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A Pilot Study of Neurocognitive Function and Brain Structures in Adolescents With Alcohol Use Disorders: Does Maltreatment History Matter?

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Abstract

Neurocognitive and brain structural differences are associated with adolescent onset alcohol use disorders (AUDs). Maltreatment histories may contribute to current results. To examine these issues, healthy adolescents ($n = 31$), adolescents without maltreatment and AUD (AUD − MAL, $n = 28$), and adolescents with AUDs with maltreatment (AUD + MAL, $n = 17$) underwent comprehensive neurocognitive assessments and MRI structural scans. Controls performed significantly better than the two AUD groups in math and language. The AUD + MAL group performed significantly lower in sustained attention compared to the AUD − MAL and control groups and lower in reading compared to controls. The AUD + MAL group had larger left pars triangularis, a region of the inferior frontal gyrus, compared to AUD + MAL and control groups, and smaller anterior corpus callosum volumes versus the AUD − MAL group. There were no group differences in other prefrontal cortex, amygdala, hippocampus, and parahippocampal volumes. The AUD + MAL group showed an inverse correlation between hippocampal volumes and age. AUD variables were associated with lower performance in fine-motor and executive function. Cannabis use variables were associated with lower performance in fine-motor, language, visual-spatial, memory, and executive function. Parahippocampal volumes positively correlated with abstinence. The preliminary results suggest adolescent AUD studies should consider examinations of maltreatment history, comorbid substance use disorders, and recovery during abstinence in their analyses.

Keywords

alcohol use disorders (AUDs), maltreatment, neuropsychology, magnetic resonance imaging, adolescence, corpus callosum

Child maltreatment is associated with increased rates of adolescent onset alcohol use disorders (AUDs), defined as *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV-TR*) alcohol dependence or abuse or *DSM-5* AUD (De Bellis, 2001; Gilbert et al., 2009; Kilpatrick et al., 2000). Maltreatment is associated with high rates of post-traumatic stress disorder (PTSD) symptoms in children and adolescents (De Bellis, 2001; De Bellis & Zisk, 2014). PTSD symptoms can contribute to a more treatment resistant AUD through the "self-medication" of stress symptoms hypothesis (De Bellis, 2001). Child maltreatment is associated with an increased odds ratio (e.g., 8.3) for alcohol and cannabis use disorders in youth (Copeland et al., 2012; Kilpatrick, et al., 2000; Scott, Smith, & Ellis, 2010), and with earlier onset and more malignant AUD course, including high rates of comorbid substance use disorders (SUDs; Clark, 2004). Adult PTSD is highly comorbid (with rates as high as 50%) with SUD (De Bellis, 2001).

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Maltreated children and adolescents without AUD histories show poorer performance than nonmaltreated controls in academic achievement, language, memory, visual-spatial, attention, and executive functions (De Bellis, Hooper, Spratt, & Woolley, 2009; De Bellis, Woolley, & Hooper, 2013). Maltreated youth without AUD histories, but who suffer from PTSD, demonstrate differences in corpus callosum and prefrontal cortex (PFC; De Bellis & Keshavan, 2003; De Bellis et al., 2002; De Bellis et al., 2008). Maltreated youth with PTSD show no differences in amygdala or hippocampus volumes compared to nonmaltreated youth (De Bellis & Keshavan, 2003; De Bellis et al., 2002; Morey, Haswell, Hooper, & De Bellis, 2016).

Results similar to those in the youth maltreatment literature described above are seen in the adolescent onset AUD literature where maltreatment histories were not examined (Jacobus & Tapert, 2013; De Bellis et al., 2005; Medina, McQueeny, Nagel, Schweinsburg, & Tapert, 2008). Alcohol affects receptors that are important in neurodevelopment (acetylcholine, serotonin, γ-aminobutyric acid, and the *N*-methyl-D-aspartate receptors for glutamate), and are distributed throughout the brain, particularly in the frontal cortex, amygdala, and hippocampus (De Bellis 2001; White & Swartzwelder, 2006). In animal studies, excessive alcohol consumption during adolescence negatively affects cortical and glial cell survival (Crews & Nixon, 2009) and brain regions involved in executive function, emotional regulation, and memory, such as the PFC, hippocampus, amygdala, and corpus callosum (White & Swartzwelder, 2006), and thus may adversely impact adolescent brain maturation (Vetreno & Crews, 2014). Adolescent primates who consumed alcohol daily demonstrated reduced hippocampal neurogenesis as well as increased hippocampal neural degeneration compared to adolescent primates whose intake of alcohol was limited (Taffe et al., 2010). In primate models of neglect, peer versus mother-reared monkeys voluntary drank more alcohol under normal living conditions, indicating that child maltreatment may contribute to AUD (Fahlke et al., 2000; Schwandt et al., 2010).

Adolescents with AUD demonstrate poorer performance in academic achievement (Moss, Kirisci, Gordon, & Tarter, 1994), fine-motor (Nguyen-Louie et al., 2015), language, memory, visual-spatial (Nguyen-Louie et al., 2015), attention, and executive functions (Jacobus & Tapert, 2013) compared to nondrinking comparison subjects. Adolescents and young adults with adolescent onset AUD have significantly smaller PFC and prefrontal white matter volumes, greater amounts of prefrontal cerebrospinal fluid (CSF; De Bellis et al., 2005; Medina et al., 2008), smaller hippocampi (De Bellis et al., 2000a; Nagel, Schweinsburg, Phan, & Tapert, 2005), and differences in the microstructure of the corpus callosum (De Bellis et al., 2008), compared with healthy comparison subjects. Some, but not all, of these adolescent AUD studies found significant relationships between drinking variables and smaller structural volumes. These data indicate that the adolescent brain may be more sensitive to the adverse effects of excessive alcohol consumption than the adult brain. In a longitudinal study, initiation of moderate to heavy alcohol use in youth was associated with accelerated frontal cortical gray matter loss (Pfefferbaum et al., 2018).

Neurocognitive and brain structural differences are associated with adolescent onset AUD; however, not all studies agree (Jacobus & Tapert, 2013). Child maltreatment, comorbid SUD, and length of abstinence prior to study enrollment may contribute to these inconsistencies. Many of the above studies did not account for maltreatment history in their samples or lacked sufficient sample sizes to examine the additive or interactive effects of maltreatment on the neurocognitive and neurobiological outcomes in adolescent onset AUD. Since individuals with a child maltreatment history have earlier ages of AUD/SUD onset, greater symptom severity, comorbidity, and are more likely to be treatment resistant, some investigators believe that AUD/SUD with and without maltreatment histories represents a clinically and biologically distinct subtype (De Bellis, 2001; Teicher & Samson, 2013). The current adolescent onset AUD literature does not address the neurobiological influence of child maltreatment on neurocognitive and brain outcomes. To comprehensively study the neurobiological consequences of alcohol on the developing adolescent brain, it is necessary to control for child maltreatment.

