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Adolescents show differential dysfunctions related to Alcohol and Cannabis Use Disorder severity in emotion and executive attention neuro-circuitries

Joseph Aloi[a,b,*], Karina S. Blair[a], Kathleen I. Crum[a], Harma Meffert[a], Stuart F. White[a], Patrick M. Tyler[a], Laura C. Thornton[a], Alita M. Mobley[a], Abraham D. Killanin[a], Kathryn O. Adams[a], Francesca Filbey[e], Kayla Pope[a,c,d], R. James R. Blair[a]

[a] Center for Neurobehavioral Research, Boys Town National Research Hospital, Boys Town, NE, United States
[b] Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, United States
[c] Department of Psychiatry, University of Nebraska Medical Center, Omaha, NE, United States
[d] Department of Psychiatry, Creighton University, Omaha, NE, United States
[e] Center for BrainHealth, School of Behavioral and Brain Sciences, University of Texas at Dallas, Dallas, TX, United States

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ABSTRACT

Alcohol and cannabis are two substances that are commonly abused by adolescents in the United States and which, when abused, are associated with negative medical and psychiatric outcomes across the lifespan. These negative psychiatric outcomes may reflect the detrimental impact of substance abuse on neural systems mediating emotion processing and executive attention. However, work indicative of this has mostly been conducted either in animal models or adults with Alcohol and/or Cannabis Use Disorder (AUD/CUD). Little work has been conducted in adolescent patients. In this study, we used the Affective Stroop task to examine the relationship in 82 adolescents between AUD and/or CUD symptom severity and the functional integrity of neural systems mediating emotional processing and executive attention. We found that AUD symptom severity was *positively* related to amygdala responsiveness to emotional stimuli and *negatively* related to responsiveness within regions implicated in executive attention and response control (i.e., dorsolateral prefrontal cortex, anterior cingulate cortex, precuneus) as a function of task performance. In contrast, CUD symptom severity was unrelated to amygdala responsiveness but *positively* related to responsiveness within regions including precuneus, posterior cingulate cortex, and inferior parietal lobule as a function of task performance. These data suggest differential impacts of alcohol and cannabis abuse on the adolescent brain.

1. Introduction

Two of the most commonly abused substances by adolescents in the US are alcohol and cannabis (Miech et al., 2016). Notably, epidemiological evidence suggests that adolescent alcohol users are twice as likely to develop Alcohol Use Disorder (AUD) while adolescent cannabis users are over three times as likely to develop Cannabis Use Disorder (CUD) by age 26 than non-users (Winters and Lee, 2008). Furthermore, adolescents who initiate substance use face a more severe disease course and a greater likelihood of relapse (Babor et al., 1992). This may reflect the deleterious neurodevelopmental impact of substance abuse on the adolescent brain (Filbey et al., 2015; Squeglia et al., 2015), which is undergoing critical changes at this time (Goddings et al., 2014).

One neuro-circuitry undergoing development during adolescence that may be disrupted by substance abuse is the neuro-circuitry mediating emotional processing (Koob and Volkow, 2016). Animal work suggests that substance dependence leads to decreased striatal response to reward and increased amygdala responsiveness to stress (Koob and Volkow, 2016). In line with this, there have been reports of increased amygdala responses to negative images in alcohol dependent adults relative to controls (Gilman and Hommer, 2008), and in undergraduate students who also demonstrated relatively low ventral striatal responsiveness to reward (Nikolova et al., 2016). Additionally, there has been at least one report of increased amygdala responsiveness to angry relative to neutral faces in adolescents with mild cannabis use histories (group average: < 5 times lifetime usage) (Spechler et al., 2015). However, other work has reported reduced amygdala responses to emotional relative to neutral faces in alcohol dependent adults (O'Daly et al., 2012) and in adult heavy cannabis smokers relative to healthy control adults (Gruber et al., 2010). In short, the human fMRI

* Corresponding author at: Center for Neurobehavioral Research, Boys Town National Research Hospital, 14100 Crawford Street, Boys Town, NE 68010, United States.
E-mail address: joseph.aloi@unmc.edu (J. Aloi).

