the males with AUD (including attention deficit hyperactivity, major depressive, post-traumatic stress, and cannabis and hallucinogen use disorders). These comorbid disorders have also been associated with brain abnormalities (Bauer & Hesselbrock, 1999; Medina, Nagel, et al., 2007; Mostofsky, et al., 2002; Steingard et al., 2002). Therefore, it difficult to disentangle the interaction of these conditions from AUD on PFC structure. For example, we found that conduct disorder was independently associated with smaller PFC volumes in the males, while AUD was associated with larger volumes. In De Bellis and colleagues' (2005) sample, 75% of the males with AUD met criteria for conduct disorder, as compared to 56% in our sample, so increased incidence of conduct disorder in an adolescent sample may result in smaller overall PFC volumes.

Consistent with De Bellis and colleagues (2005), girls with AUD had significantly smaller PFC total and white matter volumes in the anterior regions compared to female controls. Interestingly, the current results parallel previous pathology findings that demonstrated cell loss in superior, but not posterior, PFC areas (Harper, 1989). This preliminary evidence may indicate pathological processes such as neuronal death or atrophy (Pascual et al., 2007), or altered synaptic refinement. More specifically, rich concentrations of excitatory amino acid pathways in the PFC continue to develop during adolescence, alcohol consumption during adolescence may lead glutamate-mediated excitotoxicity, resulting in cell shrinkage and axonal loss (Carper-Hyland & Chandler, 2007; Freund & Anderson, 1996; Rossetti, et al., 1999; Samnick et al., 1998). Alcohol-related brain effects may also be due to an upregulation of inflammatory mediators (e.g., COX-2 and iNOS) that ultimately lead to neural cell death or injury (Blanco, et al., 2005; Pascual, et al., 2007; Valles, et al., 2004). Alternatively, the observed reduced PFC volumes among the females may have been driven exclusively by white matter pathology (Harper, Smith, & Kril, 1990; Okamoto et al., 2006). Larger studies examining PFC morphometry among adolescents with AUD are necessary to determine whether the observed volume abnormalities are primarily due to white or gray matter pathology and to assess whether these structural differences are associated with altered cognitive functioning.

Gender differences in the brain-related effects of adolescent alcohol exposure may be due to several factors, including underlying differences in PFC development rate and timing (e.g., Giedd et al., 1999; Lenroot & Giedd, 2006), differential gene expression linked to enhanced alcohol-related neurotoxicity in females (Hashimoto & Wirin, 2007), blood glucose levels (Sumida, et al., 2004), increased blood alcohol concentration among girls despite similar drinking patterns (NIAAA, 1993), alcohol dehydrogenase levels (Lieber, 2000), and hormone and receptor distributions (Emanuele, et al., 2001; Kim et al., 2003; Ogilvie & Rivier, 1996) . Comorbid disorders that affect boys and girls differently may also interact with alcohol use and PFC development during adolescence. For example, in our sample, males with AUD were more likely to be diagnosed with conduct disorder, while girls with AUD smoked more cigarettes (although this was relatively low, at an average of one cigarette per day). Both factors may affect frontal lobe function (Jacobsen et al., 2007; Kim, et al., 2001; Kruesi et al., 2004). Longitudinal studies examining PFC morphometry, hormone levels, and alcohol use among male and female adolescents are necessary to test these hypotheses.

Premorbid differences may, in part, explain the observed PFC morphometric differences. For example, executive dysfunction is a risk factor for substance use disorders (Aytaclar et al., 1999; Nigg et al., 2004). However, the current study statistically controlled for conduct disorder, had no group differences in family history of substance use disorders (which was not associated with PFC volume in this sample), and excluded individuals with premorbid psychiatric disorders such as attention deficit hyperactivity disorder. Furthermore, there were no group differences in other risk factors potentially associated with substance use such as parental SES, verbal intellectual functioning, reading ability, and education. Still, it remains possible that the observed PFC differences may be due to preexisting individual differences. For example, statistical control may be insufficient to eliminate the effects of conduct disorder on PFC morphometry, especially among the male adolescents with AUD. Future studies designed to disentangle the unique effects of alcohol use and conduct disorder on PFC structure in males are necessary, and longitudinal studies of at-risk adolescents are needed to rule out premorbid influences.

As with any study, some limitations warrant consideration. First, although comparable to other published neuroimaging studies, the current study had a low sample size. Additional studies with larger numbers of males and females with AUD are necessary. Second, reliable

parcellation of gray matter from CSF using automated segmentation methods was not possible, so the ratio of gray matter to CSF could not be established in the current study. Third, given the relatively low comorbid drug use and extensive exclusionary criteria, this sample reflects a fairly high functioning sample within the population of adolescents with AUD. Therefore, results may not generalize to adolescents with significant comorbid polydrug use or psychiatric disorders. Finally, due to the cross-sectional nature of this study, the directional and developmental relationship of PFC morphometry and alcohol use cannot be clearly ascertained. Longitudinal studies examining the developmental trajectories of male and female adolescents will help ascertain these associations.