This pilot study examined neurocognitive domains and brain structures commonly and adversely associated with stress and adolescent onset AUD and SUD (i.e., PFC regions, divisions of the corpus callosum, amygdala, hippocampus, parahippocampus gyrus). Based on the existing animal studies and the adolescent AUD and maltreatment literature, we hypothesized that adolescents with AUD + MAL would show global differences in neurocognitive function and brain structures of interest from the AUD − MAL and control groups; while the two alcohol groups would show unique differences in neurocognitive function (e.g., memory) and brain structures of interest (e.g., hippocampal volumes) compared to the controls. We hypothesized that the AUD + MAL group would show poorer neurocognitive function and lower academic achievement in all neurocognitive domains compared to the AUD − MAL and control groups (De Bellis et al., 2009; De Bellis et al., 2013) and would demonstrate smaller PFC regions and corpus callosum volumes compared to the AUD − MAL and control groups (De Bellis et al., 2000a; De Bellis et al., 2002). We hypothesized that the AUD − MAL and AUD + MAL groups would show poorer neurocognitive function in memory and smaller hippocampal and parahippocampal volumes compared to controls. We were particularly interested in differences in group measures of PFC regions (e.g., orbitofrontal cortex that is also called the ventral medial PFC) because smaller right orbitofrontal cortex volumes in youth are associated with impulsivity (Boes et al., 2009), a common symptom in both maltreated youth and youth with SUD. Adults with SUD have smaller orbitofrontal cortex volumes (Tanabe et al., 2009). Hypoactivation of the orbitofrontal cortex during response inhibition predicts early initiation of substance use (Cheetham et al., 2012). Additionally, adolescents with AUD have other substance use comorbidity that may also affect neurocognitive

function and brain structures (e.g., comorbid nicotine use, cannabis use disorder, family history of AUD/SUD). We comprehensively measured all substance use variables and controlled for family history of AUD/SUD in our planned analyses. Planned analyses were undertaken to examine the relationships between age, maltreatment status, alcohol and substance consumption variables, and outcome measures. We hypothesized that AUD/SUD consumption measures would be more negatively related to outcome variables in the AUD + MAL versus the AUD − MAL subjects.

Materials and Methods

Subjects

Adolescents (aged 13–18 years) with an adolescent onset AUD without histories of child maltreatment (AUD − MAL; $n = 28$), and adolescents with an adolescent onset AUD with a child protective services maltreatment history (AUD + MAL; $n = 17$) that occurred prior to AUD, were recruited from intensive community outpatient treatment centers specializing in youth addiction using flyers and advertisements to therapists, potential subjects, and their parents. To control for the effects of recent drinking and alcohol withdrawal, adolescents with AUD were in active outpatient treatment and alcohol- and drug-free for at least 21 days, prior to entry into the study. All AUD subjects were treatment referred for alcohol problems. Community treatment included psychoeducation, family therapy, and substance use monitoring in which urine toxicology and breathalyzer readings were obtained several times a week. All subjects were assessed for documented child protective services child abuse and neglect history prior to AUD onset, and AUD subjects were further divided into those without (AUD − MAL) and with (AUD + MAL) child protective services documented maltreatment histories. We comprehensively measured all substance use variables and controlled for family history of AUD/SUD in our planned analyses. Planned analyses were undertaken to examine the relationships between age, maltreatment status, alcohol consumption, and substance consumption variables with outcome measures.

Healthy adolescents ($n = 31$), without any *DSM-IV-TR* Type A exposure to traumatic events that involved injury or threats to self or others (American Psychiatric Association, 2000), *DSM-IV-TR* Axis I disorders, or *DSM-IV-TR* and *DSM-5* history of AUD or other SUD, were recruited through advertisements in the same communities as the AUD subjects. Parents of all potential subjects who called in response to the advertisements were given institutional review board (IRB)–approved verbal consents for screening for exclusion criteria and invited to the research program if eligible.

Exclusion criteria for all subjects were IQ < 80; pregnancy, chronic medical illness; daily prescription medication; head injury with loss of consciousness; traumatic brain injury; neurological disorder; schizophrenia; psychosis; autism; or pervasive developmental disorder; anorexia nervosa; birth weight under 5 lbs; or severe prenatal (e.g., fetal alcohol and/or drug exposure) or perinatal complications (e.g., neonatal intensive care unit stay); body weight over 250 lbs; any contraindications for safe magnetic resonance imaging (MRI) scan; and insufficient English skills for consenting to the protocol. AUD subjects were eligible for this study after at least 21 days of sobriety from alcohol, cannabis, and other drugs (except nicotine), which was confirmed with saliva and urine toxicology screens on the day of neurocognitive testing and MRI scan. After complete description of the study was given to the legal guardians and participants, written informed consent/assent were obtained to undertake this University Medical Center IRB-approved study.

Groups were similar on most demographic variables (Table 1) except: (1) socioeconomic status (SES) was lower in the AUD + MAL group compared to the two other groups, although most subjects fell within the upper middle SES. The mean scores on the Hollingshead four-factor index of SES were all within Class 4 where Class 5 is the highest social class. (2) The 2-factor full scale IQ measure was lower in the AUD + MAL group compared to the control group. Since lower IQ (De Bellis et al., 2009; De Bellis et al., 2013; Perez & Widom, 1994) is an inherent confound in maltreatment studies, statistical procedures were used to control for this factor. (3) The AUD + MAL and AUD − MAL groups had greater familial risk for AUD/SUD (Jacobus & Tapert, 2013) and were more likely to have used tobacco and cannabis (Clark, 2004; De Bellis, Broussard, Wexler, Herring, & Moritz, 2001). Analyses of outcome variables controlled for SES, FSIQ, and number of biological parents (0, 1, or 2) with lifetime AUD/SUD history.

Clinical Measures

Youth substance use disorders, other Axis I diagnoses, maltreatment type and severity, and presence or absence of PTSD were determined using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) Present and Lifetime Version (KSADS-PL; Kaufman et al., 1997) with parents as informants of their child and interviews of youth subjects. The trauma checklist of the KSADS-PL was modified as previously described (De Bellis, Hooper, Woolley, & Shenk, 2010) to include more information about life events and disorders not present in the KSADS-PL (e.g., autism). Algorithms to determine Axis I psychiatric disorders based on *DSM-IV* criteria were modified to include *DSM-5* alcohol and substance use disorders. Interviewers were individually trained to obtain over 90% agreement for the presence of any lifetime major Axis I disorder, including AUD/SUD, with a board-certified child and adolescent psychiatrist with expertise in child trauma (MDDB). Discrepancies were resolved by reviewing archival information (e.g., child protection reports, medical records) or by reinterviewing the child or caregiver. If diagnostic disagreements were not resolved with this method, consensus diagnoses were reached between a child psychiatrist (MDDB) and child psychologist (SRH) using the best estimate method (Clark, Parker, & Lynch, 1999), where a date of onset, defined as the time at which diagnostic criteria were first met, was determined for

Table 1. Demographic and Clinical Characteristics of the Study Participants.

Structure, mm^3 (Adjusted for ICV), Mean ± *SD*	Control Group (1)	AUD Group Without Child Maltreatment (2)	AUD Group With Child Maltreatment (3)	Statistic	*p* Value	Pairwise Group Difference
N	31	28	17			
Age range	16.13 ± 1.08 13.92–17.92	16.79 ± 1.08 14.58–18.08	16.41 ± 1.29 13.67–18.5	$F = 2.46$	.09	—
SES	50.52 ± 9.89	49.82 ± 10.57	41.18 ± 12.66	$F = 4.62$	<.02	3<1,2[a]
Sex (male/female)	21/10	22/6	13/4	$\chi^2 = .98$	.61	—
Right/left handed	29/2	26/2	16/1	$\chi^2 = .03$	.99	—
Race (Cauc/AA/Other)	22/4/5	25/1/2	11/4/2	$\chi^2 = 5.64$	.23	—
Body mass index (kg/m^2)	22.5 ± 3.75	22.1 ± 2.66	23.8 ± 3.18	$F = 1.49$	.23	—
Head circumference (cm)	57.00 ± 2.13	56.82 ± 1.68	56.82 ± 1.98	$F = .08$	.93	—
FSIQ	116.58 ± 14.14	109.96 ± 14.28	102.82 ± 16.93	$F = 4.84$	.01	3<1[a]
Number of biological parents with AUD/SUD history (0/1/2)	25/4/2	14/13/1	3/7/7	$\chi^2 = 27.14$	<.0001	3>2>1[c]
Ever tried alcohol? (ye s/no)	9/22	28/0	17/0	$\chi^2 = 14.82$	<.0007	2,3>1[b]
Ever tried tobacco? (yes/no)	6/25	28/0	15/2	$\chi^2 = 49.17$	<.0001	2,3>1[b]
Ever tried Cannabis? (yes/no)	4/27	26/2	16/1	$\chi^2 = 49.71$	<.0001	2,3>1[b]