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literature is somewhat inconsistent and focused on studies with adult participants.

A second putative neuro-circuitry disrupted by substance abuse is that mediating behavioral inhibition (Feldstein Ewing et al., 2014; Silveri et al., 2016; Spear, 2016); i.e., anterior cingulate/dorsomedial prefrontal cortices (ACC/dmPFC) and anterior insular cortex/inferior frontal gyrus (aIC/iFG; Criaud and Boulinguez, 2013). Moreover, substance abuse may also disrupt regions showing dense projections with ACC/dmPFC (i.e. dorsolateral prefrontal (dlPFC) and parietal cortices) which are critical for executive attention (Desimone and Duncan, 1995; Squire et al., 2013). Neuroimaging work has revealed that, relative to controls, undergraduate students and adults with heavy alcohol use histories show reduced ACC responses during NoGo trials relative to baseline (Ahmadi et al., 2013; Claus et al., 2013) and reduced dlPFC responses during successful, relative to unsuccessful, Stop trials during a Stop Signal Task (Li et al., 2009). Furthermore, ACC functional connectivity has been identified as a predictor of relapse in adults aged 18–50 with AUD (Zakiniaeiz et al., 2017). The literature in adolescents aged 18 and younger has been more mixed. One study reported an inverse relationship between prior alcohol consumption and aIC responses to incongruent relative to congruent trials during a Stroop task (Thayer et al., 2015). Another study which tracked youths from early to late adolescence reported that adolescents (ages 11–17) who later transitioned into heavy drinking showed *decreased* activity within middle frontal and parietal cortices in NoGo relative to Go trials prior to the onset of heavy drinking compared to controls who did not transition into heavy drinking (Norman et al., 2011; Wetherill et al., 2014). At a three-year follow-up after the onset of heavy drinking (at ages 14–21), adolescents who did transition to heavy drinking showed *increased* BOLD responses in these contrasts and brain regions relative to their baseline scans. However, participants who did not transition to heavy drinking showed *decreased* BOLD responses in these contrasts and brain regions relative to their baseline scans (Wetherill et al., 2014).

The empirical literature suggests a rather different relationship between cannabis usage and brain regions implicated in behavioral inhibition or executive attention, specifically *increased* (potentially compensatory) recruitment of these regions. In a Stroop task, adults with histories of heavy cannabis use showed increased ACC and dlPFC activity during interference trials relative to controls (Gruber and Yurgelun-Todd, 2005). Additionally, in a Multi-Source Interference Task, adults with histories of chronic cannabis smoking showed increased ACC recruitment during interference trials relative to control trials compared to healthy control subjects (Gruber et al., 2013). Furthermore, Filbey and Yezhuvath (2013) showed that cannabis-dependent adults showed greater connectivity between right frontal cortex and the substantia nigra/subthalamic nucleus network during successful inhibition on a Stop Signal task compared to non-dependent cannabis using adults. In a sample of adolescents, marijuana users showed increased recruitment of executive attention regions during NoGo trials relative to baseline in a Go-NoGo task (Tapert et al., 2008).

Dysfunction in executive attention neuro-circuitry may be related to increased amygdala responsiveness to threat in patients with substance abuse. Executive attention neuro-circuitry involves the dlPFC and parietal cortices and allows the priming of task-relevant representations at the expense of irrelevant ones (Desimone and Duncan, 1995). This increased priming of task-relevant stimuli inhibits the representation of emotional distractors and results in reduced amygdala responses to these distractors (Blair et al., 2007). Executive attention can be recruited explicitly within cognitive reappraisal emotion regulation paradigms (Ochsner and Gross, 2005) but also implicitly through emotion distraction paradigms (Erthal et al., 2005). Both executive attention and emotional responsiveness systems are implicated in exteroception, or processing self-relevant external stimuli, and is thought to play a role in the development and maintenance of substance abuse (DeWitt et al., 2015). If alcohol and/or cannabis abuse compromise executive attention, then representation of external task-relevant stimuli should be impaired, resulting in compromised emotion regulation and increased emotional responsiveness. Alternatively, alcohol and/or cannabis abuse may compromise neural systems underlying exteroception relatively independently, resulting in reduced representation of task-relevant stimuli regardless of emotional stimuli and/or increased emotional responsiveness regardless of task demands.

