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Adolescent heavy drinkers' amplified brain responses to alcohol cues decrease over one month of abstinence ☆

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HIGHLIGHTS

- Adolescent heavy drinkers' BOLD cue-reactivity was compared to controls.
- Adolescents were followed for 1 month of monitored abstinence and then reassessed.
- Heavy drinkers' greater BOLD response at baseline decreased after alcohol free month.

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ABSTRACT

Introduction: Heavy drinking during adolescence is associated with increased reactivity to alcohol related stimuli and to differential neural development. Alcohol cue reactivity has been widely studied among adults with alcohol use disorders, but little is known about the neural substrates of cue reactivity in adolescent drinkers. The current study aimed to identify changes in blood-oxygen level dependent (BOLD) signal during a cue reactivity task pre- and post-monitored abstinence from alcohol.
Method: Demographically matched adolescents (16.0–18.9 years, 54% female) with histories of heavy episodic drinking (HD; $n = 22$) and light or non-drinking control teens (CON; $n = 16$) were recruited to participate in a month-long study. All participants completed a functional Magnetic Resonance Imaging (fMRI) scan with an alcohol cue reactivity task and substance use assessments at baseline and after 28 days of monitored abstinence from alcohol and drugs (i.e., urine toxicology testing every 48–72 h). Repeated-measure analysis of variance (ANOVA) examined main effects of group, time, and group × time interactions on BOLD signal response in regions of interest defined by functional differences at baseline.
Results: The HD group exhibited greater ($p < .01$) BOLD activation than CON to alcohol cues relative to neutral cues in all regions of interest (ROIs; bilateral striatum/globus pallidus, left anterior cingulate, bilateral cerebellum, and parahippocampal gyrus extending to the thalamus/substantia nigra) across time points. Group × time effects showed that HD exhibited greater BOLD activation to alcohol cues than CON at baseline in left anterior cingulate cortex and in the right cerebellar region, but these decreased to non-significance after one month of monitored abstinence.
Conclusions: In all ROIs examined, HD exhibited greater BOLD response than CON to alcohol relative to neutral beverage picture cues at baseline, indicating heightened cue reactivity to alcohol cues in heavy drinking adolescents prior to the onset of any alcohol use diagnosis. Across the majority of these brain regions, differences in BOLD response were no longer apparent following a month of abstinence, suggesting a decrease in alcohol cue reactivity among adolescent non-dependent heavy drinkers as a consequence of abstaining from alcohol. These results highlight the malleability of adolescent brain function despite no formal intervention targeting cue reactivity. Increased understanding of the neural underpinnings of cue reactivity could have implications for prevention and intervention strategies in adolescent heavy alcohol users.

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1. Introduction

Alcohol use among adolescents is a pervasive issue and likely to have deleterious effects on health and well-being. Drinking to intoxication is associated with the most serious negative consequences (e.g., withdrawal symptoms relate to cognitive decline; Tapert and Brown, 1999), and this style of drinking accelerates significantly during adolescence. Recent epidemiological data indicates that 8% of American 8th graders report having been drunk in the last year, a statistic that jumps to 43% by 12th grade. Furthermore, 22% of 12th graders report heavy episodic drinking (i.e., consuming 5 or more drinks in a row) in the last 2 weeks (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2014). Heavy episodic drinking affects not only brain functioning at an acute level, but both brain development and function over time when introduced during this critical period of brain maturation (Jacobus & Tapert, 2013). Adolescent drinkers have shown diminished performances across a range of neuropsychological functioning, including on tasks of attention (Tarter, Mezzich, Hsieh, & Parks, 1995), memory (Brown, Tapert, Granholm, & Delis, 2000), information processing (Tarter et al., 1995), visuospatial functioning (Beatty, Hames, Blanco, Nixon, & Tivis, 1996; Sher, Martin, Wood, & Rutledge, 1997), language abilities (Moss, Kirisci, Gordon, & Tarter, 1994), motor speed (Ferrett, Carey, Thomas, Tapert, & Fein, 2010) and executive functioning (Montgomery, Fisk, Murphy, Ryland, & Hilton, 2012; Moss et al., 1994).

As individuals accumulate experience with substances, they tend to develop conditioned responses to cues surrounding substance use (i.e., cue reactivity), which is often characterized by craving (Rohsenow et al., 1994). Alcohol cue reactivity has been implicated as a proxy of risk for alcohol use, as adult heavy users and alcoholics exhibit increased reactivity and craving to alcohol cues, even when sober (Cooney, Litt, Morse, Bauer, & Gaupp, 1997). Exhibiting more reactivity and reporting increased subjective craving to alcohol related stimuli are indicators of the reward value and salience these stimuli have for heavy users. As such, cue reactivity has been used to predict the probability of relapse, as it may index increased incentive value that puts individuals at risk for re-initiating use (Cooney et al., 1997; Heinz, Beck, Grüsser, Grace, & Wrase, 2009).

