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Brain volume reductions in adolescent heavy drinkers

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ABSTRACT

Background: Brain abnormalities in adolescent heavy drinkers may result from alcohol exposure, or stem from pre-existing neural features.
Methods: This longitudinal morphometric study investigated 40 healthy adolescents, ages 12–17 at study entry, half of whom ($n = 20$) initiated heavy drinking over the 3-year follow-up. Both assessments included high-resolution magnetic resonance imaging. FreeSurfer was used to segment brain volumes, which were measured longitudinally using the newly developed quantitative anatomic regional change analysis (QUARC) tool.
Results: At baseline, participants who later transitioned into heavy drinking showed smaller left cingulate, pars triangularis, and rostral anterior cingulate volume, and less right cerebellar white matter volumes ($p < .05$), compared to continuous non-using teens. Over time, participants who initiated heavy drinking showed significantly greater volume reduction in the left ventral diencephalon, left inferior and middle temporal gyrus, and left caudate and brain stem, compared to substance-naïve youth ($p < .05$).
Conclusion: Findings suggest pre-existing volume differences in frontal brain regions in future drinkers and greater brain volume reduction in subcortical and temporal regions after alcohol use was initiated. This is consistent with literature showing pre-existing cognitive deficits on tasks recruited by frontal regions, as well as post-drinking consequences on brain regions involved in language and spatial tasks.

1. Introduction

Alcohol use is exceedingly common during adolescence, with rates of past year alcohol use in the US increasing from 24% to 64%, and past year drunkenness rising from 9% to 45% from ages 12 to 18 (Johnston et al., 2013). Furthermore, almost a quarter of US 18 year olds report heavy episodic drinking, defined as consuming five or more drinks on one occasion, during the past two weeks (Johnston et al., 2013). These high rates of heavy alcohol use are concerning, as the adolescent brain undergoes extensive morphometric and functional maturation, including decreases in gray matter and increases in white matter volume (Giedd, 2004; Giedd et al., 1999; Gogtay et al., 2004; Luna and Sweeney,

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2004; Spear, 2000). Gray matter reductions (i.e., cortical thinning) begin during early adolescence (approximately ages 12–14) and are generally considered to be related to pruning of excess neurons, changes in the extracellular matrix, and white matter encroachment (Paus, 2005), beginning primarily in posterior brain regions and progressing to more anterior regions (Gogtay et al., 2004) with decreases in dorsal prefrontal cortical volume continuing into early adulthood (mid-20s) (Sowell et al., 2001). In tandem with cortical thinning, white matter volume increases over adolescence, due to myelination of white matter tracts (Barnea-Goraly et al., 2005; Giedd et al., 1999; Pfefferbaum et al., 1994). These co-occurring processes are an integral component of neurocognitive development, creating more localized and efficient information processing and improved cognition (Squeglia et al., 2013). Because of these extensive maturational changes, the developing adolescent brain may be more vulnerable to the deleterious effects of alcohol (Jacobus and Tapert, 2013).

Heavy alcohol use during adolescence has been cross-sectionally associated with disadvantages on several neuropsychological domains, including memory, executive functioning, visuospatial skills, and sustained attention (Brown et al., 2000; Giancola et al., 2001; Sher et al., 1997). Importantly, longitudinal studies have suggested an adverse influence of adolescent heavy drinking (initiated around ages 15–16) on the development of visuospatial processing, attention, and working memory (Hanson et al., 2011; Squeglia et al., 2009; Tapert et al., 2002). Furthermore, deficits on tasks of inhibitory functioning in substance-naïve youth have been related to initiation of heavy alcohol use by ages 17–18 (Squeglia et al., 2014), suggesting cognitive functioning is both predictive of, and affected by, alcohol use.

The underlying mechanism of these behavioral changes may be related to morphometric anomalies in brain volume or cortical thickness. Research using structural magnetic resonance imaging (MRI) has shown smaller hippocampal (De Bellis et al., 2000; Nagel et al., 2005), prefrontal cortex (De Bellis et al., 2005; Medina et al., 2008), and cerebellum (De Bellis et al., 2005; Lisdahl et al., 2013) volumes in heavy-drinking teens compared to non-using controls. In a recent longitudinal study in youth characterized before (age ~17) and after (age ~19) initiating heavy alcohol use, adolescents who began heavy drinking over the follow-up period showed accelerated cortical thinning of right middle frontal gyrus, as well as decreased white matter volume, when compared to demographically matched non-using teens (Luciana et al., 2013). No differences were found between groups before initiation, suggesting alcohol use was related to aberrant cortical thinning, as opposed to cortical thickness being predictive of initiation of alcohol use. Furthermore, widespread cortical thinning and volume reduction has also been reported in alcohol dependent adults in frontal, temporal, and occipital regions (Fortier et al., 2011; Pfefferbaum et al., 1997).

The goals of this study were to use a set of novel analytic approaches to carefully examine within-subjects changes in morphometry and quantify cortical volume changes over time in youth who remained non-drinkers compared to those who initiated heavy drinking. We hypothesized that adolescents who transitioned into moderate to heavy drinking would show smaller cortical volumes, similar as has been seen in adolescent drinkers (Luciana et al., 2013) and adult alcoholics (Fortier et al., 2011; Pfefferbaum et al., 1997).

2. Methods

2.1. Participants

The sample was obtained from a larger ongoing neuroimaging study of 296 adolescents examining neurocognition in youth at-risk for substance use disorders (Bava et al., 2010; Squeglia et al., 2012a, 2011; Wetherill et al., 2013a). Participants were recruited through flyers sent to households of students attending local middle schools, describing the study as a project looking at adolescent brain development in youth who do or do not use alcohol, and included major eligibility criteria, financial compensation ($170 for youth, $20 for parents), and contact information. Informed consent and assent were obtained, and included approval for youth and parents be contacted for follow-up interviews and scans. Eligibility criteria, substance use history, family history of substance use, developmental, and mental health functioning data were obtained from the youth, their biological parent, and one other parent or close relative. The study protocol was executed in accordance with the standards approved by the University of California, San Diego Human Research Protections Program.

Participants for this study ($N = 40$) each had one brain scan (i.e., baseline scan) acquired before the adolescent had any significant alcohol or drug use, and one follow-up scan approximately 3 years later after half transitioned into heavy substance use, for a total of 80 scans. At baseline, inclusionary criteria included being between the ages of 12 and 17 and having minimal to no experience with substances: ≤10 total drinks in their life, never with more than 2 drinks in a week; ≤5 lifetime experiences with marijuana and none in the past three months; ≤5 lifetime cigarette uses; and no history of other intoxicant use (see Table 2). Youth with any indication of a history of a DSM-IV (American Psychiatric Association, 1994) Axis I disorder, determined by the NIMH Diagnostic Interview Schedule for Children – version 4.0 (Shaffer et al., 2000) were excluded, as were youth who had any indicator of prenatal substance exposure, any history of traumatic brain injury, loss of consciousness (>2 min), learning disorder, migraine, neurological problem, serious medical condition, or were taking a medication that could alter brain functioning or brain blood flow. After screening, approximately 12% remained eligible (see Table 1). Participants in the larger study completed substance use interviews every 3 months, and those who started heavy drinking were selected for a comprehensive annual follow-up with neuroimaging, and matched to a non-using control subject on baseline and follow-up age and pubertal development level, gender, race, family history of alcohol use disorders, and socioeconomic status. At follow-up, 20 were defined as heavy drinkers; 20 continuous non-drinkers were selected to match the characteristics of the heavy drinkers (see