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Authors

Windle, Michael
Gray, Joshua C
Lei, Karlo Mankit
et al.

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Age Sensitive Associations of Adolescent Substance Use with Amygdalar, Ventral Striatum, and Frontal Volumes in Young Adulthood

Michael Windle,
Emory University, Atlanta, Georgia

Joshua C. Gray,
Department of Psychology, University of Georgia, Athens

Karlo Mankit Lei,
Center for Family Research, University of Georgia, Athens

Allen W. Barton,
Center for Family Research, University of Georgia, Athens

Gene Brody,
Center for Family Research, University of Georgia, Athens

Steven R. H. Beach,
Center for Family Research, University of Georgia, Athens

Adrianna Galván,
Department of Psychology, University of California, Los Angeles

James MacKillop,
Peter Boris Centre for Addictions Research, McMaster University, Hamilton, Ontario, Canada

Uraina S. Clark, and
Mt. Sinai Hospital, New York

Lawrence H. Sweet
Department of Psychology, University of Georgia, Athens

Abstract

Corresponding Author: Michael Windle, PhD, Department of Behavioral Sciences and Health Education, Rollins School of Public Health, Emory University, 1518 Clifton Road NE, Atlanta, GA 30322. mwindle@emory.edu.

Contributors

MW reviewed the literature, conceptualized the study, and wrote and the manuscript. KML conducted the statistical analyses for the manuscript, and JG and LHS were involved the MRI scans and MRI data extraction. All authors contributed to reading and providing revisions to the manuscript.

Conflict of interest

No conflict declared.

Introduction—This study evaluated an age sensitive model of substance use across adolescence to determine if substance use was associated with smaller volumes for an earlier developing brain region, the amygdala, a later developing region, the inferior frontal gyrus, and the ventral striatum.

Method—Participants (*N*=110) were African American young adults who were members of a longitudinal cohort across childhood and adolescence. Measures of substance use were collected across early (ages 12–15 yrs.), middle (ages 16–18 yrs.), and later (ages 19–21 yrs.) adolescence; then, at age 25, a representative subset of the sample completed magnetic resonance imaging (MRI) that assessed regional brain volumes.

Results—Higher levels of substance use during early adolescence, but not middle or later adolescence, were significantly associated with smaller amygdalar volume in young adulthood. Higher levels of substance use during middle adolescence, but not early or later adolescence, were significantly associated with smaller pars opercularis volume. Substance use was not associated with the pars triangularis or ventral striatum.

Conclusion—These findings support age sensitive associations between substance use and smaller gray matter volumes at age 25 and are consistent with literature supporting the differential nature of substance use and brain maturation across adolescence and into young adulthood.

Keywords

Structural neuroimaging; substance use; age sensitive development; amygdala; pars opercularis; ventral striatum

1. Introduction

Neurodevelopmental research has suggested that brain maturation continues throughout adolescence and into young adulthood and that maturation, such as that associated with the limbic system, occurs earlier than those associated with regions in the prefrontal cortex (Casey et al., 2007; Galvan, 2006; Geidd et al., 1999; Geidd, 2004). These differences in brain maturation are of significance in studying adolescent and early young adult development. For example, research on substance use has suggested that an earlier age of onset for alcohol use (e.g., binge drinking) and other substances may impair the development of brain regions such as the hippocampus and amygdala; these brain regions are associated with learning, memory, and emotion, and functioning in academic and social domains (Bava & Tapert, 2010; Schneider et al., 2012; Squeglia et al., 2012; 2015). Hence, it has been suggested that there may be age sensitive periods of neurodevelopment in which exposures to psychosocial and neurobiological stressors (e.g., substance use, head trauma, child maltreatment) may have a more severe impact on specific brain regions as children mature (Jensen et al., 2015; Luby et al., 2016; Pechtel et al., 2014).

Several neuroscience perspectives on adolescent brain development have emphasized a dual systems model that consists of an earlier developing emotional intensity and lability system, often associated with the amygdala and related circuits, and a later developing cognitive regulatory system associated with the prefrontal cortex and related circuits (Steinberg, 2010; Zucker et al., 2011). The dual systems model suggests that there are rapid increases in dopaminergic activity in the socioemotional system around the time of puberty and these

increases are associated with increases in reward-seeking behavior and adolescent risk-taking, including alcohol and other substance use. These socioemotional system changes precede the structural developmental processes associated with the cognitive control system in the lateral prefrontal cortex that foster greater self-regulation and impulse control. It is argued that this age-related discrepancy in the development of emotional motivational and frontal inhibitory systems contributes to a range of adolescent risky activities such as alcohol and other substance use, externalizing behaviors (e.g., oppositional defiant behavior), and rule-breaking (e.g., at school or in the home). The subsequent developmental changes during young adulthood involve greater coordination of these dual systems that become functionally more highly integrated, thereby yielding more coordinated functioning with regard to self-regulation.

