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The Complex Interplay among Hormones, Neural Connectivity, and Real-World Risky Behaviors during Adolescence

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in Psychology

by

Diane Goldenberg

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ABSTRACT OF THE DISSERTATION

The Complex Interplay among Hormones, Neural Connectivity, and Real-World Risky Behaviors during Adolescence

by

Diane Goldenberg

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2017

Professor Adriana Galván, Chair

Adolescence is a period of dynamic change in nearly every domain. This developmental transition is characterized by dramatic alterations in hormone levels, remodeling of neural circuitry, and a number of behavioral changes including increased risk taking. In this dissertation, I present a multi-method program of research investigating the neurobiological contributors to adolescent risky decision-making in a sample of 14-18 year old adolescents (N=55). Taken together, findings suggest that the adolescent brain may be influenced by distinct hormones during specific aspects of decision making, and provide novel evidence for the possibility of a unique role for DHEA in cautious decision-making processes. Specifically, my research demonstrates that testosterone is related to trait measures in adolescents, replicating previous studies linking testosterone with sensation seeking and risk attitudes toward sexual behavior. During a novel laboratory paradigm, testosterone is associated with neural response preceding the selection of a risky choice, and DHEA with neural response preceding the

selection of a cautious choice. Moreover, DHEA is associated with greater connectivity between the dorsolateral prefrontal cortex, a region implicated in regulatory processes, and regions of the brain including the ventral striatum, a region implicated in reward processing. In other words, adolescents with higher levels of DHEA exhibit greater frontostriatal connectivity when making decisions under conditions of risk. Finally, this research demonstrates that recruitment of neural circuitry during selection of cautious choice is related to individual differences in self-reported risky sexual behavior (i.e., lifetime condom use), providing support for the ecological validity of the laboratory task and relevance to behaviors important for public health.

The dissertation of Diane Goldenberg is approved.

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PUBLICATIONS

Goldenberg, D., Telzer, E.H., Leiberman, M.D., Fuligni, A.J., & Galván, A. (2016). Greater Response Variability in Adolescents is Associated with Increased White Matter Development. *Social Cognitive and Affective Neuroscience*, nsw132.

Goldenberg, D., & Galván, A. (2015). The use of functional and effective connectivity techniques to understand the developing brain. *Developmental cognitive neuroscience*, *12*, 155-164.

Telzer, E.H., **Goldenberg, D.**, Leiberman, M.D., Fuligni, A.J., & Galván, A. (2015). Sleep Variability in Adolescence is Associated with Altered Brain Development. *Developmental Cognitive Neuroscience, 14*, 16-22.

Welborn, B. L., Lieberman, M. D., **Goldenberg, D.,** Fuligni, A. J., Galván, A., & Telzer, E. H. (2015). Neural mechanisms of social influence in adolescence. *Social Cognitive and Affective Neuroscience*, nsv095.

Telzer E.H., Qu Y., **Goldenberg D.**, Fuligni A.J., Galván A., & Lieberman M.D. (2014). Adolescents' emotional competence is associated with parents' neural sensitivity to emotions. *Frontiers in Human Neuroscience, 8(558),* doi: 10.3389/fnhum.2014.00558

Goldenberg, D., Telzer, E.H., Leiberman, M.D., Fuligni, A.J., & Galván, A. (2013). Neural Mechanisms of Cognitive Control in Sexually Risky Adolescents. *Developmental Cognitive Neuroscience, 6,* 23-29.

Mahmood, O.M., **Goldenberg, D.**, Thayer, R., Migliorini, R., Simmons, A.N., & Tapert, S.F. (2012). Adolescents' fMRI Activation to a Response Inhibition Task Predicts Future Substance Use. *Addictive Behaviors, 38(1),* 1435-1441.

Jacobus, J., **Goldenberg, D.**, Tolentino, N., Weirenga, C., Liu, T., & Tapert, S.F. (2012). Altered Cerebral Blood and Neurocognitive Correlates in Adolescent Cannabis Users. *Psychopharmacology, 222(4),* 675-684.

Bava, S., Boucquey, V., **Goldenberg, D.**, Ward, M., Jacobus, J., & Tapert., S.F. (2011). Sex Differences in Adolescent White Matter Architecture. *Brain Research, 1375,* 41-48.

Gollan, T.H., Slattery, T., **Goldenberg, D.**, Assche, E., Duyck, W., & Rayner, K. (2011). Frequency Drives Lexical Access in Reading but Not in Speaking: The Frequency-Lag Hypothesis. *Journal of Experimental Psychology: General.* 2011 May; 140(2); 186-209.

I. Introduction

"But, speaking generally, man is not meant to remain a child…As the roaring of the waves precedes the tempest, so the murmur of rising passions announces this tumultuous change..." (Jean Jacques Rousseau, 1762)

The question of how biological changes relate to adolescent behavior is not a new one. The quote above is taken from *Emile,* one of the first treatises on this stage of development, which may seem now, perhaps, a bit melodramatic and outdated. While the language we adopt when referring to adolescents has changed, a form of this sentiment remains subtly stitched into the way we conceptualize and conduct research on adolescents today. It is easy to understand why. There is consistent evidence of heightened emotional reactivity in adolescents (though not referred to with Rousseau's label of "rising passions") (e.g. Hare et al., 2008, Monk et al., 2003; Somerville, Jones, & Casey, 2010). This reactivity coincides with the overt physical changes fueled by the hormonal events of puberty (Dorn, Dahl, Woodward, & Biro, 2006) and a dramatic spike in risk taking that provides straightforward statistics that are simple to report and difficult to ignore (CDC, 2016).

For decades, a considerable amount of attention has been paid to understanding the associations between adolescent risk taking and pubertal hormones (e.g. Bauman, Foshee, Koch, Haley, & Downton, 1989; Forbes & Dahl, 2010; Martin et al., 2002) with a recent boom in neuroimaging studies probing hormonal influences on brain-behavior relations (e.g. Braams, van Duijvenvoorde, Peper, & Crone, 2015; de Macks et al., 2011; Peper, Koolschijn, & Crone, 2013). Collectively, results have provided evidence to suggest that higher levels of testosterone

in adolescents are associated with behavioral and neural correlates of risk taking, such as more sensation seeking, greater amounts of risky decisions, and increased responsivity to reward in neural regions such as the accumbens. There is an allure to these findings, as they provide scientific evidence for associations that have an intuitive appeal, using words such as *sensation seeking* that have an almost palpable intensity built into their very definitions. The incandescence of these findings may cast an unintentional and unacknowledged shadow over more subtle constructs or processes.

For example, while there is a primary focus on the effects of testosterone on adolescent behavior, no research to date has examined the influence of the pubertal hormone dehydroepiandrosterone (DHEA) on adolescent risky decision-making. DHEA is an adrenal androgen that rises during adrenarche, the first endocrinological event of puberty. It represents the most abundant circulating steroid hormone in humans (Adams, 1985), and is produced in the adrenal glands, the gonads, and the brain, where it functions as a metabolic intermediate in the biosynthesis of testosterone (Mo, Lu, & Simon, 2006). However, DHEA also exerts biological influences independent from testosterone, such as binding to a variety of cell receptor sites and acting as a neurosteroid (Baulieu & Robel, 1998). Its role in the behavior of typically-developing adolescents is currently almost entirely absent from extant literature (noted in Byrne et al., 2016).

Relatedly, another underexplored aspect of the contributors to adolescent risk taking is the neurobiological correlates of a decision *not* to take a risk, or choosing to play it safe. Although characterizing the processes that occur in the absence of a risky response is often overlooked, it can provide an important vantage point for understanding the neurobiological correlates that underlie the full spectrum of adolescent behavior. In this dissertation, I use a multi-method program of research, including surveys, hormonal assays of DHEA and

testosterone, functional magnetic resonance imaging (fMRI), and a novel experimental paradigm to investigate the underexplored neurobiological contributors to adolescent risky decision-making.

Pubertal Hormones and Adolescent Risky Behavior

The pubertal process is a cascade of distinct but overlapping endocrinological events (Dorn et al, 2006). The most-often examined event is gonadarche, a process which most directly relates to the primary biological goal of puberty, the attainment of reproductive maturity. During gonadarche, the reproductive organs (testes and ovaries) begin to secrete testosterone and estrogen (respectively) and attain reproductive capacity. Previous research suggests that high levels of testosterone are associated with increased approach-related behaviors in rodents (Amstislavskaya and Popova, 2004; Cooper, Goings, Kim, & Wood, 2014) and increased risk taking in human boys and girls (Vermeersch, T'sjoen, Kaufman, & Vincke, 2008a; de Water, Braams, Crone, & Peper, 2013). Adrenarche is the process through which circulating levels of DHEA begin to increase. It occurs before gonadarche, and its biological purpose is far less understood. Interestingly, humans and the great apes are the only species demonstrated to exhibit this endocrine event (Campbell, 2011). Its unique role in human development suggests that DHEA plays a key evolutionary role, but there is a dearth of research on the developmental contributions of this hormone to adolescent behavior (noted in Byrne et al., 2016). Increases in estradiol, the primary estrogen released from the gonads, also represent an important component of the pubertal cascade (Pettersson & Gustafsson, 2001). Circulating values exist at very low concentrations and are difficult to accurately measure using immunoassay techniques (Rosner, Hankinson, Sluss, Vesper, & Wierman, 2013). Estradiol values are particularly low in males, rendering assessments invalid. Studies examining the influence of estradiol typically recruit only

females for inclusion to have enough power to detect effects (Vermeersch, T'sjoen, Kaufman, & Vincke, 2008b). Given the inclusion of equal numbers of males and females in the current research, measures of estradiol are not assessed in this dissertation.

Pubertal Hormones and the Adolescent Brain

Evidence from animal work demonstrates that pubertal hormones can exert influences on neural circuits at cellular levels (Schulz, Molenda-Figueira, & Sisk, 2009), particularly in reward-related systems of the brain (Romeo, 2003; Sato, Schulz, Sisk, & Wood, 2008). In humans, a recently-increasing number of neuroimaging studies (e.g. Forbes et al., 2010; Op de Macks et al., 2011, Braams et al., 2015) suggest that pubertal hormones exert significant effects on limbic response to reward during adolescence in boys and girls. Specifically, the published studies on this topic have suggested that greater levels of testosterone are associated with increased activation in reward circuitry when participants are performing a risk-taking or rewarding computer task. For example, a recent longitudinal study demonstrated that increases in testosterone levels were linearly related to neural activity in the ventral striatum during a risk-taking task in boys and girls, over and above the effects of age, suggesting a driving factor of testosterone in the increased response to rewards (Braams et al., 2015). Collectively, these studies suggest that gonadal hormones "sensitize" the brain's reward system, making adolescents more reactive to rewards in general. However, there is no information on how DHEA relates to brain-behavior relations with respect to risk taking. Thus far, two anatomical studies have found preliminary evidence that DHEA is related to structural development of the dorsolateral prefrontal cortex (DLPFC), indexed by cortical thickness (Nguyen et al., 2013) and white matter volume (Klauser et al., 2015) in children and adolescents. Given the hypothesized role that the protracted development of the prefrontal cortex plays in adolescent risk taking (Casey, 2015), it

is surprising that no research has examined the association between DHEA and adolescent neural correlates of risky decision-making.

Real-world Risk-Taking Behaviors

There is limited research on the association between pubertal hormones and the brain as it relates to self-reported engagement in real-world adolescent behaviors. A major goal of the current program of research is to understand neurobiological contributors to adolescent risky decision-making through the lens of real-world behaviors that teens are engaging in. While prior work has primarily focused on measures of substance use (Braams, Peper, van der Heide, Peters, & Crone, 2016 and de Water et al., 2013), few studies have included measures of other phenotypic manifestations of risk taking, such as risky sexual behavior or reckless driving. Engagement in sexual relationships and driving during adolescence demonstrate how certain behaviors can serve a motivated purpose during this time (e.g., exploration of new roles and relationships, transition to the independence of adulthood), yet have the potential for severe negative consequences if not engaged in safely. Examining the neurobiological correlates that relate to individual variability in self-reported riskier versus safer sexual and driving practices in adolescents has the potential to be directly applicable to real-world problems. Gaining a better understanding of the neurobiological correlates of real-world forms of adolescent risk-taking may inform social policies designed to improve adolescent health.

Overview of Studies

All studies were conducted as part of one research project on a sample of adolescents (N=55) who underwent fMRI and completed questionnaires, and a subsample (n=33) that provided salivary assays for hormones. Participants were 14 – 18 years, a fairly narrow age range of mid- to- late adolescents, and a period of time during which there is a high level of individual

variability in both hormone levels and engagement in real world risk taking behaviors. All analyses controlled for age, as the purpose of this program of research was to investigate how individual variability in neurobiological measures relate to differences in risk taking, over and above possible developmental contributors of chronological age.

Study 1. This study examines the influence of DHEA as well as testosterone on traits related to risky decision-making. Adolescents collected saliva samples at home upon waking that were assayed for DHEA and testosterone levels. Testosterone levels were z-scored for males and females separately and collapsed within a single variable that represented a participant's hormone level with respect to his or her same-sex peer in the sample. The same procedure was followed for DHEA. Additionally, adolescents also completed questionnaire measures evaluating traits related to adolescent risk taking (impulsivity, sensation seeking, risk attitudes for different behavioral domains) and real-world engagement in risky activities (risky sexual behavior and reckless driving). Adolescents with relatively greater levels of testosterone endorsed significantly higher amounts traits related to risk taking across several measures, including sensation seeking and risk perceptions for risky sexual behavior. Additionally, neither pubertal hormone was related to indices of frequency of engagement in real-world risk taking. Findings do not provide evidence for a direct association between pubertal hormones and risky behavior in adolescent's daily lives. This is concurrent with prior literature, which has suggested that adolescents are not likely to be victims of raging hormones, and engagement in risk taking is highly influenced by potential moderating contextual or environmental variables. However, testosterone does appear to be linked with traits and attitudes related to behavioral approach tendencies, consistent with previous studies. Finally, given prior research linking DHEA to structural changes in the prefrontal cortex, we speculate that the lack of significant associations with DHEA in the current

study may not be due to a lack of association with adolescent behavior in general, but rather that this hormone may not relate specifically to the approach-related behaviors often assessed in studies of adolescent risk taking.

Study 2. This study used fMRI to understand how DHEA and testosterone related to neural activation during risky decision-making on a laboratory task. Behaviorally, higher levels of testosterone were related to faster reaction time when making risky decisions. At the neural level, higher levels of testosterone was associated with greater neural activation preceding the selection of a risky choice, specifically in the putamen. Given the putamen's role in automatic motor response, behavioral and neuroimaging findings suggest that higher relative levels of testosterone is associated with selection of risky choices as a potential automatic or habitual response. Interestingly, DHEA was also positively associated with neural activation in the putamen preceding the selection of a response, but for selection of cautious choices. Moreover, higher levels of DHEA were associated with greater functional connectivity of the dorsolateral prefrontal cortex (DLPFC) and a number of cortical regions including the ventral striatum during selection of cautious versus risky choices. Frontostriatal connections may be particularly important for adolescent decision-making, supporting exertion of goal-directed behavior based on motivational states. Findings provide novel evidence for an important role of DHEA in frontostriatal coupling during cautious decision-making processes.

Study 3. Given the importance of understanding the neurobiological correlates of adolescent risk taking within the context of the behaviors adolescents actually engage in, we sought to explore how neural activation on the laboratory task was related to real-world measures of risky behavior. Participants completed self-report measures evaluating frequency of engagement in risky sexual behavior and reckless driving. Only sexually experienced adolescents

or those with driver's permits or licenses were included in analyses conducted on variables measuring "risky sexual behavior" and "reckless driving", respectively. As the purpose of the current study was to examine individual differences that relate to variability in self-reported riskier versus safer sexual and driving practices in adolescents, only adolescents who engaged in these behaviors had the opportunity to make decisions varying in levels of risk. While there were no significant findings with respect to reckless driving, individual differences in risky sexual behavior was related to differential patterns of functional connectivity during selection of a cautious compared to risky choice. Specifically, adolescents who reported engaging in safer practices, indexed with higher reported levels of condom use, demonstrated greater functional coupling of the caudate and cortical regions such as the anterior cingulate cortex (ACC) during cautious decision-making. Conversely, individuals who reported engaging in riskier practices demonstrated greater functional coupling of the caudate and subcortical regions involved in affective response, particularly when choosing to play it safe. Findings provide evidence that adolescents with greater subcortico-subcortical coupling (and less cortico-subcortical coupling) may have greater difficulty translating knowledge into action during affectively salient contexts when making decisions in their daily lives.

II. Adolescent Risk Taking: Behavioral Associations with Testosterone but not DHEA

Adolescence is a developmental period characterized by instability and transformation. The natural tendency to venture, explore, and take risks is normative as individuals transition away from primary caregivers (Spear, 2000). The increased risk taking observed in adolescence is, at times, depicted as stemming from the "storm and stress" of this stage (Hall, 1904) or the raging hormones of puberty, contributing to cartoonish views of teens acting impulsively and irrationally (as noted by Reyna and Farley, 2006). Simple characterizations of adolescent behavior ignore the rich complexity inherent to this developmental stage. Multiple endocrinological changes comprise the hormonal events of puberty, which likely influence behavior in complex ways. However, previous research has largely focused on associations between testosterone and risk taking in adolescents. DHEA is the hormonal byproduct of adrenarche, the initial endocrinological event of the pubertal process, and its role in the behavior of typically-developing adolescents is currently almost entirely absent from extant literature (recently noted in Byrne et al., 2016). The purpose of the current study was to examine associations between DHEA and measures related to risky behavior in adolescents.

Surges in pubertal hormones occur relatively early in the transition into adolescence, providing a loose anchor to the beginning of this period, but the sustained hormonal increases are intimately tied to many of the subsequent changes that occur during this time (Sisk & Foster, 2004). Pubertal hormones act not only on peripheral tissues to cause the appearance of secondary sex characteristics that are the overt signs of puberty, but they may also influence behavior in adolescence such as risk taking (Sisk & Zehr, 2005). For example, previous research suggests that endogenously high levels of testosterone are associated with increased approach-related behaviors in adolescents (Martin et al., 2002; Quevedo, Benning, Gunnar, & Dahl, 2009). From

an evolutionary perspective, it makes intuitive sense that the hormonal changes of puberty are linked to the activation of motivational drives and approach-related behaviors, as these changes increase the likelihood that adolescents will leave the natal environment to mate outside the family (Peper & Dahl, 2013).

The hormonal processes of puberty are a set of endocrinological changes that result in the attainment of reproductive maturity (Dorn et al., 2006). Increases in testosterone occur with the initiation of gonadarche, during which the reproductive organs begin increasing the production of sex steroids in response to pituitary gonadotropins. After the attainment of biologically mature gametes that occurs with gonadarche, the dramatic increases in endogenous levels of testosterone remains high, likely to sustain motivational drives and approach-related behaviors that will provide a behavioral means of bringing mature gametes together (Sato et al., 2008). The initiation of adrenarche occurs long before gonadarche and in a far more quiescent manner. In fact, the invisible signs of puberty occur as early as age six with the initiation of adrenarche (Remer, Boye, Hartmann, & Wudy, 2005). During this process, the adrenal glands are activated by an unknown trigger and begin secreting increased levels of DHEA, which steadily continue rising up until the third decade of life and ultimately represent the most abundant steroid hormone in circulation across the lifespan (Adams, 1985).