Note. AUD = alcohol use disorder; SUD = substance use disorder; Cauc = Caucasian; AA = African American; Other = Multiracial; SES = socioeconomic status measured by the Hollingshead four-factor index, where higher numbers mean higher SES; FSIQ = Full Scale IQ estimated from two factors.
[a]Comparisons tests for all pairs using Tukey–Kramer honestly significant difference $q = 2.37$, $p < .05$. [b]Post hoc analysis of means of proportion. [c]Post hoc correspondence analysis.

each disorder (Clark, Pollock, Mezzich, Cornelius, & Martin, 2001). The AUD + MAL group was defined by history of a positive forensic investigation with child protective services that indicated neglect or physical, sexual, or emotional abuse as defined by state criteria. Because multiple sources of information are needed to gather accurate maltreatment history and related symptoms (Kaufman, Jones, Stieglitz, Vitulano, & Mannarino, 1994), we also reviewed archival records (e.g., birth records, pediatric records, school attendance records, forensics records, and child protective services records) and our KSADS-PL interview as sources of mental health symptoms, trauma history, birth history, and pediatric health for inclusion/exclusion criteria. These records were collected on all participants and in some cases lead to exclusion of subjects (e.g., controls excluded from the study for maltreatment history, subject initially assigned to any of the three groups were excluded for positive urine toxicology at birth).

Child maltreatment was defined as an adolescent having a lifetime history of a positive investigation and intervention from the state's child protective services and confirming one or more of the following on interview: witnessing domestic violence, experiencing physical, sexual, or emotional abuse, and/or neglect (defined as failure to supervise or failure to provide). These data were gathered on all adolescent subjects during the KSADS-PL parent and youth interviews along with reviews of archival records as described above. The AUD + MAL ($n = 17$) consisted of individuals who suffered from the following maltreatment types: witnessing domestic violence ($n = 14$), experiencing physical ($n = 12$), sexual ($n = 3$), or emotional abuse ($n = 14$), neglect defined as failure to supervise ($n = 16$), or failure to provide ($n = 6$). The mean number of types of maltreatment experiences in this group was 3.8 ± 1.2. The AUD − MAL and control groups did not include any subjects who reported child protective services involvement or who responded positively to any of the maltreatment questions above.

Substance use information was gathered by direct interviews with the adolescents. For each symptom, age of onset was estimated to the nearest month. Methods from the Lifetime History of Alcohol Use Interview were incorporated into the KSADS-PL and used to collect supplemental information on alcohol and other abused substances including cannabis, nicotine, and eight other drug classes (stimulants, sedatives/hypnotics/anxiolytics, cocaine, opioids [heroin, morphine, codeine], hallucinogens, phencyclidine, solvents/inhalants, and other [e.g., nitrous oxide, ecstasy, other prescription drugs]). Variables collected included average quantity and frequency of use, age of onset of regular use (defined as use of at least twice a month for 2 months), maximum frequency and quantity of use, and age of maximum frequency and quantity of use. Quantity variables were based on 0.6-oz. (17 g) ethanol "standard drinks" (one 12-oz. [340 g] beer, one 5-oz. [142 g] glass of table wine [12% alcohol by volume], or one 1.5 oz. [42.5 g] of 80-proof hard liquor). Frequency variables were calculated as the mean number of drinks (or substances used) per week during the 6 months prior to enrollment in treatment. Cannabis use was translated into a standard joint (Chung, Martin, Winters, Cornelius, & Langenbucher, 2004). We also collected information on the number of days of sobriety from each substance used. The AUD − MAL and AUD + MAL groups did not differ in the total number or types of all major Axis I disorders or AUD/SUD variables including age of onset, duration, or comorbid cannabis, nicotine, or other drug use. All AUD subjects also met *DSM-5* criteria for AUD and other SUDs.

The diagnostic assessments and neurocognitive testing occurred in a single day, and the MRI scan was scheduled

within 3 weeks of these evaluations. The mean length of time between last alcohol and cannabis use and the diagnostic procedures/neurocognitive testing and the MRI scan were similar between groups. The AUD group had to maintain sobriety for this entire time period for scanning eligibility.

Neuropsychological measures. The neurocognitive tasks were age-appropriate, psychometrically sound, comprehensive, and appropriate for a maltreatment sample (Gabowitz, Zucker, & Cook, 2008). The neuropsychological domains consisted of fine-motor, language, visual-spatial, memory/retrieval, attention, executive functions, and academic achievement as these measures were previously demonstrated to show differences between maltreated youth and controls, and AUD youth and controls. The outcome variables from each of the measures were age-based standard scores.

The fine-motor domain consisted of the Trail-Making Test Part A (Reitan & Wolfson, 1992) and Grooved Pegboard Test (Heaton, Grant, & Matthews, 1992). The language domain consisted of the Controlled Oral Word Association Test–Animals (Loonstra, Tarlow, & Sellers, 2001), Peabody Picture Vocabulary Test-III (Dunn & Dunn, 1997), and the Concepts and Directors Subtest from the Clinical Evaluation of Language Fundamentals (Semel, Wiig, & Secord, 2003), which provides measures of receptive language and verbal fluency. The visual-spatial domain consisted of the Rey–Osterrieth Complex Figure Test–Copy Condition (Duley et al., 1993) and the Judgment of Line Orientation Test (Benton, Varney, & Hamsher, 1978), which provides measures of higher order visuoconstructive abilities and two-dimensional visual-spatial functions, respectively. The memory/retrieval domain consisted of the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1994) and the Test of Learning and Memory (TOMAL) Paired Recall Subtest (Reynolds & Bigler, 1996) to provide assessments of both visual and verbal memory. The attention domain consisted of the Conners' Continuous Performance Test-II (Conners, 2000) that provides estimates of sustained attention, inhibitory control, and performance variability. The executive domain consisted of tasks that reflected the complexity of this domain. Inhibitory control was measured with the Stroop Color and Word Test interference score (Stroop, 1935). Cognitive flexibility was measured with the categories and perseverative response measure of the computerized Wisconsin Card Sorting Test (WCST; Fortuny & Heaton, 1996) and Trail-Making Test Part B (Reitan & Wolfson, 1992). Working memory was measured with the Woodcock Johnson Test of Cognitive Abilities-III Numbers Reversed Subtest (Woodcock, McGrew, & Mather, 2001b). Participants were administered the abbreviated version (Vocabulary and Block Design) of the age-appropriate Wechsler Intelligence Scale for IQ (Wechsler, 1991, 1997). The Academic Achievement domain consisted of the Woodcock Johnson-III Tests of Academic Achievement Reading and Mathematics subtests (Woodcock, McGrew, & Mather, 2001a).

MRI

Anatomical images were acquired using the Siemens Trio 3.0 Tesla MRI system (Trio, Siemens Medical Systems) scanner (3D, GRE [MPRAGE], axial, TR = 1,750 ms, T1 = 1,100 ms, 25.6 cm FOV, 1.0-mm slice thickness, flip = 20°, bandwidth: 220 [Hz/pixel], 256 [phase] × 256 [frequency], number of excitations = 1). All T1 images were visually inspected to assure appropriate quality. Automated segmentation and labeling of the PFC regions of interest, amygdala, hippocampus, parahippocampus gyrus, and corpus callosum division volumes, and estimation of total intracranial volume from participants' T1 images were performed using the FreeSurfer image analysis suite (version 5.1.0; http://surfer.nmr.mgh.harvard.edu/) and its library tool recon-all as previously described (Desikan et al., 2006; Destrieux, Fischl, Dale, & Halgren, 2010; Fischl et al., 2004). PFC regions of interest included the superior frontal gyrus, middle frontal gyrus (rostral and caudal divisions), inferior frontal gyrus (pars opercularis, pars triangularis, and pars orbitalis), orbitofrontal cortex (lateral and medial divisions), anterior cingulate gyrus (rostral and caudal divisions), precentral gyrus, and frontal pole. Spatial normalization by affine registration to Talairach space and skull stripping were performed on the T1 images. FreeSurfer registration, segmentation, and labeling of structures were described previously (Morey et al., 2016). Briefly, registration and segmentation of the regions of interest were overlaid on original T1 images and visually inspected (CCH, RAM) slice-by-slice for correct location and shape (editing) before entry into the FreeSurfer pipeline to improve the validity of intensity normalization and segmentation. All scans were reviewed by a neuroradiologist who ruled out clinically significant abnormalities. Subjects tolerated the procedure well. No sedation was used.