A corollary of this adolescent brain developmental orientation has been the inclusion of a focus on age sensitive periods of brain growth that may be impaired due to external adverse consequences from substance use or child maltreatment (e.g., Jensen et al., 2015; Pechtel et al., 2014; Teicher & Samson, 2016). According to the age sensitive notion, brain system development may be differentially impaired contingent on *when* the exposures occur. For example, findings by Prechtel et al. (2014) indicated that child maltreatment, specifically at ages 10–11 years, contributed to variation in amygdala volume in young adulthood. Likewise, findings summarized by Luby et al. (2016) have suggested that the preschool period is a sensitive period for the impact of maternal support on the trajectory of hippocampal development.

Guided by literature on adolescent brain development, we focused on three brain regions: (a) the amygdala as the central structure associated with emotional processing; (b) the inferior frontal gyrus (specifically the pars opercularis and pars triangularis), a region with a well-documented role in response inhibition and cognitive regulatory control (Aron et al., 2003; 2004; Batty et al., 2010; Chambers et al., 2006); and (c) the ventral striatum that has been associated with risk-taking and reward processing (Ernst, 2014; Galvan, 2010). There have been conceptual frameworks (Bava & Tapert, 2010; Galvan, 2010; Jacobus & Tapert, 2012; Steinberg, 2010) and empirical studies suggesting linkage between disinhibitory behavior, including substance use, and amygdala size. Moreover, there is evidence that the amygdala plays a role in executive functions implicated in the development of substance use behaviors (Schaefer & Grey, 2007). Therefore, the focus of this study was on key nodes of a frontolimbic network that have independently and collectively been implicated in emotional and cognitive regulation as well as reward seeking behaviors such as substance use (Casey & Jones, 2010; Ernst, 2014).

Research focused on the association between substance use and either the pars opercularis or the pars triangularis has not been forthcoming. However, studies of brain functioning associated with the inferior frontal gyrus (IFG), which encompasses both of them (and the pars orbitalis), have suggested some links between response inhibition in the IFG and substance use and dependence (Moeller et al., 2016; Wiers et al., 2015; Wilcox et al., 2016). The pars opercularis is associated with language production and also has been associated with executive cognitive functions related to inhibition (Wilcox et al., 2016). Studies and reviews conducted by other investigators focused on ADHD (Batty et al., 2010; Mulligan et

al., 2011) and adult cognitive functioning (Aron et al., 2003; 2004; Chambers et al. 2006) have identified the pars opercularis with impairments in response inhibition. While not a structural imaging study, a meta-analysis of fMRI connectivity modeling in ADHD has indicated hypoactivation of the pars opercularis for those with ADHD; this hypoactivation has been mapped to executive function tasks related to working memory, planning, problem solving, and inhibitory control (Cortese et al., 2016).

Adolescent risk-taking and deficits in reward processing have been associated with the ventral striatum and associated neural regions (Ernst, 2014; Schnieder et al., 2012). Two alternative hypotheses have been proposed for the relationships between the ventral striatum and substance use. The more dominant hypothesis is that the striatum is hyper-sensitive to rewards (e.g., a “high” from using substances) and yields a motivated pattern of reward seeking behavior. An alternative hypothesis is that the striatum is hypo-sensitive to rewards during adolescence and contributes to increased efforts (motivation) for heightened reward seeking. In Ernst’s triadic model of adolescent motivation, the striatum is viewed as part of the Cognitive Impulsivity and Risk Seeking dimension that results in approach, reward–seeking behavior such as substance use (Ernst, 2014). Given the potential significance of the striatum region for reward seeking and substance use during adolescence, we also measured the ventral striatum volume as a region of interest.

In this study, analyses were performed on data collected from rural African American youths (ages 12 to 21 years) who had participated in a longitudinal study of families (Brody et al., 2013; 2016). Imaging data were obtained when the participants were 25 years of age to determine brain volumes. The study was guided by an age sensitive developmental perspective. Specifically, substance use exposures were based on the summation of substance use across three developmental periods of early- (ages 12–15 years), middle- (ages 16–18 years), and later-adolescence (19–21 years). Using path analysis modeling, each of these three developmental periods was specified to predict volumes of the three identified regions that were measured in early adulthood via an MRI assessment. This enabled an evaluation of the age sensitive hypothesis in that tests of specific predictive relations between the timing of substance use exposure (i.e., which phase of adolescence) and volumetric measures of the amygdala, IFG, and ventral striatum.

