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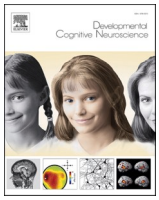

Sex and pubertal variation in reward-related behavior and neural activation in early adolescents

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ABSTRACT

This study aimed to characterize the role of sex and pubertal markers in reward motivation behavior and neural processing in early adolescence. We used baseline and two-year follow-up data from the Adolescent Brain and Cognitive Development[SM] study (15844 observations; 52% from boys; age 9–13). Pubertal development was measured with parent-reported Pubertal Development Scale, and DHEA, testosterone, and estradiol levels. Reward motivation behavior and neural processing at anticipation and feedback stages were assessed with the Monetary Incentive Delay task. Boys had higher reward motivation than girls, demonstrating greater accuracy difference between reward and neutral trials and higher task earnings. Girls had lower neural activation during reward feedback than boys in the nucleus accumbens, caudate, rostral anterior cingulate, medial orbitofrontal cortex, superior frontal gyrus and posterior cingulate. Pubertal stage and testosterone levels were positively associated with reward motivation behavior, although these associations changed when controlling for age. There were no significant associations between pubertal development and neural activation during reward anticipation and feedback. Sex differences in reward-related processing exist in early adolescence, signaling the need to understand their impact on typical and atypical functioning as it unfolds into adulthood.

1. Introduction

Risk taking and reward seeking are common behaviors in adolescence compared to childhood and adulthood. These behavioral patterns coincide with a heightened neural sensitivity to rewards that begins to increase and then peak during adolescence (Braams et al., 2015; Shulman et al., 2015; Spear, 2011). A marked increase in the onset of mental illnesses characterized by low sensitivity to reward (e.g. anhedonia, avolition) also occurs during adolescence (Costello et al., 2011). Among illnesses that present with low reward sensitivity, the onset of mood and psychotic disorders in particular tracks with pubertal maturation and presents with sex differences (Barendse et al., 2023; Conley et al., 2012; Mancuso et al., 2015). Despite the important role of sex-assigned-at-birth (hereafter sex) and puberty in mental illness onset, it remains unclear how typical patterns of reward processing by the brain during adolescence vary as a function of sex and of pubertal changes. Thus, characterizing the contribution of sex and pubertal markers to reward-related behaviors and neural processing in a large and diverse sample of early adolescents is an essential step to more fully understanding risk for mental health disorders with features of low reward sensitivity.

1.1. Rewards and the brain

The frontostriatal system in the brain plays a major role in motivated behaviors, and adolescence involves substantial changes in its structure and function. Such behaviors include approach or avoidance responses to rewarding or aversive stimuli that facilitate attaining a goal (Ernst

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and Fudge, 2009). Neural activation to rewards in humans has been commonly studied with monetary rewards, in task designs that require enacting a behavior to gain a reward (i.e. reward anticipation) and learning the outcome of the behavior (i.e. reward feedback). During both the anticipation and feedback phases of reward processing, activation has been consistently documented in the striatum, especially ventral striatum, as well as the ventromedial prefrontal cortex (vmPFC). This has been established in both adults and adolescents (Bartra et al., 2013; Silverman et al., 2015), including in the 9–10-year-olds of the ABCD study (Chaarani et al., 2021). Additionally, the receipt of rewards engages the posterior cingulate cortex (PCC) (Bartra et al., 2013; Chaarani et al., 2021). The dorsomedial prefrontal cortex (dmPFC) has been found to respond to both reward and loss anticipation, but potentially more strongly to rewards (Bartra et al., 2013; Chaarani et al., 2021).

Age-related changes have been found in these neural signatures of reward processing. Meta-analytic evidence supports the proposition that adolescents have a heightened response in striatal and medial frontal regions when anticipating and receiving rewards as compared to adults (Silverman et al., 2015). Furthermore, a longitudinal study suggests ventral striatum response to reward feedback peaks in around age 16 (Braams et al., 2015). These age-related changes in striatal function, along with gradual development of cognitive control abilities, are posited to explain adolescent risk taking in theoretical models like the dual systems model and maturation imbalance model (B. J. Casey et al., 2008; Steinberg, 2010). These models often hypothesize the development of the striatal reward component to be tied to pubertal development (Shulman et al., 2016). Open questions remain, however, about how sex and pubertal markers are related to behavioral and neural reward response patterns, as we explain below.