Statistical Methods

Background characteristics of the AUD and control groups were compared using ANOVA or χ^2 for categorical measures. Distributions of the neurocognitive and brain outcome measures were examined for normality using Shapiro and Wilk's W statistic. Residuals were inspected in cases where the distributions were not normal. Statistical methods were used to control for significantly different sociodemographic characteristics between groups as seen in Table 1 (i.e., SES, IQ, and number of biological parents with AUD/SUD history). As described above, these covariates are known to influence the neuropsychological and brain regions examined in this study. This modeling strategy of including appropriate covariates improved the efficiency of the models, so that typical parametric procedures were determined to be adequately robust in our exanimation of the neurocognitive and brain outcome measures where the raw data distributions were not normal (Kleinbaum, Kupper, & Muller, 1988).

To address the research questions regarding hypothesized neurocognitive differences between groups, we first engaged in data reduction strategies for each of the a priori conceptual

neuropsychological domains. Cronbach's α for the neurocognitive domains were achievement = 1.95, fine-motor = .70, language = .73, visual-spatial = .71, memory/retrieval = .77, attention = .60, and executive function = .67. To address the research questions pertaining to group differences in each of the neurocognitive domains, we undertook a series of multivariate analyses of covariance (MANCOVAs) for each of the domains to control for multiple comparisons, controlling for SES, IQ, and parental history of AUD/SUD as described above. For any significant MANCOVA, univariate procedures were conducted to examine which tasks produced the group differences with follow-up pairwise comparisons to determine which groups were different from one another. Partial Eta Square (η^2) was reported to reflect effect sizes for significant group differences (*small* = .01 to .0, *medium* = .06 to .13; *large* > .14; Cohen, 1988).

For the brain structural measures, individual volumes were covaried by their individual intracranial volumes as measured by FreeSurfer, one of the standard practices for adjusting for brain size differences in youth (Giedd & Rapoport, 2010). Our imaging sample size was decreased for controls, $n = 28$; AUD − MAL, $n = 22$; and AUD + MAL, $n = 9$; due to scan refusal (control $n = 1$; AUD − MAL, $n = 2$; AUD + MAL, $n = 2$), movement (control, $n = 2$; AUD − MAL, $n = 2$; AUD + MAL, $n = 2$), pregnancy noted between interview/neurocognitive assessment and MRI scan day (AUD − MAL, $n = 1$; AUD + MAL, $n = 2$), or relapse (AUD − MAL, $n = 1$; AUD + MAL, $n = 2$). The groups with MRI data were similar to the three groups in the entire sample in all variables including FSIQ, alcohol and substance use variables, and types of *DSM-IV-TR* Axis I disorder. However, within this subanalysis of MRI structural data, the control group was significantly younger (AUD + MAL mean age: 16.7 ± 1.5 years, age range 13.7–18.5 years; AUD − MAL mean age: 16.9 ± 1.04 years, age range 15.0–18.0 years; and control mean age: 16.1 ± 1.1 years, age range 13.9–17.9 years) and had higher SES and less positive family history of AUD/SUD than the AUD − MAL and AUD + MAL groups. The AUD groups were similar to each other on all demographic and clinical variables. Therefore, in the planned analyses of brain measures, we used general linear models to examine brain regions of interest, adjusted for intracranial volume, SES, IQ, and parental history of AUD/SUD and the covariates that differed between these three groups (i.e., age) with follow-up pairwise comparisons to determine which of the three groups were different from one another.

We examined the relationship between AUD and other substance variables and neurocognitive and brain volume outcome measures in all AUD subjects using Pearson's or Spearman's ρ correlations, as appropriate. We did not examine the relationship between AUD/SUD variables and outcome measures between the AUD + MAL and AUD − MAL groups separately because these two groups were similar in their mental health and other SUD comorbidity. Planned examinations were done to examine the interactive effects of age and sex within our three groups. The Fisher *r*-to-*z* transformation test was used to test for significant differences between the independent correlation coefficients of the three correlations of groups. The value of α was .05 (two tailed), given our a priori hypotheses and planned comparisons (Rothman, 1990). Analyses were undertaken using IBM SPSS Statistics for Windows (Version 20.0, computer software; IBM Corporation [2011], Armonk, NY) or JMP Pro (Version 11.0, computer software; SAS Institute Incorporated [2013], Cary, NC).

Results

Neurocognitive Measures

As shown in Table 2, the healthy control group performed significantly better than the two AUD groups in math and language. Both the AUD − MAL and the healthy control group performed significantly better than the AUD + MAL group in sustained attention. The control group performed significantly better than AUD + MAL group in reading and math fluency. There were no group differences in fine-motor, visual-spatial, memory/retrieval, and executive function. We also compared all AUD subjects with the controls. The healthy control group performed significantly better than the AUD group in Academic Achievement (particularly math) and language. There were no group differences in fine-motor, visual-spatial, memory/retrieval, attention, and executive function. Group × Gender analyses showed that control females performed better in Achievement in Broad Reading than control males. We saw no other Group × Gender or Group × Gender × Age effects in our analyses.

Brain Measures

Intracranial volume did not differ between the three groups ($F_{2, 51} = 1.4$, $p = .26$). As shown in Table 3, larger left pars triangularis, a region of the inferior frontal gyrus, were seen in the AUD + MAL compared to AUD + MAL and control groups (parameter estimate: 501.0, $t = 2.78$, $p < .006$), while smaller anterior corpus callosum volumes were seen in the AUD + MAL compared to the AUD − MAL groups (parameter estimate: 74.75, $t = 2.58$, $p = .01$). There were no other group differences in brain measures between the AUD − MAL, AUD + MAL, and control groups. Because of the small number of subjects in the AUD + MAL group, we also compared the full AUD group (with and without maltreatment) with the controls and found no group differences. In accord with the imaging literature, males had larger intracranial and amygdala volumes (Giedd & Rapoport, 2010). There was a significant interaction of Age × Group, $F(2, 50) = 3.3$, $p < .05$, for total hippocampal volumes after adjusting for intracranial volume indicating that: (A) The slope of total hippocampal volumes showed a trend to increase significantly with age in the control group ($r = .33$, $p = .08$), (B) overall the slope of total hippocampal volumes showed no association with age in the AUD − MAL group ($r = -.12$, $p = .59$). However, there was one subject whose data were an outlier (3 *SD* from the mean). We examined this correlation without the outlier and also found that total hippocampal volumes showed no association with age (total

Table 2. Three Group Comparisons Across the Achievement and Neurocognitive Measures Controlling for SES, IQ, and Parental History of AUD/SUD.