2. METHODS

2.1 Participants

A total of119 right-handed rural African Americans age 25 years were recruited from the 667 participants in a randomized prevention trial (Brody et al., 2013; 2016). The sample was recruited from rural Georgia communities when the participants were 11 years of age (mean age at pretest = 11.2 years, $SD = 0.34$). At age 11 years, the sample was characterized as working poor (73.8% at or below the Federal poverty level); 64.3% were single parent households, 35.7% two-parent households; and 21% of families had 1 child, 40% had two children, and 39% had three or more children. At age 21 (most recent wave when demographic data were collected), 6% of the sample was married, 1% was separated, and 93% reported never married. Regarding highest educational level, 4.3% did not finish high school, 35.4% had completed high school or passed G.E.D., 48.3% had some college or

went to a technical or trade school, 10.3% had a B.A., and 1.7% had a Masters' degree. Regarding employment status, 47.5% were employed full-time, 18% part-time, 2.6% full-time homemakers, and 31.9% were unemployed. Average monthly income from all sources was $1,050 (*SD*=$787).

The age 25 data collection included 461 participants from the original sample and a random selection of 119 participants received an MRI scan. The 119 participants were screened for standard imaging contraindications and right-handedness prior to enrollment. Subsequent to the imaging session, data from three participants were excluded due to image quality and motion artifacts, and six participants were excluded because of outlier scores (i.e., scores more than three standard deviations from the mean). The remaining 110 participants (56 females and 54 males) were included in the analyses. Missing data (less than 2%) were estimated via maximum likelihood estimation (Muthén & Muthén, B.O. 1998–2015). The University of Georgia's Institutional Review Board approved and monitored all study procedures, and all participants provided written informed consent.

2.2 Measures

Age groups—Because the focus of this study was on testing age sensitive periods, three aggregated age groups were formed that corresponded with early adolescence (ages 12–15 years; four assessments), middle adolescence (ages 16–18 years; three assessments), and later adolescence (ages 19–21 years; three assessments).

Substance use—At all waves of data collection, adolescents reported their use during the previous month of cigarettes, alcohol, and marijuana, as well as excessive (binge) drinking on a widely used survey instrument from the Monitoring the Future Study (Johnston et al., 2007). For alcohol, binge drinking, and marijuana, response options varied from 0 "none" to 6 "used 30 or more times". For cigarettes, response options varied from 0 "not at all" to 6 "about 2 packs a day". We derived both individual summed scores for each of the substances as well as an aggregate score across substances. To provide a common scale across substances, z-scores were derived for each substance use variable and combined to form a composite substance use measure. Analyses were conducted for both the composite measure and each of the substances. Using an aggregated composite score is consistent with our own and others' prior research (Newcomb & Bentler, 1988; Windle et al., 2016).

Child maltreatment—Five items selected from the CDC's Adverse Childhood Experiences measure that is used in the Behavioral Risk Surveillance Survey were used to measure child maltreatment (CDC, 2014). The 5-items were emotional neglect, physical neglect, emotional abuse, physical abuse, and sexual abuse and referred to experiences of participants that occurred prior to age 18 years. Response options were 0 "No" and 1 "Yes".

Depressive symptoms—Self-reports of depressive symptoms at age 18 were obtained using the Center for Epidemiologic Studies Depression scale (CES–D; Radloff, 1977), which is widely used with community samples. Youths rated each of 20 symptoms on a scale of 0 (*rarely or none of the time*), 1 (*some or a little of the time*), 2 (*occasionally or a moderate amount of the time*), or 3 (*most or all of the time*). The alpha coefficient was .86.

Externalizing problems—Mothers assessed adolescents' externalizing symptoms when the youths were age 18 years using the parent form of the Child Behavior Checklist (CBCL; Achenbach, 1991). The Aggressive and Rule Breaking subscales were combined to index externalizing symptoms; coefficient alpha for these 35 items was .92.

2.3 MRI Acquisition

Imaging data were collected using a GE Signa HDx 3-Tesla scanner at the University of Georgia's Bio-Imaging Research Center. A high-resolution T_1-weighted, fast spoiled gradient echo sequence was conducted during a 30 minute scanning session (repetition time [TR] = 7.8 ms, echo time [TE] = 3.1 ms, flip angle = 20°; field of view [FOV] = 25.6 cm, matrix = 256 × 256, 160 contiguous 1 mm axial slices, voxel size = 1 mm^3).

