Brain and Cognition 111 (2017) 51–62

Contents lists available at ScienceDirect

Brain and Cognition

journal homepage: www.elsevier.com/locate/b&c

Adolescent neural response to reward is related to participant sex and task motivation

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ARTICLE INFO

Article history:
Received 4 March 2016
Revised 6 October 2016
Accepted 7 October 2016
Available online 2 November 2016

Keywords:
Reward
Risk taking
Adolescence
Sex hormones
Sex differences
Motivation

ABSTRACT

Risky decision making is prominent during adolescence, perhaps contributed to by heightened sensation seeking and ongoing maturation of reward and dopamine systems in the brain, which are, in part, modulated by sex hormones. In this study, we examined sex differences in the neural substrates of reward sensitivity during a risky decision-making task and hypothesized that compared with girls, boys would show heightened brain activation in reward-relevant regions, particularly the nucleus accumbens, during reward receipt. Further, we hypothesized that testosterone and estradiol levels would mediate this sex difference. Moreover, we predicted boys would make more risky choices on the task. While boys showed increased nucleus accumbens blood oxygen level-dependent (BOLD) response relative to girls, sex hormones did not mediate this effect. As predicted, boys made a higher percentage of risky decisions during the task. Interestingly, boys also self-reported more motivation to perform well and earn money on the task, while girls self-reported higher state anxiety prior to the scan session. Motivation to earn money partially mediated the effect of sex on nucleus accumbens activity during reward. Previous research shows that increased motivation and salience of reinforcers is linked with more robust striatal BOLD response, therefore psychosocial factors, in addition to sex, may play an important role in reward sensitivity. Elucidating neurobiological mechanisms that support adolescent sex differences in risky decision making has important implications for understanding individual differences that lead to advantageous and adverse behaviors that affect health outcomes.

1. Introduction

Following perinatal neural organization, adolescence marks a second wave of plasticity, during which numerous behavioral, social, and physiological changes occur that act to re-organize and activate the brain (Spear, 2013). This extended brain plasticity can be viewed as a double-edged sword, serving to augment vulnerability to biological and psychological insult, as well as support healthy neurodevelopment (Telzer, 2016). Processing of rewarding stimuli is particularly relevant during the adolescent period, given the rise in sensation seeking, which may contribute to increased reward sensitivity and risk taking in some youth (Romer & Hennessy, 2007). Dysregulated reward processing has been linked with affective and substance use disorders, the incidence of which increase substantially during adolescence (Davey, Yucel, & Allen, 2008; Ernst, Pine, & Hardin, 2006; Fairchild, 2011; MacPherson, Magidson, Reynolds, Kahler, & Lejuez, 2010). As such, elucidating the neural mechanisms underlying adolescent reward sensitivity may help in promoting beneficial, rather than adverse, neuroplastic change.

Psychobiological models of adolescent risk taking posit an imbalance between reward processing and self-control, mirrored by enhanced functional activation of reward-sensitive regions (i.e. striatum, including nucleus accumbens) and diminished activation of self-regulatory brain regions (i.e. medial prefrontal cortex), which drives risk taking via inefficient regulation of reward-sensitive brain regions by self-regulatory regions (Casey, 2015; Ernst, 2014; Smith, Chein, & Steinberg, 2013; Somerville, Jones, & Casey, 2010). However, there is a paucity of data showing a direct relationship between reward sensitivity and risk taking (Braams, Peper, van der Heide, Peters, & Crone, 2016; Braams, van Duijvenvoorde, Peper, & Crone, 2015; Galvan et al., 2006; van Duijvenvoorde et al., 2014, 2015; Vorobyev, Kwon, Moe, Parkkola, & Hamalainen, 2015), likely because there is substantial

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http://dx.doi.org/10.1016/j.bandc.2016.10.003
0278-2626/

individual variability in reward sensitivity (Bjork & Pardini, 2015; Braams et al., 2015; Chick, 2015; Cservenka, Herting, Seghete, Hudson, & Nagel, 2012). Some of this variability may be due to individual differences in personality traits, such as sensation seeking (Cservenka et al., 2012; van Duijvenvoorde et al., 2014) and impulsivity (Forbes et al., 2009; Piray, den Ouden, van der Schaaf, Toni, & Cools, 2015). Moreover, the link between reward sensitivity and risk taking may be partly explained by pubertal influences (Forbes et al., 2010; Urosevic, Collins, Muetzel, Lim, & Luciana, 2014), given that puberty has been shown to correlate with sensation seeking (Forbes & Dahl, 2010; Martin et al., 2002, 2006; Steinberg, 2004; Steinberg et al., 2008), reward sensitivity (Urosevic et al., 2014) and nucleus accumbens activity in response to rewards (Braams et al., 2015). Indeed, there is evidence that pubertal increases in sensation seeking predict real-world risky behavior, such as substance use (Kirillova, Vanyukov, Gavaler, Pajer, & Tarter, 2001; Martin et al., 2002).