Brain imaging studies of cue reactivity, primarily in adults, have reliably shown increased reactivity in heavy users in areas associated with reward processing (e.g., striatal and limbic regions), and have shown differences between heavy users and light- or non-drinking controls in parietal and temporal regions (Schacht, Anton, & Myrick, 2013). Likewise, several studies link brain regions associated with addiction processes in cue reactivity responses, including reward learning (nucleus accumbens [NA] and striatum; Ihssen, Cox, Wiggett, Fadardi, & Linden, 2011; Schacht et al., 2011; Vollstädt-Klein et al., 2011), reward salience (anterior cingulate cortex [ACC] and orbitofrontal cortex [OFC]; Grüsser et al., 2004; Vollstädt-Klein et al., 2011), and decision-making (dorsolateral prefrontal cortex [DLPFC]; Grüsser et al., 2004). Beyond simply differentiating between heavy and non-users, cue-elicited BOLD response in these brain regions has also been correlated with self-report craving ratings (Myrick et al., 2004; Park et al., 2007), substantiating BOLD responses as valid indices of cue-reactivity.

Adolescent heavy drinkers with varying levels of alcohol use disorder severity have exhibited increased BOLD responses to alcohol words (Tapert, Brown, Baratta, & Brown, 2004) and pictures (Tapert et al., 2003) in similar brain regions identified in studies of adults discussed above (e.g., ACC and DLPFC). These BOLD differences in adolescents were also associated with behaviors of interest including average number of drinks per month and the self-reported desire to drink alcohol (Tapert et al., 2003). Cue reactivity represents one of the core alterations to neurobiology elicited by alcohol use (Heinz et al., 2009), and serves as a promising focus for intervention (Vollstädt-Klein et al., 2011). The presence of similar effects in adolescents as those seen in adults may represent either challenges (e.g., changes occurring early in development may be more deeply ingrained into the neural architecture) or opportunities (e.g., adolescent brains are more malleable and more likely to overcome the neural alterations associated with increased cue reactivity). Gaining a better understanding of how individuals at risk for developing alcohol use disorders react to alcohol stimuli, and monitoring how those reactions change over time, may be particularly important for developing prevention and intervention strategies aimed at reducing alcohol use disorders in adolescents and young adults.

The aim of the current study was to elucidate neural substrates associated with cue reactivity in adolescent heavy episodic drinkers (HD) compared to non-drinking controls (CON), and to evaluate responses pre- and post-monitored abstinence. Areas of the brain associated with reward processing and decision-making were of primary interest and identified as regions of interest (ROI) a priori including the NA, dorsal striatum and globus pallidus (DSGP), ACC, OFC, and DLPFC. We hypothesized that heavy drinking adolescents would show increased BOLD response to alcohol relative to neutral cues compared to non-drinking adolescents prior to prolonged abstinence (e.g., Tapert et al., 2003), but differences would diminish after a month of monitored abstinence, representing a decrease in the motivational salience of alcohol cues over the course of the abstinence period.

2. Method

2.1. Participants

Participants (16.0–18.9 years) were recruited from local high schools, colleges, and community settings via mailings and fliers (Bekman, Winward, Lau, Wagner, & Brown, 2013; Winward, Bekman, Hanson, Lejuez, & Brown, 2014). The study was advertised as an "adolescent development project," and no information regarding alcohol or drug use criteria was described in the fliers or discussed prior to screening. Interested students responding by phone were independently screened to determine eligibility. Each interested teen and one parent underwent a structured interview to confirm eligibility. In accordance with the University of California, San Diego (UCSD) Human Research Protections Program and high school district policies, written informed assent (adolescent participant) and consent (parent/legal guardian) were obtained before participation. To minimize confounds, individuals were excluded if they had: history of a psychiatric disorder; extensive marijuana (>50 lifetimes) or other drug use (>15 times); head trauma; learning disorder; neurological dysfunction or serious medical illness; family history of bipolar I or psychotic disorder; significant prenatal alcohol exposure (>7 drinks in a week or >2 drinks in a day); sensory problems; use of psychoactive medications; and substance use during the abstinence protocol.

Participants were classified as HD or CON. HD participants reported ≥100 lifetime drinking episodes, ≥3 past month heavy episodic drinking occasions (with at least 1 within 2 weeks prior to study initiation), and 1 or more recent alcohol withdrawal symptoms. CON teens reported <5 lifetime drinking episodes, no history of heavy drinking episodes (i.e., >4/5 standard alcoholic drinks on one occasion for females/males) or alcohol withdrawal symptoms, and no previous marijuana or other drug use (see Table 1 for detailed alcohol use characteristics). None of the participants met criteria for Diagnostic and Statistical Manual of Mental Disorders-Fourth edition (DSM-IV) alcohol dependence and none were seeking treatment for their alcohol use.

A total of 51 participants were enrolled in the study (HD = 32; CON = 19). Five HD participants did not complete the protocol (4 due to toxicology confirmed alcohol or drug use, 1 due to schedule conflicts/inability to fulfill protocol). An additional 8 participants' data were excluded due to excessive artifacts in their fMRI data (i.e., >15% of trials contained artifacts; 3 CON and 5 HD), leaving a final sample of 38 adolescents (HD = 22; CON = 16). The HD group was approximately 6 months older than the CON group, but the groups did not differ significantly in pubertal development or in the distribution of males and females (see Table 1). Of the 16 CON, 3 reported ever having