Structure, mm^3 (Adjusted for ICV), Mean ± *SD*	Control Group (1)			AUD Group without Child Maltreatment History (2)			AUD Group WithChild Maltreatment History (3)						Pairwise Comparisons	Partial η^2
	N	Mean	*SD*	*N*	Mean	*SD*	*N*	Mean	*SD*	*F*	*p*	*df*		
Achievement										2.257**	.006	16/126	—	.223
Broad reading	31	118.26	17.88	28	110.36	14.27	17	98.35	15.17	4.188*	.019	2/70	3<1	.107
Letter-word Identif.	31	106.29	11.57	28	103.68	10.40	17	94.82	13.73	2.468	.092	2/870	3<1	.066
Reading fluency	31	120.74	22.50	28	110.57	16.48	17	99.76	15.25	3.403*	.039	2/70	3<1	.089
Passage comp.	31	112.29	11.02	28	109.04	12.04	17	97.47	11.92	2.670	.076	2/70	—	.071
Broad math	31	116.97	13.56	28	101.54	14.01	17	92.41	13.00	11.474***	.001	2/70	2,3<1	.247
Calculation	31	118.81	13.23	28	100.61	15.48	17	90.24	15.44	12.130***	.001	2/70	2,3<1	.257
Math fluency	31	107.19	12.78	28	98.50	17.66	17	88.53	13.33	4.886**	.010	2/70	3<1	.123
Applied problems	31	113.35	12.68	28	102.18	10.80	17	96.76	10.25	6.421**	.003	2/70	2,3<1	.155
Fine-motor										1.803	.104	6/118	—	.084
Trail-making part A	26	106.40	12.95	27	104.06	6.18	14	104.63	12.71	1.485	.235	2/61	—	.046
GPT: Dominant hand	26	100.74	11.29	27	94.76	15.68	14	91.65	11.03	2.497	.091	2/61	—	.076
GPT: Nondominant hand	26	99.67	11.77	27	96.88	14.73	14	91.25	16.74	0.704	.499	2/61	—	.023
Language										2.177*	.049	6/136	—	.088
COWAT-Animals	31	102.79	11.98	28	103.83	15.13	17	99.46	13.16	1.196	.309	2/70	—	.033
PPVT-III	31	118.87	11.26	28	110.93	12.43	17	103.00	12.94	3.960*	.023	2/70	2,3<1	.102
CELF-3 Con. & Dir.	31	111.45	12.12	28	108.04	11.17	17	99.41	15.19	1.777	.177	2/70	—	.048
Visual-spatial										0.559	.693	4/138	—	.016
Rey–Osterrieth Copy	31	80.50	24.90	28	70.61	29.88	17	65.32	28.36	0.654	.523	2/70	—	.018
Judgment of line	31	107.38	16.22	28	103.22	13.97	17	97.05	24.77	0.045	.956	2/70	—	.001
Memory/retrieval										0.885	.531	8/132	—	.051
CVLT-total recall	31	111.27	13.01	27	111.61	17.37	17	103.53	12.24	1.018	.367	2/69	—	.029
CVLT-long delay	31	109.19	10.73	27	108.06	12.98	17	99.56	14.39	0.877	.421	2/69	—	.025
CVLT-Learn	31	93.71	12.71	27	89.72	15.16	17	87.21	11.18	0.679	.510	2/69	—	.019
TOMAL object recall	31	107.90	10.39	27	102.04	10.58	17	99.71	14.84	0.677	.512	2/69	—	.019
Attention										2.737*	.031	4/136	—	.075
CPT-omission	30	106.97	8.24	28	102.98	10.34	17	102.49	13.52	1.077	.346	2/69	—	.030
CPT-variability	30	108.82	9.03	28	104.66	13.92	17	95.76	19.86	4.776*	.011	2/69	3<1,2	.122
Executive										0.849	.583	10/112	—	.070
Stroop-interference	26	110.38	16.68	26	104.79	11.19	14	109.54	14.12	1.317	.276	2/60	—	.042
WCST-perseverations	26	120.92	14.17	26	113.73	13.68	14	109.00	17.24	0.514	.601	2/60	—	.017
WCST-categories	26	106.04	4.49	26	105.59	4.98	14	101.15	13.39	0.869	.425	2/60	—	.028
WJ-III numbers rev.	26	111.15	18.05	26	105.92	14.29	14	99.21	17.77	0.053	.948	2/60	—	.002
Trail-making part B	26	102.92	13.87	26	95.01	15.85	14	96.94	13.99	1.322	.274	2/60	—	.042

Note. Means = age-based standard scores. All scores have been scaled to have a mean = 100, *SD* = 15, with higher scores reflecting a more intact performance. AUD, SUD = alcohol, substance use disorders; IQ = intelligence as defined by the Wechsler Abbreviated Scale of Intelligence; GPT = Grooved Pegboard Test; WISC-III = Wechsler Intelligence Scale for Children–Third Edition; COWA-Animals = Controlled Oral Word Association Test–Animal Naming; PPVT-III = Peabody Picture Vocabulary Test–Third Edition; CELF-3 = Clinical Evaluation of Language Fundamentals–Third Edition; CVLT = California Verbal Learning Test; TOMAL = Test of Memory and Learning; CPT = Conners' Continuous Performance Test; WCST = Wisconsin Card Sorting Test; WJ-III = Woodcock–Johnson–Third Edition.
*$p < .05$. **$p < .01$. ***$p < .001$.

hippocampal volume = 8,684.5 ± 541.6 mm^3 × Age, $r = .18$, $p = .46$), and (C) the slope of total hippocampal volumes decreased significantly with age in the AUD + MAL group ($r = -.76$, $p < .02$). When compared to the AUD + MAL group, there were significant differences between the correlations of the control ($z = 2.95$, $p = .003$) and AUD − MAL ($z = 2.38$, $p < .02$) groups (Figure 1). However, we saw no other Age × Group effects and no Group × Gender interactions in our analyses of brain structures. Maltreatment variables did not correlate with any of the neurocognitive and academic achievement variables.

Correlations of AUD and SUD Variables With Neurocognitive Outcomes in AUD Subjects

Correlations with alcohol-related variables. In the fine-motor domain, the longer the duration of an AUD, the poorer the performance on the grooved pegboard for the nondominant

Table 3. Three Group Comparisons of Brain Measures Controlling for Intracranial Volume, SES, Age, IQ, and Parental History of AUD/SUD.