While DHEA does not have the same dramatic rise as testosterone that overlaps with the developmental period of adolescence (Boyar et al., 1974), DHEA levels during adolescence are associated with individual differences in the physical changes of puberty (e.g. secondary sex characteristics) during this period (Shirtcliff, Dahl, & Pollack, 2009). There is some evidence to suggest that DHEA may be associated with emotional regulation or mood in childhood and adolescence, a process that is likely important for adolescent risky decision-making; however,

this work has only been conducted in clinical populations (Bloch, Ish-Shalom, Greenman, Klein, & Latzer, 2012; Goodyer, Tamplin, Herbert, & Altham, 2000). There is a lack of understanding regarding how DHEA relates to behavior and decision-making in typically-developing populations.

The primary aim of the present study was to examine the association between DHEA levels and behavioral measures that relate to adolescent risk taking. Participants completed questionnaire measures, which consisted of traits such as impulsivity, sensation seeking, and risk attitudes for different behavioral domains. Additionally, testosterone levels were assessed to understand current findings within the context of prior literature. Finally, as it is important to understand adolescent behavior and decision-making as it manifests in adolescents' daily lives, self-reported frequency of engagement in real world risky behaviors, such as risky sexual behavior and reckless driving, was assessed as well. We hypothesized that testosterone would be associated with measures such as sensation seeking and real-world engagement in risky sexual behavior, given the biological role of this hormone in reproductive maturity. Hypotheses regarding the association between DHEA and behavioral measures were exploratory.

Methods

Participants. Fifty-five healthy right-handed adolescents (ages 14-18, M_{Age} = 16.25 years, *SD* = 1.08, 29 female) were recruited as part of a larger neuroimaging study through poster and internet advertisements approved through the UCLA Institutional Review Board (IRB) and through the Galván Lab participant database. While all participants underwent fMRI and completed questionnaire measures, a subset provided salivary assays for pubertal hormones, which comprised a subset of hormonal and behavioral data described in the current study. All participants provided informed consent, and participants under the age of 18 provided assent

while their parent or guardian completed the informed consent procedure. All participants were high school students. Participants were excluded from participation if they had a previous diagnosis of psychiatric or neurologic illness or developmental delay, were taking psychoactive medication at the time of the study, or had metal in their bodies.

Materials

Salivary hormone assays. Testosterone and DHEA levels were assessed for a subsample of participants who collected saliva by passive drool (n=33, 17 male). We used salivary hormonal assays rather than serological assays to minimize invasive testing. To minimize effects of diurnal fluctuations of hormonal levels, saliva samples were collected immediately upon waking in all participants, before brushing their teeth, eating, or drinking. We verified that these instructions had been followed by parental report. To minimize effects of cyclical fluctuations, salivary assays were collected during the follicular phase of the menstrual cycle in post-menarchal girls (*n*=14), as in prior studies implementing the same methodology (e.g. Peters et al., 2015). One participant reported birth control use. After collection, samples were stored at −80°C and later analyzed by the Dresden Lab Service. Duplicate assays for testosterone and DHEA were performed for each participant, with intra-assay variation of <7% for all results. Therefore, the mean values were used. Given sexual dimorphisms in sex hormones (Dorn et al., 2006), values for testosterone were z-scored separately for males and females and then collapsed within a single variable. This process was repeated for DHEA. In other words, values for testosterone and DHEA were not raw hormone levels, rather standardized scores for each individual with respect to his or her same-gender peers in the sample. All analyses used z-scored values of testosterone and DHEA and controlled for age.

Questionnaire Measures. Participants completed questionnaires to assess impulsivity, sensation seeking, and risk attitudes, which are each traits hypothesized to contribute to adolescent risky decision-making (Steinberg, 2008).

Impulsivity. The UPPS-P Impulsivity Scale (Lynam, Smith, Whiteside, & Cyders, 2006), a 59-item inventory designed to measure five distinct features of impulsive behavior: negative urgency, lack of perseverance, lack of premeditation, sensation seeking, and positive urgency. Participants rated each item on a 4-point Likert scale ranging from 1 (*strongly agree*) to 4 (*strongly disagree*).

Sensation seeking. The Sensation Seeking Scale (Zuckerman, 1994) is a 34-item scale that assesses four factors involved in sensation seeking: seeking thrill and adventure, disinhibition (that is, tendency to express impulses), seeking experience, and susceptibility to boredom. Participants rated each item on a scale of 0 (*strongly disagree*) to 10 (*strongly agree*).

Risk attitudes and perceptions. A modified version of the Cognitive Appraisal of Risk Activities (CARE) (Fromme, Katz, & Rivet, 1997) was used to assess evaluation of risks and perception of consequences for specific types of risk behaviors. Participants were asked to provide ratings on six factors, including Risky Sexual Behavior, Heavy Drinking, Illicit Drug Use, Aggressive and Illegal Behaviors, Irresponsible Academic/Work Behaviors, and High Risk Sports. There were a total of 34 items. For each item, participants were asked to provide three ratings from 1 to 7 (1 = Not likely at all; 7 = Extremely likely): (1) the likelihood of engaging in this activity in the next 6 months; (2) the likelihood of a negative consequence and (3) the likelihood of a positive consequence. This risk-taking measure was originally developed in a sample of young adults and test-retest reliability and construct validity of the measure have been established (Fromme et al., 1997).

Self-reported real-world risk taking. Participants were also asked to complete questionnaires assessing frequency of engagement in real-world risk taking behaviors (i.e., risky sexual behavior and reckless driving). Instructions explicitly stated that participant's answers were confidential and would not be disclosed to anyone. Only sexually experienced adolescents or those with driver's permits or licenses were included in analyses conducted on variables measuring "risky sexual behavior" and "reckless driving", respectively. As the purpose of the current study was to examine individual differences that relate to variability in self-reported riskier versus safer sexual and driving practices in adolescents, only adolescents who engage in these behaviors have the opportunity to make decisions that vary in levels of risk.

Risky sexual behavior. Sexually experienced adolescents (n=18) provided information on frequency of engagement in risky sexual behavior. The rate of sexually active adolescents in our sample (34%) is similar to national trends (CDC, 2016). Participants ranged in age from 15-18 years (M_{age}=17.04, 13 males). Although multiple variables were collected to assess risky sexual behavior (e.g. number of partners, age of first sexual intercourse), lifetime condom use was selected to assess risky sexual decision-making because this behavior most directly relates to contraction of STIs or unintended pregnancy (CDC, 2016) and in-the-moment impulsive decisions (Donohew et al., 2000). Participants were asked to describe their lifetime condom use on a 5-point Likert Scale (1=never used a condom; 5=used a condom every time). Lower levels of lifetime condom use indexed higher frequency of risky sexual behavior.

Reckless driving. Adolescents with driver's permits or licenses (n=21) provided information on frequency of engagement in reckless driving behavior. The rate of adolescents with driver's licenses in our sample (38%) is similar to national trends for urban areas (Shults, Olsen, & Williams, 2013). Participants ranged in age from 16-18 years (M_{age}=17.05, 13 males).

To assess reckless driving, participants were asked to rate frequency of engagement in risky behaviors while driving on a 5-point Likert Scale (0=never; 4=almost always). Risky driving behaviors consisted of 13 items such as speeding up to make a yellow light, running a red light, receiving a ticket, and driving over the speed limit. For analyses, reckless driving was operationalized as the sum of self-reported frequency across all items. The possible range was 0 (reporting "never" on all 13 items) to 52 (reporting "almost always" on all 13 items).

Results

Hormonal Measures

Testosterone and DHEA levels were assessed for a subsample of participants who provided saliva samples (N=33, 17 male). Males and females did not differ in age (females M_{Age} = 16.65, *SD* = 1.22, range = 14-18 years; males M_{Age} = 16.19 years, *SD* = 1.17, range = 14-18 years). For DHEA, mean levels for boys was 325.83 pg/ml (*SD*=249.76) and mean levels for girls was 316.03 pg/ml (*SD*=193.66). For testosterone, mean levels for boys was 81.53 pg/ml (*SD*=52.61) and mean levels for girls was 13.07 pg/ml (*SD*=52.61). Mean levels were similar to previously reported norms for adolescents (Granger, Schwartz, Booth, Curran, & Zakaria, 1999; Shirtcliff, Dahl, & Pollack, 2009). There was a significant difference between testosterone by gender $t(16.43)=-5.33$, $p<.001$, equal variances not assumed) and a significant positive association between DHEA and age ($r=.37$, $p<.05$). No significant association was found between DHEA and gender, or testosterone and age. Given sexual dimorphisms in pubertal hormones, values for testosterone were z-scored separately by self-reported gender and then collapsed within a single standardized variable, which was used for all subsequent analyses. The same procedure was followed for DHEA. Testosterone and DHEA were significantly associated ($r=.61$, $p<.001$) (see Figure 1).

Correlations between hormonal measures and self-report

Associations between self-report measures and pubertal hormones were examined and are reported in Table 1. Testosterone was significantly associated (r=.39, p<.05) with several traits related to approach-related tendencies, such as the disinhibition subscale of the Sensation Seeking Scale (e.g. "I like to have new and exciting experiences and sensations even if they are a little unconventional or illegal."). Figure 2 provides a scatterplot depicting one representative example of the several associations found between testosterone and approach-related tendency. Other examples include a positive association with measures on the UPPS-P that relate to difficulty inhibiting impulses in affective contexts. For example, higher levels of testosterone was related to increased positive urgency (e.g. "When I am very happy, I can't seem to stop myself from doing things that can have bad consequences.") (r=.65, p<.001) and increased negative urgency (e.g. "When I am upset I often act without thinking.") (r=.5, p<.01). Additionally, testosterone was associated with risk attitudes towards traits related to risky sexual behavior and aggressive behavior. Specifically, adolescents with relatively higher levels of testosterone reported lower expected risks (r=-.53, p<.01) and greater expected benefits (r=.65, p<.001) of engaging in risky sexual behavior (e.g. "Sex with multiple partners.") (Figure 3A and 3B). Additionally, higher levels of testosterone were associated with greater expected benefits of aggressive and illegal behavior (e.g. "Punching or hitting someone with a fist.") (r=.49, p<.01).

With respect to real-world measures of risk taking behavior, participants' reckless driving ranged from 0 – 20 on the 0-52 scale (M= 9.19, SD=6.28), with higher numbers representing greater frequency of engagement in risky driving. Risky sexual behavior ranged from 1 – 4 on the 0-4 scale indicating lifetime condom use, with higher numbers indicating greater frequency of condom use (M= 3.94, SD=1.00). There were no associations between either hormone and

real-world measures of risk (i.e., risky sexual behavior or reckless driving). There were no significant differences by gender on real-world measures of risk taking. There were no associations between DHEA and any behavioral measures. All analyses are corrected for age.

Discussion

While the primary purpose of this study was to investigate associations between DHEA and traits related to risk taking in adolescents, significant associations were only found with testosterone, a measure that was included for replication purposes. Largely consistent with prior literature, higher levels of testosterone were found to relate to increased sensation-seeking and approach-related tendencies, particularly within the domains of sexual and aggressive behavior. While testosterone was associated with traits and risk attitudes, it was not significantly related to frequency of engagement in self-reported measures of real-world risk taking. Findings do not provide evidence for a direct association between pubertal hormones and risky behavior in adolescent's daily lives. The robust set of results demonstrated for testosterone and the lack of associations with DHEA are considered within the context of the larger literature.

Testosterone was significantly associated with several measures, which collectively suggest that relatively higher levels of testosterone are associated with a greater drive to experience novelty and excitement, in addition to more difficulty controlling impulses during affectively salient contexts. Sensation-seeking, or the pursuit of high-intensity, exciting experiences, occurs more frequently in adolescents than in either children or adults (Steinberg, 2008) and is correlated more strongly with measures of pubertal maturation than age (Spear, 2000; Steinberg & Morris, 2001). Previous work has related greater testosterone with increased motivation and approach-related tendencies (Aluja & Torrubia, 2004; Campbell et al., 2010), which may encourage adolescents to attain novel experiences (Forbes & Dahl, 2010). Sensation

seeking is correlated with risk taking, such that individuals high in sensation seeking tend to engage in behaviors that increase the amount of stimulation they experience; however, the two constructs are not overlapping as sensation seekers do not seek out risk for its own sake (Zuckerman, 1994).

With respect to risk attitudes, testosterone was associated with evaluation of risks and benefits, particularly for domains emphasized in prior literature, risky sexual and aggressive behaviors. These behaviors are most related to the increased salience and pursuit of social goals that are central to adolescence (Crone & Dahl, 2012). In general, shifts in testosterone appear to activate motivational tendencies, especially appetitive motivations in the realm of social goals and rewards, which help to facilitate social re-orientation during adolescence. In animals, testosterone at puberty appears to influence sexual and aggressive behavior (Schulz & Sisk, 2006), which are both important for the evolutionary goals of reproduction and establishment of social dominance. In humans this association is likely reflected in adolescents' increasing motivation to attract friends and romantic partners, to attain social status, and more generally, in their natural tendencies to pay more attention to peer, romantic, and sexual contexts (Forbes & Dahl, 2010).

In the present study, there were no significant associations between testosterone or DHEA and self-reported real-world engagement in risk-taking behaviors. In other words, although there were associations between testosterone and risk attitudes in domains including sexual risk taking, there was no relation between testosterone and actual behaviors as they manifested in adolescents' daily lives and decisions, such as lifetime condom use. These findings are also fairly consistent with prior literature, which has suggested that while reproductive hormones are critical to social behaviors, the behaviors they influence are sensitive to social

context (Ballonoff Suleiman, Johnson, Shirtcliff, & Galvan, 2015). For example, one study found the association between testosterone and adolescent sexual behavior was mediated by frequent attendance at religious services (Halpern, Udry, and Suchindran, 1997), pointing to a role for environment-behavior-development interactions. Additionally, evidence from human and non-human primate research indicates that testosterone does not necessarily have a direct relation to aggressive behavior. Rather, testosterone increases motivation to attain higher status, and the effect of testosterone level on behavior is dependent on social context (Wallen, 2001). Collectively, it appears that many of the behavioral changes associated with pubertal hormones are linked to activational effects on specific motivational tendencies, such as increased sensation seeking and increased orientation to peer and romantic contexts, though the subsequent influences on behavior are highly variable depending upon social context as well as underlying individual differences.

Not only was the pattern of findings for testosterone and behavior largely reflective of the larger literature, so was the lack of significant associations between DHEA and behavior. To date, no research has reported significant associations between DHEA and behavior with respect to adolescent risk taking. Our rationale for focusing on DHEA and behaviors related to adolescent risky decision-making was guided by a set of fairly recent studies that used structural neuroimaging techniques to demonstrate an association between DHEA and structural development of the prefrontal cortex (PFC) in children and adolescents (Nguyen et al., 2013; Klauser et al., 2015). These studies offer a glimpse of evidence that DHEA may play a role in the maturation of the PFC, a process that has been hypothesized to be important for adolescent risky decision-making (Casey, Galvan, & Somerville, 2016), yet neither study assessed behavioral correlates associated with these neurobiological changes. Overall, it is unknown if the absence of

DHEA in the broader literature is because measures of DHEA have been included and not reported due to lack of results, or if measures of this hormone have simply not been included.

A strength of this study is that we attempt to address a gap in literature that has been virtually ignored; yet, this very same feature is related to a substantial limitation of the study. Our methodological approach was guided by prior work on adolescent risky decision-making, and we selected measures to assess impulsivity, sensation seeking, and risk attitudes, given the literature relating these traits with risk taking at this time (Bornovalova et al., 2009; Figner & Weber, 2011; Romer, 2010; Steinberg 2007). Incidentally, these are the same traits that appear to be associated with the approach-related tendencies most often associated with testosterone (Aluja, Garcia, Garcia, & Blanco, 2016; Cooper, Goings, Kim, & Wood, 2014; Wood et al., 2013). We speculate that the current null DHEA findings may be related to a lack of measures that appropriately reflect constructs related to this particular hormone. In other words, perhaps it is not that DHEA is unrelated to adolescent risk-taking behaviors, but rather, that DHEA is not related to the particular risk-taking measures included in the current study. As DHEA administration in adults has been linked to optimal performance on tests of emotion regulation and attention (Sripada et al., 2013) and precocious puberty defined as early adrenarche has been linked to mood disorders in children and adolescents (Rose et al., 2008), future work should include measures of attentional and emotional regulation in typically-developing populations. Another limitation of this work is a relatively small sample size, which precludes separate investigations for males and females. However, although testosterone is typically considered a "male hormone", levels of this pubertal hormone roughly double in girls over the course of puberty, with the highest increases occurring just before menarche (Halpern et al., 1997), suggesting that testosterone plays an important role for females as well. It is important to note

that the use of z-scored values in the current study constrains interpretations of findings relative to same-sex peers in the sample. Another challenge of a small sample size is limited power to explore variables that may mediate the association between hormones and behavior. As noted in the discussion, the association between hormones and behavior is not often direct, and numerous other social and environmental cues may contribute to these associations along with other potential biological factors. Additionally, the current study design cannot determine cause (hormones) and effect (behavior), as engagement in behaviors may be altering the hormonal milieu.

Despite limitations, this study offers a novel perspective toward obtaining a broader understanding of the biological contributors of behavior during adolescence. Consistent inclusion of approach-related behaviors and measures of testosterone provides fairly consistent findings in the current study and in prior research. However, the entire endocrine system is altered during puberty, and adrenarche and gonadarche are thought to be independent events controlled by different mechanisms. The relative absence of DHEA from research on adolescent risk taking is important to begin to address, and the current study provides a first step toward that goal.

Figure 1. Significant positive association between testosterone and DHEA (r=.61, p<.001). Values for pubertal hormones z-scored separately for males and females to standardize by sex. All analyses corrected for age.

