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Substance abuse risk in emerging adults associated with smaller frontal gray matter volumes and higher externalizing behaviors

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ABSTRACT

Background: During emerging adulthood, alcohol and substance use peak. Previous research has suggested that prefrontal and subcortical brain volumes may relate to risk for development of substance abuse. Epidemiological studies indicate that early initiation of alcohol or drug use significantly increases the likelihood of later substance use disorder diagnoses. We hypothesized that frontal regions would be smaller in young adults with early substance use and related problems (early-risk, ER), compared with a control group without early use/problems (C). We further hypothesized that these volumes would be associated with more externalizing behaviors, an additional robust predictor of substance abuse.
Methods: One hundred and six subjects, ages 18–23, underwent high-resolution anatomical magnetic resonance image scanning. Individuals were categorized as C ($n = 64$) or ER ($n = 42$) using a composite-score of early alcohol/drug use and problems based on prospectively collected assessments; externalizing behaviors were also previously assessed during adolescence. Neuroanatomical volumes were compared between groups and correlated with behavioral measures.
Results: ER subjects exhibited more externalizing behaviors than their control counterparts. Total left frontal cortex and left superior frontal cortex volumes were significantly smaller in the ER group, controlling for family history of alcoholism and current substance use. Total gray matter volumes were negatively associated with substance risk score. Further, externalizing behavior score was negatively correlated with both left superior cortical and left total cortical volumes.
Conclusions: These findings suggest that smaller frontal cortical volumes, specifically the left superior frontal cortex, represent an underlying risk factor for substance abuse in emerging adults.
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1. Introduction

The transition years to adulthood, between the late teens and early twenties, is the developmental interval during which alcohol and drug use are at their highest levels and when the highest prevalence of substance use disorder (SUD) occurs (Johnston et al., 2004; Substance Abuse and Mental Health Services Administration (SAMHSA, 2006, 2010). Risk for SUD has been associated with family history and impulsive or externalizing behaviors (see recent reviews by Bava and Tapert, 2010; Stone et al., 2012). Externalizing behaviors, including aggression or delinquency, have been linked by numerous studies to both early onset and frequency of substance use (i.e., Boyle et al., 1992; Brook et al., 1996; Tarter et al., 1999; King et al., 2004; Olson et al., 2007; Hayatbakhsh et al., 2008). Further, early initiation of substance use is associated with subsequent problem use and dependence (Brook et al., 2007; King and Chassin, 2007; Roche et al., 2008), highlighting the interdependence of risk factors.

Much important work has looked at morphological differences in youth at high-risk for substance abuse based on a family history of alcoholism (FH+). For example, high-risk adolescents (average age 17) were found to have smaller right amygdala volumes than a matched group of FH− adolescents with no familial liability (FH−) – a difference not explained by past month alcohol consumption

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(Hill et al., 2001). Similarly, high-risk adolescents had decreased right-to-left hemisphere orbitofrontal volume ratio, which was not accounted for by a history of SUD – used as a proxy for alcohol and drug exposure (Hill et al., 2009). Related work hrevealed larger cerebellum and total intracranial and gray matter (GM) volumes in high-risk subjects aged 14–23 (Hill et al., 2007) and in high-risk subjects aged 8–29, when controlling for a history of SUD (Hill et al., 2011).

Other work has focused specifically on the relationships between substance use/abuse and brain structure. The most robust finding, summarized in a recent review, is prefrontal GM deficits in individuals with alcohol use disorders (AUD), particularly those under the age of 40 (Welch et al., 2013). For example, 14–21 year olds with early-onset AUD had smaller prefrontal cortex volumes than matched controls (De Bellis et al., 2005). AUD has also been associated with smaller hippocampal volume (De Bellis et al., 2000) but no cerebellar volume differences compare with controls (De Bellis et al., 2005) in this same age range. As the authors discuss, it is difficult to know whether these differences are a result of alcohol use or are a pre-existing risk factor for AUD. One approach to investigate this issue is to study high-risk youth with no alcohol exposure. Benegal et al. (2007) conducted a study of alcohol naïve high-risk (FH+) males aged 9–23 and found smaller volumes of superior frontal cortex, cingulate and parahippocampal gyri, thalamus, and cerebellum compared with FH− controls, which negatively correlated with externalizing behaviors (Benegal et al., 2007). These studies converge to suggest heritable anatomical differences related to risk for AUD.

We sought to build on this work, using a narrow age range to minimize variability in brain maturation. In addition, we sought to take into account that, while family history is a powerful predictor of later SUD, it is likely that there are neurobiological contributions to outcome differences even within a high-risk sample. Early onset of drinking has been shown to be a robust predictor of later AUD, even when controlling for family history (Dawson et al., 2008). Therefore, we examined early indicators of risky substance involvement, including early initiation and problems associated with use (Webb et al., 1991; Grant and Dawson, 1997; Zucker et al., 2003; Heitzeg et al., 2008), which we refer to as early-risk/endorsement (ER). We focused on emerging adulthood (18–23 years) including subjects with a range of substance use, taking this use, as well as family history, into account in our analyses. We expected that, compared with a less risky control (C) group, ER subjects would have smaller frontal and cingulate cortices and smaller subcortical structures including the thalamus and amygdala, supporting prior work indicating volumes in these regions are related to risk. We further hypothesized that the volumes of these regions would be negatively associated with externalizing behavior scores, linking anatomy to a known risk marker (Crews and Boettiger, 2009). We also report supplementary analyses investigating familial risk as a point of comparison with the existing literature.