In the current study, we implemented an emotion distraction task, the Affective Stroop task (aST; Blair et al., 2007) in adolescents showing varying levels of AUD and CUD symptomatology. In the aST, participants are instructed to determine the quantity of numbers displayed on the screen that are temporally bracketed by either emotional or neutral distracters. Work with healthy adolescents (Hwang et al., 2014) and adults (Blair et al., 2007) reveals that task performance is associated with decreased amygdala responsiveness to emotional distracters and increased recruitment of regions mediating behavioral inhibition (ACC, dmPFC, aIC, and iFG) and executive attention (dlPFC and parietal cortices) to task-relevant stimuli. The aST has been extensively used in work with both adolescent and adult clinical populations (Blair et al., 2013, 2012; Hwang et al., 2016, 2015; White et al., 2014). Specifically, adults with GAD, SAD, and PTSD show compromised recruitment of ACC and/or parietal cortices during task relative to view trials (Blair et al., 2013, 2012) while adolescents with ADHD, show reduced dmPFC activity during incongruent trials relative to typically developing (TD) adolescents (Hwang et al., 2015). Furthermore, in adolescents with disruptive behavior disorders (DBDs), there is decreased recruitment of aIC in incongruent relative to view trials and the degree to which this is compromised relates to impulsivity symptoms within this sample (Hwang et al., 2016). In addition, adolescents with DBDs and high levels of callous-unemotional traits showed reduced vmPFC and amygdala responsiveness to negatively valenced stimuli (Hwang et al., 2016). In short, the aST has been successfully used to show dysfunction in emotion processing, behavioral inhibition, and executive attention neuro-circuitries in adult and adolescent clinical populations.

We hypothesized that: (i) participants with high levels of AUD and CUD symptoms would show increased recruitment of the region implicated in emotional responding to both positively and negatively valenced stimuli (amygdala); and (ii) participants with at least high levels of AUD symptomatology would show reduced recruitment of regions implicated in behavioral inhibition (dmPFC/ACC and/or aIC/iFG) and/or executive (dlPFC and/or parietal cortices) to task relative to view trials.

2. Materials and methods

2.1. Participants

Study participants included 96 youths aged 14–18 years from both a residential treatment facility and the community. 14 participants were excluded due to excessive movement (> 10% volumes censored at > 1 mm motion across adjacent volumes) or low accuracy on the task (< 60% accuracy; average AUDIT of excluded participants = 4.2, average CUDIT of excluded participants = 5.0). This resulted in a final sample of 82 youths (47 youths from the residential treatment facility and 35 from the community); average age = 16.1 (SD = 1.32), IQ = 100.6 (SD = 10.13) and 51 male. Clinical characterization was done through psychiatric interviews by licensed and board-certified psychiatrists with the participants and their parents. Youths with significant substance abuse histories were residents of the residential treatment facility and were abstinent for at least four weeks prior to scanning.

49 youths endorsed having used, and 33 youths denied having used, alcohol and/or cannabis on the Alcohol Use Disorder Identification Test (AUDIT) and the Cannabis Use Disorder Identification Test (CUDIT), respectively (Adamson et al., 2010; Fairlie et al., 2006; Saunders et al., 1993). The range of AUDIT scores and CUDIT scores was 0–22 (M = 2.9; SD = 4.65) and 0–32 (M = 7.0; SD = 8.96), respectively. AUDIT scores, but not CUDIT scores, were significantly related with age