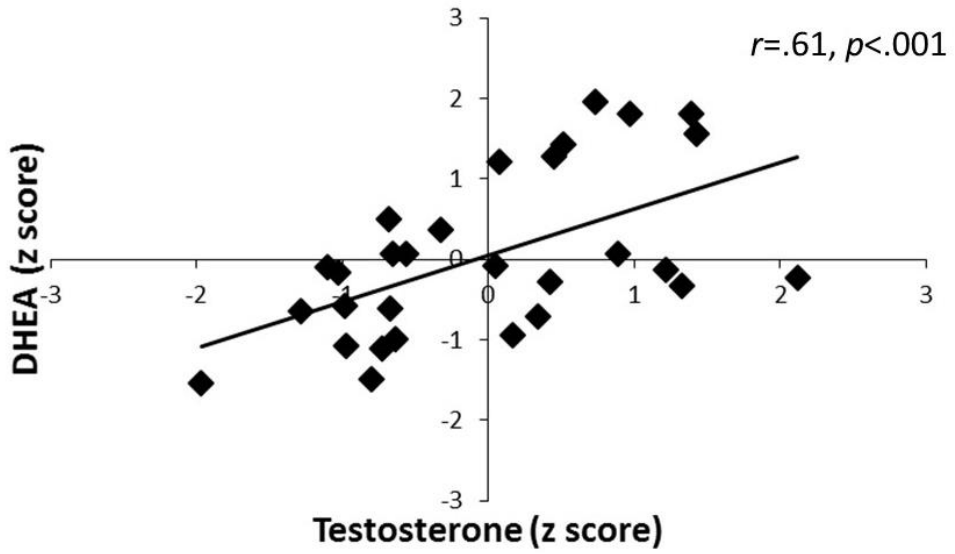

Figure 2. Significant positive association illustrating the link between testosterone and disinhibition (r=.39, p<.05). Values for pubertal hormones z-scored separately for males and females to standardize by sex. All analyses corrected for age.

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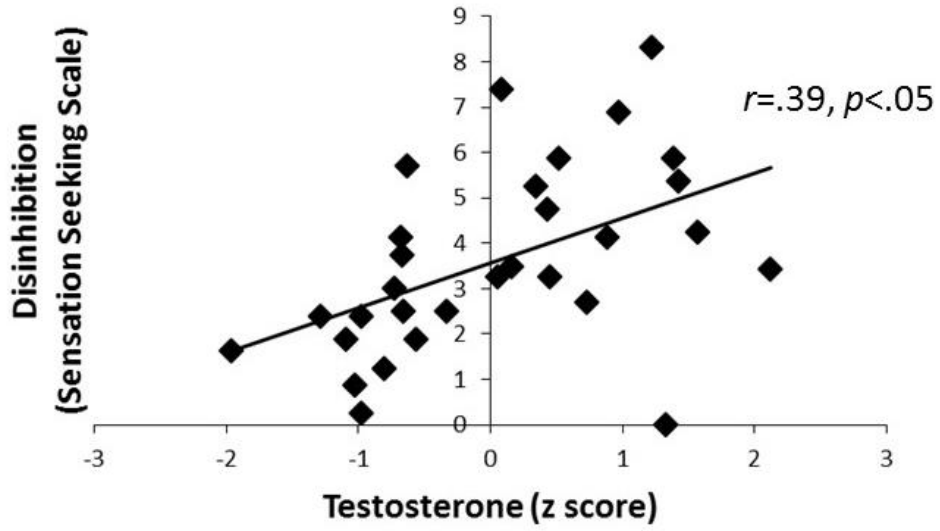

Figure 3. Significant association between testosterone and risk attitudes toward risky sexual behavior. (A) Adolescents with relatively higher levels of testosterone reported lower expected risks (r=-.53, p<.01) and (B) greater expected benefits (r=.65, p<.001) for engaging in risky sexual behavior Values for pubertal hormones z-scored separately for males and females to standardize by sex. All analyses corrected for age.

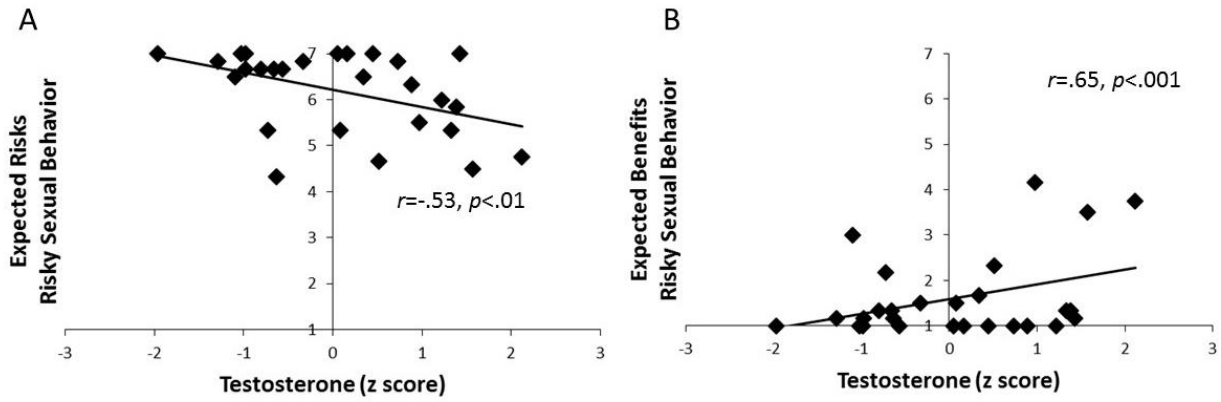

Table 1. Correlations between pubertal hormones and self-report questionnaires

	Testosterone (z-score)	DHEA (z-score)
CARE-R (Likelihood)		
Illicit Drug Use	.10	.02
Aggressive and Illegal Behaviors	.18	.21
Risky Sexual Behaviors	.09	-.04
Drinking	.21	.13
High Risk Sports	.13	-.14
Academic/Work Behaviors	-.04	.13
CARE-R (Expected Risk)		
Illicit Drug Use	.05	-.01
Aggressive and Illegal Behaviors	-.07	-.04
Risky Sexual Behaviors	-.52**	-.21
Drinking	-.22	-.09
High Risk Sports	-.08	.04
Academic/Work Behaviors	.14	.06
CARE-R (Expected Benefit)		
Illicit Drug Use	.06	.02
Aggressive and Illegal Behaviors	.50**	.13
Risky Sexual Behaviors	.66***	.37
Drinking	.28	.11
High Risk Sports	-.03	-.20
Academic/Work Behaviors	.19	.20
Sensation Seeking Scale		
Boredom Susceptibility	.18	-.08
Disinhibition	.42*	.31
Experience Seeking	-.20	.07
Thrill and Adventure Seeking	.09	.17
UPPS-P		
Negative Urgency	.50**	-.01
Lack of Premeditation	.17	.11
Lack of Perseverance	.13	-.07
Sensation Seeking	.10	.10
Positive Urgency	.66***	.25
Reckless Driving	.27	-.40
Risky Sexual Behavior	-.66	-.99

Note: *=p<.05,**=p<.01,***=p<.001. Values for pubertal hormones z-scored separately for males and females to standardize by sex. All analyses corrected for age.

III. The Unique Role of DHEA in Frontostriatal Connectivity during Cautious Decision Making in Adolescence

Adolescence is defined as the transition between childhood and adulthood and is characterized by profound change across multiple cognitive and psychosocial domains. Surges in pubertal hormones occur relatively early in the transition into adolescence, providing a loose anchor to the beginning of this period (Dorn et al., 2006), but the sustained hormonal increases are intimately tied to many of the subsequent developmental changes that occur during this time (Sisk & Foster, 2004). Insights from animal work suggest that pubertal hormones shape adolescent brain development via their ability to organize neural circuits (Sisk & Zehr, 2005), evidence that has been supported by neuroimaging work in human adolescents (Peper & Dahl, 2013). Organizational effects appear to be most significant in limbic regions associated with motivational and reward-related response (Sato et al., 2008). As the biological purpose of puberty is the attainment of reproductive maturity, it makes adaptive sense that increases in pubertal hormones, such as testosterone, relate to neurobehavioral changes in motivational drives at this time. The increased tendency to approach, explore, and take risks during adolescence is normative and may facilitate successful transition to the independence of adult roles (Spear, 2000). At the same time, adolescent risky decision-making is a complex construct, and these same tendencies can confer points of vulnerability for maladaptive behavior and negative trajectories. For these reasons, it is of value to investigate the neurobiological contributors of adolescent risk taking.

While a quickly burgeoning literature is beginning to explore the role of gonadal hormones (e.g. testosterone) on brain-behavior relations in adolescence, there is a striking dearth of research on the potential role of adrenarche and its hormonal byproducts in human

neurobiological development (Byrne et al., 2016). Adrenarche is the earliest phase of pubertal development, associated with dramatic increases in circulating levels of the androgen dehydroepiandrosterone (DHEA), secreted by the adrenal cortex. This endocrinological event is specific to humans and the great apes (Campbell, 2011), suggesting a unique evolutionary role for DHEA in human development. Thus far, two anatomical studies have found preliminary evidence that DHEA is related to structural development of the dorsolateral prefrontal cortex (DLPFC), indexed by cortical thickness (Nguyen et al., 2013) and white matter volume (Klauser et al., 2015) in children and adolescents. Given the hypothesized role that the protracted development of the prefrontal cortex plays in adolescent risk taking (Casey, 2015), it is surprising that no research has examined the association between DHEA and adolescent neural correlates of risky decision-making.

The majority of research investigating the role of pubertal hormones on the behavioral and neural correlates of adolescent risk taking has primarily focused on testosterone. Specifically, the published studies on this topic have suggested that greater levels of testosterone are associated with increased activation in reward circuitry when participants are performing a risk-taking or rewarding computer task. For example, increased levels of testosterone in boys was associated with enhanced activation in the ventral striatum after high-risk gambles (de Macks et al., 2011), reproducing results from a separate study reporting that testosterone levels were positively related to activation in reward-related regions during reward anticipation in boys (Forbes et al., 2010). Additionally, a longitudinal study demonstrated that increases in testosterone levels were linearly related to neural activity in the ventral striatum during a risk-taking task in boys and girls, over and above the effects of age, suggesting a driving factor of testosterone in the increased response to rewards (Braams et al., 2015). Collectively, these

studies suggest that gonadal hormones "sensitize" the brain's reward system, making adolescents more reactive to rewards in general.

In the present study, our goal was to build upon and extend this prior literature by examining the role of DHEA in neural reactivity during adolescent risky decision-making. To achieve this aim, we collected measures of salivary DHEA in addition to testosterone in a sample of adolescent participants. Based on prior literature, we predicted that higher levels of testosterone would be associated with greater striatal activation during risk taking. We also hypothesized that DHEA would be related to neural activation in the DLPFC during task performance, though hypotheses were exploratory given the lack of previous studies using measures of DHEA. A second goal of this study was to examine whether testosterone or DHEA are associated with functional connectivity during risk-taking. Prior research suggests that neural connectivity (assessed through resting state) may mediate the link between testosterone and self-reported levels of risk taking in adolescents (Peters, Jolles, Van Duijvenvoorde, Crone & Peper, 2015), though it is particularly important to understand neural co-activation in the moment risky decisions are made, given the context-dependent nature of frontostriatal coupling during adolescence (Crone and Dahl, 2012). For this reason, we assessed levels of functional connectivity during risky decision-making on a laboratory task. An adapted version of the Stoplight Task (Chein, Albert, O'Brien, Uckert, & Steinberg, 2011) was used, which has successfully elicited ventral striatal response during risky decision-making in adolescents in previous research (Kahn, Peak, Dishion, Stormshak, & Pfeifer, 2015; Kim-Spoon et al., 2016). In the current study, the Stoplight Task was modified to include a response inhibition component in addition to risky decision-making trials. It is unclear to what extent adolescent risk taking is a result of an inability to inhibit impulses or a deliberate choice in pursuit of reward. Thus, a final

goal of the current study was to investigate how different pubertal hormones (testosterone and DHEA) are related to neural activation during distinct components of adolescent task performance (response inhibition, decision-making during risk).

Methods

Participants. Fifty-five healthy right-handed adolescents (ages 14-18, M_{Age} = 16.25 years, *SD* = 1.08, 29 female) were recruited through poster and internet advertisements approved through the UCLA Institutional Review Board (IRB) and through the Galván Lab participant database. All participants provided informed consent, and participants under the age of 18 provided assent while their parent or guardian completed the informed consent procedure. All participants were high school students. Participants were excluded from participation if they had a previous diagnosis of psychiatric or neurologic illness or developmental delay, were taking psychoactive medication at the time of the study, or had metal in their bodies.

Materials

Salivary hormone assays. Participants collected saliva samples at home on the morning of the scan. See Study 1 Methods for details on collection and processing of hormone data.

Risky Decision-Making fMRI Task. During the fMRI scan, participants completed the Driving Game, an adapted version of the Stoplight Task originally designed by Chein et al., (2011). The version implemented in the current study was modified to include a response inhibition component in addition to the risky decision-making trials present in the original task (see Figure 1). In the task, participants moved a car along a computerized track and were instructed to reach the finish line as soon as possible to receive up to a $15 bonus. Every trial began with a series of 2-4 green lights. Participants used a button box to go ("1" button) for green lights, with the goal of building a prepotent response. Fifty percent of trials ended with a

red light, for which participants were instructed to stop ("2" button) as fast as possible without making a mistake (successful response inhibition). False alarms were defined as pressing the "1" button for a red light, failing to inhibit the pre-potent response to go. Negative outcomes (a 3 s crash) occurred after false alarms. Fifty percent of trials ended with a yellow light, for which participants could choose to either stop ("2" button) or go ("1" button). Stopping (i.e., cautious choice) resulted in a short 3 s delay at the light before proceeding. Going (i.e., risky choice) resulted in either continuing without delay for greater reward or experiencing a crash with a 6 sec delay. Either outcome to risky choice had a 50% random probability of occurring, though participants were not informed of this. Red and yellow light trials were presented in random and interspersed order throughout the task.

Participants completed 2 runs lasting approximately 8 mins each. Given the self-paced nature of the task, each participant experienced a different number of trials, though on average, participants were presented with a total of 70 trials (35 red, 35 yellow) summed across both functional runs. The inter-trial interval (ITI) was jittered according to a random gamma distribution (M=2 s). Each block of 10 trials was separated by a ten-second rest period. Behavioral data from the scanner were acquired and temporally aligned to fMRI acquisitions using E-Prime (Psychology Software Tools, Pittsburgh, PA) interfaced on a projector display.

fMRI Data Acquisition. Imaging data were collected using a 3 Tesla Siemens TrioMRI scanner at the UCLA Staglin Center for Cognitive Neuroscience. Parameters for image acquisition were voxel size = 3.0 x 3.0 x 4.0 mm, slices = 34, slice thickness = 4.0 mm, TR = 2 s, TE = 30 ms, flip angle = 90 degrees, interleaved slice geometry, field of view = 192 mm, 270 volumes. A T2*weighted, matched bandwidth (MBW), high-resolution, anatomical scan and magnetization-prepared rapid-acquisition gradient echo (MPRAGE) scan were acquired for

registration purposes (TR: 1900 ms; TE 2.26 ms; FOV: 250 mm; slice thickness: 1mm; 176 slices).

fMRI Data Preprocessing and Analysis. Preprocessing and statistical analyses were carried out using FSL 6.0 (www.fmrib.ox.ac.uk/fsl). No participants exceeded > 2mm in translational movement. Preprocessing consisted of motion-correction using MCFLIRT, removal of non-brain matter using BET, and spatial smoothing (5 mm FWHM Gaussian kernel). EPI images were registered to the MBW, then to the MPRAGE, and finally into standard MNI space (MNI152, T1 2 mm) using linear registration with FSL FLIRT.

Data analysis was conducted using FEAT, first at an individual subject-level and then using a mixed-effects model at the group analysis level. Z-statistic images were thresholded at a cluster-level of $z > 2.3$ and a corrected significance threshold of $p \leq 0.05$.

One general linear model (GLM) was defined for the Driving Game task, which included multiple regressors for each event type. Two decision regressors were created for yellow light trials (Cautious and Risky) and two response regressors were created for red light trials (Response Inhibition and False Alarm). A response regressor was created for green light trials (Go). The ITI after a risky choice served as an outcome regressor (Reward Anticipation) and outcomes to risky choice were created as well (Reward Receipt and Crash). Finally, a variable was created that included (1) trials with no button presses, (2) crashes after false alarms, and (3) the wait time after a cautious choice. The inclusion of this variable served to remove these items from the implicit baseline. All events were modeled at stimulus presentation and convolved with double gamma HRF in FSL. Duration for outcome events (anticipation and receipt of reward, crash) was the duration of the stimulus. Duration for events defined by a button press (e.g., risky and cautious choice, response inhibition, false alarm, go) was reaction time. The rest periods and

jittered inter-trial intervals were not explicitly modeled and therefore served as an implicit baseline. Six motion parameters were also included as covariates in the model for each run for each of the participants. The two runs for each participant were combined using a fixed effects voxel-wise analysis at the second level.

At the group level, fMRI analyses of greatest interest were for participant choice during yellow lights (risky or cautious) and participant response during red lights (response inhibition). To examine the neural correlates of risk taking, the following contrasts were modeled: Risky Choice (relative to baseline), Cautious Choice (relative to baseline), Risky Choice > Cautious Choice, and Cautious Choice > Risky Choice. To examine the neural correlates of successful response inhibition, the following contrast was modeled: Response Inhibition > Go. This measure isolated successful overriding of the pre-potent response, and is the typical contrast used to measure response inhibition (Aron & Poldrack, 2006). To examine differences between directed inhibition (stopping at a red light) and elected inhibition (stopping at a yellow light), the following contrasts were modeled: cautious > response inhibition, and response inhibition > cautious. Specifically, the contrast for cautious > response inhibition was of interest, as it allowed for an examination of neural activation preceding a decision to stop (cautious choice), relative to stopping an impulsive action (response inhibition). Additional contrasts examined main effects for outcome types: reward anticipation (relative to baseline), reward receipt (relative to baseline), and crash (relative to baseline). Values for testosterone and DHEA were z-scored by gender and entered as regressors in separate whole brain regression analyses with age included as a covariate. Tests were corrected for family-wise errors (FWE).

Psychophysiological interaction (PPI) analyses (Friston et al., 1997) were conducted to examine whether functional coupling between the dorsolateral prefrontal cortex (DLPFC) and

subcortical regions was affected by 1) testosterone or 2) DHEA during decision-making in adolescents. The DLPFC was selected as a region of interest because of its role in higher-level, flexible control of behavior (Miller & Cohen, 2001). The seed region for the PPI analyses was defined as a small mask (6 mm radius) around the peak voxel of DLPFC activation elicited during the Cautious > Inhibition contrast. This mask was drawn within the functional space of each participant and the deconvolved time-series was extracted for the ROI. The first-level design for each run consisted of three regressors of interest: 1) the physiological regressor, 2) the psychological variable, and 3) their product. The physiological regressor comprised the time-series for the DLPFC. The psychological (task) regressor modeled the contrast of cautious choice versus response inhibition, convolved with a double-gamma hemodynamic response function (HRF). The product regressor modeled the interaction between of the psychological regressor and the physiological regressor, with the psychological regressor zero-centered about the minimum and maximum values and the physiological regressor demeaned. This interaction term identified regions that covaried in a task-dependent manner with the seed region. The remaining task and motion regressors were included as regressors of no interest. The first-level PPIs were then entered into a group-level regression analysis using the FMRIB Local Analysis of Mixed Effects module in FSL (Beckmann, Jenkinson, & Smith, 2003) to investigate differences by pubertal hormone levels, with age as a covariate. Values for z-scored DHEA levels were entered as a regressor in one whole brain regression analysis and z-scored testosterone levels in the second analysis. Thresholded Z statistic images were prepared to show clusters determined by a corrected, cluster-forming threshold of $z > 2.3$ and an extent threshold of $p<.05$ familywise error corrected

Results

Hormone assays. Please refer to Study 1 Results for descriptive statistics on DHEA and testosterone.

