NeuroImage xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Binge drinking impacts dorsal striatal response during decision making in adolescents

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ARTICLE INFO

Article history:
Received 21 August 2015
Accepted 20 January 2016
Available online xxxx

Keywords:
Adolescence
Decision making
Alcohol
Binge
Dorsal striatum

ABSTRACT

Adolescence is a time of both increased risk taking and increased vulnerability to the neurotoxic effects of alcohol. However, it is unclear whether brain functioning abnormalities in adolescent binge drinkers are a result of alcohol use itself or whether they represent premorbid risk characteristics. The current study addresses this question by using a modified version of the Wheel of Fortune (WOF) task, during functional magnetic resonance imaging (fMRI), at both baseline, while all subjects were alcohol-naïve, and revisit, when half of the subjects had emerged into regular binge drinking (n = 13) and half remained alcohol and substance-naïve (n = 13). Region of interest (ROI) analysis revealed that during decision making, there was a significant binge-drinking related reduction in brain activation in the dorsal striatum, an effect associated with degree of recent use. Furthermore, whole brain analysis revealed a decrease in fronto-parietal brain activation prior to initiation of alcohol use, in adolescents who went on to binge drink. Additionally, there were numerous regions, both cortical and subcortical, in which there was a significant time-related developmental change, across groups. These results demonstrate how abnormalities in decision-making related circuitry might both lead to and perpetuate alcohol drinking behavior. These findings help aid in our ability to disentangle consequences of binge drinking from potential risk markers for future binge drinking, and may help guide future prevention and intervention strategies.

Introduction

Adolescence is a time of significant neurodevelopment (for review, see Blakemore, 2012) and is also a time of increased risk taking, including experimentation with drugs and alcohol (Eaton et al., 2012). This tendency towards novel exploration and risk taking is believed to stem from continued development of both reward processing and executive control regions during this time (for review, see Geier, 2013). For example, in a cross-sectional analysis, Van Leijenhorst et al. (2010) found that from late childhood to early adulthood, during risky decision making, there was a linear decrease in activation in dorsal anterior cingulate cortex (dACC) and an inverted-U shaped trajectory of activation in the ventral medial prefrontal cortex (vmPFC), with a peak during late adolescence. This finding coincides with findings from a recent longitudinal structural neuroimaging study that revealed a mismatch between the development of reward and cognitive control regions, with the nucleus accumbens (NAc) showing relatively earlier maturation than the PFC (Mills et al., 2014). Furthermore, pre-clinical models indicate that during adolescence there is a peak in dopamine receptor levels and binding in the striatum (Seeman et al., 1987), accompanied by an increase in the density of dopaminergic projections to the PFC (Kalsbeek et al., 1988; Rosenberg and Lewis, 1994). Taken together, these findings highlight the dynamic changes taking place in prefrontal and striatal regions of the brain, areas thought to be important for decision making (for review, see Balleine et al., 2007).

Adolescence is also a time of increased vulnerability to the neurotoxic effects of alcohol. Pre-clinical models have found that adolescent rats are more susceptible than adult rats to neuronal cell death as a result of an alcohol binge (Crews et al., 2000). More specifically, neural cells in the PFC are particularly sensitive to binge-like exposure to alcohol during adolescence (Koss et al., 2012). The striatum also responds differently to alcohol in adolescence compared to adulthood. For example, during acute alcohol exposure, increased dopamine release in the striatum is more prominent in adolescents (Pascual et al., 2009; Philpot et al., 2009) and appears to be associated with greater rewarding effects of alcohol (Pautassi et al., 2008; Ristuccia and Spear, 2008). Additionally, alcohol exposure differentially affects cognitive performance, with adolescent, but not adult rodents, showing decreases in learning and memory due to alcohol exposure (Land and Spear, 2004; Markwiese et al., 1998; White et al., 2000). These results suggest that exposure to alcohol, even in seemingly modest doses, may have a greater impact on the

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http://dx.doi.org/10.1016/j.neuroimage.2016.01.044
1053-8119/

developing adolescent brain than on a mature adult brain, and that both prefrontal and striatal regions may be particularly susceptible to these effects. With up to 68% of adolescents having reported drinking alcohol by the 12th grade, and over 22% reporting binge drinking (Johnston et al., 2014), gaining a better understanding of alcohol's effects on these developing regions is extremely relevant, as it may help provide us with better targets for future prevention and intervention strategies.

Numerous cross-sectional studies have been conducted comparing binge-drinking adolescents to their alcohol-naïve peers to assess the effects of alcohol at a structural and functional neurobiological level. Magnetic resonance imaging (MRI) studies have revealed that binge drinking during adolescence is associated with significantly thicker (females) and thinner (males) frontal lobe cortices (Squeglia et al., 2012), reductions in cerebellar volume (Lisdahl et al., 2013), and widespread reductions in white matter integrity (McQueeny et al., 2009). Furthermore, functional MRI studies (fMRI) have revealed that binge-drinking adolescents have decreased brain response in the right superior and inferior frontal gyri during working memory (Squeglia et al., 2011), and numerous regions of differential activation during verbal encoding, including increased posterior parietal cortex activation (Schweinsburg et al., 2010; Schweinsburg et al., 2011). However, to our knowledge, few studies have attempted to look at binge-drinking related effects on adolescent brain response during decision making, despite the likelihood that decision making-related neurobiological alterations, in particular, may be highly relevant for choosing to misuse alcohol. Johnson et al. (2008) found that during affective decision making, binge-drinking adolescents performed significantly worse than their alcohol-naïve counterparts on the decision making portion of the Iowa Gambling Task (IGT), with this result linked to dysfunction in the vmPFC; however, this result was more closely related to a hypersensitivity to reward outcome, as opposed to risky choice selection. Furthermore, Xiao et al. (2013) found that binge-drinking adolescents showed higher activation than non-drinkers in bilateral insula during the IGT; however, this finding was also not specific to the selection phase of risk taking and included other aspects of decision making, such as anticipation and reward processing. Failure to separate decision making from response to outcome makes the interpretation of neuroimaging findings difficult, as there are likely many processes that underlie these complex tasks.