2. Methods

2.1. Subjects

Participants were 106 right-handed adolescents (64 males, 42 females) aged 18.0–22.8 years (mean 20.5 ± 1.4). Subjects were recruited from the MLS, an ongoing study of families with parental alcoholism (FH+, 2/3 of sample) and contrast nonalcoholic families (FH−, 1/3 of sample; Zucker et al., 2000). Detailed description regarding MLS recruitment and assessments can be found elsewhere (Zucker et al., 1996).

Exclusionary criteria were: any neurological, acute, uncorrected, or chronic illness; any current or recent (within six months) treatment with centrally active medications including sedative hypnotics; and history of psychosis or schizophrenia in first-degree relatives. The presence of most Axis I psychiatric or developmental disorders was exclusionary. Externalizing disorders, including conduct disorders, attention deficit/hyperactivity disorder (ADHD), or substance use disorder (SUD), were not exclusionary as these may lie on a developmental spectrum with alcoholism risk (Krueger, 1999). This sample represents the first 106 neuroimaging participants within the age range of interest. Subject characteristics are summarized in Table 1. Written informed consent, approved by the University of Michigan Medical School Institutional Review Board, was obtained.

2.2. Measures

2.2.1. Substance risk score. Substance use, including abuse or dependence, was assessed using DSM-IV criteria from responses obtained from each subject's Drinking and Drug History (DDHx) Questionnaire (Zucker et al., 1990; Zucker, 1991; Zucker and Fitzgerald, 1994) assessing onset of use, content–quantity, frequency, and variability of alcohol consumption; frequency of other drug use; and consequences/problems related to use. The measure was administered yearly since age 11 so responses were relatively contemporaneous to the drinking experience.

A substance risk variable was created from five binary (yes/no) measures ascertained from DDHx responses: (1) onset of drinking by age 14; (2) onset of drunkenness by age 15; (3) onset of marijuana use by age 14; (4) onset of other drug use by age 16; and (5) more than four (>30th percentile) problems associated with alcohol use by age 17. The resultant variable ranged from 0 to 5. Subjects were categorized in either the control (C, substance risk = 0–1, $n = 64$) or ER (substance risk = 2–5, $n = 42$) groups. Scores were based on cumulative data up until benchmark ages; all participants had sufficient annual assessments between benchmark ages and the MRI scan to allow calculation of this variable despite missing data. The number of missed assessments did not differ between the risk groups (completed assessments age 11 to scan age: C: 72.9 ± 17.0%; ER: 71.5 ± 15.9%; $t = 0.41$, $p = 0.684$).

2.2.2. Substance use. Measures derived for covariates for analyses were:

(1) Cumulative drink volume (CDV), calculated from annual drink volume (DV):

DV=((drinking days/month past 6 months ∗ drink/day past 6 months) ∗ 6)
+((drinking days/month in the previous 6 months ∗
drink/day in the previous 6 months) ∗ 6))

CDV = sum of DV until and including current age

If data was missing for a year, DV was calculated as an average of the adjacent years.

(2) Pack years (PY) was calculated from the most recent assessment: How frequently have you smoked cigarettes during the past 30 days (converted to packs/day), current age, and age at first cigarette (fcig):

$PY = 0.5 * packs/day * (age - fcig)$.

The 0.5 multiplier assumes a monotonic increase in use from first cigarette until the most recent assessment.

A urine drug screen was administered to each subject prior to scanning to test for current/recent marijuana use.

2.2.3. Externalizing behaviors. Participants completed the Youth Self Report (YSR) questionnaire (Achenbach, 1991) as part of the ongoing MLS when they were 11.8–15.0 years (mean 13.4 ± 0.9) and again at 14.8–18.4 years (mean 16.4 ± 0.9). The YSR provides standardized scores of a respondent's social and emotional functioning, and has been used extensively demonstrating strong reliability and validity (Achenbach and Rescorla, 2001). Internal consistency of the YSR across assessments was adequate (Cronbach's alpha = 0.88). We used the broadband scale of externalizing behavior (EXT) given previous work associating these early behaviors with problem alcohol involvement (SAMHSA, 2005; Zucker et al., 2008).

2.2.4. Family history (FH) and family history density (FHD). Seventy-five participants study were FH+, having one or both parents with a lifetime history of alcoholism, based on a diagnosis of alcohol abuse or dependence, while 31 participants were FH−, consistent with the entire MLS. FHD was derived from genogram data on parents, aunts/uncles, grandparents and great aunts/uncles. Identified alcoholic relatives were weighted by degree within each generation (1°, 0.5; 2°, 0.25; 3°, 0.125) and summed across generations. FHD cannot be considered a pure measure of genetic load for alcoholism but provides some estimate of heritable risk (Zucker et al., 1996).

2.3. Anatomical data acquisition

High-resolution anatomical T1 scans were acquired on a 3.0 Tesla GE Excite2 scanner (Milwaukee, WI). Motion was minimized with foam pads and an emphasis on the importance of keeping still. FreeSurfer Version 5.1 (Fig. 1), a volumetric segmentation program, was used for 3-D reconstruction of anatomical images for the purpose of statistical analysis.

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