Behavioral results on laboratory task. Given the self-paced nature of the task, each participant experienced a different number of total trial types. On average, adolescents successfully inhibited a response on 95% of red lights (*SD*=5.63, range=70-100%) and selected a cautious choice on 62% of yellow lights (*SD*=26.66, range=0-100%) (Figure 2A). Additionally, significant differences in reaction time (RT) by trial type were identified (Figure 2B) by a repeated-measures ANOVA, [$F(2.85, 88.21)=34.16$, $p<.01$]. Pairwise comparisons revealed significant differences between trial types of interest *(*$p<.001$, Bonferroni correction for multiple comparisons). Participants had longer RT for Cautious versus Risky Choices, Cautious versus False Alarms, and for Cautious versus Inhibition trials.

Gender and age differences on task behavior were examined. Although females made more cautious choices (by 8.43%) than males, and younger adolescents made more cautious choices than older adolescents, these differences were not statistically significant. There was a significant gender difference for RT on risky choice $t(53)=3.23$, $p<.002$, such that males were faster (.48 s) than females (.57 s). No other significant age or gender differences were observed.

Associations between pubertal hormones and task behavior. Measures of interest for task behavior were: percent cautious choices (number cautious divided by total number of yellow light trials), percent risky choices (number risky divided by total number of yellow light trials), percent response inhibition (number successful stop at red divided by total number of red light trials), and RT for cautious, risky, and response inhibition trials. Higher levels of testosterone were significantly associated with faster RT on risky choice ($r=-.33$, $p<.05$) (Figure 3). No other

significant associations were found between testosterone and task behavior. There were no associations between DHEA and task behavior. All analyses controlled for age.

fMRI Results

Decisions on yellow light trials. First, main effects of risky and cautious decisions on neural activation were examined. Whole-brain omnibus analyses of the contrast of Risky Choice > Baseline revealed activation in the striatum, including caudate and accumbens, and anterior cingulate cortex (ACC) (Figure 4A). Next, the omnibus GLM analysis for the Cautious Choice > Baseline contrast identified extensive cortical activation, including the dorsolateral prefrontal cortex (DLPFC) (Figure 4B). The list of whole-brain results and peak coordinates for these contrasts (Risky > Baseline and Cautious > Baseline) are listed in Table 1.

Response inhibition trials. Response inhibition was operationalized as successful inhibition at a red light relative to pressing to go at a green light (overriding of the pre-potent response). The omnibus GLM analysis for the Inhibition > Go contrast identified activation in regions typically active during response inhibition, such as the right inferior frontal gyrus (r-IFG) and insula (Figure 5). Finally, main effects for the Cautious > Inhibition contrast revealed greater activation in prefrontal regions such as the DLPFC and orbitofrontal cortex (OFC), in addition to insula, thalamus, and paracingulate gyrus. The list of whole-brain results and peak coordinates for these contrasts (Inhibition > Go and Cautious > Inhibition) are listed in Table 2.

Correlations between pubertal hormones and neural activation during decision making on yellow light trials. To test whether pubertal hormones were associated with neural activation during task performance, correlation analyses were conducted with DHEA and testosterone as regressors of interest in separate models, controlling for age. The contrasts examined were Risky > Baseline, Cautious > Baseline, Inhibition > Go, Cautious > Inhibition.

There was a significant positive association between testosterone and neural activation during Risky > Baseline in the right putamen, right paracingulate gyrus, left IFG, and right middle frontal gyrus (Figure 6A and 6B, Table 3). There were no negative associations between testosterone and neural activation during Risky > Baseline. There were no significant positive or negative correlations between testosterone and neural activation for Cautious > Baseline, Inhibition > Go, and Cautious > Inhibition. With respect to DHEA, there was a significant positive association with neural activation during Cautious > Baseline in the bilateral putamen (Figure 6C and 6D, Table 3). There were no negative associations between DHEA and neural activation during Cautious > Baseline. There were no significant positive or negative correlations between DHEA and neural activation for Risky > Baseline, Inhibition > Go, and Cautious > Inhibition. In other words, testosterone and DHEA appear to have differential roles on neural activation, specifically in the putamen, during distinct aspects of decision making (risky and cautious choice).

PPI Results

The seed used for PPI analyses was defined as a sphere with 6 mm radius around the peak voxel of the left DLPFC (MNI coordinates: x=-34, y=52, z=8). During Cautious > Inhibition, the DLPFC was functionally coupled (positively correlated) with other prefrontal regions, such as the right medial prefrontal cortex and a region in the left frontal lobe, in addition to the left occipital cortex and middle temporal gyrus. (Table 4).

When DHEA was added a regressor to the GLM, analyses revealed that, on average, higher levels of DHEA was positively associated with functional coupling between the DLPFC and a number of subcortical regions, including bilateral putamen and ventral striatum, and right amygdala. Other regions identified during this analysis were bilateral insula, r-IFG, ACC, left

precuneus, left angular gyrus, right superior temporal gyrus, and right supramarginal gyrus (Figure 7, Table 4). That is, adolescents with higher levels of DHEA have greater functional frontostriatal connectivity during cautious decision making relative to exertion of response inhibition. When testosterone was examined as a regressor, no brain regions differentially functionally interacted with the DLPFC during Cautious > Inhibition. Age was controlled for in all analyses.

Discussion

This study used fMRI to investigate the relation between testosterone and DHEA and the neural correlates of distinct aspects of risky decision-making in a group of adolescents. Participants comprised a relatively narrow age range of mid- to late- adolescents (14 - 18 years), and all analyses controlled for age to isolate the effects of pubertal hormones independent of chronological age. Pubertal hormones were associated with neural activation on the laboratory task, such that testosterone correlated with neural response preceding the selection of a risky choice, and DHEA correlated with neural response preceding a cautious choice. Moreover, DHEA was associated with greater functional coupling between the DLPFC and a number of subcortical regions, including the ventral striatum. This functional coupling was observed specifically during selection of a cautious choice relative to exertion of response inhibition. Findings suggest the possibility of a unique role for DHEA in cautious decision-making processes.

Adolescents with higher levels of testosterone demonstrated significantly faster reaction times when selecting a risky choice and greater putamen activation preceding that decision, relative to peers with lower levels of testosterone. The putamen is implicated in learning of automatic motor response or habitual action (Tricomi, Balleine, & O'Doherty, 2009), which

suggests that making a risky decision may be more of an automatic response for adolescents with high levels of testosterone. These findings are consistent with prior research associating higher testosterone levels with increased striatal response (Braams et al., 2015; Forbes et al., 2010; de Macks et al., 2011) and greater levels of risk taking (de Water et al., 2013; Vermeersch, T'Sjoen, Kaufman, & Vincke, 2008a) in adolescent boys and girls.

Interestingly, levels of DHEA were also associated with putamen response, but only during cautious choice. Specifically, adolescents with higher levels of DHEA relative to their peers had greater activation in the putamen preceding the selection of a cautious decision. Current findings provide evidence suggesting that specific pubertal hormones have differential influences on the adolescent brain during distinct components of decision making (risky and cautious choice). While there is a growing literature on the influence of testosterone on brain-behavior relations in adolescence, the potential effects of DHEA are currently extremely under-examined. Thus far, a total of two studies report inclusion of DHEA measures in fMRI research on adolescence. One of the studies demonstrated that adolescents with higher DHEA had greater activity in the anterior temporal cortex while reading social emotion scenarios compared to basic emotion scenarios (Goddings, Burnett Heyes, Bird, Viner, & Blakemore, 2012) while the other reported a lack of statistically significant findings related to DHEA (Klapwijk et al., 2013). Results from the former study provide tentative evidence that this hormone may play a role in processes important for adolescent development (e.g., association of DHEA with social emotional processing), an interpretation that is supported by results from the current study (e.g. association of DHEA with cautious decision-making).

The selection of cautious choices are rarely examined in investigations of adolescent risky decision-making, as most studies focus on decision-making under conditions of risk

irrespective of the actual choices made (i.e., collapsing across risky and cautious choices to examine decision-making processes in general) with only a handful of recent exceptions (Kahn et al., 2015; Telzer, Ichien, & Qu, 2015; Guassi Moreira & Telzer, 2016). In the current study, the same stimulus (i.e., a yellow light) elicited significant differences in reaction time by decision type and elicited distinct neural activation patterns preceding the decision. Specifically, risky choice yielded extensive striatal activation, including bilateral caudate and accumbens activation. Cautious choice yielded greater prefrontal engagement, including DLPFC, IFG and insula. Results suggest there are behavioral and neurobiological differences in the ways adolescents engage in distinct aspects of risky decision-making. Adolescents are often characterized by how risky they are, yet the participants in the current study selected the cautious choice, on average, nearly two thirds of the time. Characterizing the processes that subserve the decision to play it safe provides an important vantage point for understanding the neurobiological correlates that underlie the full spectrum of adolescent behavior.

Additionally, current findings provide evidence for differential processes underlying cautious decision-making and successful exertion of response inhibition. Although selecting a cautious choice and inhibiting a prepotent response involved the same observable behavior in the laboratory task (pressing the "2" button to stop), there were significant behavioral and neural differences preceding that behavior depending on trial type. Behavioral data demonstrate that stopping as a cautious choice elicits slower reaction time compared to inhibition of an impulsive action, suggesting greater amounts of cognitive processing required for stopping as a deliberative choice not to take a risk. Neuroimaging findings support behavioral data, such that significantly more activation was elicited in regions such as the DLPFC, OFC, and insula for the Cautious > Inhibition contrast. The prefrontal cortex continues developing well into adolescence (Giedd et

al., 1999; Sowell et al., 2001), and the DLPFC is the highest cortical area that is involved in regulation of goal-directed behavior (Miller & Cohen, 2001). The insula is an important hub for integration of cognitive information and affective states (Smith, Steinberg, & Chein, 2014). Collectively, this suggests that choosing to play it safe requires greater cognitive control of attentional and emotional states than exertion of impulse control. While this is an intuitive finding, it is an important one. Risk taking and impulsivity are often conflated in examinations of adolescent behavior (as noted in Casey, 2015), and the novel design of the current paradigm provides the ability to directly examine behavioral and neural differences between the decision not to take a risk and the inhibition of an impulsive action.

Adolescents with higher levels of DHEA had greater functional coupling of the DLPFC and a number of regions during cautious decision making relative to exertion of response inhibition. Although research on DHEA and neural response in the adolescent brain is quite limited, animal work has identified associations between DHEA and dendritic growth (Compagnone & Mellon, 2000; Li et al., 2009) and neuroprotective effects (Maninger, Wolkowitz, Reus, Epel, & Mellon, 2009). Adrenarche has thus been speculated to play an important role in the extended period of synaptic pruning in humans (Campbell, 2011). Interestingly, the specific regions that co-activated with DLPFC during cautious decision-making in the current study included subcortical areas such as the putamen, amygdala, and ventral striatum. Frontostriatal connections appear to be particularly important for adolescent behavior and decision-making (Somerville, Hare, & Casey, 2010), supporting complex cognitive functions relevant to this developmental period, such as adjusting goal-directed behavior given changing motivational states (Crone & Dahl, 2012). Although the evidence presented in the current study is preliminary due to the rather limited sample size, findings suggest that DHEA is associated

with the neural correlates of cautious decision-making, particularly the frontostriatal connections hypothesized to support this behavior.

It is important to understand these results within the context of the limitations of the current work. First, the current sample was not large enough to examine differential effects by sex, which is particularly relevant for research questions on pubertal hormones. However, although testosterone levels significantly differed by sex, DHEA levels did not, consistent with prior literature (e.g. Shirtcliff et al., 2009). DHEA is an adrenal hormone, and its influences are likely less directly related to sexually dimorphic effects than gonadal hormones such as testosterone. Additionally, there is utility to using z-scored values for hormones, as analyses provide information on individual differences in hormone levels relative to same-sex peers. Second, the process of adrenarche occurs quite early in childhood, beginning as early as 6 years of age. DHEA levels increase steadily throughout the lifespan and then decline in old age. While the current study is conducted in a sample of adolescents, the influences of DHEA are not specific to this period. These analyses do not characterize longitudinal trajectories or provide comparisons with child or adult groups. However, the purpose of the current research was to characterize how individual differences in levels of pubertal hormones, above and beyond potential effects of chronological age, related to neural correlates of risky decision-making. The research was conducted in adolescents, as this research question is of particular relevance to this period. Finally, DHEA was not associated with behavioral measures in the present study. Prior literature has focused primarily on the influences of testosterone during adolescence, likely because the behavioral and neural correlates of testosterone are clearly noticeable and related to a "go" response. Assessing a "stop," or the lack of taking a risk, is a more subtle endeavor. In the present study, selection of a cautious choice and exertion of response inhibition are both actions

to stop, and they are indistinguishable behaviors in terms of observed response. However, differential patters of neural activation and correlations between DHEA and functional connectivity for this contrast highlight the utility of using neuroimaging methods to uncover differences in processing that may not be revealed by behavior alone.

Despite limitations, the present study contributes to our growing understanding of the neurobiological contributors to risky decision-making in adolescents in novel and important ways. Prior literature has focused primarily on measures of testosterone and neural response to risk or reward, providing a foundational understanding of how pubertal hormones influence the adolescent brain, yet offering a view of only one aspect of this association. The current study provides novel evidence that DHEA may play a unique role in neural processes preceding the selection of a cautious choice and the frontostriatal connections hypothesized to subserve this behavior.

Figure 1. Example of green, red, and yellow light events on the laboratory task. Participants had 1 s to use a button box to press "1" to go for green, "2" to stop for red, and could choose whether to go (risky choice) or stop (cautious choice) for yellow. A jittered inter-trial stimulus followed presentation of each event. Potential outcomes to risky choices had equal and random probabilities of occurring. All trials began with 2-4 green lights and ended with either a red or yellow light.

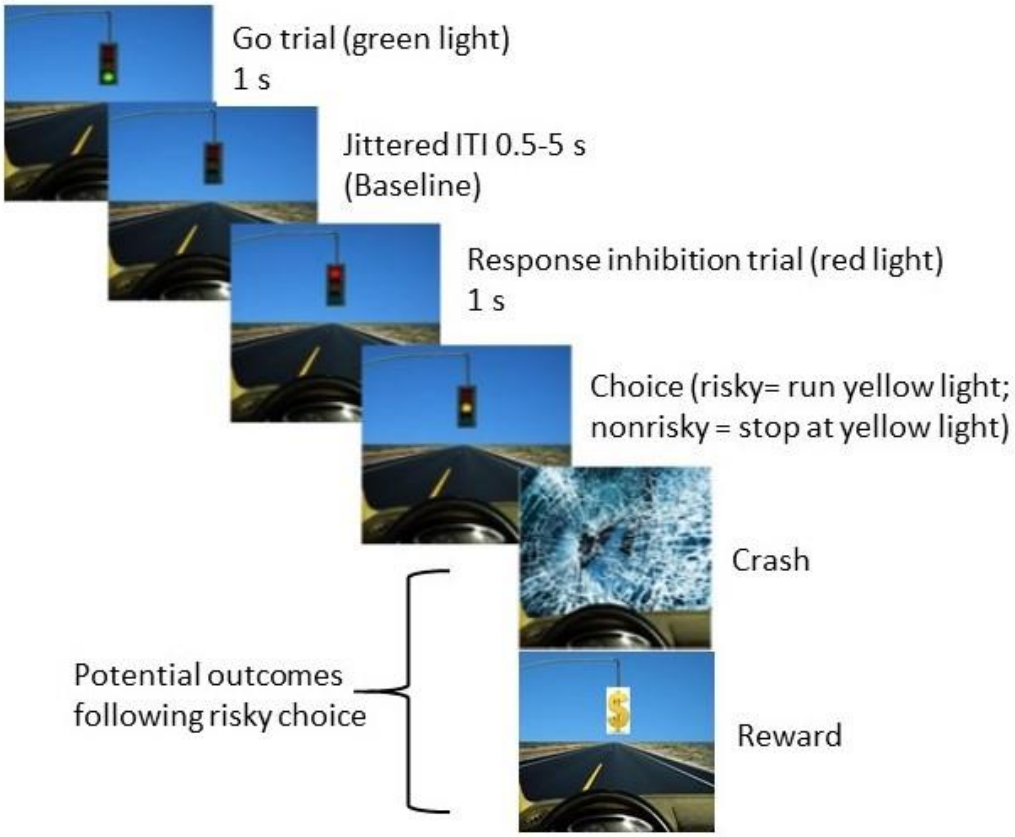

Figure 2. (A) On average, participants successfully inhibited a response on 94% of red lights and selected a cautious choice on 62% of yellow lights. (B) A repeated-measures ANOVA identified significant differences in reaction time (RT) by trial type [$F(2.85, 88.21)=34.16$, $p<.01$].

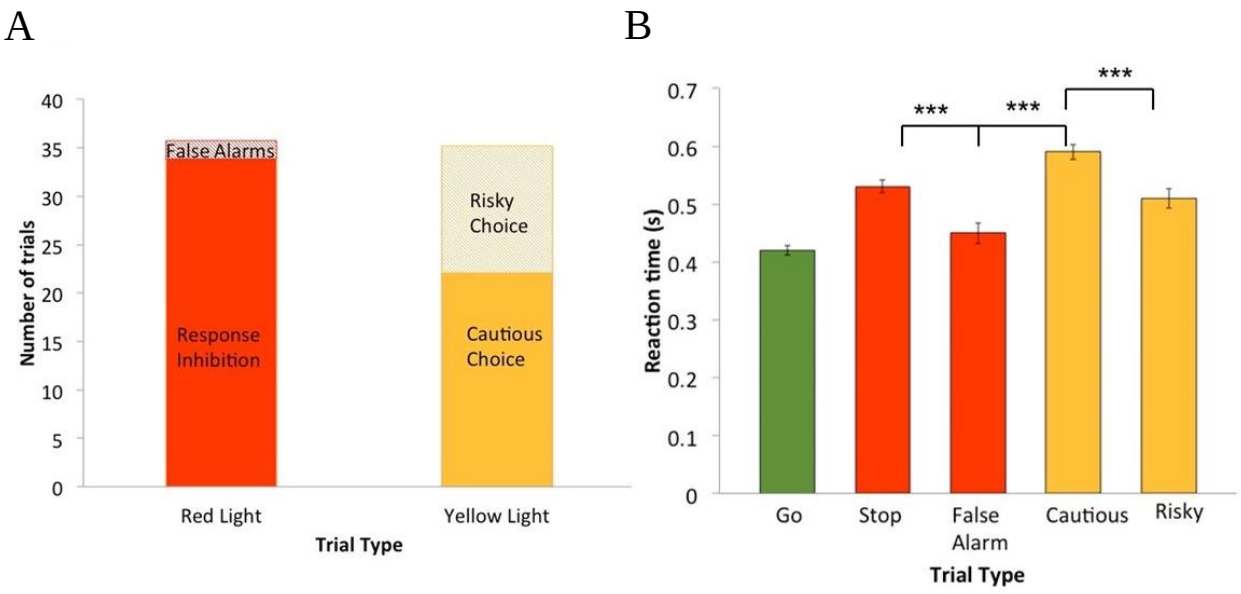

Figure 3. There was a significant association between pubertal hormones and behavior on task, such that higher levels of testosterone were significantly associated with faster RT on risky choice (r=-.33, p<.05).