Structure, mm^3 (Adjusted for ICV), Mean ± *SD*	Healthy Controls (Group 1), *N* = 28	All AUD subjects (*N* = 31)	AUD Group Without Maltreatment History (Group 2), *N* = 22	AUD Group With Maltreatment History (Group 3) *N* = 9	All AUD vs. Controls Statistic	*p* Value	Three-Group Statistic	*p* Value	Pair-wise[a]
Prefrontal cortex									
Left superior frontal gyrus	25,864.8 ± 2,101.7	25,493.5 ± 2,031.8	25,493.9 ± 2,239.3	25,492.6 ± 1,522.5	$F(2, 51) = 0.0$	.99	$F(2, 50) = 1.04$	.36	
Right superior frontal gyrus	24,946.9 ± 2,058.6	24,251.0 ± 2,557.0	24,370.2 ± 2,616.2	23,959.6 ± 2,533.2	$F(2, 51) = 0.06$	.80	$F(2, 50) = .36$	.70	
Left rostral middle frontal gyrus	19,095.9 ± 1,730.7	19,166.6 ± 1,947.5	19,312.1 ± 2,059.8	18,811.0 ± 1,698.7	$F_{2,51} = 1.78$	.19	$F(2, 50) = .89$	.42	
Right rostral middle frontal gyrus	19,454.0 ± 1,624.8	19,829.8 ± 2,125.9	20,305.9 ± 2,042.2	18,665.9 ± 1,962.8	$F(2, 51) = 2.3$	.13	$F(2, 50) = 1.63$	.21	
Left Caudal middle frontal gyrus	7,737.7 ± 1,155.6	7,644.7 ± 1,150.1	7,511.2 ± 1,124.3	7,970.8 ± 1,213.7	$F(2, 51) = 0.45$	.51	$F(2, 50) = 1.66$	.20	
Right caudal middle frontal gyrus	6,884.9 ± 1,157.8	6,874.4 ± 1,129.4	6,822.2 ± 1,245.8	7,002.1 ± 826.9	$F(2, 51) = 0.45$	.50	$F(2, 50) = .94$	.40	
Left pars opercularis	6,100.1 ± 976.9	5,783.8 ± 795.4	5,644.0 ± 816.1	6,125.5 ± 662.6	$F(2, 51) = 0.25$	.62	$F(2, 50) = 2.19$	.12	
Right pars opercularis	4,946.1 ± 816.6	4,697.3 ± 821.2	4,512.2 ± 694.0	5,149.8 ± 969.5	$F(2, 51) = 0.11$	.74	$F(2, 50) = .54$	.58	
Left pars triangularis	4,367.0 ± 680.3	4,202.4 ± 606.5	4,056.3 ± 430.4	4,559.5 ± 831.3	$F(2, 51) = .61$	.44	$F(2, 50) = 3.87$	.03	1,2<3
Right pars triangularis	5,340.1 ± 810.4	5,211.7 ± 674.7	5,080.3 ± 569.5	5,532.8 ± 831.9	$F(2, 51) = 0.0$	.99	$F(2, 50) = .80$	.45	
Left pars orbitalis	2,541.4 ± 271.8	2,508.6 ± 351.9	2,553.1 ± 325.9	2,399.5 ± 408.4	$F(2, 51) = 0.0$	.98	$F(2, 50) = .22$	.81	
Right pars orbitalis	3,295.4 ± 429.4	3,041.6 ± 440.4	3,005.0 ± 358.8	3,131.0 ± 613.8	$F(2, 51) = 2.2$	.14	$F(2, 50) = 1.9$	.16	
Left lateral orbitofrontal cortex	9,040.9 ± 554.1	8,929.1 ± 756.54	9,052.9 ± 644.1	8,626.6 ± 955.1	$F(2, 51) = 0.0$	.99	$F(2, 50) = .12$	.89	
Right lateral orbitofrontal cortex	8,869.2 ± 766.3	8,799.3 ± 755.4	8,822.3 ± 663.6	8743.1 ± 989.5	$F(2, 51) = 0.1$	.90	$F(2, 50) = .09$	.91	
Left medial orbitofrontal cortex	5,862.9 ± 544.8	5,780.1 ± 676.1	5,797.3 ± 663.3	5,738.1 ± 746.0	$F_{2,51} = 0.1$	.93	$F(2, 50) = .41$	.67	
Right medial orbitofrontal cortex	5,975.2 ± 557.8	5,829.7 ± 559.9	5,825.2 ± 624.1	5,840.9 ± 391.3	$F(2, 51) = 0.54$	.47	$F(2, 50) = .26$	.77	
Left anterior cingulate cortex (rostral)	3,252.2 ± 522.7	3,145.7 ± 502.3	3,203.1 ± 535.7	3,005.5 ± 401.9	$F(2, 51) = 0.09$	.10	$F(2, 50) = .82$	.44	
Right anterior cingulate cortex (rostral)	2,711.9 ± 499.5	2,576.8 ± 377.1	2,529.1 ± 365.9	2,693.5 ± 400.4	$F(2, 51) = 2.84$	.14	$F(2, 50) = 1.40$	.26	
Left anterior cingulate cortex (caudal)	2,162.2 ± 506.3	2,050.8 ± 483.2	2,166.9 ± 423.6	1,767.2 ± 526.3	$F(2, 51) =0.70$	.41	$F(2, 50) = 2.02$	.14	
Right anterior cingulate cortex (caudal)	2,600.2 ± 518.9	2,637.8 ± 504.2	2,606.9 ± 491.3	2,713.3 ± 557.5	$F(2, 51) = 0.1$	.96	$F(2, 50) = .37$	.69	
Left precentral gyrus	14,524.9 ± 1,362.7	14,428.9 ± 993.7	14,558.5 ± 1,082.7	14,112.3 ± 683.5	$F(2, 51) = 0.07$	.80	$F(2, 50) = .33$	.72	
Right precentral gyrus	14,235.8 ± 1,345.8	13,971.0 ± 1,229.1	14,200.8 ± 1,289.1	13,409.5 ± 896.4	$F(2, 51) = 0.36$	.55	$F(2, 50) = .24$	.79	
Left frontal pole	882.8 ± 184.3	901.6 ± 172.8	864.4 ± 173.9	992.4 ± 140.1	$F(2, 51) = 0.75$	.39	$F(2, 50) = 1.75$	.18	
Right frontal pole	1,196.1 ± 187.2	1,169.1 ± 216.9	1,174.0 ± 208.3	1,157.0 ± 249.7	$F(2, 51) = 0.04$	.84	$F(2, 50) = .05$	.96	
Left amygdala	1,595.7 ± 162.6	1,645.2 ± 159.7	1,646.2 ± 147.0	1,642.7 ± 197.2	$F(2, 51) = 0.37$	.54	$F(2, 50) = .19$	.82	
Right amygdala	1,703.8 ± 193.5	1,760.0 ± 145.3	1,763.6 ± 106.2	1,751.1 ± 222.3	$F(2, 51) = 0.91$	.35	$F(2, 50) = .52$	.60	
Left hippocampus	3,999.7 ± 486.1	4,192.7 ± 357.1	4,265.8 ± 365.1	4,014.2 ± 279.2	$F(2, 51) = 1.23$	.27	$F(2, 50) = .68$	.51	
Right hippocampus	4,204.2 ± 329.2	4,317.5 ± 344.6	4,389.8 ± 347.1	4,140.6 ± 281.9	$F(2, 51) = 1.21$	.28	$F(2, 50) = .86$	.43	
Left para-hippocampal gyrus	2,488.5 ± 324.8	2,406.7 ± 310.3	2,420.4 ± 333.7	2,373.2 ± 258.7	$F(2, 51) = 0.25$	.62	$F(2, 50) = .15$	.86	
Right para-hippocampal gyrus	2,379.1 ± 277.9	2,315.1 ± 242.1	2,346.6 ± 238.5	2,238.1 ± 246.9	$F(2, 51) = 0.22$	.64	$F(2, 50) = .17$	.85	

(continued)

Table 3. (continued)

Structure, mm^3 (Adjusted for ICV), Mean ± *SD*	Healthy Controls (Group 1), *N* = 28	All AUD subjects (*N* = 31)	AUD Group Without Maltreatment History (Group 2), *N* = 22	AUD Group With Maltreatment History (Group 3) *N* = 9	All AUD vs. Controls Statistic	*p* Value	Three-Group Statistic	*p* Value	Pair-wise[a]
Corpus callosum									
Anterior	845.6 ± 124.8	860.9 ± 139.8	897.7 ± 132.3	771.2 ± 120.8	$F(2, 51) = 1.48$	.23	$F(2, 50) = 3.3$	.04	2>3
Midanterior	502.9 ± 127.5	500.2 ± 104.2	498.7 ± 103.2	503.9 ± 112.8	$F(2, 51) = 0.95$	.33	$F(2, 50) = .77$	.47	
Central	476.6 ± 110.9	472.9 ± 89.2	475.5 ± 96.9	466.5 ± 71.8	$F(2, 51) = 0.31$	.58	$F(2, 50) = .22$	.80	
Midposterior	443.4 ± 90.3	454.4 ± 69.3	459.1 ± 78.8	442.7.8 ± 38.3	$F(2, 51) = 1.06$	.31	$F(2, 50) = 1.31$	.28	
Posterior	889.7 ± 100.2	912.9 ± 128.3	913.7 ± 132.1	911.2 ± 126.0	$F(2, 51) = 3.18$	.08	$F(2, 50) = 1.64$	.20	

Note. AUD = alcohol use disorders; SUD = substance use disorders; SES = socioeconomic status; ICV = intracranial volume.
[a] Least means differences Dunnett test, $Q = 2.24$, $p \leq .05$.

