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Reduced cerebellar brain activity during reward processing in adolescent binge drinkers

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ABSTRACT

Due to ongoing development, adolescence may be a period of heightened vulnerability to the neurotoxic effects of alcohol. Binge drinking may alter reward-driven behavior and neurocircuitry, thereby increasing risk for escalating alcohol use. Therefore, we compared reward processing in adolescents with and without a history of recent binge drinking. At their baseline study visit, all participants (age = 14.86 ± 0.88) were free of heavy alcohol use and completed a modified version of the Wheel of Fortune (WOF) functional magnetic resonance imaging task. Following this visit, 17 youth reported binge drinking on ≥3 occasions within a 90 day period and were matched to 17 youth who remained alcohol and substance-naïve. All participants repeated the WOF task during a second visit (age = 16.83 ± 1.22). No significant effects were found in a region of interest analysis of the ventral striatum, but whole-brain analyses showed significant group differences in reward response at the second study visit in the left cerebellum, controlling for baseline visit brain activity ($p/\alpha < 0.05$), which was negatively correlated with mean number of drinks consumed/drinking day in the last 90 days. These findings suggest that binge drinking during adolescence may alter brain activity during reward processing in a dose-dependent manner.

1. Introduction

Adolescence is a period marked by continued structural and functional development in the brain (for review, see Blakemore, 2012), as well as many associated behavioral and cognitive changes (for review, see Paus, 2005). Adolescence is also a time of increased risk-taking behavior, including experimentation with drugs and alcohol (Eaton et al., 2012). One possible explanation for increased risk-taking observed during adolescence involves the continued development of reward-related neurocircuitry (Galvan, 2010). Brain regions, such as the orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC), and striatum have been implicated as key components in the brain's reward system (McClure et al., 2004; Schultz, 2000) and are regions that undergo development during adolescence (Goddings et al., 2014; Gogtay et al., 2004). For example, dopamine receptor levels and binding in the striatum are higher during adolescence than adulthood (Seeman et al., 1987) and are accompanied by an increase in density of dopaminergic projections to the prefrontal cortex (Kalsbeek et al., 1988; Rosenberg and Lewis, 1994; Tunbridge et al., 2007). These developmental changes in the reward system during adolescence may impact how the brain responds to reward. Specifically, some neuroimaging studies have found greater reward-related activation during adolescence, compared to that seen in adults and children, in regions such as the ventral striatum and mPFC (Van Leijenhorst et al., 2010), which may be associated with an increase in ventral striatal dopamine release observed during rewarding events (Jonasson et al., 2014; Koepp et al., 1998). This heightened plasticity of the reward system during adolescence may render the adolescent brain more vulnerable to the neurotoxic effects of drugs of abuse.

Currently, the most common form of substance use among adolescents is the use of alcohol. In the United States, by the end of the 12th grade, 68% of adolescents have reported drinking alcohol, 52% report being drunk in their lifetime, and 26% report being drunk within the last 30 days (Johnston et al., 2014). Furthermore, binge drinking, the most common form of alcohol misuse among adolescents (Deas, 2006), is reported by over 22% of adolescents (Johnston et al., 2014). In line with findings of continued development of the reward system during adolescence, pre-clinical models have found that the reward system in adolescence responds differently to alcohol than during adulthood. Increased dopamine release

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within the ventral striatum during acute alcohol exposure is prominent in adolescents (Pascual et al., 2009; Philpot et al., 2009) and appears to be associated with greater rewarding effects of alcohol during this developmental stage (Pautassi et al., 2008; Ristuccia and Spear, 2008), which may promote future drinking. In support of this notion, rodent models indicate that alcohol exposure during adolescence, compared to adulthood, increases reward driven behavior (McMurray et al., 2014; Schindler et al., 2014).

A growing body of literature has documented numerous abnormalities in brain structure and functioning among adolescent alcohol users. Binge drinking during adolescence has been associated with differences in frontal lobe cortical thickness (Squeglia et al., 2012) and reductions in cerebellar volume (Lisdahl et al., 2013), as well as widespread reductions in white matter integrity with and without comorbid marijuana use (Jacobus et al., 2013). Additionally, binge drinking has been shown to have an effect on brain activity during affective decision making (Xiao et al., 2013) and spatial working memory (Schweinsburg et al., 2008; Squeglia et al., 2011). Cross-sectional neuroimaging studies have begun to explore the effects of alcohol on reward processing in the brain, but this work has been limited to adults. Alcohol-dependent adults have shown increased activation in the ventral striatum and mesial frontal cortex during reward notification compared to controls (Bjork et al., 2008b), as well as reduced reward outcome-related positivity in the brain, measured with event-related potentials, suggestive of deficient reward processing (Kamarajan et al., 2010). This latter "reward deficiency" finding is further supported by studies in adult alcoholics which found hyporesponsive activity in the ventral striatum during reward anticipation (Beck et al., 2009; Wrase et al., 2007). While both hyper- and hyporesponsive activity in the ventral striatum have been seen in human adults, preclinical models in adolescents primarily support the idea of reward deficiency, such that repeated alcohol exposure leads to a hypodopaminergic state (Philpot et al., 2009), and alcohol-induced changes to the reward system correlate with increased alcohol seeking behavior and voluntary consumption in adult rats that experienced adolescent alcohol exposure (Pascual et al., 2009). No longitudinal study, to our knowledge, has investigated the effects of binge-level alcohol use on reward-related brain activation in an adolescent population.