The current study used fMRI and a modified version of the Wheel of Fortune (WOF) task (Ernst et al., 2004), a reward-based decision-making task, to assess risk-taking behavior and the blood oxygen level-dependent (BOLD) response in binge-drinking adolescents and matched controls. Unlike previous studies (Johnson et al., 2008; Xiao et al., 2013), this task separated the decision making, anticipation, and reward outcome phases of risk-taking behavior, so as to more accurately examine BOLD response during decision making. In fact, brain regions previously shown to have altered BOLD response during decision making among adolescent alcohol users, such as the vmPFC and insula (Johnson et al., 2008; Xiao et al., 2013), have also been shown to be more heavily recruited during reward anticipation using the WOF task (Ernst et al., 2004). Meanwhile, dorsal control regions, including the dorsolateral PFC and dorsal striatum, appear to be more heavily recruited during the selection phase of this task (Ernst et al., 2004), and during decision making in general (Balleine et al., 2007). Based on this, and the increased susceptibility of the PFC and striatum to the neurotoxic effects of alcohol during adolescence (Crews et al., 2000; Koss et al., 2012; Pascual et al., 2009; Philpot et al., 2009), we hypothesized that following emergence into binge drinking, the dorsolateral PFC and dorsal striatum would show less activation in binge-drinking adolescents than controls, above and beyond any premorbid differences seen at baseline in these regions. Additionally, utilization of a longitudinal design allowed us to also explore pre-existing differences, an effect that has yet to be reported on, as well as developmental effects which have previously only been looked at cross-sectionally (e.g. Van Leijenhorst et al., 2010).

Methods

Participants

Recruitment and exclusionary criterion

Healthy adolescent participants (13 to 16 years old) were recruited from the local community as part of an ongoing longitudinal study on adolescent neurodevelopment. After a telephone pre-screen to determine initial eligibility, written consent and assent were obtained from parents and youth, respectively, followed by separate comprehensive screening interviews of participants and their parents. Exclusionary criteria during this screening interview included left-handedness [Edinburgh Handedness Inventory (Oldfield, 1971)], diagnosis of a DSM-IV psychiatric disorder [Diagnostic Interview Schedule for Children Predictive Scales (Lucas et al., 2001)], inability to obtain family history information, serious medical problems (including head trauma), mental retardation or learning disability, psychotic illness in a biological parent, known prenatal drug or alcohol exposure, MRI contradictions, and pregnancy. Furthermore, at baseline, adolescents were excluded for prior drug or alcohol use that exceeded >10 lifetime alcohol drinks, >2 drinks on any one occasion, >5 uses of marijuana, >4 cigarettes per day, or any other drug use [Brief Lifetime version of the Customary Drinking and Drug Use Record (CDDR) (Brown et al., 1998)]. The study was approved by the Oregon Health & Science University (OHSU) Institutional Review Board.

Participant characteristics

To assess socioeconomic status (SES), parents were administered the Hollingshead Index of Social Position, a measure based on the educational attainment and occupation of each parent (Hollingshead and Redlich, 1958). To provide an estimate of overall intellectual functioning, youth were administered the 2-subtest version of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). To measure pubertal development, self-assessment of puberty was obtained using a modified line drawing version of the Tanner's Sexual Maturation Scale (Taylor et al., 2001), with drawings ranging from stage 1 (pre-adolescent) through stage 5 (adult-like maturation). To evaluate family history of alcohol use disorders (AUDs), a known risk factor for alcoholism shown to be associated with unique neurobiological features (Cservenka et al., 2014a; Cservenka et al., 2014b; Cservenka and Nagel, 2012), a family history density (FHD) score was calculated for each participant using the Family History Assessment Module (Rice et al., 1995). FHD was based on how many and how closely related an adolescent was to the relative(s) with an AUD; parents contributed 0.5, grandparents 0.25, and aunts and uncles a weighted ratio of 0.25 divided by the number of their siblings, with higher scores indicating greater prevalence of familial AUDs.

Follow-ups and binge-drinking criterion

Following initial recruitment and collection of baseline neuropsychological and neuroimaging measures, follow-up phone interviews were conducted with youth approximately every 90 days, during which the CDDR and 90-day Timeline Followback (Sobell et al., 1996) were administered to assess substance use. Once a participant reported binge drinking (≥5 drinks for males or ≥4 drinks for females, in one occasion), as well as had ≥3 total occasions of ≥4 drinks within the last 90 days, they were brought in for re-assessment with neuropsychological and neuroimaging measures analogous to those conducted at baseline. For every binge-drinking adolescent that was re-assessed after initiation of alcohol use, a time-since-baseline and developmentally (based on sex, age and pubertal stage) matched non-using control was also brought in for re-assessment. This procedure resulted in a total of 13 binge-drinking youth and 13 non-using controls. Youth were instructed to refrain from any drug and alcohol use for 72 h prior to their revisit, and a negative breathalyzer prior to their imaging session was used to confirm absence of acute alcohol intoxication.

Please cite this article as: Jones, S.A., et al., Binge drinking impacts dorsal striatal response during decision making in adolescents, NeuroImage (2016), http://dx.doi.org/10.1016/j.neuroimage.2016.01.044