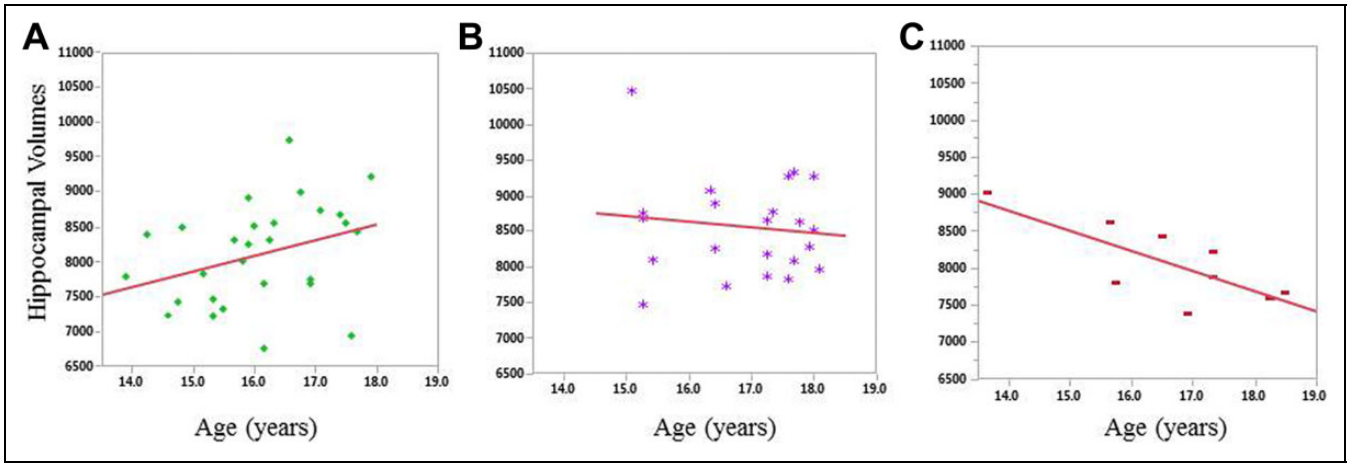

Figure 1. There was a significant interaction of Age × Group ($F_{2,50} = 3.3$, $p < .05$) for total hippocampal volumes after adjusting for intracranial volume, age, SES, and familial history of AUD/SUD indicating that: (A) The slope of total hippocampal volumes showed a trend to increase significantly with age in the control group ($r = .33$, $p = .08$), (B) the slope of total hippocampal volumes showed no association with age in the AUD − MAL group ($r = -.12$, $p = .59$), and (C) the slope of total hippocampal volumes decreased significantly with age in the AUD + MAL group ($r = -.76$, $p < .02$). There was a significant difference between the correlations of the control ($z = 2.95$, $p = .003$) and AUD − MAL ($z = 2.38$, $p < .02$) groups with the AUD + MAL group. SES = socioeconomic status; AUD = alcohol use disorder; SUD = substance use disorder; AUD − MAL = adolescents with AUDs without maltreatment and AUD; AUD + MAL = adolescents with AUDs with maltreatment.

hand ($r = -33$, $p = .03$). Performance on the grooved pegboard for the dominant hand positively correlated with abstinence (the number of days since the last drink; $r = .30$, $p < .05$). In the attention domain, the greater the number of weekly drinks consumed, the more omission errors made on the CPT ($r = -.37$, $p < .02$) and the lower the Attention Variability on the CPT ($r = -.37$, $p < .02$). In the executive domain, the number of drinks consumed in a day significantly correlated with lower performance on the Stroop-Interference Task ($r = .40$, $p < .007$). All of these correlations were of a moderate degree of magnitude.

Correlations with cannabis-related variables. The number of symptoms of cannabis withdrawal inversely correlated with slower performance of the grooved pegboard for the dominant hand ($r = -.35$, $p = .03$) and nondominant hand ($r = -.42$, $p = .009$). In the language domain, the younger the age of onset of cannabis use disorder, the lower the performance on the Peabody Picture Vocabulary Test–Third Edition ($r = .41$, $p < .02$). In the visual-spatial domain, the younger the age of onset of cannabis use disorder, the lower the performance on the Judgment of Line Orientation task ($r = .41$, $p < .02$). The younger the age of onset of cannabis use disorder, the lower the performance on the CVLT Total Recall ($r = .35$, $p < .05$), and the more joints smoked in a day, the lower the performance on the TOMAL Object Recall ($r = -.34$, $p < .03$). The younger the age of onset of cannabis dependence, the lower the WCST-perseverations ($r = .56$, $p = .002$) and WCST-categories completed ($r = .52$, $p = .005$) scores. The longer the duration of cannabis dependence, the lower the WCST-Perseveration ($r = -.39$, $p < .03$) and the more joints smoked per week, the slower the performance on the Trail-Making Part B ($r = -.34$, $p < .05$). Taken together, these correlations were within the moderate to large range.

Correlations with nicotine-related variables. In the memory/retrieval domain, the younger the age of onset of nicotine dependence, the lower the performance on the TOMAL Object Recall ($r = .42$, $p < .03$). The number of cigarettes consumed daily correlated with lower performance on the Stroop-Interference Task ($r = -.36$, $p < .02$). The longer the duration of nicotine dependence ($r = -.39$, $p = .04$) and the younger the age of onset of nicotine dependence ($r = .52$, $p = .004$), the lower the performance on the WCST-Perseverations score. In the academic domains, broad reading and math did not significantly correlate with any of the AUD/SUD variables.

Correlations of AUD and SUD variables with brain volume outcomes. Total left amygdala volume ($r = -.38$, $p < .04$) was negatively correlated to a moderate degree with mean number of drinks per week. Total ($r = -.38$, $p < .04$) and right parahippocampal ($r = -.43$, $p < .02$) volumes were negatively correlated to a moderate degree with mean number of drinks per week. Total ($r = .47$, $p < .009$) and left parahippocampal ($r = .50$, $p = .004$) volumes positively correlated to a moderate to strong degree with abstinence (the number of days since the last drink). Brain measures did not significantly correlate with any other of the AUD/SUD or maltreatment variables.

Discussion

This study used a three-cell design to examine neurocognitive function, academic achievement, and brain structures in abstinent adolescents with an AUD controlling for child maltreatment. The two AUD groups were similar in their comorbid *DSM-IV-TR* and *DSM-5* Axis I psychopathology and on alcohol, nicotine, cannabis, and other substance use variables. We found that some neurocognitive differences associated with