In summary, the present study found that adolescents with AUD demonstrated prefrontal cortex (PFC) structural abnormalities, especially in the white matter anterior to the genu of the corpus callosum. Gender significantly moderated the relationship between alcohol use and PFC morphometry. These results highlight the need for additional animal and human research examining the interaction between gender and alcohol use on PFC neurodevelopment during adolescence.

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Table 1: Demographics, Cognitive Function, and Substance Use Characteristics by Alcohol Use Group and Gender.

	Female Controls (*n*=7) M(SD) or % [range]	AUD Females (*n*=5) M(SD) or % [range]	Male Controls (*n*=10) M(SD) or % [range]	AUD Male (*n*=9) M(SD) or % [range]
Age	16.5 (1.0) [15.3 – 17.75]	17.1 (0.6) [16.4 – 17.7]	16.6 (0.7) [15.7 – 17.9]	16.6 (0.7) [15.2 – 17.5]
% Caucasian	86%	100%	80%	100%
% Family history negative [a]	43%	20%	44%	44%
% Conduct disorder positive [£]	0%	0%	0%	56%
Hollingshead socioeconomic index	26.0 (10.1) [18 – 47]	17.0 (6.6) [11 – 27]	21.4 (11.9) [11 – 47]	26.1 (16.1) [11 – 53]
WRAT-3 Reading standard score	109.6 (6.9) [103 – 123]	110.2 (4.4) [105 – 115]	104.9 (8.2) [93 – 115]	104.4 (9.4) [90 – 120]
Vocabulary scaled score	13.6 (3.7) [9 – 18]	13.6 (1.8) [12 – 16]	11.7 (2.2) [8 – 14]	12.3 (1.3) [11 – 14]
Days since last drink [b h]	652.8 (473.8) [90 – 998]	9.0 (4.6) [5 – 14]	356.7 (483.0) [5 – 998]	21.0 (17.3) [5 – 60]
Lifetime alcohol use episodes [c i k]	1.0 (4.1) [0 – 11]	164.2 (131.6) [45 – 505]	5.8 (7.7) [0 – 20]	137.8 (160.1) [45 – 505]
Drinks/month, past 3 months [f]	0.0	49.0 (42.2) [3 – 108]	4.67 (7.2) [0 – 18]	43.5 (26.1) [17 – 98]
Regular drinking age of onset	n/a	15.2 (1.3) [14 – 17]	n/a	14.6 (0.9) [14 – 16]
Lifetime alcohol withdrawal symptoms	0 (0) [0 – 0]	2.0 (1.6) [0 – 4]	1.3 (3.8) [0 – 12]	2.5 (2.1) [0 – 6]
Alcohol abuse and dependence criteria, past 3 months [d i]	0.0	2.0 (1.0) [1 – 3]	0.3 (0.5) [0 – 1]	3.0 (2.3) [0 – 6]
Lifetime marijuana use episodes [c k]	0.1 (0.4) [0 – 1]	17.0 (17.2) [0 – 40]	3.2 (7.8) [0 – 25]	7.7 (8.5) [0 – 20]
Marijuana use/month, past 3 months	0.0	0.8 (1.3) [0 – 3]	0.6 (1.1) [0 – 3]	0.8 (1.6) [0 – 5]
Days/month smoked cigarettes [j]	0.0	6.4 (6.0) [0 – 15]	0.8 (2.3) [0 – 7]	0.9 (2.0) [0 – 6]
Cigarettes per day [b]	0.0	1.2 (1.6) [0 – 4]	0.3 (1.0) [0 – 3]	0.0
Lifetime other drug use episodes	0.0	2.2 (4.4) [0 – 10]	0.0	0.0

Notes:

[£] Chi-Square ($p<.05$), males with AUD more likely than other groups.

[a] Family history negative=no biological 1st or 2nd degree relatives with substance use disorder.

[b] Figures include only those who reported use.

[c] Maximum allowed was 998.

[d] Number of abuse/dependent symptoms do not necessarily indicate a positive DSM-IV diagnosis.

[e] Groups significantly different ($p<.05$).

[f] Controls less than users ($p<.05$)

[g] Female controls different than male controls ($p<.05$)

[h] Female controls different than users ($p<.05$)
[i] Male AUD different than male controls ($p<.05$)
[j] Female AUD different than all others ($p<.05$)
[k] Female AUD different than controls ($p<.05$)

Table 2: Prefrontal Cortex Morphometry and Composition by Alcohol Use Group and Gender.