The current study sought to expand on this body of literature by examining neural activation to reward in a group of binge-drinking adolescents compared to alcohol/drug-naïve controls using a prospective, longitudinal approach. Adolescents performed a modified version of the Wheel of Fortune (WOF) task (Ernst et al., 2004), a reward-based decision-making task, during functional magnetic resonance imaging (fMRI). Based on previous findings in adult alcoholics of decreased reward-related activation (Beck et al., 2009; Wrase et al., 2007), as well as alcohol's propensity to affect the reward system during adolescence (Pascual et al., 2009; Philpot et al., 2009), we hypothesized that binge-drinking adolescents would show reduced brain activation to reward outcome, compared to their non-using peers, in reward processing regions, such as the mPFC and ventral striatum.

2. Materials and methods

2.1. Participant recruitment and screening

Over 200 participants, ages 12–16, were recruited as part of a longitudinal study on risk factors for and consequences of alcohol use on brain and behavior during adolescence (Cservenka et al., 2012, 2013, 2014a,b; Cservenka and Nagel, 2012; Mackiewicz Seghete et al., 2013). Recruitment was conducted through community mailings and local advertising. The participating youth and one of their parents or guardians were interviewed by phone during a pre-screen to determine initial eligibility, following which study consent and assent were obtained from parents and youth, respectively. Next, a longer telephone screening interview was conducted with the youth and parent, separately. During this screen, the Structured Clinical Interview (Brown et al., 1994), the Diagnostic Interview Schedule for Children Predictive Scales (Lucas et al., 2001), and the Family History Assessment Module (Rice et al., 1995) were administered to assess the presence of psychiatric conditions in the youth, and determine family history of psychopathology. Youth who met DSM-IV criteria for an Axis I disorder were not included in the study. Other exclusionary criteria for study participation were (1) lack of family history information, (2) presence of psychotic disorders in first-degree biological parents (i.e. schizophrenia or bipolar I), (3) parent report of prenatal alcohol exposure, (4) MRI contraindications (including pregnancy), (4) head injury with loss of consciousness, (5) use of psychotropic medication, (6) left-handedness (Oldfield, 1971), and (7) serious medical/neurological conditions. Furthermore, since this study was aimed at understanding the neural consequences of initiating heavy drinking during adolescence, youth were excluded from the initial study visit if they reported >10 lifetime alcoholic beverages, >2 drinks/occasion, >5 lifetime uses of marijuana, or >4 cigarettes/day (Brief Lifetime version of the Customary Drinking and Drug Use Record (CDDR, Brown et al. (1998)). Finally, the Hollingshead Index of Social Position (Hollingshead, 1957) was administered to the participating parent or guardian to estimate socioeconomic status (SES) of the youth, based on the parents' educational and occupational attainment. All procedures were in accordance with the ethical guidelines of the Oregon Health & Science University (OHSU) Institutional Review Board.

2.2. Study procedures and follow-up assessments

Eligible male youth were scheduled for study visits at any time, while female youth were scheduled during the first 10 days of their menstrual cycle (follicular phase) to account for cycle-related variations in hormone levels. At the initial baseline study visit (age range: 13.15–16.34), participants underwent neuroimaging, during which they completed a modified version of the WOF fMRI task (Cservenka et al., 2013; Cservenka and Nagel, 2012; Ernst et al., 2004) and a structural MRI scan for co-registration of functional data (other components of the MRI scan are not reported in this study). Furthermore, youth completed a neuropsychological battery within one week of the imaging session, which included estimates of intellectual functioning using the Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler (1999)). Pubertal status was assessed with gender-specific line drawings representing pubertal development with Tanner's Sexual Maturation Scale (Taylor et al., 2001). The Children's Depression Inventory (Kovacs, 1985) and the State-Trait Anxiety Inventory (Spielberger et al., 1973) were administered at each study visit to assess depressive symptoms and state anxiety, respectively.

Following completion of the initial study visits, participants could elect to participate in the longitudinal portion of the study. If youth assented to participating, they were contacted by phone approximately every 3 months. During these phone interviews, youth were asked to provide information on drinking behavior in the past 90 days with the CDDR (Brown et al., 1998), following which the 90-day Timeline Followback (TLFB) (Sobell and Sobell, 1992; Sobell et al., 1986) was used to collect detailed information on alcohol, marijuana, nicotine, and other drug use, if any use was reported. Based on these interviews, youth who reported binge drinking ($\geq$5 drinks/occasion for males and $\geq$4 drinks/occasion for females) on at least one occasion in the past 90 days, and had at least two other occasions of $\geq$4 drinks/occasion in that 3-month