drinking may be related to a history of maltreatment, such as poorer performance in broad reading and math fluency and difficulties with sustained attention. Thus, these findings agree with previous studies of maltreated children and adolescents who did not have a history of AUDs or SUDs (De Bellis et al., 2009; De Bellis et al., 2013). We found poorer sustained attention in the AUD + MAL group compared to the AUD − MAL group and controls. Attention problems are commonly seen in maltreated youth who do not have AUD/SUD (De Bellis et al., 2009; De Bellis et al., 2013). Our pilot data showed that AUD + MAL group had smaller anterior corpus callosum volumes compared to the AUD − MAL group, an area of the corpus callosum that houses axons from the prefrontal cortex, which is part of the complex dorsal frontoparietal network that governs sustained attention (Corbetta & Shulman, 2002). Smaller corpus callosum areas were reported in maltreated youth with PTSD (De Bellis et al., 1999; De Bellis et al., 2002). It is possible that the results in the literature demonstrating poorer attention in adolescents with an AUD are preexisting and related to child maltreatment, other types of early trauma, or are neurodevelopmental in nature secondary to genetic influences. Maltreated youth with PTSD and no AUD/SUD history demonstrated prefrontal deficits in anterior cingulate neural integrity (De Bellis, Keshavan, Spencer, & Hall, 2000b), orbitofrontal cortex volume (Hanson et al., 2010; Keding & Herringa, 2015; Morey et al., 2016), and PFC function (Carrion, Garrett, Menon, Weems, & Reiss, 2008; Hanson et al., 2013). However, we saw no orbitofrontal cortex group differences in this study. Inattention was predictive of future AUD in a longitudinal study, which supports the idea that inattention is a premorbid risk factor for AUD (Tapert, Baratta, Abrantes, & Brown, 2002). Further, since we showed that the number of weekly drinks consumed was positively associated with attention dysfunction in the entire AUD sample, we also speculate that alcohol may have subtle toxic effects on attention networks that improve with abstinence and are independent of premorbid inattention. We note that the AUD + MAL group showed larger left pars triangularis volumes than controls. This is a region of the inferior frontal gyrus that is involved in language, word retrieval, and working memory. AUD + MAL group showed poorer reading skills compared to the controls but did not differ in the language memory/retrieval domains. The hippocampus is responsible for attention and memory. We found that there was a significant interaction of Age × Group for total hippocampal volumes demonstrating that the slope of hippocampal volumes decreased significantly with age in the AUD + MAL group compared to the control and AUD − MAL groups, suggesting that early maltreatment experiences may increase the risk to the hippocampus of the adverse effects of alcohol. However, larger longitudinal epidemiological studies, which examine maltreatment variables and hippocampal volumes before drinking onset, are needed to examine these issues further.

The findings reported here, of lower academic achievement in math and language in both the AUD − MAL and AUD + MAL groups, agree with the previous literature demonstrating poorer academic achievement (Moss et al., 1994) and language (Jacobus & Tapert, 2013) in adolescents with an AUD. Our results did not replicate the results of others showing that adolescents with AUD show poorer fine-motor (Nguyen-Louie et al., 2015), language, memory, visual-spatial (Nguyen-Louie et al., 2015), attention, and executive functions (for review, see Jacobus & Tapert, 2013). However, we did see correlations that suggest that the longer the duration of an AUD, the poorer the fine-motor performance, and the greater the number of drinks consumed in a day, the lower performance on selected executive functions (i.e., Stroop-Interference Task). Since correlations suggested that fine-motor performance improved with more days of abstinence, it is possible that alcohol had subtle negative effects on cognitive function, which are reversible once abstinent due to the adolescent age of our sample. We have found a similar effect in a separate sample of adolescents with cannabis use disorders once they became abstinent (Hooper, Woolley, & De Bellis, 2014).

AUD is frequently comorbid with cannabis use disorder (CUD; Clark, 2004). Our study suggested that CUD variables were predictive of neurocognitive function. CUD variables negatively predicted performance in fine-motor, language, memory, and executive function. Furthermore, the younger the age of CUD onset, the poorer the performance on tests of language, visual-spatial, memory, and executive functions. Neurocognitive measures did not show significant correlations with number of days of cannabis abstinence.

AUD is also frequently comorbid with nicotine dependence (Clark, 2004). Although we required 21 days of abstinence from alcohol and illicit drugs for study entry, we did not require that participants stop using cigarettes to be study eligible. Greater severity of nicotine dependence was negatively associated with performances on tests in the memory and executive function domains; the younger the age of onset of nicotine dependence, the poorer the performance on tests of memory and executive functions.

In contrast to our previous study (De Bellis et al., 2000a), where adolescents were required to be abstinent from alcohol and drugs for only 14 days, we did not find hippocampal (including parahippocampal) volume differences in the AUD groups who were required to be abstinent for at least 21 days prior to study entry compared with controls. We did see a negative correlation between left amygdala volume and mean number of drinks consumed per week. Total and right parahippocampal volumes were positively associated with the number of days of abstinence, which may suggest that alcohol induced neurotoxicity in adolescents is reversible with abstinence and/or treatment during this developmental time period. Animal studies suggest that alcohol may be toxic to neurons through the mechanisms involving glutamate, oxidative stress, neuroinflammatory mediators, and inhibition of cortical and hippocampal neurogenesis (see Crews et al., 2005). In a rat model, neurogenesis occurs in the hippocampal regions within weeks of a 4-day binge treatment of rats (Nixon & Crews, 2004), suggesting that recovery from the toxic neural effects of alcohol may be responsible for our positive correlations between

days since last alcohol intake, parahippocampal volumes, and performance in fine-motor domains. Our requirement of 21 days of abstinence and our recruitment from outpatient clinics specializing in the treatment of youth addictions prior to study entry may also be responsible for the lack of significant findings between AUD subjects and controls in this study compared to the existing literature as most adolescent AUD/SUD studies have not required 3 weeks of abstinence prior to study enrollment.

This study has a number of limitations. It employed a cross-sectional design that limits inferences about the causal relationships between alcohol effects, maltreatment, neurocognitive functions, academic achievement, and brain structures. We were only able to scan a small number of AUD + MAL subjects (due to higher numbers of pregnancy and relapse in this group) compared to the AUD − MAL group. This limited our power to detect significant differences in the brain structures studied. The AUD + MAL group differed from the control group in FSIQ and SES, which may have contributed to results independently. The IQ limitation is inherent in child maltreatment studies where both cross-sectional (De Bellis et al., 2009; De Bellis et al., 2013) and longitudinal studies demonstrate lower IQ in victims of maltreatment (Perez & Widom, 1994). Since higher IQ participants demonstrate a linear relationship with neural efficiency compared with lower IQ participants in the IQ range of our participants (Neubauer & Fink, 2009), we believe FSIQ group differences were appropriately addressed using statistical methods. We note that mean SES for all three groups was within Class 4 of 5, where Class 5 is the highest class on the Hollingshead four-factor index. Thus, the significant differences in SES, even though controlled for statistically in our results, were not likely to be real world differences reflecting extremes of wealth and poverty. We did not recruit a maltreated group without AUD. Therefore, we do not know if our results suggest that individuals with an AUD and documented maltreatment history are more sensitive to the negative effects of alcohol or that some of the findings in the adolescent alcohol literature are related to trauma histories that were not examined prior to alcohol consumption. Although we controlled for age in our analyses, we studied adolescents aged 13–18 years, maturation effects that are not directly related to age could have influenced our results. Finally, this was a pilot study where sample sizes were relatively small (particularly for brain volume measures) and the number of comparisons undertaken is a potential methodological limitation. Thus, our results should be interpreted with caution. It will be important for larger scale longitudinal epidemiological studies to measure maltreatment variables to address neurobiological hypotheses concerning predictors and causation of AUD/SUD.

This study has numerous strengths. We examined maltreatment as a factor that may have influenced the current adolescent literature on the effects of an AUD on neurocognitive function and PFC, corpus callosum, and limbic volumes. Although maltreatment is a common risk factor for AUD, previous AUD investigations have not addressed the effects of AUD from maltreatment on neurocognitive function and brain regions. We studied two groups of adolescents who were in outpatient treatment and abstinent from alcohol and substance use for 21 days prior to study entry and had similar clinical and AUD/SUD presentations. We also controlled for number of biological parents with an AUD/SUD in all our analyses.

Conclusions

The results of this pilot study suggest that differences between adolescents with AUD and controls are complex, particularly with regard to attention regulation and brain structural measures. Prior child maltreatment history may independently or additively contribute to the adverse effects of adolescent drinking on cognitive function and brain measures. Preexisting problems with sustained attention in youth with AUD + MAL may contribute to their high rate of AUD and SUD treatment resistance and relapse once a period of sobriety is obtained. Therefore, successful treatment of individuals with addictions and maltreatment history may require building attention regulation skills. Comorbid SUD and possible recovery of some cognitive functions and parahippocampal volumes during abstinence are factors that may also contribute to the current conflicting findings in the existing literature.

Authors' Note

Stephen R. Hooper, PhD, has provided consultation to Eli Lilly not related to this work, so there is no conflict of interest identified in this work.

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