	Female Controls (*n*=7) M(SD) or % [range]	AUD Females (*n*=5) M(SD) or % [range]	Male Controls (*n*=10) M(SD) or % [range]	AUD Male (*n*=9) M(SD) or % [range]
Intracranial volume (ICV) (cc^3) [a]	1519.1 (117.1) [1374.0 – 1703.1]	1549.0 (86.0) [1430.0 – 1636.6]	1674.2 (158.0) [1438.4 – 2015.9]	1658.9 (80.2) [1551.7 – 1842.1]
Posterior PFC/ICV (cc^3)	0.1040 (0.0071) [0.0908 – 0.1135]	0.1007 (0.0084) [0.0939 – 0.1149]	0.1026 (0.0112) [0.0843 – 0.1178]	0.1039 (0.0134) [0.0809 – 0.1248]
Anterior dorsal PFC/ICV (cc^3)	0.0663 (0.0058) [0.0577 – 0.0749]	0.0643 (0.0064) [0.0568 – 0.0725]	0.0656 (0.0095) [0.0482 – 0.0784]	0.0709 (0.0093) [0.0585 – 0.0894]
Anterior ventral PFC/ICV (cc^3) [b]	0.0554 (0.0064) [0.0477 – 0.0678]	0.0473 (0.0040) [0.0446 – 0.0541]	0.0531 (0.0071) [0378 – 0.0642]	0.0586 (0.0063) [0.0515 – 0.0684]
Posterior PFC WM/ICV (cc^3)	0.0364 (0.0031) [0.0321 – 0.0405]	0.0354 (0.0032) [0.0327 – 0.0408]	0.0372 (0.0049) [0.0302 – 0.0437]	0.0373 (0.0053) [0.0282 – 0.0463]
Anterior dorsal PFC WM/ICV (cc^3)	0.0164 (0.0023) [0.0140 – 0.0197]	0.0152 (0.0029) [0.0116 – 0.0185]	0.0165 (0.0031) [0.0117 – 0.0210]	0.0182 (0.0033) [0.0124 – 0.0231]
Anterior ventral PFC WM/ICV (cc^3) [c]	0.0140 (0.0024) [0.0113 – 0.0172]	0.0113 (0.0010) [0.0100 – 0.0125]	0.0139 (0.0020) [0.0093 – 0.0163]	0.0149 (0.0019) [0.0123 – 0.0170]

Notes: WM= White matter volume, PFC= Prefrontal cortex volume.

[a] Females significantly smaller than males ($p<.05$).

[b] Female AUD different than controls ($p<.05$)

[c] Male AUD different than female AUD ($p<.05$)

Figure 1: 3D sagittal view of prefrontal cortex (PFC) boundary delineation.

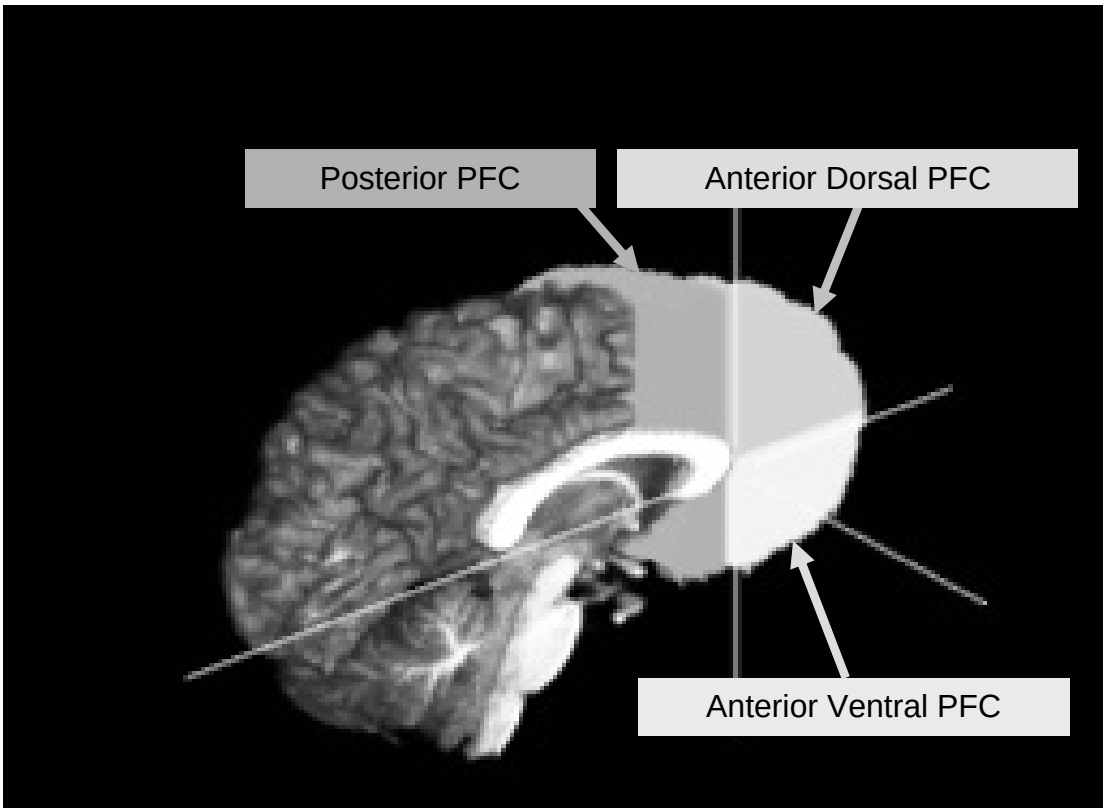

Figure 2: Means (± 1SE) of the anterior ventral prefrontal cortex volume/intracranial volume by alcohol use disorder (AUD) group and gender