2.4 Image Analysis

Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer 5.3 image analysis suite, which is well documented and freely available online for download (http://surfer.nmr.mgh.harvard.edu/). FreeSurfer morphometric procedures have demonstrated good test-retest reliability across scanner manufacturers and field strengths (Han et al. 2006; Reuter et al., 2012). The standard FreeSurfer pipeline (discussed in detail in prior publications, e.g., Reuter et al., 2012) was used to derive intracranial volume (ICV) and segment cortical and subcortical gray matter volumes, including quantification of the left and right amygdala, pars opercularis, pars triangularis, and ventral medial gray matter. The Freesurfer processing pipeline explicitly considers individual variability in regions across participants during the data extraction (Pintzka et al., 2015). Pars opercularis and pars triangularis boundaries were defined using the Desikan-Killiany Atlas (Desikan et al., 2006). The ventral striatum (i.e., accumbens area) and amygdala were defined by the atlas of Fischl et al. (2002). The regions of interest were estimated from these atlases using probabilistic labeling procedures in FreeSurfer. Briefly, a neuroanatomical label (e.g., accumbens area) was assigned to each voxel based on probabilistic information automatically estimated from manually labeled training sets. We controlled for intracranial volume in order to assess the effects of each brain region relative to whole brain volume.

2.5 Data Analysis Plan

2.5.1. Path analysis—Path analysis is a flexible modeling procedure that facilitates the specification of proposed relationships among observed (or manifest) variables, including direct and indirect effects, and then provides statistical testing and evaluation of the proposed model for adequacy of fit (Kline, 1998; Muthén & Muthén, 1998–2015). Statistical assumptions largely parallel those of standard regression analyses, though model specifications are more flexible. For example, path analysis is useful in our analyses because it permits the specification of some variables to be both predicted (e.g., early adolescent substance use predicts middle adolescent substance use) and to function as a predictor (middle adolescent substance use predicts brain volumes). Furthermore, in our application, there are multiple dependent variables (brain volumes) that are correlated and may be estimated simultaneously in path analysis rather than one at a time. Testing correlated dependent variables one at time assumes independence of the separate equations; such

univariate modeling would violate the independence assumption. Path analysis also provides overall model fit statistics to facilitate the adequacy of the model specified (Kline, 1998). Structural equation modeling, of which path analysis is one type, has been used in other imaging applications related to brain volume, connectivity, and fMRI (Bowman, 2014; Colibazzi et al., 2008; Yeh et al., 2010).

2.5.2. Sensitivity analysis—In addition, for our specified path model it is recognized that omitted variables may serve as alternative explanations for our obtained findings; therefore, we conducted sensitivity analyses. For example, our findings could be due to emotional or behavioral problems (Muetzel et al., in press), or to antecedent childhood maltreatment (Gold et al., 2016; Pechtel et al., 2014). Likewise, there may be sex differences in our path model that is masked by the pooled across sex specification (Goddings et al., 2014; Lind et al., 2017). Unfortunately, our sample size is restricted (N=110) and underpowered to fully test and confidently interpret these more complex models. Nevertheless, for purposes of evaluating the robustness of the age-sensitive associations between substance use and the regional brain volumes, we conducted two additional sensitivity analyses that included: (a) childhood maltreatment, internalizing and externalizing problems; and (b) the investigation of sex differences for the path model.

3. Results

3.1 Path analytic models

A path analysis model was used to evaluate associations between substance use during early, middle, and later adolescence and brain volume measures of the amygdala, pars opercularis, and ventral striatum. Initial screening analyses also examined the pars triangularis, another component of the IFG, but there were no significant associations with substance use during any stage of adolescence and it was excluded from subsequent analyses. The correlation matrix used for the path model is provided in Table 1.

The path analysis model was specified, estimated, and evaluated using Mplus software (Muthén & Muthén, 1998–2015). We used maximum likelihood estimation with robust standard errors (MLR). The MLR estimates are robust to non-normality and standard errors were computed using sandwich estimators. The path model was specified such that early, middle, and late adolescent substance use predicted left and right volumes for the amygdala, pars opercularis, and ventral striatum while controlling for total brain volume. Because the bivariate correlations between the left and right amygdala and early adolescent substance use were similar in magnitude, we constrained them to equivalence in our specified model. Constrained and unconstrained model comparisons via the chi-square difference test indicated no decrement in model fit for the constrained model and hence the constraint was retained in the path model.

The specified model fit the data well (χ^2 with 4 *df* =6.48, p=.166, CFI=.994) and Figure 1 provides a summary of the substantive findings. Higher substance use during early adolescence was significantly associated with lower volume of the left and right amygdala, whereas higher substance use during middle adolescence was significantly associated with

lower volume of the left pars opercularis. None of the age of substance use variables significantly predicted the ventral striatum.