1.2. Sex differences in reward-related behavior and neural activation

A large meta-analysis reported no sex differences in self-reported reward sensitivity, but higher self-reported punishment sensitivity in girls than boys (Cross et al., 2011). Measures of reward sensitivity covered attraction to rewards and motivation to approach/obtain rewards, and punishment sensitivity measures covered sensitivity to (potential) negative consequences and to lack of reward (note: in reward tasks, punishment sensitivity is mainly relevant to avoid losing money on loss trials). Sex differences in reward sensitivity might depend on the type of reward: girls scored higher when questions focused on social and attachment-related rewards, whereas boys reported higher reward sensitivity when questions related to status and money. Men and boys also reported more sensation seeking and showed more risk taking on lab tasks (Cross et al., 2011), which is confirmed by research specific to adolescence (Shulman et al., 2015).

Sex differences have also been reported in the development of brain structure and function of regions involved in reward processing. The volume of striatal regions decreases with age, especially in girls (Herting et al., 2018; Wierenga et al., 2018). Animal research suggests pruning in the medial PFC in adolescence in females only (Willing and Juraska, 2015), although human MRI studies have found similar cortical thinning in both sexes (Mills et al., 2014). Morgan et al. (2013) demonstrated higher striatal (caudate) response to reward feedback and medial PFC activation to reward anticipation in girls compared to boys, whereas Alarcón et al. (2017) reported higher ventral striatum activation in boys, and two other studies (Braams et al., 2015; Op de Macks et al., 2011) found no sex difference in neural response to reward feedback (anticipation was not examined in either study). Thus, it is unclear if sex differences exist in the early adolescent period in the function of striatal and frontal regions. Also, little research has tested the effects of sex on striatal and frontal activation to both reward feedback and anticipation in a sample size large enough to ensure power to detect small effects. This is important since mental illnesses that present with low reward sensitivity become more prevalent with pubertal maturation (which is a sex-dependent process) and present with marked sex differences.

1.3. Pubertal differences in reward-related behavior and neural activation

Pubertal development is theorized to be a contributor to the adolescent-specific increases in behavioral and neural reward sensitivity (Poon et al., 2019; Walker et al., 2017). Pubertal changes can be assessed using different markers, including self-report or other-report of pubertal stage and levels of sex hormones. Androgen and estrogen sex hormones, such as testosterone and estradiol, have been of interest in neuroimaging given that they are primarily responsible for secondary sexual characteristics maturation and act via steroid receptors throughout the brain (Almey et al., 2015; Sarkey et al., 2008).

On the behavioral level, a large study (N=810) reported that boys and girls at more advanced pubertal stages show higher reward sensitivity (note: only tested separately from age; Harden et al., 2018). This aligns with other findings, such as a positive association between pubertal stage and reward approach behavior in humans (Icenogle et al., 2017) and between pubertal development and reward sensitivity for food in rats (Friemel et al., 2010). A comprehensive meta-analysis found a small, positive association between testosterone levels and risk taking, as well as sensation seeking and novelty seeking in boys and girls and adults (Kurath and Mata, 2018). Also, greater testosterone levels in early adolescence have been related to heightened sensitivity to immediate rewards (Laube et al., 2017). The impact of estradiol on behavioral reward sensitivity has generally not been confirmed (Harden et al., 2018; Kurath and Mata, 2018; Ladouceur et al., 2019), and animal research suggests it might be specifically relevant for sexual and social rewards (Yoest et al., 2014).

At the neural level, several studies (mostly with small sample sizes) have reported positive associations between adolescents' testosterone levels and striatal activation during reward feedback (Alarcón et al., 2017; Braams et al., 2015; Op de Macks et al., 2011), although negative and null findings have also been reported (Forbes et al., 2010; Ladouceur et al., 2019; Poon et al., 2019). In line with this, animal work has demonstrated that testosterone enhances midbrain dopamine synthesis and receptor expression and normalizes medial PFC dopamine when administered following gonadectomy (Sinclair et al., 2014). Also, young adult women who were administered testosterone demonstrated increases in ventral striatum activity during anticipation of rewards (Hermans et al., 2010).

Work in rodents shows that estradiol strengthens dopamine release in the striatum and enhances dopamine synthesis in female animals (Diekhof, 2018). Estradiol also strengthens dopamine release in the PFC, enhances PFC activation after stimulation, and reduces inhibitory neuron expression in the medial PFC (Cholanian et al., 2014; Sárvári et al., 2014). In humans, a small experimental study showed that combined estradiol and progesterone administration during menopause strengthens putamen and caudate activation during reward anticipation and vmPFC activation during reward feedback (Thomas et al., 2014). Correlational work additionally indicates that neural responses during reward anticipation fluctuate across the menstrual cycle in adult women (Bayer et al., 2013; Dreher et al., 2007; Ossewaarde et al., 2011). However, research on adolescents relating estradiol levels to neural activation during reward processing is limited, underpowered, and has led to conflicting results (Ladouceur et al., 2019; Op de Macks et al., 2011, 2016).