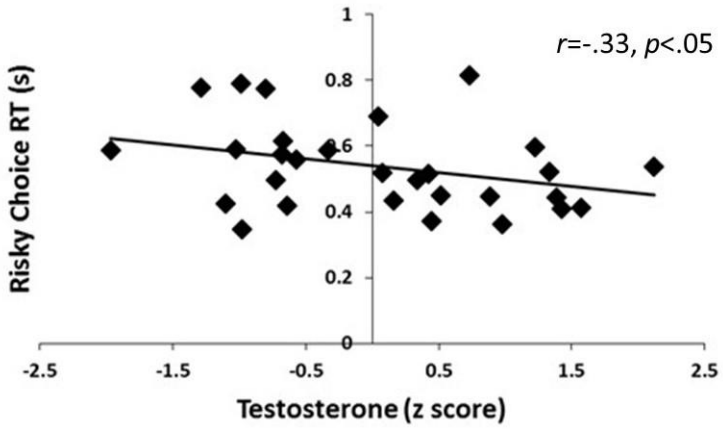

Figure 4. Differential activation preceded the decision to make a risky or cautious choice on yellow light trials. (A) The contrast for Cautious > Baseline identified extensive cortical activation, including in the dorsolateral prefrontal cortex (DLPFC). (B) The contrast for Risky > Baseline revealed activation in the striatum, including caudate and accumbens. All analyses cluster-corrected at z=2.3, p<.05. *R=right; L=left.*

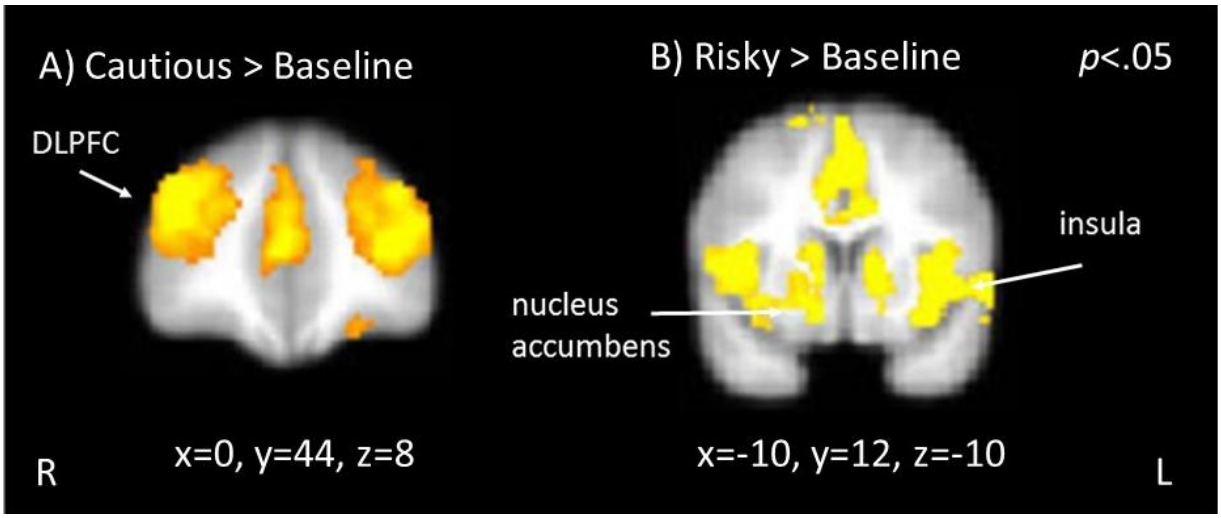

Figure 5. The contrast for Inhibition > Go identified activation in regions implicated in successful response inhibition, such as the right inferior frontal gyrus (R-IFG). All analyses cluster-corrected at z=2.3, p<.05. *R=right; L=left.*

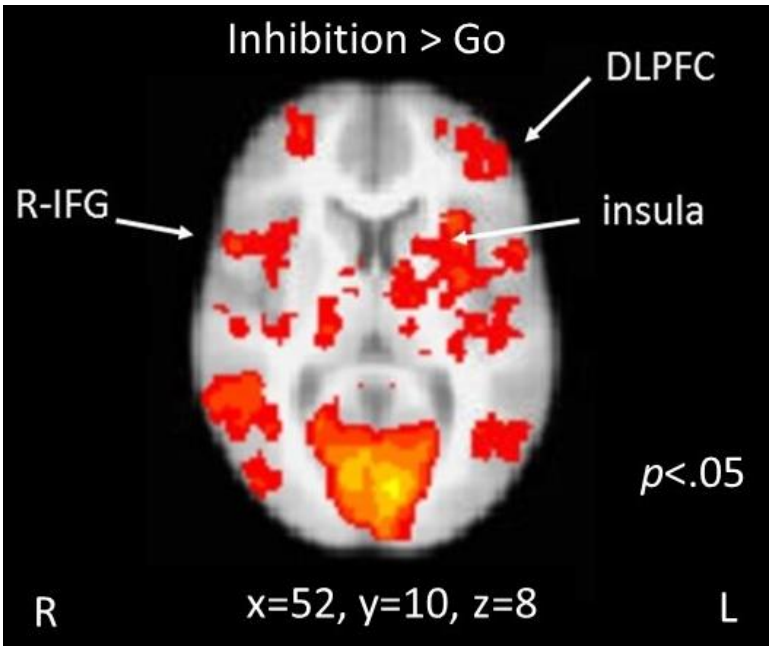

Figure 6. Neural response during risky (A) and cautious (C) choice positively correlated with testosterone and DHEA, respectively. Scatterplots are for visualization purposes, illustrating the correlation between hormones and parameter estimates extracted from clusters in the putamen during risky (r=.42, p<.05) (B) and cautious (r=.67, p<.001) (D) choice. All analyses cluster-corrected at z=2.3, p<.05, corrected for age. *R=right; L=left.*

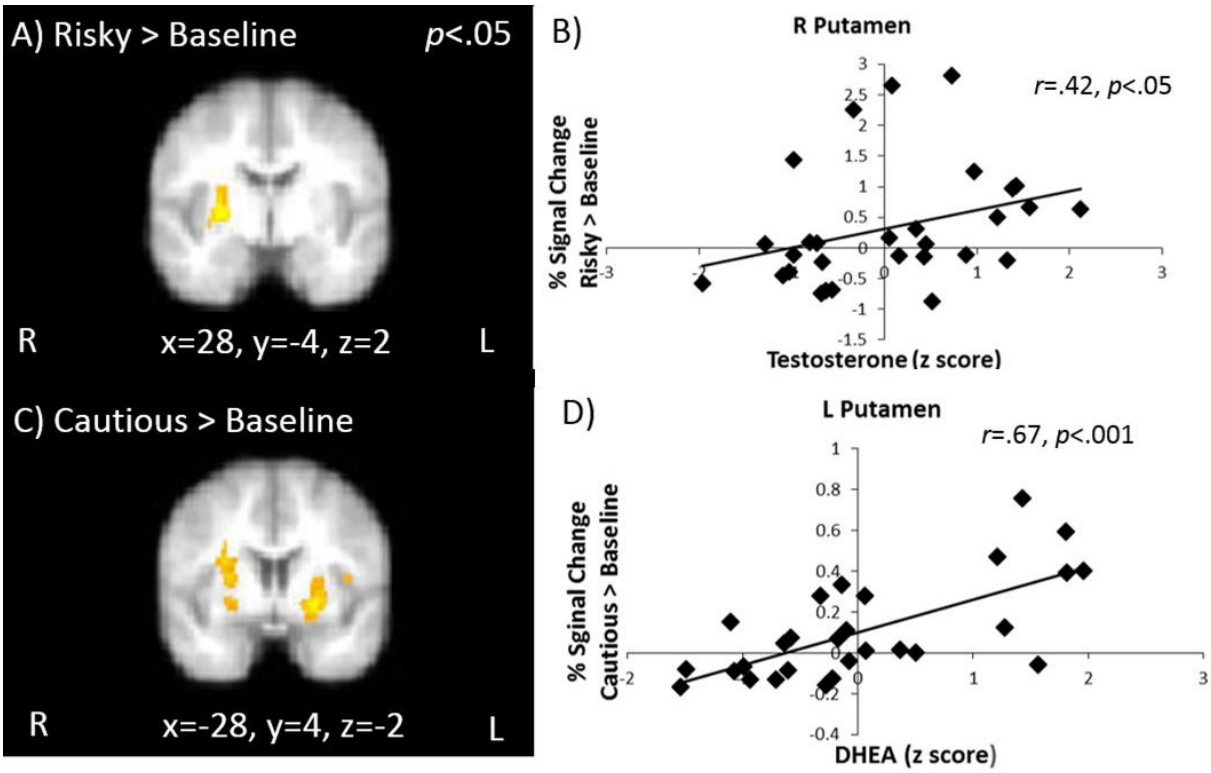

Figure 7. (A) DHEA was positively associated with functional connectivity between the left DLPFC and a number of subcortical regions such as ventral striatum, amygdala, and insula for the Cautious > Inhibition contrast. (B) For descriptive purposes, parameter estimates of intensity were extracted from the peak voxel in the left ventral striatum (VS) to depict the positive correlation between DHEA and DLPFC-VS functional connectivity during Cautious > Inhibition in the scatterplot. All analyses cluster-corrected at z=2.3, p<.05, corrected for age. *R=right; L=left.*

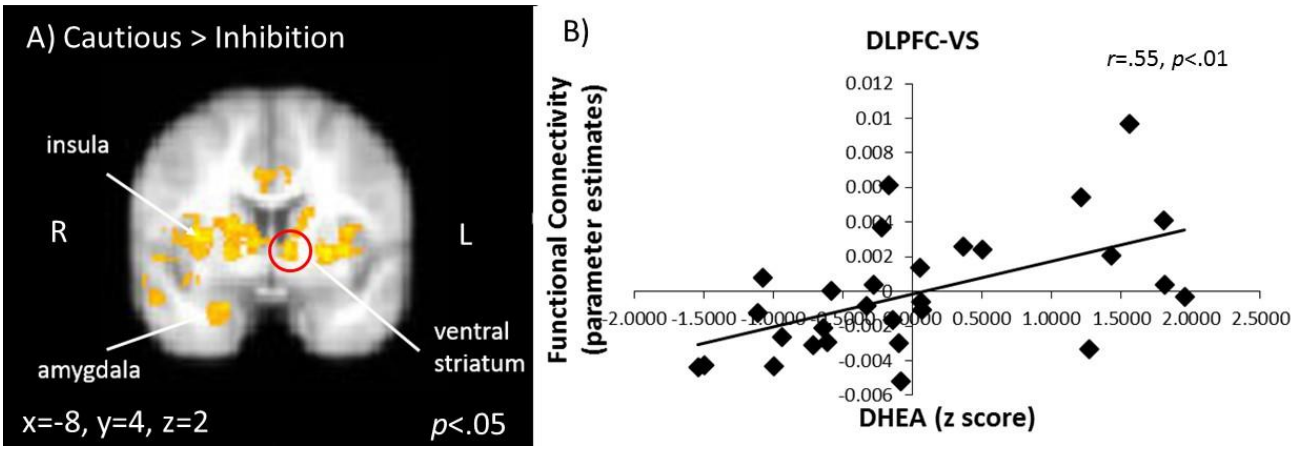

Table 1. Neural activation preceding risky and cautious choices at yellow lights

Trial Type	Region	*x*	*y*	*z*	*Z-max*	Voxels
Main Effects						
Risky Choice						
	R precuneus	6	-74	44	6.22	32376
	L insula	-32	22	6	5.43	
	R insula	32	22	6	3.59	
	R anterior cingulate cortex	6	36	22	5.29	
	L superior parietal lobule	-46	-42	56	5.15	
	R nucleus accumbens	12	12	-8	2.60	
	R caudate	10	12	6	2.41	
	L caudate	-10	12	6	3.81	
	L thalamus	-8	-12	6	4.46	
	R thalamus	8	-12	6	3.54	
	R putamen	16	12	-6	2.85	
	L putamen	-16	12	-6	2.50	
	R occipital cortex	8	-100	6	2.35	
	R inferior frontal gyrus	48	12	8	3.40	
	L precentral gyrus	-54	6	24	2.60	
	R dorsolateral prefrontal cortex	34	54	22	2.46	
	L dorsolateral prefrontal cortex	-26	54	22	3.6	
	R orbitofrontal cortex	28	54	-14	2.97	
Cautious Choice						
	R precuneus	12	-68	46	8.26	67598
	Posterior cingulate gyrus	0	-24	28	8.05	
	Paracingulate gyrus	0	26	38	7.83	
	R superior parietal lobule	38	-48	46	7.95	
	L superior parietal lobule	-42	-52	56	7.87	
	L postcentral gyrus	-44	-30	48	7.84	
	R insula	32	26	-2	4.91	
	L insula	-32	26	-2	4.97	
	R putamen	20	6	4	3.54	
	L putamen	-20	6	4	3.88	
	R caudate	12	8	14	4.44	
	L caudate	-12	8	14	4.14	
	R inferior frontal gyrus	56	12	14	4.13	
	R dorsolateral prefrontal	36	52	16	5.62	

cortex				
L dorsolateral prefrontal cortex	-36	52	16	5.97

Note: x, y, and z refer to MNI coordinates; Z-max refers to the peak level of activation intensity; Voxels refers to the number of voxels in each significant cluster; L and R refer to left and right hemispheres.

Table 2. Neural activation during response inhibition contrasts

Trial Type	Region	*x*	*y*	*z*	*Z-max*	Voxels
Main Effects						
Inhibition > Go						
	L superior parietal lobule	-38	-42	48	7.52	63371
	R superior parietal lobule	38	-42	48	4.75	
	R temporal occipital cortex	32	-48	-14	4.12	
	L temporal occipital cortex	-32	-48	-14	3.55	
	R lateral occipital cortex	-54	-66	2	3.70	
	L lateral occipital cortex	52	-66	2	2.48	
	L precentral gyrus	-52	6	26	4.80	
	R inferior frontal gyrus	56	14	26	2.88	
	Anterior cingulate gyrus	0	26	26	3.22	
	L insula	-32	12	10	3.35	
	L putamen	-28	-6	2	3.71	
	R thalamus	20	-26	2	3.93	
	L thalamus	-20	-26	2	2.66	
	R supramarginal gyrus	58	-28	26	2.98	
	L supramarginal gyrus	-58	-28	26	4.04	
	R dorsolateral prefrontal cortex	32	56	24	3.36	
	L brain stem	-8	-48	-42	4.02	408
Cautious > Inhibition						
	Paracingulate gyrus	0	28	38	7.10	11143
	L angular gyrus	-42	-56	50	6.31	6210
	L dorsolateral prefrontal cortex	-42	54	6	4.55	1516
	R dorsolateral prefrontal cortex	42	54	6	3.09	
	L orbitofrontal cortex	-28	60	-8	3.10	
	R orbitofrontal cortex	28	60	-8	3.12	
	L insula	-32	22	0	5.58	894
	R insula	32	22	0	3.88	
	Posterior cingulate gyrus	0	-26	30	6.12	765
	L middle frontal gyrus	-40	30	34	3.84	606
	R middle temporal gyrus	60	-32	-8	4.15	477
	R occipital cortex	28	-92	-6	3.89	455
	R thalamus	4	-20	10	3.42	446

Note: x, y, and z refer to MNI coordinates; Z-max refers to the peak level of activation intensity; Voxels refers to the number of voxels in each significant cluster; L and R refer to left and right hemispheres.

Table 3. Associations between pubertal hormones and neural activation preceding risky and cautious choices

Trial Type	Region	*x*	*y*	*z*	*Z-max*	Voxels
Positive correlation with testosterone						
Risky Choice						
	R paracingulate gyrus	4	44	30	3.25	453
	L inferior frontal gyrus	-44	30	8	3.64	404
	R putamen	28	-4	2	3.85	294
	R middle frontal gyrus	50	8	44	3.28	276
Positive correlation with DHEA						
Cautious Choice						
	L putamen	-24	8	-4	4.08	618
	R putamen	26	6	-8	2.75	556

Note: x, y, and z refer to MNI coordinates; Z-max refers to the peak level of activation intensity; Voxels refers to the number of voxels in each significant cluster; L and R refer to left and right hemispheres.

Table 4. Functional connectivity with the DLPFC during Cautious > Inhibition

Trial Type	Region	*x*	*y*	*z*	*Z-max*	Voxels
Increased connectivity						
	R frontal medial cortex	6	36	-12	3.86	2020
	L frontal lobe	-18	28	16	3.88	991
	L occipital cortex	-26	-74	2	3.74	897
	L middle temporal gyrus	-54	-12	-14	3.68	393
Positive correlation with DHEA						
	R putamen	30	-20	6	4.86	19540
	L putamen	-30	-20	6	2.83	
	R ventral striatum	8	4	0	3.10	
	L ventral striatum	-8	4	0	3.10	
	R insula	34	0	6	2.71	
	L insula	-34	0	6	2.55	
	R inferior frontal gyrus	48	26	6	3.26	
	Anterior cingulate gyrus	0	18	36	2.7	
	R amygdala	20	2	-30	2.62	
	R superior temporal gyrus	62	-20	2	3.70	
	R supramarginal gyrus	58	-48	14	3.94	
	L angular gyrus	-56	-54	14	3.24	
	L precuneus	-18	-38	40	3.52	354

Note: x, y, and z refer to MNI coordinates; Z-max refers to the peak level of activation intensity; Voxels refers to the number of voxels in each significant cluster; L and R refer to left and right hemispheres.

IV. Sexually Riskier Adolescents Engage Subcortical Neural Circuitry, rather than Cortico-Subcortical, when Choosing to Play it Safe

Adolescent risk taking is a topic of public and scientific interest. Rates of risky behavior increase at this time (Steinberg, 2008) and range from exploratory and normative to dangerous and destructive. One of the primary tasks of adolescence is to gain knowledge and experience that will facilitate successful transition into adult roles. Adolescent engagement in sexual relationships is an example that illustrates how a behavior can serve a motivated and adaptive purpose during this life stage (e.g., exploration of new roles and relationships) and also have the potential for negative outcomes. Another illustrative example is engagement in driving, a behavior that facilitates transition to independence during adolescence, but can also have the potential for significant consequences for public health and personal safety. Adolescent decision-making processes contribute to the potential for negative outcomes related to these behaviors, as adolescents engage in these behaviors in ways that are either reckless or safe (e.g., consistent contraceptive use). Thus, the purpose of the current study was to examine the individual differences in decision-making processes that relate to self-reported riskier versus safer sexual and driving practices in adolescents.