The path model in Figure 1 was specified also for each of the four separate substances (i.e., alcohol use, binge drinking, cigarette use, and marijuana use) to evaluate the specificity of the composite substance use findings. The results of these models are summarized in Table 2 and figures for each are provided in the Supplemental Materials. The findings indicated some specificity in that alcohol use and binge drinking were statistically significant predictors of the left amygdala in early adolescence and the left pars opercularis in middle adolescence. In addition, cigarette and marijuana use significantly predicted lower right amygdala volume in early adolescence.

3.2 Sensitivity Analyses

To evaluate if our parameter estimates in Figure 1 from substance use to brain volumes were confounded by child maltreatment, internalizing problems, or externalizing problems, we specified a path model that included these measures. The findings for this model are presented in Figure 2 and indicated that that our age sensitive findings were robust. Parameter estimates for the early adolescent substance use to left and right amygdala volumes remained statistically significant, as they did for the middle adolescent substance use to left pars opercularis volume. In addition, smaller right ventral striatum volume was significantly predicted via an externalizing pathway from childhood maltreatment to middle adolescent externalizing problems to late adolescent substance use. Higher depressive symptoms in middle adolescence also significantly predicted smaller volume of the left pars opercularis.

Because the respective sample sizes for males and females were too small (underpowered) to specify, test, and evaluate the complex model described above, we did test a simultaneous group model across sex groups for our model findings presented in Figure 1. We also conducted single degree of freedom Wald tests to evaluate the equality of each parameter estimate across males and females. The findings for this model and the Wald test statistics are provided in the Supplemental Material. Briefly, they indicated that all but three paths did not differ significantly between males and females. The three paths that did differ significantly were: (1) substance use between middle adolescence and later adolescence was higher for males relative to females (though the paths were significant for both males and females); (2) substance use in middle adolescence was more strongly related to right ventral striatum volume for males relative to females (only the male path was significant); and (3) substance use in early adolescence was more strongly related to right amygdala volume for females (though paths were significant for both males and females). Thus, while based on an underpowered sample, sex differences were not a prominent feature distinguishing males and females for the path model specified.

4. Discussion

The findings from this study were supportive of age sensitive associations between adolescent substance use and brain volume in specific brain regions. First, higher levels of early adolescent substance use were significantly associated with smaller left and right

amygdala volumes in young adulthood. The amygdala is a central component of the brain's emotional processing system that develops earlier than brain's cognitive control systems that are associated with the lateral prefrontal cortex. Although the sensitivity of the amygdala to external exposures (e.g., child maltreatment, disinhibitory behaviors including substance use) has not been universally supported in the literature (Silveri et al., 2016; Teicher & Samson, 2016), our findings are consistent with findings that have provided support for this association (Hill et al., 2001; Pardini et al., 2011). Findings based on individual substances relative to the composite measure indicated that alcohol use and binge drinking were the most prominent substance-specific predictors of the left amygdala in early adolescence, and cigarette and marijuana use were specific predictors of the right amygdala in early adolescence. Hence, higher exposure to all four of these substance use indicators was relevant to reduced volume in the amygdala.

Second, higher levels of middle adolescent substance use were significantly associated with smaller left pars opercularis volume in young adulthood. The pars opercularis is a prefrontal region that develops later than the emotional processing systems, which center on the amygdala. Prior to the current study, the potential sensitivity of the pars opercularis to heavier substance use had yet to be reported in the literature; however, the pars opercularis has been reported in relation to inhibitory processes in ADHD (Batty et al., 2010; Cortese et al., 2016). Findings based on individual substances relative to the composite measure indicated that alcohol use and binge drinking were the most prominent substance-specific predictors of the left pars opercularis in early adolescence. Future research will need to replicate the current study findings and further explore the mechanisms of how the pars opercularis may be associated with substance use, specifically alcohol use and binge drinking, via inhibitory processes and poorer executive functioning (e.g., impulsive decision-making, poor problem solving).

Third, in our primary path model (Figure 1) our findings did not support significant associations between substance use and the ventral striatum. However, in our sensitivity analysis a life-course pathway from childhood maltreatment to adolescent externalizing problems to late adolescent substance use was associated with smaller volume of the right ventral striatum. These findings are of interest to the field but are limited due to statistical power considerations and our path model needs replication to buttress our findings. Our sensitivity analysis did support the robustness of our findings in that the adolescent age-specific associations between substance use and the brain regions remained significant after including the potentially important omitted variables of child maltreatment, internalizing problems, and externalizing problems.