Dehydroepiandrosterone (DHEA), a neurosteroid and adrenal hormone, has been associated with several aspects of structural brain development (Byrne et al., 2017); but studies on its role in reward processing are lacking. Findings on the association between secondary sex characteristics (e.g. Tanner Stage) and neural response to rewards are mostly null (Braams et al., 2015; Cao et al., 2019; Ladouceur et al., 2019; Morgan et al., 2013; Op de Macks et al., 2016; van Duijvenvoorde et al., 2014). Reports of associations between activation in PCC, ventromedial and dorsomedial PFC, and pubertal development are

scarce and inconsistent (Vijayakumar et al., 2018).

There is also a paucity of research on the association between pubertal stage or pubertal hormone levels and reward *anticipation* in particular, as the majority of studies have focused on the feedback stage. Since reward feedback and anticipation elicit partially distinct neural activation patterns, examination of both reward subprocesses in the same dataset would be valuable.

1.4. Sex and pubertal development interactions

Prior studies on pubertal stage or hormone levels in relation to adolescents' reward processing have almost always tested if there are effects specific to sex, but these studies have not explained heterogeneity in findings. Only two studies in adolescent samples found sex differences in the association between hormone levels or pubertal stage and neural response to rewards: one negative association with testosterone specific to boys (Forbes et al., 2010) and one negative association with estradiol specific to girls (Ladouceur et al., 2019). The majority of studies in adolescents found no sex differences (Alarcón et al., 2017; Braams et al., 2015; Morgan et al., 2013; Op de Macks et al., 2011; Poon et al., 2019; van Duijvenvoorde et al., 2014). However, the gaps in the research mentioned in the section about pubertal differences (e.g. limited research on reward anticipation and on DHEA levels in relation to neural activation to rewards) also hold for interactions with sex, warranting more comprehensive research on the interaction between pubertal development and sex in relation to reward-related neural activation.

1.5. Current study

This study tested hypotheses about the association of sex and puberty markers with behavioral as well as striatal and frontal neural response during reward anticipation and receipt in early adolescence. We sought to provide much-needed context to enhance understanding of the risk for mental health disorders with presenting features of low reward sensitivity. Importantly, to aid in resolving inconsistencies across studies using relatively small samples of adolescents and of children at different stages of adolescence, we tested our research questions in a well-powered, large sample of adolescents (i.e. the ABCD study) studied at age 9–10 years and again at age 11–13 years. This encompasses the years of early adolescence and provides sufficient variability in pubertal markers, without making the age range so wide that age and indices of pubertal development become too correlated. To address the questions, we focused on reward motivation behaviors and six regions of interest (ROIs) of the reward network, given past work documenting their consistent activation to anticipating and receiving rewards (Bartra et al., 2013; Chaarani et al., 2021; Silverman et al., 2015), including the baseline ABCD study data (Chaarani et al., 2021). These ROIs consisted of the nucleus accumbens (NAcc), caudate, ventromedial PFC, medial OFC, dorsomedial PFC, and PCC. We also comprehensively examined both the anticipatory and feedback phases of reward processing, given that most previous studies examining sex or puberty markers as predictors of reward function focused on feedback and not the anticipation phase.

1.6. Research questions and hypotheses

Using baseline and two-year follow-up ABCD study data, we addressed the following research questions, with hypotheses italicized under each question. These hypotheses and our methods were preregistered at https://osf.io/astc8/ on 28th of January 2023.

1.6.1. Sex differences in reward-related behavior and neural activation

11. Are there sex differences in reward motivation behavior?

Boys were expected to have higher reward sensitivity for money (Cross et al., 2011), which might be reflected in more on-time responses to reward trials. However, girls were expected to have higher punishment sensitivity than boys (Cross et al., 2011), which is useful in the task to avoid losing money by responding on time to loss trials. These patterns together might equalize earnings on the task between sexes.

12. Are there sex differences in neural activation in regions of the reward network during anticipation of rewards (win cues vs neutral cue)?

Previous research on this topic is scarce (Morgan et al., 2013), thus limiting our ability to form a directional hypothesis.

13. Are there sex differences in neural activation in regions of the reward network during reward feedback (win feedback vs no-win feedback on win cue trials)?