While previous research has focused on potential social, lifestyle, and contextual factors that may contribute to risky sexual (Aalsma, Fortenberry, Sayegh, & Orr, 2006) and driving (Bina, Graziano, & Bonino, 2006; Hartos, Eitel, & Simons-Morton, 2002) behavior in adolescents, the role of decision-making processes is less clear. Some models of adolescent decision-making posit that risk taking at this time is subserved by relatively high inclinations for reward-seeking coupled with still-developing capacities for self-control (Steinberg et al., 2008). This hypothesis is supported by a wealth of studies implementing functional magnetic resonance

imaging (fMRI) techniques to understand the neurocognitive correlates of adolescent risk taking (e.g. Eshel, Nelson, Blair, Pine & Ernst, 2007; Galvan et al., 2006; Geier, Terwilliger, Teslovich, Velanova, & Luna, 2009; van Leijenhorst, Zanolie, Van Meel, Westenberg, & Crone, 2010). A prominent theory that has emerged from this work is that adolescent risk taking is associated with a heightened reactivity of subcortical regions related to reward and affective response that coincides with a fine-tuning of connections between cortical regions implicated in regulatory control of behavior (Casey, Getz, & Galvan, 2008; Crone & Dahl, 2012; Smith, Chein, & Steinberg, 2010). In other words, adolescents may have an increased tendency to seek out rewards that coincides with a still-developing ability to regulate that reward-seeking behavior.

This research suggests that adolescent engagement in risk taking is not due to irrationality or ignorance, but is intimately intertwined with motivational and contextual factors (Somerville & Casey, 2010). Specifically, emotionally charged or rewarding contexts can diminish control of behavior or influence decision-making in adolescents (Crone & Dahl, 2012). Indeed, when considering real-world forms of adolescent risky decision-making such as risky sex or reckless driving, they appear to be a result of a proclivity to seek out thrills and rewards that interacts with a difficulty exerting cognitive control in affectively-salient contexts (e.g. failure to use a condom in the heat of the moment; speeding through yellow lights for the thrill of it). Risky sexual decisions, in particular, often occur under emotionally and motivationally salient contexts, and may render adolescents vulnerable to difficulties in regulation of behavior in the "heat of the moment" (Reyna & Farley, 2006).

For this reason, it is important to include real-world and context-dependent measures of risk taking in fMRI studies, but ecological validity is a challenge in the scanning environment. Very few neuroimaging studies have included naturalistic measures of real-world risky

behaviors, as indexed through self-report, to relate activation during basic laboratory paradigms to the behaviors adolescents engage in during their daily lives (an issue discussed in Berkman & Falk, 2013). Thus, the neural correlates related to frequency of engagement in risky sexual behavior or reckless driving in adolescents are largely underexplored, despite the prevalence of these behaviors and the gravity of their negative consequences. Strides have been made in approximating reckless driving in the scanning environment with the use of laboratory paradigms designed to mimic driving behavior (Chein et al., 2011; Cascio et al., 2014). These advances allow for an examination of the neural correlates of more ecologically relevant tasks, yet there is still little information on how this activation relates to adolescent behavior outside the laboratory. With respect to adolescent risky sexual behavior, only two studies have examined how self-reported measures of contraceptive use relate to the adolescent brain (Ewing, Houck, & Bryan, 2015; Goldenberg, Telzer, Lieberman, Fuligni, & Galvan, 2013). In both studies, sexually riskier adolescents had differential activation in the right inferior frontal gyrus (R-IFG) during response inhibition on a go/no-go task, compared to their less risky peers. These consistent findings suggest that neural correlates of impulse control during response inhibition are related to risky sexual behavior in teens. However, the role of reward-related processes during a risky decision-making task in adolescents with respect to self-reported risky sexual behavior or reckless driving measures remain unknown.

The goal of the present study was to examine the association between self-reported real-world risk-taking behaviors (risky sex and reckless driving) in adolescents and the neural correlates subserving risky and cautious choice in a laboratory task. We performed functional connectivity analyses to examine co-activation of cortical regions involved in regulatory processes and subcortical structures implicated in reward during selection of risky and cautious

choices. Given the integrative and interactive roles of affective and regulatory neural processes in adolescent decision-making and behavior, incorporating circuit-based accounts of the neural correlates of adolescent risk taking may improve our understanding of why adolescents engage in the behaviors they do and how this can vary by emotional context (Casey, Galvan, & Somerville, 2016). We hypothesized that adolescents with higher self-reported engagement in real-world risk taking would exhibit less connectivity between cortical and subcortical regions during risky decision-making.

Methods

Participants. Fifty-five healthy right-handed adolescents (ages 14-18, M_{Age} = 16.25 years, *SD* = 1.08, 29 female) were recruited through poster and internet advertisements approved through the UCLA Institutional Review Board (IRB) and through the Galván Lab participant database. All participants provided informed consent, and participants under the age of 18 provided assent while their parent or guardian completed the informed consent procedure. All participants were high school students. Participants were excluded from participation if they had a previous diagnosis of psychiatric or neurologic illness or developmental delay, were taking psychoactive medication at the time of the study, or had metal in their bodies.

Materials

Self-reported real-world risk taking. Please refer to Study 1 Methods for a description of self-report measures assessing engagement in risky sexual behavior and reckless driving.

Risky Decision-Making fMRI Task. During the fMRI scan, participants completed the Driving Game, an adapted version of the Stoplight Task originally designed by Chein et al., (2011). Results reported in the current study focus on decisions rendered on yellow light trials

(see Figure 1). A detailed description of the fMRI Task, Data Acquisition, Data Preprocessing, and Level 1 Data Analysis can be found in the Methods section of Study 2.

fMRI Data Analysis. At the group level, fMRI analyses of greatest interest were for participant choice rendered at yellow lights (risky or cautious). To examine the neural correlates of decision making on this task, the following contrasts were modeled: Risky Choice (relative to baseline), Cautious Choice (relative to baseline), Risky Choice > Cautious Choice, and Cautious Choice > Risky Choice. Additional contrasts examined main effects for outcome types: reward anticipation (relative to baseline), reward receipt (relative to baseline), and crash (relative to baseline). Values for self-reported real-world risk taking measures (reckless driving and risky sexual behavior) were demeaned and entered as regressors in separate whole brain regression analyses with age included as a covariate. Tests were corrected for family-wise errors (FWE).

Psychophysiological interaction (PPI) analyses (Friston et al., 1997) were conducted to examine whether functional coupling between regions of interest were affected by individual differences in real-world amounts of 1) risky sexual behavior or 2) reckless driving during decision-making in adolescents. The seed region for the PPI analyses was defined as a small mask (6 mm radius) around the peak voxel of caudate activation identified from the main effects of the Risky > Baseline contrast. The caudate was selected as the seed regions given its role in goal-directed action during motivationally significant events (Tanaka, Balleine, & O'Doherty, 2008). This mask was drawn within the functional space of each participant and the deconvolved time-series was extracted for the ROI. The first-level design for each run consisted of three regressors of interest: 1) the physiological regressor, 2) the psychological variable, and 3) their product. The physiological regressor comprised the time-series for the caudate. The psychological (task) regressor modeled the contrast of cautious choice versus risky choice,

convolved with a double-gamma hemodynamic response function (HRF). The product regressor modeled the interaction between of the psychological regressor and the physiological regressor, with the psychological regressor zero-centered about the minimum and maximum values and the physiological regressor demeaned. This interaction term identified regions that covaried in a task-dependent manner with the seed region. The remaining task and motion regressors were included as regressors of no interest. The first-level PPIs were then entered into a group-level regression analysis using the FMRIB Local Analysis of Mixed Effects module in FSL (Beckmann, Jenkinson, & Smith, 2003) to investigate whether functional connectivity with the caudate was affected by individual differences in self-reported amounts of 1) risky sexual behavior or 2) reckless driving during decision-making in adolescents. Demeaned values of lifetime condom use and reckless driving were entered as regressors in separate whole brain regression analyses. Thresholded Z statistic images were prepared to show clusters determined by a corrected, cluster-forming threshold of $z > 2.3$ and an extent threshold of $p<.05$ familywise error corrected

Results

Self-reported real-world risk taking. Please refer to Study 1 Results for descriptive statistics on risky sexual behavior and lifetime condom use.

Behavior on risky decision-making task. Please refer to Study 2 Results for descriptive statistics on task behavior.

Associations between real-world measures of risky behavior and task behavior. Since this study focused on differences between cautious and risky choices, measures of interest for task behavior were: percent cautious choices (number cautious divided by total number of yellow light trials), percent risky choices (number risky divided by total number of yellow light

trials), and RT for cautious and risky choices. Adolescents reporting higher levels of lifetime condom use demonstrated significantly faster reaction time (RT) when making a cautious choice (r=-.52, p<.05), suggesting that selection of cautious decisions may be more of an automatic response for these individuals. There were no other associations between task behavior and self-reported real-world measures of risk taking. All analyses controlled for age.

fMRI Results

Decisions on yellow light trials. First, main effects of risky and cautious decisions on neural activation were examined. Please refer to Study 2 fMRI Results for a description of main effects for Risky > Baseline and Cautious > Baseline (also represented in Table 1 and Figure 4A and 4B, Study 2). In study 3, the omnibus GLM analysis for the Risky > Cautious contrast was examined and revealed activation in the left paracingulate gyrus, medial prefrontal cortex (mPFC), anterior cingulate gyrus (ACC), and right lateral occipital cortex. There was no significant activation for the contrast Cautious > Risky (Table 1).

Correlations between real-world risky behaviors and neural activation during decision making on yellow light trials. To test whether self-reported engagement in real-world risky behaviors was associated with neural activation during task performance, correlation analyses were conducted with risky sexual behavior and reckless driving as regressors of interest in separate models. The contrasts examined were Risky > Baseline, Cautious > Baseline, Risky > Cautious, Cautious > Risky. There were no significant positive or negative associations between real-world manifestations of risk taking and neural activation during decision-making on the laboratory task.

PPI Results

The seed used for PPI analyses was defined as a sphere with 6 mm radius around the peak voxel of the left caudate (MNI coordinates: x=-12, y=8, z=10). During Cautious > Risky, the caudate was functionally coupled (positively correlated) with prefrontal regions such as the orbitofrontal cortex, bilateral dorsolateral prefrontal cortex (DLPFC), and right inferior frontal gyrus (R-IFG), in addition to the anterior cingulate cortex (ACC), right caudate, left putamen, left occipital pole, and left middle and inferior temporal gyri (Table 2).

To assess the association between real-world measures of risky behavior and functional coupling with the caudate during selection of cautious compared to risky choices on the task, the measures for reckless driving and lifetime condom use were demeaned and included as behavioral regressors. When reckless driving was added as a regressor to the GLM, there were no significant associations. When risky sexual behavior was added as a regressor to the GLM, analyses revealed that, on average, higher levels of lifetime condom use was positively associated with functional coupling between the caudate and the left ACC, precuneus, middle and superior frontal gyri, and bilateral precentral gyri (Figure 2A and 2B, Table 2). That is, among sexually active adolescents, those reporting higher levels of lifetime condom use (i.e., less risky sexual behavior) had greater functional coupling between the caudate and regions such as the ACC when choosing to play it safe (Cautious > Risky). Additionally, the variable of lifetime condom use was negatively associated with functional coupling between the caudate and a number of subcortical regions, such as the left nucleus accumbens and hippocampus, right amygdala and putamen, in addition to left middle and superior temporal gyri, brainstem, and right lingual gyrus (Figure 2C and 2D, Table 2). In other words, adolescents reporting lower levels of lifetime condom use (i.e., more risky sexual behavior) had greater functional coupling

between the caudate and subcortical regions important for affective salience (e.g. nucleus accumbens and amygdala) when choosing to play it safe (Cautious > Risky).

Discussion

In this study, we examined the association between functional connectivity during a risky decision-making task and self-reported frequency of engagement in real-world measures of risky behavior in adolescents. Individual differences in self-reported frequency of risky sexual behavior was related to differential patterns of functional connectivity during selection of a cautious compared to risky choice. Specifically, adolescents who reported engaging in safer practices, indexed with higher reported levels of condom use, demonstrated greater functional coupling of the caudate and cortical regions such as the anterior cingulate cortex (ACC) during cautious decision-making. Conversely, individuals who reported engaging in riskier practices demonstrated greater functional coupling of the caudate and subcortical regions involved in affective response, particularly when choosing to play it safe. Results remained significant when including age as a covariate, suggesting that findings are independent of possible influences from chronological age. Findings provide evidence that adolescents with greater subcortico-subcortical coupling (and less cortico-subcortical coupling) may have greater difficulty translating knowledge into action during affectively salient contexts when making decisions in their daily lives.

Among sexually active adolescents, those reporting higher levels of condom use demonstrated greater caudate-ACC coupling during cautious decision-making, compared to their sexually riskier peers. The caudate is a region that appears to play a critical role in supporting the planning and execution of motor behavior required for achieving motivated goals (Tanaka et al., 2008). It is highly interconnected with multiple corticostriatal loops that form parallel circuits

(Alexander, DeLong, & Strick, 1986). Evidence suggests that the caudate and its associated corticostriatal circuitry underlies goal-directed action, which is the selection of behavior based on the changing values of goals and a knowledge of which actions lead to what outcomes (Grahn, Parkinson, & Owen, 2008). Specifically, connections with the ACC may facilitate the generation of appropriate strategies, taking account internal motivation and environmental cues that provide information on potential outcomes to actions (de Wit et al., 2012). In the current study, adolescents with higher reported rates of lifetime condom use demonstrated greater functional coupling between the caudate and ACC during task performance, which we interpret to reflect greater ability to exert goal-directed action control compared to their more risky peers.

Conversely, adolescents reporting lower lifetime condom use (i.e., sexually riskier) exhibited greater co-activation of the caudate and subcortical structures during task performance. Given that caudate loops receiving major connections from other subcortical structures such as the nucleus accumbens mediate information related to internal states (Tekin & Cummings, 2002), we interpret these findings to reflect selection of goal-directed action based primarily on internal motivation in sexually riskier adolescents. In other words, the caudate and its associated circuitry is implicated in initiation and maintenance of goal-directed response based on internal motivation and potential outcomes to actions in the external environment. Sexually riskier adolescents appear to engage circuitry implicated in the former while their safer peers engage circuitry implicated in the latter. This makes intuitive sense, given that engaging in sexual behavior typically occurs under contexts of high motivational salience and requires the evaluation of potential outcomes to lack of contraceptive use.

These functional connectivity results are specific to selection of a cautious relative to risky choice on the task. We posit that this contrast reflects the process of cautious decision

making, or choosing to play it safe. It is also important to consider that this contrast reflects reward sensitivity because selection of the certain response (cautious choice) could reflect an unwillingness to take a risk that may delay receipt of reward, even if that reward may ultimately be larger. However, functional connectivity analyses in the current study revealed that selection of a cautious choice was, on average, associated with greater co-activation of the caudate and regulatory regions, such as the dorsolateral prefrontal cortex (DLPFC) and right inferior frontal gyrus (R-IFG), compared to selection of risky choice. This is fairly convergent with prior work on a similar task, in which main effects for the Cautious > Risky contrast yielded significant activation in the R-IFG (Kahn et al., 2014). These results support interpretation that the Cautious > Risky contrast reflects a decision not to take a risk through exertion of regulatory control.

Thus, findings provide evidence for differential recruitment of functional circuitry during cautious decision-making in sexually risky adolescents. Specifically, these individuals demonstrate greater functional coupling of the caudate and subcortical regions involved in affective response, such as the nucleus accumbens and amygdala. Both of these structures are crucial to motivated behavior, though the nucleus accumbens is often attributed to positive valence (approach response) and the amygdala to negative valence (avoid response) (Ernst, Pine, & Hardin, 2006). Recently, a study found that individual variability in functional response of the nucleus accumbens and amygdala is predictive of sexual risk behavior in young adult college students (Victor, Sansosti, Bowman, & Hariri, 2015). The authors speculate that neural circuit functions contributing to approach and avoidance are relevant to the expression of risky behaviors, particularly sexual risk taking. In the current study, we hypothesize that the increased caudate-accumbens and caudate-amygdala connections during cautious decision-making may reflect competing “approach” and “avoid” signals for making a cautious choice, as the adolescent

deliberates prior to selection of the response. This interpretation is supported by behavioral data, as adolescents who are sexually riskier exhibit significantly slower reaction times when making a cautious choice. This suggests greater processing time, perhaps to resolve motivational conflicts. Ultimately, the decision-making process terminates with a cautious choice, which would suggest that the caudate-accumbens co-activation prevailed. Indeed, the signal intensity of caudate-accumbens coupling in the current data was stronger than that of caudate-amygdala. Alternatively, it is possible that increased functional co-activation of the caudate and subcortical regions simply reflects greater connectivity among subcortical regions in general in riskier participants.

This pattern of functional connectivity during cautious decision making may be related to a failure to select the cautious choice when decisions are made during contexts of high affective arousal in adolescents' daily lives. For example, the vast majority of sexually active people across age groups are aware of the preventative efficacy of condom use, yet many do not use them on a consistent basis (Browne & Minichielli, 1994), particularly during adolescence (Parsons, Halkitis, Bimbi, & Borkowski, 2000). There is some evidence that adolescents pre-contemplate, deliberate, and prepare for sexual encounters (Reece et al., 2010), though they are often unable to translate forethought into action in the heat of the moment (Reyna & Farley, 2006). The original intention of the current work was not to investigate the neural correlates of sexual risk taking in adolescents, but to explore the associations between neural activation on a laboratory task and real-world engagement in risky behavior. Results were specific to risky sexual behavior, rather than reckless driving. Adolescents appear to have the most difficulty regulating behavior during contexts of affective arousal (Somerville & Casey, 2010), and decision making related to sexual behavior represents a uniquely affectively salient context.

Although this study has strengths, there are a few limitations to note. The sample of adolescents used for the current analyses was part of a larger dataset not recruited on the basis of engagement in sexual activity, which limited our sample size. This relatively small sample size did not allow for a comparison of sex differences in the relation between risky sexual behavior and brain activation during decision making. This will be important for future work to address, as level of riskiness and ramifications of engaging in unprotected sexual intercourse may vary for males and females. The current findings are meant to serve as a preliminary exploration to address a question that has not been examined in the literature previously. Additionally, questionnaires in the current study did not assess sexual orientation; youth in same sex relationships may choose to not report contraceptive use because they reason there is no biological risk of pregnancy. However, failure to use contraceptives may still be considered risky due to concerns about sexually transmitted infections (STIs). Finally, we recognize that the decision-making process is merely one aspect of several that contribute to adolescent risky sexual behavior (e.g. peer norms, length and type of relationship, religion and religiosity).

