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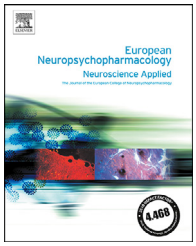

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Nucleus accumbens connectivity at rest is associated with alcohol consumption in young male adults

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Abstract
Alcohol consumption during adolescence might impede normal brain development, while more excessive drinking during this period poses a risk for developing alcohol use disorder. Here it was tested whether nucleus accumbens (NAcc) resting-state functional connectivity could be associated with lifetime drinking behavior in young adults, and whether it could predict their alcohol consumption during a one-year follow-up period. The current investigation was part of the bicentric *Learning and Alcohol Dependence* (LeAD) population-based prospective cohort study. One hundred and eighty-four 18-year-old male social drinking volunteers without a lifetime diagnosis of psychotic, bipolar, or alcohol use disorder were recruited from the general population. Seed-based resting-state functional connectivity was calculated for the bilateral NAcc in

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each participant. Across the group, the association between NAcc functional connectivity and lifetime alcohol consumption was assessed ($p < .05$, whole-brain FWE-corrected). Individual connectivity values were then extracted from regions that demonstrated a significant association to predict drinking behavior during a one-year follow-up period ($n = 143$), correcting for lifetime alcohol consumption. Weaker connectivity between the left NAcc and bilateral dorsolateral prefrontal cortex, inferior frontal gyrus, left caudate nucleus, left putamen, and left insula was associated with greater lifetime alcohol consumption, as well as with greater alcohol consumption during the one-year follow-up period. Our findings underscore the relevance of fronto-striatal connectivity to the field of alcohol research. Impaired prefrontal cognitive control might mediate excessive drinking behavior and may prove a promising biomarker for risk of future alcohol (ab)use.

1. Introduction

Alcohol is the most frequently used psychoactive substance worldwide (Gowing et al., 2015). Although its negative consequences are widely acknowledged, the use of alcohol is socially accepted across many cultures, even in adolescence. It is this developmental stage in particular that is characterized by marked changes in motivated behavior, during which an increased focus on rewarding outcomes is generally demonstrated (van Duijvenvoorde et al., 2016). Such reward-driven behavior, together with the presence of associated personality traits was shown to be a risk factor for early alcohol use (Nees et al., 2012). At the same time, frontal control areas are not yet fully developed, which is thought to underlie reduced behavioral control (Mills et al., 2014). Consequently, this brain developmental mismatch may lead to risky behavior, such as exploration of recreational, but intoxicating substances, including alcohol, which might ultimately endanger one's health in the case of substance abuse. However, most alcohol-consuming adolescents do not develop a sustained *alcohol use disorder* (AUD), although several variables, such as the starting age of alcohol use, a (steadily increasing) drinking load, and the number of binge episodes during adolescence are clear risk factors for developing AUD (Feldstein Ewing et al., 2014).

As the brain still undergoes significant structural (Gogtay et al., 2004) and functional (Grayson and Fair, 2017) maturation throughout adolescence and into early adulthood, it might be particularly vulnerable to the toxic effects of alcohol. Previous research has indeed demonstrated that excessive alcohol use is associated with structural brain changes in adolescents: areas identified to be most susceptible to such changes are the cerebellum and prefrontal cortex, which are relevant to behavioral fine-tuning and mediation of higher-order cognitive control, as well as regions of the limbic and mesolimbic system, which are involved in motivation, emotion, learning, and reward processes (Cservenka and Brumback, 2017; Feldstein Ewing et al., 2014). Specifically, accelerated gray matter volume decreases (Heikkinen et al., 2017), attenuated white matter volume increases (Squeglia and Gray, 2016), and smaller overall brain volume (Squeglia et al., 2014) and cortical thinning have been reported in (heavy) drinking adolescents (Cservenka and Brumback, 2017; Silveri et al., 2016).

On the other hand, reduced top-down modulation of subcortical structures by prefrontal areas has been linked to increased substance use (Silveri et al., 2016; van Duijvenvoorde et al., 2016), and to alcohol use in specific (Goldstein and Volkow, 2011), as well as to the pathogenesis of substance use disorders, including AUD (Park et al., 2010). For example, in healthy adolescents and young adults it was shown that weaker functional connectivity between the amygdala and orbitofrontal cortex was associated with recent alcohol use, while it could predict future alcohol consumption during a two-year follow-up period as well: Although lesser integration of fronto-limbic circuits may initially have been caused by previous alcohol intake, the prospective results illustrate the potential of using connectivity measures to better understand and predict future alcohol use (Peters et al., 2017).

To date, the nucleus accumbens (NAcc), implicated in incentive motivation and reward processing (Hikida et al., 2016), has been underrepresented in developmental research, especially with respect to substance use during adolescence. Nucleus accumbens function has repeatedly been implicated in the development and maintenance of AUD (Claus et al., 2011; Garbusow et al., 2016), as well as connectivity between the NAcc and prefrontal areas (Forbes et al., 2014; Park et al., 2010). Although NAcc connectivity has been studied in patients and in substance-naïve young adults with a family history of AUD (Camchong et al., 2014; Cservenka et al., 2014; Squeglia et al., 2015), no study has looked at its association with alcohol consumption during adolescence so far.

Here we tested whether lifetime drinking behavior is associated with NAcc resting-state functional connectivity (RSFC), and whether NAcc connectivity predicts the use of alcohol during a one-year follow up period. Given the importance of prefrontal-striatal connectivity for cognitive control, we hypothesized that weaker NAcc connectivity to the prefrontal cortex would be associated with higher lifetime drinking behavior, as well as with more alcohol consumption during the year after scanning.

2. Experimental procedures

2.1. Participants

For the current study, 199 healthy 18-year-old male adolescents were recruited by mail via local resident registration offices in Berlin ($n = 92$) and Dresden ($n = 107$) as part of a large-scale bi-

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