Previous research on this topic is a limited set of small, cross-sectional studies that have conflicting results (Alarcón et al., 2017; Braams et al., 2015; Morgan et al., 2013; Op de Macks et al., 2011), therefore no hypothesis can be formed.

1.6.2. Puberty measures and reward motivation behavior

21. How is pubertal stage related to reward motivation behavior, and is this moderated by sex?

We expected a positive association between pubertal stage and reward motivation behavior, in terms of more on-time responses to reward trials and higher earnings, in both sexes. [1] *This is based on previous human and animal research (Friemel et al., 2010; Harden et al., 2018; Icenogle et al., 2017).*

22. How are testosterone levels related to reward motivation behavior, and is this moderated by sex?

We expected a positive association between testosterone levels and reward motivation behavior in both sexes[1] *(Kurath and Mata, 2018; Laube et al., 2017).*

23. How are DHEA levels related to reward motivation behavior, and is this moderated by sex?

Given that there is no previous research to guide hypotheses for this question, we treated this as an exploratory analysis.

24. How are estradiol levels related to reward motivation behavior in girls?

We did not expect a significant association between estradiol levels and reward motivation behavior (Harden et al., 2018; Kurath and Mata, 2018; Ladouceur et al., 2019), but we examined this question to be able to provide a comprehensive picture of each aspect of pubertal development with each element of reward processing. Estradiol was not measured in boys, thus no sex difference is tested here.

1.6.3. Puberty measures and neural activation during reward anticipation

31. How is pubertal stage related to neural activation in regions of the reward network during anticipation of rewards (win cue vs neutral cue), and is this moderated by sex?

Prior research that tested this question has reported null results (Braams

[1] When we state 'in both sexes', this means no moderation by sex is expected. This footnote was added after preregistration.

et al., 2015; Ladouceur et al., 2019; Morgan et al., 2013; Op de Macks et al., 2016; van Duijvenvoorde et al., 2014), but most of these studies lacked the power to detect small effects. Therefore, we examined this question here with a focus on effect size in the result and interpretation, expecting a small positive effect based on these previous studies.

32. How is testosterone related to neural activation in regions of the reward network during anticipation of rewards (win cue vs neutral cue), and is this moderated by sex?

Based on animal research (summarized in Diekhof, 2018) and experimental adult research (Hermans et al., 2010), we hypothesized there will be a positive association between testosterone levels and striatum activation during reward anticipation in both sexes.

33. How is DHEA related to neural activation in regions of the reward network during anticipation of rewards (win cue vs neutral cue), and is this moderated by sex?

Given that there is no previous research to guide hypotheses for this question, we treated this as an exploratory analysis.

34. How is estradiol related to neural activation in regions of the reward network during anticipation of rewards (win cue vs neutral cue) in girls?

Based on animal research (summarized in Diekhof, 2018) and experimental adult research (Thomas et al., 2014), we expected a positive association between estradiol levels and striatum activation during reward anticipation.

1.6.4. Puberty measures and neural activation during reward feedback

41. How is pubertal stage related to neural activation in regions of the reward network during reward feedback (win feedback vs no-win feedback), and is this moderated by sex?

The prior research that has examined this question reported null results (Braams et al., 2015; Ladouceur et al., 2019; Morgan et al., 2013; Op de Macks et al., 2016; van Duijvenvoorde et al., 2014), but often did not have the power to detect small effects. Therefore, we examined this question here with a focus on effect size in the result and interpretation, expecting a small effect size based on these previous studies.

42. How is testosterone related to neural activation in regions of the reward network during reward feedback (win feedback vs no-win feedback), and is this moderated by sex?

Based on correlational studies with adolescents (Alarcón et al., 2017; Braams et al., 2015; Op de Macks et al., 2011), we hypothesized that higher testosterone will be associated with greater striatal activation during reward feedback in both sexes.

43. How is DHEA related to neural activation in regions of the reward network during reward feedback (win feedback vs no-win feedback), and is this moderated by sex?

Given that there is no previous research to guide hypotheses on this question, we treated this as an exploratory analysis.

44. How is estradiol related to neural activation in regions of the reward network during reward feedback (win feedback vs no-win feedback) in girls?

Based on a combination of previous findings from animal research (Cholanian et al., 2014; Sárvári et al., 2014), human experimental research (Thomas et al., 2014), and adolescent correlational research (Op de Macks et al., 2011), we hypothesized that estradiol is positively associated with ventromedial PFC activation during reward feedback.