Our study findings are generally consistent with the dual systems model of asynchronous brain development that is associated with higher levels of risky behavior, including substance use (Steinberg, 2010; Zucker et al., 2011). Higher levels of early adolescent substance use were associated with lower amygdala volumes of the socioemotional system in young adulthood, whereas higher levels of middle adolescent substance use were associated with lower pars opercularis volume in the cognitive control system in young adulthood. There are three different models that may account for our study findings. First, according to an exposure model, age sensitive exposure to substances may have

differentially influenced the size of brain systems associated with emotional sensitivity (amygdala) and cognitive control (pars opercularis). Second, according to a premorbid model, it is possible that the observed differences in volumes as indicated in young adulthood were already evident in early adolescence (i.e., premorbid) and that these premorbid reduced volumes predicted substance use or intervening mechanisms (e.g., reward processes, rapid decision making) across adolescence. This interpretation is consistent with the findings of Hill et al. (2001) who reported smaller amygdala volumes among high risk (family history positive for alcohol) youth who had yet to initiate substance use. Third, according to a bidirectional model, it is possible that there were bidirectional relationships between premorbid brain volumes and substance use exposure that interacted across time to yield the pattern of findings that were indicated in this study. Longer-term repeated measures prospective data are required to disentangle these alternative explanations and await data collected from current studies such as the National Consortium of Alcohol and Cognitive Development (Brown et al., 2015) and the Adolescent Brain Cognitive Development Study (https://abcdstudy.org, 2017).

Several limitations of this study should be noted. First, this longitudinal family study was not designed with age sensitive periods of neurodevelopment as an endpoint. Hence, there were no data collection points for neuroimaging across the course of the study until the age 25 follow-up. Any proposed causal linkage cannot be inferred from our findings; rather, as described previously, these findings are consistent with prior neurodevelopmental observations and await confirmation via validated, longitudinal research. Our sensitivity analysis did support the robustness of the findings and this is important given the limited sample size. Second, whereas left and right amygdala volumes were associated with early adolescent substance use, associations in middle adolescence were indicated only for a smaller volume for the left hemisphere of the pars opercularis. Left side hemispheric functioning of the pars opercularis has been associated with language development and the right side with inhibitory control (Aron et al., 2003; 2004), although some functional imaging findings have indicated bilateral IFG associations with poor inhibitory control (Liddle et al., 2001). Furthermore, language is a component of the larger cognitive control system and involved in self-regulation. Nevertheless, the reason for this lateralized finding is not clear and awaits future inquiry. Third, our findings did not support significant associations between substance use and the ventral striatum. However, our sensitivity analysis suggested that a longer–term externalizing pathway may strengthen associations for substance use and the ventral striatum (Zucker et a., 2011). Fourth, our investigation of sex differences revealed few differences in the substance use-brain volume associations; however, sample size prevented more robust tests of possible sex differences. Future research should be designed to replicate these findings and determine the mechanisms and functional outcomes (e.g., academic, work, and social functioning) associated with these substance use-brain volume findings. Fifth, our findings are based on rural African American young adults and our findings may not generalize to other racial groups or to individuals at higher income levels. To the extent that these findings are confirmed in subsequent research, early identification of higher exposure to substance use (especially alcohol) or premorbid characteristics may be further targeted in interventions to prevent earlier onset substance use and its impact on brain development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- MRI brain volumes were assessed among young adult African Americans.
- Early adolescent substance use was associated with smaller amygdalar volume.
- Middle adolescent substance use was associated with smaller pars opercularis volume.
- Findings support age sensitive periods of brain development for substance use.

