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The link between testosterone and amygdala—orbitofrontal cortex connectivity in adolescent alcohol use

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Abstract Alcohol consumption is one of the most problematic and widespread forms of risk taking in adolescence. It has been hypothesized that sex hormones such as testosterone play an important role in risk taking by influencing the development of brain networks involved in emotion and motivation, particularly the amygdala and its functional connections. Connectivity between the amygdala and the orbitofrontal cortex (OFC) may be specifically related to alcohol use, given the association of this tract with top-down control over behavioral approach tendencies.

In line with this, prior studies in adults indicate a link between alcohol use and functional connectivity between the amygdala and the orbitofrontal cortex (OFC), as well as between testosterone and amygdala—OFC connectivity. We consolidated these research lines by investigating the association between alcohol use, testosterone and resting state functional brain connectivity within one large-scale adolescent sample ($n = 173$, aged 12—25 years). Mediation analyses demonstrated an indirect effect of testosterone levels on alcohol use through amygdala—OFC intrinsic functional connectivity, but only in boys. That is, increased testosterone in

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boys was associated with reduced amygdala—OFC connectivity, which in turn was associated with increased alcohol intake. This study is the first to demonstrate the interplay between adolescent alcohol use, sex hormones and brain mechanisms, thus taking an important step to increase our understanding of the mechanisms behind this form of adolescent risk-taking.

1. Introduction

Adolescents are prone to increased risk taking and impulsive behavior (Steinberg, 2008). Although risk-taking behavior in adolescence can be adaptive (Crone and Dahl, 2012), it is also associated with negative consequences for health and safety. Alcohol use is one of the most widespread forms of risk taking in adolescence (Hibell et al., 2012). Adolescent alcohol use is associated with impaired cognitive functioning and school performance (Zeigler et al., 2005) and alcohol-related problems in adulthood (Grant et al., 2006). Understanding the mechanisms behind alcohol use in adolescence is an important step toward preventing alcohol-related problems.

Risk-taking behavior, including alcohol use, has been related to the dramatic rise in sex hormones at puberty (Forbes and Dahl, 2010). Indirect evidence for a link between increased sex hormonal production during puberty and increased alcohol use comes from studies showing that adolescents with advanced pubertal maturation show relatively higher levels of alcohol intake (Bratberg et al., 2005; Biehl et al., 2007; Westling et al., 2008). Moreover, a direct association was found between higher production of the sex hormone testosterone and an earlier onset of alcohol consumption in adolescent boys (de Water et al., 2013). Consequently, a prominent hypothesis predicts that sex hormones affect risk taking by influencing the development of limbic brain areas involved in emotion and motivation (Peper and Dahl, 2013).

The amygdala is one such limbic brain area that plays a key role in adolescent functional brain organization (Scherf et al., 2013) and is associated with both testosterone and alcohol use. For instance, the amygdala is among the brain areas with the highest density of androgen receptors as shown in animal studies (Simerly et al., 1990). Moreover, the amygdala response to emotional faces can be modulated by testosterone, (Stanton et al., 2009; Hermans et al., 2008; Derntl et al., 2009; Manuck et al., 2010). With regard to alcohol, the amygdala is one of the key regions of interest in animal studies on alcohol use (McBride, 2002) and human research shows that alcohol ingestion leads to reduced amygdala activity for fearful/angry faces (Gilman et al., 2008, 2012; Sripada et al., 2011) and a lower amygdala response to fearful faces is linked to increased risk for future alcohol abuse (Glahn et al., 2007).

Since the amygdala is highly interconnected with other brain regions (Cole et al., 2010), it is important to also take into account the functional connections of the amygdala. The connection with the orbitofrontal cortex (OFC) is of particular interest, as the OFC is directly connected to the amygdala through the uncinate fasciculus (Von Der Heide et al., 2013), an association tract that develops well into adolescence (Lebel and Beaulieu, 2011). In adults, it has been demonstrated that functional connectivity between the amygdala and the OFC during emotional face processing was reduced after alcohol ingestion (Gorka et al., 2013). Interestingly, testosterone administration (van Wingen et al., 2010; Bos et al., 2012a) and high endogenous testosterone (Spielberg et al., 2014) showed similar reducing effects on amygdala—OFC functional connectivity.

We therefore argue that it is vital to study the interplay between testosterone and amygdala—OFC connectivity in adolescents to explain individual differences in alcohol consumption. We tested this in a large cross-sectional adolescent sample using a resting state paradigm, which is a valuable tool to investigate functional networks in the developing brain (Uddin et al., 2011) and has several advantages over task-based brain activity, including high test-retest reliability (Zuo and Xing, 2014) and broader generalizability. We hypothesized that higher levels of testosterone would be associated with increased alcohol consumption, mediated through lower amygdala—OFC connectivity.

2. Methods

2.1. Participants

The included sample consisted of 173 healthy participants (86 girls, 87 boys), between 12.05 and 25.95 years old ($M = 15.85$, $SD = 3.10$), for whom data on alcohol consumption, brain imaging and hormonal samples were available. Because this study was part of a larger project also involving younger participants, we collected complete resting state scans, high-resolution functional scans and T1 scans for 295 participants between 8 and 25 years old. Only participants who were 12 years and older ($n = 209$) were asked to fill out the alcohol questionnaire and younger participants were therefore excluded from further analyses. Other reasons for exclusion were: not completing the alcohol questionnaire ($n = 11$), missing testosterone levels ($n = 16$), excessive movement in the MRI scanner (>3 mm; $n = 3$) and excessive micromovements (>20% of volumes with >05 mm movement; $n = 5$). Note that several participants were excluded for multiple reasons, e.g. both excessive movement and missing testosterone data.

Participants were recruited through local schools and advertisements. IQ was estimated with two subtests of the WAIS-III or WISC-III (Similarities and Block Design). All estimated IQ scores were within the normal range ($M = 109.39$, $SD = 9.67$, range: 80—135) and there was no correlation with age ($r = .05$, $p = .53$). Adults (18 years and older) received payment (60 euros) for participation, children received presents and their parents received 30 euros for travel reimbursement. The study was approved by the Institutional Review Board at the Leiden University Medical Center. The