Gonadal hormones, which are re-activated at the onset of puberty, have also been linked to reward processing. Previous work in adolescents showed a positive association between striatal activity in response to reward and endogenous levels of testosterone (Braams et al., 2015; Op de Macks et al., 2011) and estradiol (Op de Macks et al., 2011) in both males and females. Moreover, sex hormone levels have been positively associated with risk-taking behavior in adolescence (de Water, Braams, Crone, & Peper, 2013; Martin, Mainous, Curry, & Martin, 1999; Peper, Mandl, et al., 2013; Peters, Jolles, Van Duijvenvoorde, Crone, & Peper, 2015; Vermeersch, T'Sjoen, Kaufman, & Vincke, 2008a, 2008b). In studies that compared boys and girls directly, there is more evidence of a positive relationship between sex hormones and risky behavior in boys relative to girls (de Water et al., 2013; Peper, de Reus, van den Heuvel, & Schutter, 2015; Peters et al., 2015), or compared to evidence indicating no sex difference (Peper, Koolschijn, & Crone, 2013). In young adults, sex hormone levels have been shown to predict risky behavior in both sexes to the same degree (Braams et al., 2016; Mehta, Welker, Zilioli, & Carre, 2015; Nguyen et al., 2016; Stanton, Liening, & Schultheiss, 2011). The majority of this research supports a link between testosterone and risk taking (Braams et al., 2016; de Water et al., 2013; Martin et al., 1999; Mehta et al., 2015; Nguyen et al., 2016; Peper et al., 2015; Peper, Koolschijn, et al., 2013; Peters et al., 2015; Stanton et al., 2011; Vermeersch et al., 2008b), while a subset of studies also support a positive association between estradiol and risk taking (de Water et al., 2013; Martin et al., 1999; Peper et al., 2015; Vermeersch et al., 2008a). Only two studies have examined the relationship between reward sensitivity, as indexed by nucleus accumbens activity, sex hormones and risk taking (Braams et al., 2015, 2016). One of these studies reported that puberty, testosterone and risk taking explained nucleus accumbens activation during a gambling game in both males and females (Braams et al., 2015). The second study indicated that testosterone levels, but not nucleus accumbens activation during the same gambling task, predicted risky behavior, as indexed by self-reported alcohol use, two years later in males and females (Braams et al., 2016). The mechanism linking sex hormones, reward sensitivity and risk taking remains to be fully elucidated; however, the extant literature suggests that both testosterone and estradiol may be important in explaining risk-taking behavior during adolescence, particularly in boys.

Intriguingly, sex differences in striatal reactivity during reward processing have not been reported or examined in previous studies of adolescents (Braams et al., 2015, 2016; Forbes et al., 2010; Op de Macks et al., 2011). This is somewhat surprising, given the presence of sex differences in pubertal maturation, sex hormone levels (Tanner & Whitehouse, 1976), prefrontal cortical maturation (on average, girls mature approximately two years earlier than boys) (Lenroot et al., 2007) and sensation seeking (on average, boys report more sensation seeking than girls) (Romer & Hennessy, 2007; Steinberg et al., 2008; Zuckerman & Kuhlman, 2000). Thus, sex may be an important variable to consider for understanding individual differences in reward sensitivity and risk taking during adolescence. Indeed, one of the primary neurotransmitters involved in reward processing - dopamine (Berridge & Kringelbach, 2008) - develops in a sexually dimorphic manner during adolescence. Studies in rodents demonstrate enhanced dopamine release in females compared to males due to elevations in estradiol levels during puberty (Di Paolo, Rouillard, & Bedard, 1985; Sarvari et al., 2014; Xiao & Becker, 1994). In contrast, testosterone metabolites have been shown to mediate reward response following direct administration into the nucleus accumbens, which may be mediated by binding at γ-Aminobutyric acid (GABA) (Frye, Park, Tanaka, Rosellini, & Svare, 2001) and dopamine (Mhillaj et al., 2015) receptors. Additionally, both sex hormones have been shown to influence sensation seeking in adolescence (Kerschbaum, Ruemer, Weisshuhn, & Klimesch, 2006; Vermeersch, T'Sjoen, Kaufman, & Vincke, 2009), indicating a role for sex hormones in dopamine activity and sensation seeking. Thus, examining the influence of sensation seeking and sex hormones on potential sex differences in reward sensitivity may inform psychobiological models of risk taking in adolescence.

The current study adds to this literature by examining sex differences in reward processing in a large sample of healthy adolescents, as well as the potentially mediating influence of sex hormones on observed sex differences. We hypothesized boys would show increased blood oxygen level-dependent (BOLD) response in the striatum, including nucleus accumbens, during reward receipt feedback, as well as heightened risky behavior during a risky decision-making task, compared to girls. These hypotheses were based on research showing higher sensation seeking in adolescent boys (Romer & Hennessy, 2007; Steinberg et al., 2008) and delayed prefrontal gray matter maturation in boys, compared to age-matched girls (Lenroot et al., 2007). We also predicted testosterone and estradiol would mediate sex differences in nucleus accumbens BOLD response, given their important role in pubertal development, sensation seeking and in modulating reward-relevant brain regions (Braams et al., 2015; Di Paolo et al., 1985; Frye et al., 2001; Op de Macks et al., 2011; Sarvari et al., 2014; Xiao & Becker, 1994).

2. Material and methods

2.1. Participant screening and exclusionary criteria

Participants underwent comprehensive structured interviews by trained research assistants to determine eligibility. Youth and parents completed separate structured telephone interviews that included the Diagnostic Interview Schedule for Children Predictive Scales (Lucas et al., 2001), the Family History Assessment Module (Rice et al., 1995), and the Brief Lifetime version of the Customary Drinking and Drug Use Record (Brown et al., 1998). Exclusionary criteria included current diagnosis of DSM-IV disorders (lifetime history of DSM-IV disorders was not assessed), significant substance use (>10 lifetime alcoholic drinks or >2 drinks/occasion, >5 uses of marijuana, any other drug use, or >4 cigarettes per day), neurological illness/head trauma, serious medical problems, prenatal exposure to drugs or alcohol, reported history of psychotic disorders in biological parents, current medication that may affect neural (e.g. psychoactive medication) or endocrine (e.g. birth control) function, the inability of a parent to provide family history information, left-handedness (Edinburgh Handedness Inventory, Oldfield, 1971), pregnancy, and MRI contraindications. This study