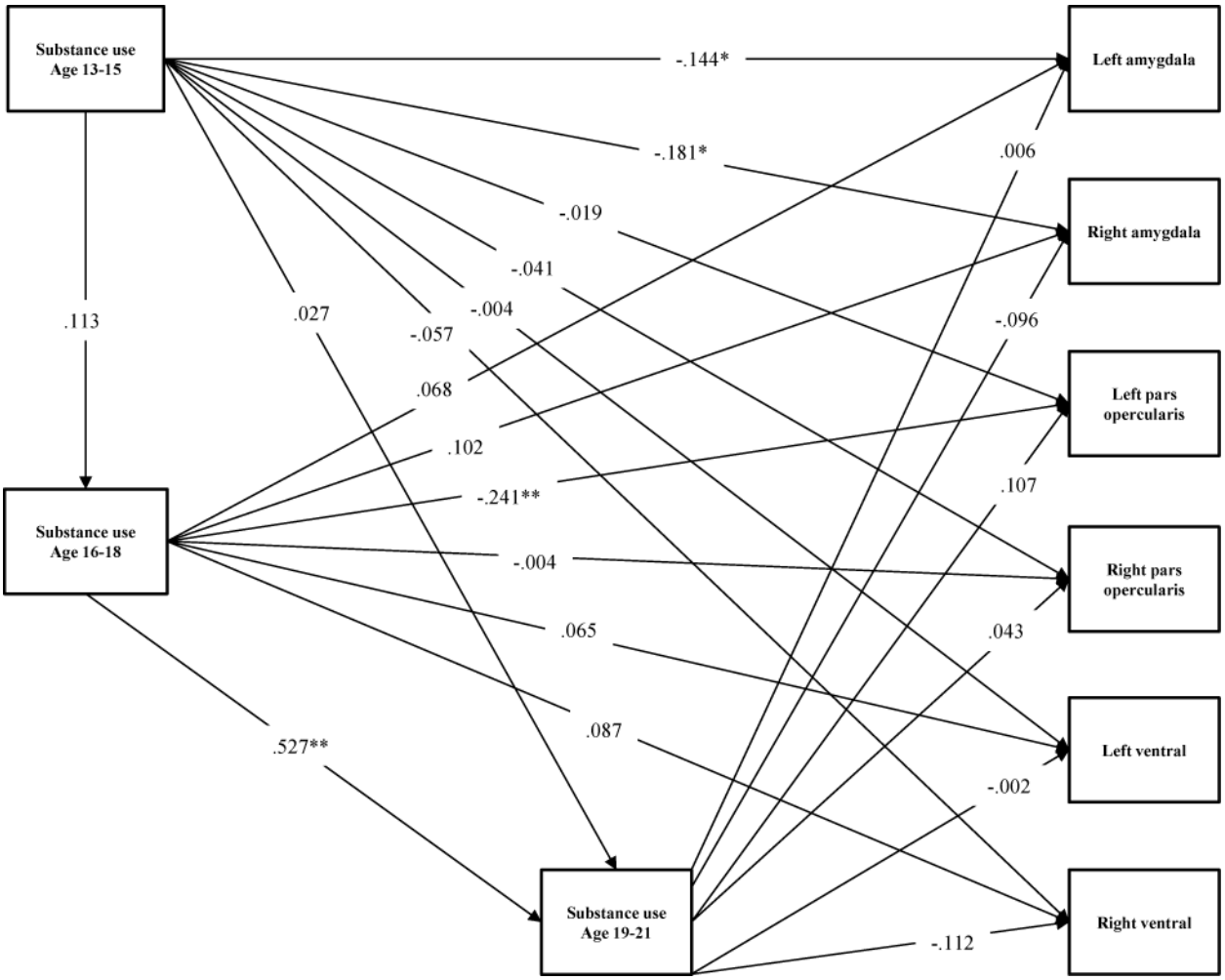

Figure 1.

Path analysis model showing the effects of substance use on amygdala, pars opercularis, and ventral striatum.

Note: Chi-square = 6.480, $df = 4$, $p = .166$; CFI = .994. Values are standardized parameter estimates. Total volume is controlled. $N = 110$. * $p \leq .05$; ** $p \leq .01$ (two-tailed tests).