In summary, current findings provide initial support for the importance of variability in functional connectivity during decision making in the expression of adolescent sexual risk behavior. Although the initiation of sexual behavior is common among adolescents and young adults, some individuals express this behavior in a manner that significantly increases risk for negative outcomes with far-reaching and long-lasting consequences, such as STIs and unplanned pregnancy. Identifying biological mechanisms of risk is important because it has the potential to not only direct the search for novel intervention targets but also inform strategies for prevention. As such, current results suggest the importance of considering individual variability in functional

neural circuits supporting regulatory and affective response in the expression of sexual risk behavior in adolescents.

Figure 1. Example of a yellow light event on the laboratory task. Participants were presented with an average of 35 yellow lights over 2 functional runs during fMRI. At each yellow light, participants rendered a decision to either stop the car (cautious choice) or run the yellow light (risky choice) with a goal of reaching the finish line as quickly as possible for greater monetary reward. Cautious choices resulted in a short delay. Successful risk taking resulted in no delay. Unsuccessful risk taking resulted in a crash, and a relatively long delay.

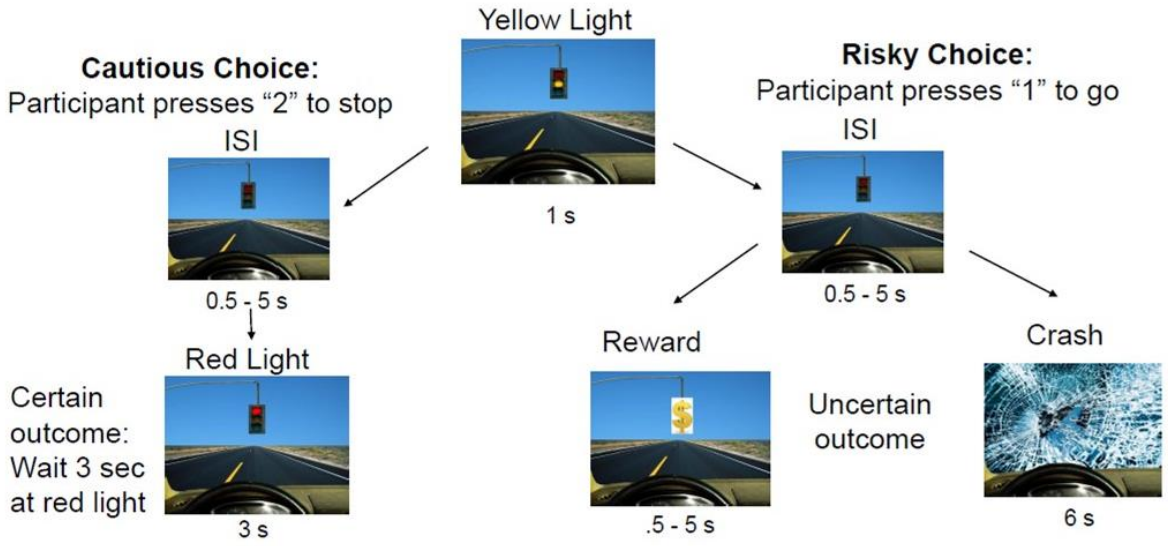

Figure 2. For the contrast Cautious > Risky, adolescent sexual riskiness was positively (A) and negatively (B) associated with functional coupling of the left caudate with cortical and subcortical regions, respectively. Specifically, among sexually active adolescents, those reporting higher levels of lifetime condom use (i.e., less risky) had greater caudate-ACC functional coupling when playing it safe, an association visually depicted in the scatterplot (B). Those reporting lower levels of lifetime condom use (i.e., more risky) had greater functional connectivity between the caudate and a number of subcortical regions. This association is depicted in the scatterplot illustrating strength of caudate-accumbens functional coupling decreasing with higher levels of self-reported condom use (D). All analyses cluster-corrected at z=2.3, p<.05, corrected for age. *R=right; L=left.*

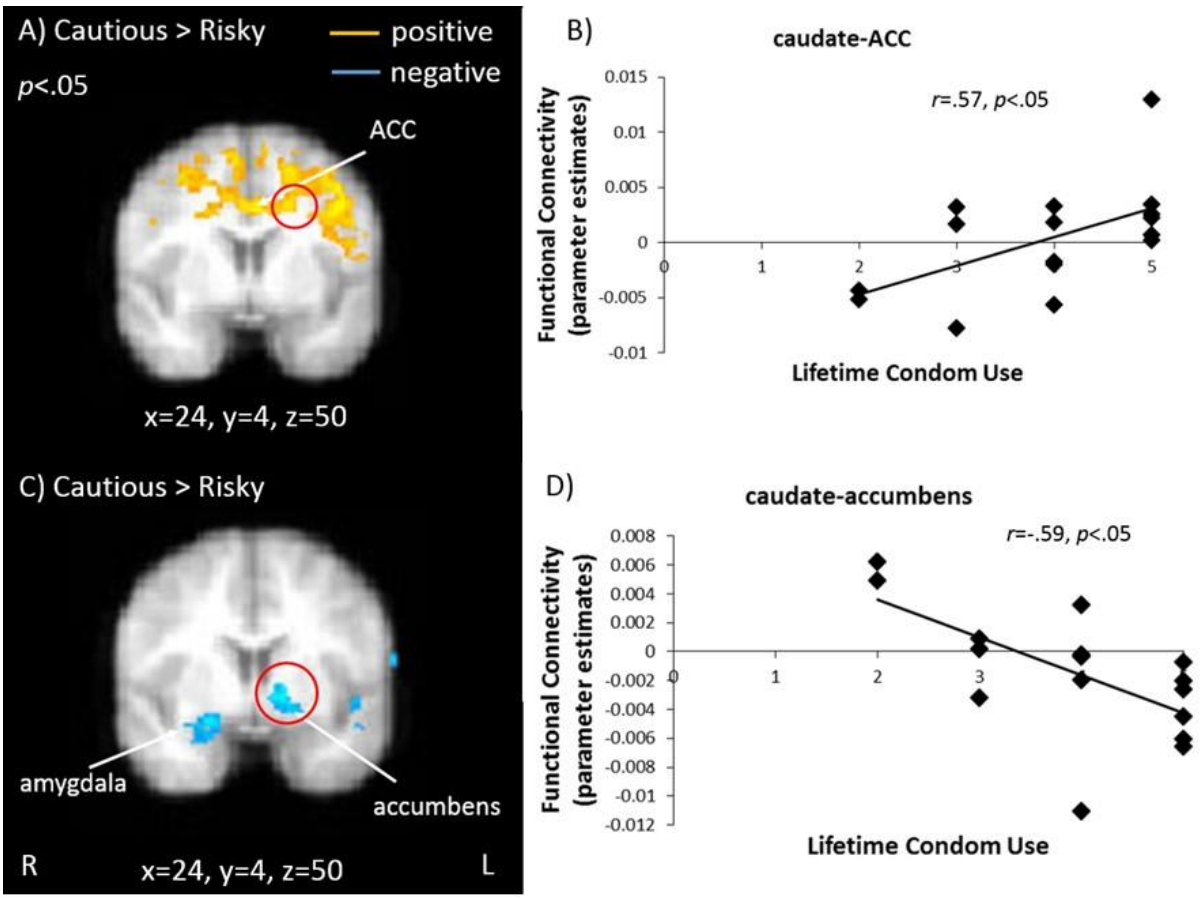

Table 1. Neural activation for yellow light contrasts

Trial Type	Region	*x*	*y*	*z*	*Z-max*	Voxels
Main Effects						
Risky > Cautious						
	L paracingulate gyrus	-14	48	18	3.4	516
	anterior cingulate cortex	0	38	19	2.63	
	medial prefrontal cortex	0	46	-6	2.38	
	R lateral occipital cortex	18	-86	36	3.45	346
Cautious > Risky						
	none					

Note: x, y, and z refer to MNI coordinates; Z-max refers to the peak level of activation intensity; Voxels refers to the number of voxels in each significant cluster; L and R refer to left and right hemispheres.

Table 2. Functional connectivity with the caudate during Cautious > Risky

Trial Type	Region	*x*	*y*	*z*	*Z-max*	Voxels
Increased connectivity						
	L occipital pole	-12	-94	6	4.33	3600
	R dorsolateral prefrontal cortex	46	40	10	2.63	
	L dorsolateral prefrontal cortex	-46	40	10	2.47	
	R inferior frontal gyrus	46	34	4	2.63	
	L anterior cingulate cortex	-4	32	-4	2.82	
	L middle temporal gyrus	-62	-24	-10	3.07	
	L inferior temporal gyrus	-50	-60	-10	4.26	
	L putamen	-30	-26	2	3.69	
	R caudate	8	24	0	3.74	
	L orbitofrontal cortex	-12	50	-10	3.94	1334
Positive correlation with lifetime condom use						
	R precuneus	10	-50	52	4.36	9615
	L anterior cingulate cortex	-4	2	36	3.74	
	L middle frontal gyrus	-46	6	36	3.39	
	L superior frontal gyrus	-22	6	44	2.65	
	L lateral occipital cortex	-22	-68	42	3.28	
	R precentral gyrus	34	-16	54	3.80	
	L precentral gyrus	-34	-16	54	2.73	
Negative correlation with lifetime condom use						
	L middle temporal gyrus	-50	-44	2	4.58	5560
	L nucleus accumbens	-10	4	-4	3.52	
	L hippocampus	-34	-28	-8	4.12	
	R amygdala	26	2	-18	2.63	
	R putamen	28	-14	-4	3.76	
	L insula	-40	-6	4	2.91	
	R lingual gyrus	16	-60	-8	4.08	
	L superior temporal gyrus	-64	-28	4	3.20	
	L brainstem	-2	-24	-16	3.64	324

Note: x, y, and z refer to MNI coordinates; Z-max refers to the peak level of activation intensity; Voxels refers to the number of voxels in each significant cluster; L and R refer to left and right hemispheres.

V. General Discussion

The research presented in this dissertation helps illuminate the underexplored aspects of the neurobiology of adolescent risky decision-making. These studies primarily focused on aspects of adolescent biology, decision-making, and behavior that have previously received little attention. They provide novel evidence that DHEA may play a role in the functional corticostriatal circuits that subserve cautious decision-making processes, and that corticostriatal circuits may relate to the ability to play it safe in adolescents' daily lives.

These studies suggest a more nuanced interpretation of existing literature on the neurobiological contributors of adolescent risky decision-making. To date, studies have primarily focused on the association between testosterone and the approach-related tendencies related to risk taking, such as sensation seeking. This inclination to approach, venture, and explore facilitates attainment of novel experiences during a period important for learning. However, current findings provide novel evidence for complementary, co-occurring processes that are relevant for adolescent decision-making. While we have tended to dichotomize adolescent biology and behavior with respect to testosterone and approach response (i.e., more or less testosterone related to more or less risk taking), present results suggest a bigger picture of testosterone-related approach *and* DHEA-related regulatory processes. In other words, adaptive behavior requires flexible control of response. Importantly, DHEA was not related to behavior in the current research, though robust results were found with neuroimaging measures. The neural activation for which DHEA was most related to contrasted two behaviors (selection of a cautious choice and exertion of impulse control) that are outwardly indistinguishable. Additionally, there was no direct link between hormones and risk taking as it manifested in adolescent's daily lives in the current work. Collectively, these findings underscore the importance of examining other

biological factors besides hormones that may be informative in understanding adolescent risk taking.

Indeed, functional neural circuitry subserving decision-making processes on the laboratory task was associated with real-world measures of risk in adolescents. Among sexually active adolescents, corticostriatal circuits underlying cautious decision-making were found to be significantly related to greater regulatory control of behavior in the form of more consistent condom use. There is often a focus on risky decision-making, yet the adolescents in our sample selected the cautious choice more often than not during task performance and had a demonstrated variability in self-reported condom use, such that many teens reported always or almost always using contraceptives. Investigating the underlying mechanisms for cautious decision making is important for informing efforts to promote positive development and safer engagement with exploratory and reward-seeking behaviors during this period. Additionally, characterizing the neural correlates of cautious decision making in adolescents who are not always able to regulate response during affectively salient contexts (i.e., sexually riskier) is an important first step to understanding when and why these processes may fail.

The current research offers initial evidence to highlight the importance of obtaining a broader perspective on the neurobiological correlates of adolescent behavior. Avenues for future work should continue to build on the understanding of the hormonal cascade of puberty as a complex and multi-component process. For example, it will be interesting to see how testosterone and DHEA are related to each other through the use of relative ratios. Does DHEA have differential influences on brain-behavior relations depending on whether an individual has low levels versus high levels of testosterone? Investigations of these questions will help us attain an understanding of the complementary and independent associations of DHEA and testosterone

with adolescent brain and behavior. Another potential avenue for future work is assessing how individual levels in hormone reactivity, above and beyond basal levels, may influence brain-behavior relations in adolescents. For example, testosterone levels have been found to increase after interactions that are perceived as challenges to social status (Eisenegger, Haushofer, & Fehr, 2011), which highlights that (1) the association between hormones and behavior is not unidirectional and (2) hormones may be important for in-the-moment ramping of response and behavior. This example also highlights the role of social environment, which is particularly important for adolescents (Crone & Dahl). Numerous potential social and environmental cues may contribute to the role of hormones on brain-behavior relations, and future work should include measures (e.g., peer norms, parent-child relationship, home environment) within larger samples to explore these associations.

There are multiple layers of complexity to the adolescent period, and no single study can assess all elements, but the current work provides a valuable first step to addressing a broader range of adolescent neurobiology and behavior largely missing from prior research. Collectively, findings suggest that the adolescent brain may be influenced by distinct hormones during specific aspects of decision making, and provide novel evidence for the possibility of a unique role for DHEA in cautious decision-making processes. Moreover, this research demonstrates that recruitment of neural circuitry during selection of cautious choice is related to individual differences in self-reported risky sexual behavior, providing support for the ecological validity of the laboratory task and relevance to behaviors important for public health. This understanding is an important first step towards the development and implementation of successful programs and policies to promote positive development during this period.

REFERENCES

Aalsma, M. C., Fortenberry, J. D., Sayegh, M. A., & Orr, D. P. (2006). Family and friend closeness to adolescent sexual partners in relationship to condom use. *Journal of Adolescent Health*, *38*(3), 173-178.

Adams JB (1985) Control of secretion and the function of C19-delta 5-steroids of the human adrenal gland. *Molecular and Cellular Endocrinology*, 41**,** 1–17.

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual review of neuroscience*, *9*(1), 357-381.

Aluja, A., & Torrubia, R. (2004). Hostility-aggressiveness, sensation seeking, and sex hormones in men: re-exploring their relationship. *Neuropsychobiology*, *50*(1), 102-107

Aluja, A., García, L. F., García, Ó., & Blanco, E. (2016). Testosterone and disinhibited personality in healthy males. *Physiology & behavior*, *164*, 227-232..

Amstislavskaya, T. G., & Popova, N. K. (2004). Female-induced sexual arousal in male mice and rats: behavioral and testosterone response. *Hormones and Behavior*, *46*(5), 544-550.

Aron, A. R., & Poldrack, R. A. (2006). Cortical and subcortical contributions to stop signal response inhibition: role of the subthalamic nucleus. *Journal of Neuroscience*, *26*(9), 2424-2433.

Ballonoff Suleiman, A., Johnson, M., Shirtcliff, E. A., & Galván, A. (2015). School-Based Sex Education and Neuroscience: What We Know About Sex, Romance, Marriage, and Adolescent Brain Development. *Journal of School Health*, *85*(8), 567-574.

Baulieu, E. E., & Robel, P. (1998). Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) as neuroactive neurosteroids. *Proceedings of the National Academy of Sciences*, *95*(8), 4089-4091.

Bauman, K. E., Foshee, V. A., Koch, G. G., Haley, N. J., & Downton, M. I. (1989). Testosterone and cigarette smoking in early adolescence. *Journal of behavioral medicine*, *12*(5), 425-433.

Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2003). General multilevel linear modeling for group analysis in FMRI. *Neuroimage*, *20*(2), 1052-1063.

Berkman, E. T., & Falk, E. B. (2013). Beyond brain mapping using neural measures to predict real-world outcomes. *Current Directions in Psychological Science*, *22*(1), 45-50.

Bina, M., Graziano, F., & Bonino, S. (2006). Risky driving and lifestyles in adolescence. *Accident Analysis & Prevention*, *38*(3), 472-481.

Bloch, M., Ish-Shalom, S., Greenman, Y., Klein, E., & Latzer, Y. (2012). Dehydroepiandrosterone treatment effects on weight, bone density, bone metabolism and mood in women suffering from anorexia nervosa—a pilot study. *Psychiatry research*, *200*(2), 544-549.

Bornovalova, M. A., Cashman-Rolls, A., O'donnell, J. M., Ettinger, K., Richards, J. B., & Lejuez, C. W. (2009). Risk taking differences on a behavioral task as a function of potential reward/loss magnitude and individual differences in impulsivity and sensation seeking. *Pharmacology Biochemistry and Behavior*, *93*(3), 258-262.

Boyar, R. M., Rosenfeld, R. S., Kapen, S., Finkelstein, J. W., Roffwarg, H. P., Weitzman, E. D., & Hellman, L. (1974). Human puberty simultaneous augmented secretion of luteinizing hormone and testosterone during sleep. *Journal of Clinical Investigation*, *54*(3), 609.

Braams, B. R., van Duijvenvoorde, A. C., Peper, J. S., & Crone, E. A. (2015). Longitudinal changes in adolescent risk-taking: a comprehensive study of neural responses to rewards, pubertal development, and risk-taking behavior. *Journal of Neuroscience*, *35*(18), 7226-7238.

Braams, B. R., Peper, J. S., van der Heide, D., Peters, S., & Crone, E. A. (2016). Nucleus accumbens response to rewards and testosterone levels are related to alcohol use in adolescents and young adults. *Developmental cognitive neuroscience*, *17*, 83-93.

Browne, J., & Minichiello, V. (1994). The condom: why more people don't put it on. *Sociology of Health & Illness*, *16*(2), 229-251.

Byrne, M. L., Whittle, S., Vijayakumar, N., Dennison, M., Simmons, J. G., & Allen, N. B. (2016). A systematic review of adrenarche as a sensitive period in neurobiological development and mental health. *Developmental Cognitive Neuroscience*.

Campbell, B. C., Dreber, A., Apicella, C. L., Eisenberg, D. T., Gray, P. B., Little, A. C., ... & Lum, J. K. (2010). Testosterone exposure, dopaminergic reward, and sensation-seeking in young men. *Physiology & behavior*, *99*(4), 451-456.

Campbell, B. C. (2011). Adrenarche and middle childhood. *Human Nature*, *22*(3), 327.