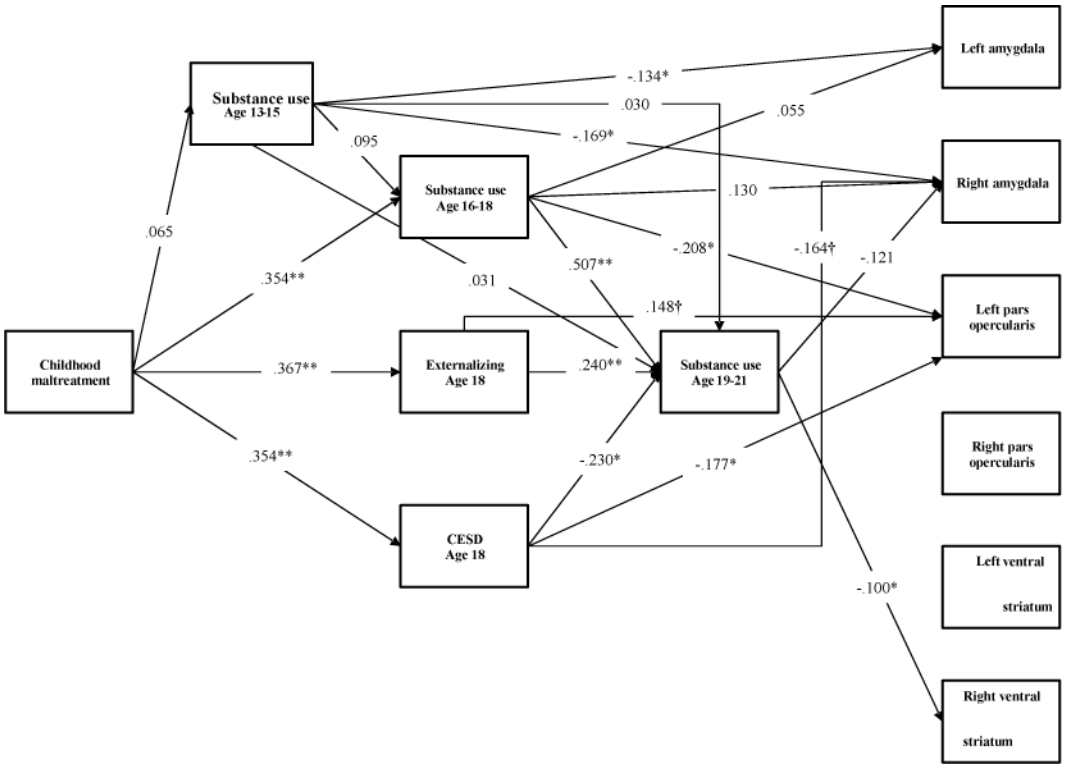

Figure 2.

Path analysis model showing the effects of childhood maltreatment, internalizing and externalizing problems, and substance use on amygdala, pars opercularis, and ventral striatum.

Note: Chi-square = 17.897, $df = 36$, $p = .995$; CFI = 1.000; RMSEA = .000. Values are standardized parameter estimates. Total volume is controlled. $N = 110$. * $p \leq .05$; ** $p \leq .01$ (two-tailed tests).

Table 1

Correlation matrix for the study variables

	1	2	3	4	5	6	7	8	9	10
1. Substance use EA[1]	—									
2. Substance use MA[2]	.024	—								
3. Substance use LA[3]	−.047	.691**	—							
4. Left amygdala	−.246**	.138	.148	—						
5. Right amygdala	−.206*	.037	.044	.504**	—					
6. Left pars opercularis	−.038	−.091	.037	.399**	.346**	—				
7. Right pars opercularis	−.107	.119	.129	.362**	.316**	.545**	—			
8. Left ventral striatum	−.037	.173	.145	.541**	.460**	.358**	.339**	—		
9. Right ventral striatum	−.085	.130	.040	.446**	.535**	.378**	.304**	.874**	—	
10. ICR[4] volume	−.061	.180	.185	.565**	.421**	.447**	.495**	.622**	.600**	—
Mean	.097	.770	2.374	1.250	1.356 6	4.510	3.700	4.132	4.058	1.415
SD	.339	1.911	2.353	.223	.174	.825	.584	.410	.369	.192

*$p \leq .05$;

**$p \leq .01$; (two-tailed tests).

[1]Early adolescence;

[2]Middle adolescence;

[3]Later adolescence;

[4]Intracranial volume

Table 2

Parameter estimates for aggregated and disaggregated substance use in predicting brain volume regions

	L-amygdala	R-amygdala	L-pars opercularis	R-pars opercularis	L-ventral striatum	R-ventral striatum
Age 12–15:						
Alcohol	−.19^{d}	−.07	−.09	−.10	−.01	−.04
Binge	−.20**	−.01	−.07	−.05	−.05	−.07
Cigarette	−.06	−.23*	−.14^{d}	−.03	−.09	−.09
Marijuana	−.07	−.13*	−.02	.03	.40	−.09
Composite Score	−.14*	−.18*	−.02	−.04	−.01	−.06
Age 16–18:						
Alcohol	−.03	.05	−.21**	−.08	−.01	−.06
Binge	.03	.07	−.16*	−.08	.08	.13
Cigarette	.32**	.06	−.09	−.08	.03	−.07
Marijuana	.11	.02	−.15	−.09	.01	−.05
Composite Score	.07	.10	−.24**	−.01	.06	.09
Age 19–21:						
Alcohol	.06	−.11	.04	.04	−.06	−.14^{d}
Binge	.02	−.14	.01	−.09	−.02	−.10
Cigarette	−.30*	−.06	−.10	.25**	.08	.03
Marijuana	.01	.11	.16	.05	.09	.08
Composite Score	.01	−.10	.11	.04	−.01	−.11

*p <.05

**p < .01

^{d}p < .10