Cascio, C. N., Carp, J., O'Donnell, M. B., Tinney Jr, F. J., Bingham, C. R., Shope, J. T., ... & Falk, E. B. (2014). Buffering social influence: neural correlates of response inhibition predict driving safety in the presence of a peer. *Journal of cognitive neuroscience*.

Casey, B. J., Getz, S., & Galvan, A. (2008). The Adolescent Brain. *Developmental Review*, *28*, 62–77.

Casey, B. J. (2015). Beyond simple models of self-control to circuit-based accounts of adolescent behavior. *Annual review of psychology*, *66*, 295-319.

Casey, B. J., Galván, A., & Somerville, L. H. (2016). Beyond simple models of adolescence to an integrated circuit-based account: A commentary. *Developmental cognitive neuroscience*, *17*, 128-130.

Centers for Disease Control and Prevention. (2016, June). *CDC Releases Youth Risk Behaviors Survey*. Retrieved from https://www.cdc.gov/features/yrbs/

Chein, J., Albert, D., O'Brien, L., Uckert, K., & Steinberg, L. (2011). Peers increase adolescent risk taking by enhancing activity in the brain's reward circuitry. *Developmental science*, *14*(2), F1-F10.

Compagnone, N. A., & Mellon, S. H. (2000). Neurosteroids: biosynthesis and function of these novel neuromodulators. *Frontiers in neuroendocrinology*, *21*(1), 1-56.

Cooper, S. E., Goings, S. P., Kim, J. Y., & Wood, R. I. (2014). Testosterone enhances risk tolerance without altering motor impulsivity in male rats. *Psychoneuroendocrinology*, *40*, 201-212.

Crone, E. A., & Dahl, R. E. (2012). Understanding adolescence as a period of social–affective engagement and goal flexibility. *Nature Reviews Neuroscience*, *13*(9), 636-650.

de Macks, Z. A. O., Moor, B. G., Overgaauw, S., Güroğlu, B., Dahl, R. E., & Crone, E. A. (2011). Testosterone levels correspond with increased ventral striatum activation in response to monetary rewards in adolescents. *Developmental Cognitive Neuroscience*, *1*(4), 506-516.

de Water, E., Braams, B. R., Crone, E. A., & Peper, J. S. (2013). Pubertal maturation and sex steroids are related to alcohol use in adolescents. *Hormones and behavior*, *63*(2), 392-397.

de Wit, S., Watson, P., Harsay, H. A., Cohen, M. X., van de Vijver, I., & Ridderinkhof, K. R. (2012). Corticostriatal connectivity underlies individual differences in the balance between habitual and goal-directed action control. *Journal of Neuroscience, 32*(35), 12066-12075.

Dorn, L. D., Dahl, R. E., Woodward, H. R., & Biro, F. (2006). Defining the boundaries of early adolescence: A user's guide to assessing pubertal status and pubertal timing in research with adolescents. *Applied Developmental Science*, *10*(1), 30-56.

Figner, B., & Weber, E. U. (2011). Who takes risks when and why? Determinants of risk taking. *Current Directions in Psychological Science*, *20*(4), 211-216.

Forbes, E. E., & Dahl, R. E. (2010). Pubertal development and behavior: hormonal activation of social and motivational tendencies. *Brain and cognition*, *72*(1), 66-72.

Forbes, E. E., Ryan, N. D., Phillips, M. L., Manuck, S. B., Worthman, C. M., Moyles, D. L., ... & Dahl, R. E. (2010). Healthy adolescents' neural response to reward: associations with puberty, positive affect, and depressive symptoms. *Journal of the American Academy of Child & Adolescent Psychiatry*, *49*(2), 162-172.

Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., & Dolan, R. J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage*, *6*(3), 218-229.

Fromme, K., Katz, E. C., & Rivet, K. (1997). Outcome expectancies and risk-taking behavior. *Cognitive Therapy and Research*, *21*(4), 421-442.

Eisenegger, C., Haushofer, J., & Fehr, E. (2011). The role of testosterone in social interaction. *Trends in cognitive sciences*, *15*(6), 263-271.

Ernst, M., Pine, D. S., & Hardin, M. (2006). Triadic model of the neurobiology of motivated behavior in adolescence. *Psychological medicine*, *36*(03), 299-312.

Eshel, N., Nelson, E. E., Blair, R. J., Pine, D. S., & Ernst, M. (2007). Neural substrates of choice selection in adults and adolescents: development of the ventrolateral prefrontal and anterior cingulate cortices. *Neuropsychologia*, *45*(6), 1270-1279.

Ewing, S. W. F., Houck, J. M., & Bryan, A. D. (2015). Neural activation during response inhibition is associated with adolescents' frequency of risky sex and substance use. *Addictive behaviors*, *44*, 80-87.

Galvan, A., Hare, T. A., Parra, C. E., Penn, J., Voss, H., Glover, G., & Casey, B. J. (2006). Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *Journal of Neuroscience*, *26*(25), 6885-6892.

Geier, C. F., Terwilliger, R., Teslovich, T., Velanova, K., & Luna, B. (2009). Immaturities in reward processing and its influence on inhibitory control in adolescence. *Cerebral Cortex*, bhp225.

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., ... & Rapoport, J. L. (1999). Brain development during childhood and adolescence: a longitudinal MRI study. *Nature neuroscience*, *2*(10), 861-863.

Goddings, A. L., Burnett Heyes, S., Bird, G., Viner, R. M., & Blakemore, S. J. (2012). The relationship between puberty and social emotion processing. *Developmental science*, *15*(6), 801-811.

Goldenberg, D., Telzer, E. H., Lieberman, M. D., Fuligni, A., & Galván, A. (2013). Neural mechanisms of impulse control in sexually risky adolescents. *Developmental cognitive neuroscience*, *6*, 23-29.

Goodyer, I. M., Tamplin, A., Herbert, J., & Altham, P. M. E. (2000). Recent life events, cortisol, dehydroepiandrosterone and the onset of major depression in high-risk adolescents. *The British Journal of Psychiatry*, *177*(6), 499-504.

Grahn, J. A., Parkinson, J. A., & Owen, A. M. (2008). The cognitive functions of the caudate nucleus. *Progress in neurobiology*, *86*(3), 141-155.

Granger, D. A., Schwartz, E. B., Booth, A., Curran, M., & Zakaria, D. (1999). Assessing dehydroepiandrosterone in saliva: a simple radioimmunoassay for use in studies of children, adolescents and adults. *Psychoneuroendocrinology*, *24*(5), 567-579.

Guassi Moreira, J. F., & Telzer, E. H. Mother still knows best: Maternal influence uniquely modulates adolescent reward sensitivity during risk taking. *Developmental Science*.

Hall, G. S. (1904). Adolescence (Vols. 1 & 2). *New York: Appleton*.

Halpern, C. T., Udry, J. R., & Suchindran, C. (1997). Testosterone predicts initiation of coitus in adolescent females. *Psychosomatic Medicine*, *59*(2), 161-171.

Hare, T. A., Tottenham, N., Galvan, A., Voss, H. U., Glover, G. H., & Casey, B. J. (2008). Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. *Biological psychiatry*, *63*(10), 927-934.

Hartos, J., Eitel, P., & Simons-Morton, B. (2002). Parenting practices and adolescent risky driving: A three-month prospective study. *Health education & behavior*, *29*(2), 194-206.

Kahn, L. E., Peake, S. J., Dishion, T. J., Stormshak, E. A., & Pfeifer, J. H. (2014). Learning to play it safe (or not): Stable and evolving neural responses during adolescent risky decision-making. *Journal of cognitive neuroscience*.

Kim-Spoon, J., Kahn, R., Deater-Deckard, K., Chiu, P., Steinberg, L., & King-Casas, B. (2016). Risky decision making in a laboratory driving task is associated with health risk

behaviors during late adolescence but not adulthood. *International journal of behavioral development*, *40*(1), 58-63.

Klapwijk, E. T., Goddings, A. L., Heyes, S. B., Bird, G., Viner, R. M., & Blakemore, S. J. (2013). Increased functional connectivity with puberty in the mentalising network involved in social emotion processing. *Hormones and behavior*, *64*(2), 314-322.

Klauser, P., Whittle, S., Simmons, J. G., Byrne, M. L., Mundy, L. K., Patton, G. C., ... & Allen, N. B. (2015). Reduced frontal white matter volume in children with early onset of adrenarche. *Psychoneuroendocrinology*, *52*, 111-118.

Li, Z., Cui, S., Zhang, Z., Zhou, R., Ge, Y., Sokabe, M., & Chen, L. (2009). DHEA-neuroprotection and-neurotoxicity after transient cerebral ischemia in rats. *Journal of Cerebral Blood Flow & Metabolism*, *29*(2), 287-296.

Lynam, D. R., Smith, G. T., Whiteside, S. P., & Cyders, M. A. (2006). The UPPS-P: Assessing five personality pathways to impulsive behavior. *West Lafayette, IN: Purdue University*.

Maninger, N., Wolkowitz, O. M., Reus, V. I., Epel, E. S., & Mellon, S. H. (2009). Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). *Frontiers in neuroendocrinology*, *30*(1), 65-91.

Martin, C. A., Kelly, T. H., Rayens, M. K., Brogli, B. R., Brenzel, A., Smith, W. J., & Omar, H. A. (2002). Sensation seeking, puberty, and nicotine, alcohol, and marijuana use in adolescence. *Journal of the American academy of child & adolescent psychiatry*, *41*(12), 1495-1502.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual review of neuroscience*, *24*(1), 167-202.

Mo, Q., Lu, S. F., & Simon, N. G. (2006). Dehydroepiandrosterone and its metabolites: differential effects on androgen receptor trafficking and transcriptional activity. *The Journal of steroid biochemistry and molecular biology*, *99*(1), 50-58.

Monk, C. S., McClure, E. B., Nelson, E. E., Zarahn, E., Bilder, R. M., Leibenluft, E., ... & Pine, D. S. (2003). Adolescent immaturity in attention-related brain engagement to emotional facial expressions. *Neuroimage*, *20*(1), 420-428.

Nguyen, T. V., McCracken, J. T., Ducharme, S., Cropp, B. F., Botteron, K. N., Evans, A. C., & Karama, S. (2013). Interactive effects of dehydroepiandrosterone and testosterone on cortical thickness during early brain development. *Journal of Neuroscience*, *33*(26), 10840-10848.

Parsons, J. T., Halkitis, P. N., Bimbi, D., & Borkowski, T. (2000). Perceptions of the benefits and costs associated with condom use and unprotected sex among late adolescent college students. *Journal of adolescence*, *23*(4), 377-391.

Peper, J. S., & Dahl, R. E. (2013). The teenage brain: Surging hormones—Brain-behavior interactions during puberty. *Current directions in psychological science*, *22*(2), 134-139.

Peper, J. S., Koolschijn, P. C. M., & Crone, E. A. (2013). Development of risk taking: contributions from adolescent testosterone and the orbito-frontal cortex. *Journal of cognitive neuroscience*, *25*(12), 2141-2150.

Peters, S., Jolles, D. J., Van Duijvenvoorde, A. C., Crone, E. A., & Peper, J. S. (2015). The link between testosterone and amygdala–orbitofrontal cortex connectivity in adolescent alcohol use. *Psychoneuroendocrinology*, *53*, 117-126.

Pettersson, K., & Gustafsson, J. Å. (2001). Role of estrogen receptor beta in estrogen action. *Annual Review of Physiology*, *63*(1), 165-192.

Quevedo, K. M., Benning, S. D., Gunnar, M. R., & Dahl, R. E. (2009). The onset of puberty: Effects on the psychophysiology of defensive and appetitive motivation. *Development and psychopathology*, *21*(01), 27-45.

Reece, M., Herbenick, D., Schick, V., Sanders, S. A., Dodge, B., & Fortenberry, J. D. (2010). Condom use rates in a national probability sample of males and females ages 14 to 94 in the United States. *The journal of sexual medicine*, *7*(s5), 266-276.

Remer, T., Boye, K. R., Hartmann, M. F., & Wudy, S. A. (2005). Urinary markers of adrenarche: reference values in healthy subjects, aged 3–18 years. *The Journal of Clinical Endocrinology & Metabolism*, *90*(4), 2015-2021.

Reyna, V. F., & Farley, F. (2006). Risk and rationality in adolescent decision making: Implications for theory, practice, and public policy. *Psychological science in the public interest*, *7*(1), 1-44.

Romer, D. (2010). Adolescent risk taking, impulsivity, and brain development: Implications for prevention. *Developmental psychobiology*, *52*(3), 263-276.

Rosner, W., Hankinson, S. E., Sluss, P. M., Vesper, H. W., & Wierman, M. E. (2013). Challenges to the measurement of estradiol: an endocrine society position statement. *The Journal of Clinical Endocrinology & Metabolism*, *98*(4), 1376-1387.

Romeo, R. D. (2003). Puberty: a period of both organizational and activational effects of steroid hormones on neurobehavioural development. *Journal of neuroendocrinology*, *15*(12), 1185-1192.

Rose, L. D. D. S. R., Rotenstein, D., Susman, E. J., Huang, B., Loucks, T. L., & Berga, S. L. (2008). Differences in endocrine parameters and psychopathology in girls with premature

adrenarche versus on-time adrenarche. *Journal of Pediatric Endocrinology & Metabolism, 21*, 439-448.

Rousseau, J.J. (1911) Emile: Or, on education. New York, New York: Dutton. (Orig. work published in 1762)

Sato, S. M., Schulz, K. M., Sisk, C. L., & Wood, R. I. (2008). Adolescents and androgens, receptors and rewards. *Hormones and behavior*, *53*(5), 647-658.

Schulz, K. M., & Sisk, C. L. (2006). Pubertal hormones, the adolescent brain, and the maturation of social behaviors: lessons from the Syrian hamster. *Molecular and cellular endocrinology*, *254*, 120-126.

Schulz, K. M., Molenda-Figueira, H. A., & Sisk, C. L. (2009). Back to the future: the organizational–activational hypothesis adapted to puberty and adolescence. *Hormones and behavior*, *55*(5), 597-604.

Shirtcliff, E. A., Dahl, R. E., & Pollak, S. D. (2009). Pubertal development: correspondence between hormonal and physical development. *Child development*, *80*(2), 327-337.

Shults, R. A., Olsen, E., Williams, A. F., & Centers for Disease Control and Prevention (CDC). (2015). Driving among high school students-United States, 2013. *MMWR Morb Mortal Wkly Rep*, *64*(12), 313-7.

Sisk, C. L., & Foster, D. L. (2004). The neural basis of puberty and adolescence. *Nature neuroscience*, *7*(10), 1040-1047.

Sisk, C. L., & Zehr, J. L. (2005). Pubertal hormones organize the adolescent brain and behavior. *Frontiers in neuroendocrinology*, *26*(3), 163-174.

Smith, A. R., Chein, J., & Steinberg, L. (2013). Impact of socio-emotional context, brain development, and pubertal maturation on adolescent risk-taking. *Hormones and Behavior*, *64*(2), 323-332.

Smith, A. R., Steinberg, L., & Chein, J. (2014). The role of the anterior insula in adolescent decision making. *Developmental neuroscience*, *36*(3-4), 196-209.

Somerville, L. H., & Casey, B. J. (2010). Developmental neurobiology of cognitive control and motivational systems. *Current opinion in neurobiology*, *20*(2), 236-241.

Somerville, L. H., Jones, R. M., & Casey, B. J. (2010). A time of change: behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. *Brain and cognition*, *72*(1), 124-133.

Somerville, L. H., Hare, T., & Casey, B. J. (2011). Frontostriatal maturation predicts cognitive control failure to appetitive cues in adolescents. *Journal of cognitive neuroscience*, *23*(9), 2123-2134.

Sowell, E. R., Thompson, P. M., Tessner, K. D., & Toga, A. W. (2001). Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: inverse relationships during postadolescent brain maturation. *Journal of Neuroscience*, *21*(22), 8819-8829.

Spear, L. P. (2000). Neurobehavioral changes in adolescence. *Current directions in psychological science*, *9*(4), 111-114.

Sripada, R. K., Marx, C. E., King, A. P., Rajaram, N., Garfinkel, S. N., Abelson, J. L., & Liberzon, I. (2013). DHEA enhances emotion regulation neurocircuits and modulates memory for emotional stimuli. *Neuropsychopharmacology*, *38*(9), 1798-1807.

Steinberg, L. (2007). Risk taking in adolescence: New perspectives from brain and behavioral science. *Current directions in psychological science*, *16*(2), 55-59.

Steinberg, L. (2008). A social neuroscience perspective on adolescent risk-taking. *Developmental review*, *28*(1), 78-106.

Steinberg, L., & Morris, A. S. (2001). Adolescent development. *Annual review of psychology*, *52*(1), 83-110.

Tanaka, S. C., Balleine, B. W., & O'Doherty, J. P. (2008). Calculating consequences: brain systems that encode the causal effects of actions. *Journal of Neuroscience*, *28*(26), 6750-6755.

Tekin, S., & Cummings, J. L. (2002). Frontal–subcortical neuronal circuits and clinical neuropsychiatry: an update. *Journal of psychosomatic research*, *53*(2), 647-654.

Telzer, E. H., Ichien, N. T., & Qu, Y. (2015). Mothers know best: redirecting adolescent reward sensitivity toward safe behavior during risk taking. *Social cognitive and affective neuroscience*, nsv026.

Tricomi, E., Balleine, B. W., & O'Doherty, J. P. (2009). A specific role for posterior dorsolateral striatum in human habit learning. *European Journal of Neuroscience*, *29*(11), 2225-2232.

Van Leijenhorst, L., Zanolie, K., Van Meel, C. S., Westenberg, P. M., Rombouts, S. A., & Crone, E. A. (2010). What motivates the adolescent? Brain regions mediating reward sensitivity across adolescence. *Cerebral cortex*, *20*(1), 61-69.

Vermeersch, H., T'sjoen, G., Kaufman, J. M., & Vincke, J. (2008a). The role of testosterone in aggressive and non-aggressive risk-taking in adolescent boys. *Hormones and behavior*, *53*(3), 463-471.

Vermeersch, H., T'sjoen, G., Kaufman, J. M., & Vincke, J. (2008b). Estradiol, testosterone, differential association and aggressive and non-aggressive risk-taking in adolescent girls. *Psychoneuroendocrinology*, *33*(7), 897-908.

Victor, E. C., Sansosti, A. A., Bowman, H. C., & Hariri, A. R. (2015). Differential patterns of amygdala and ventral striatum activation predict gender-specific changes in sexual risk behavior. *Journal of Neuroscience*, *35*(23), 8896-8900.

Wallen, K. (2001). Sex and context: hormones and primate sexual motivation. *Hormones and behavior*, *40*(2), 339-357.

Wood, R. I., Armstrong, A., Fridkin, V., Shah, V., Najafi, A., & Jakowec, M. (2013). 'Roid rage in rats? Testosterone effects on aggressive motivation, impulsivity and tyrosine hydroxylase. *Physiology & behavior*, *110*, 6-12.

Zuckerman, M. (1994). *Behavioral expressions and biosocial bases of sensation seeking*. Cambridge university press.