2. Methods

2.1. Participants

Participants were enrolled at baseline (age 9–10) and 2-year (age 11–13) follow up in the Adolescent Behavior Cognitive Development (ABCD) Study®, release 4.0. The ABCD study recruited a baseline sample of 11,878 children in the United States using school-based and community-based recruitment (Volkow et al., 2018). Children had to be 9 or 10 years of age at baseline enrollment and fluent in English. Exclusion criteria were: MRI contraindication (e.g. irremovable ferromagnetic implants, claustrophobia, pregnancy), major neurological disorder, gestational age < 28 weeks or birthweight < 1200 g, history of traumatic brain injury, or current diagnosis of schizophrenia, autism spectrum disorder, intellectual disability, or alcohol/substance use disorder. Our pre-specified exclusion criteria specific to this study were: intersex or transgender identity reported by child and/or parent at any of the included time points. This is because we were interested in sex and its interactions with pubertal variables, but the intersex and transgender groups were too small to examine separately. For neuroimaging analyses, we excluded any scans failing ABCD recommended imaging quality assurance criteria (see further detail below). For behavioral analyses, participants were only included if they responded to at least 20 trials per run to exclude participants who did not understand the task or were not paying attention. Specifically for hormone analyses, we followed a stepwise protocol to quality check saliva samples and their hormone levels (see *Hormones*), which led to additional exclusions for those analyses.

Data were collected at 21 research sites distributed across the US (see https://abcdstudy.org/). Centralized institutional review board (IRB) approval was obtained from the University of California, San Diego. In addition, study sites obtained approval from their local IRBs. Caregivers provided written informed consent and the child provided written assent. Participants received monetary compensation for their study participation.

2.2. Measures

2.2.1. The monetary incentive delay task

The Monetary Incentive Delay (MID) task (Knutson et al., 2000) measures both anticipation and receipt of reward and losses. There are 5 trial types: small win ($0.20), large win ($5.00), small loss (-$0.20), large loss (-$5.00), and neutral (no-win-or-loss). Each trial has a cue indicating the trial type, a target the participant must respond to as fast as possible with a button press, and feedback indicating the outcome of the trial (win, lose, neutral). Targets are presented for 150–500 ms. Correct trials are when the participant responds before the target disappears, and lead to a win on win trials, avoidance of loss on loss trials, and have no consequence on neutral trials. To maintain 60% accuracy across participants, the response window was calibrated to each participant and adjusted over the task. Participants completed 100 trials (20 of each trial type) and could win up to $60.

2.2.2. Reward motivation behavior

Total earnings on the task were used as a behavioral outcome. Total earnings are dependent on how fast participants respond to reward and loss trials, and by how well they take into account the size of the reward. We should note that earnings are thus also influenced by punishment sensitivity as participants need to try to avoid losses on loss trials. Additionally, we calculated the within-person difference in proportion of on-time responses between large win trials and neutral trials, and small win trials and neutral trials. This served as another measure of

motivation for reward, where a greater (positive) accuracy difference indicates the child is more likely to respond in time when anticipating a win.

2.2.3. Imaging data

Multiband echo-planar imaging (EPI) fMRI volumes were acquired during the MID task. Acquisition parameters were harmonized to allow collection on Philips, Siemens and GE 3 T scanners. Main EPI parameters were: 90 × 90 matrix, 60 slices, 216 × 216 field of view, TR = 800 ms, TE = 30 ms, flip angle = 52°, multiband factor = 6 and voxel size = 2.4 × 2.4 × 2.4 mm. For more details on the imaging acquisition protocol, including the anatomical scan, see Casey et al. (B. Casey et al., 2018).

2.2.4. Sex

Sex was based on baseline parent-reported sex assigned at birth.

2.2.5. Pubertal development scale

Physical markers of pubertal maturation were assessed at baseline and at 2-year follow-up via self- and parent-report of the Pubertal Development Scale (PDS)(Petersen et al., 1988), comprising 5 items assessing pubertal maturation on a 4-point scale (not yet begun, barely started, definitely underway, seems complete). Height growth spurt, pubic hair growth, and skin changes are assessed in both sexes; menarche and breast development in girls; and facial hair growth and voice changes in boys. Scores were converted to Tanner Stages (ranging from 1 to 5) using syntax described in Shirtcliff et al. (2009) and treated as a continuous variable. Because parent-report PDS had 93% complete data at baseline versus 50% for self-report, we only use parent-report PDS. Parents who reported on the child were mostly the biological mother (85% of observations), followed by biological fathers (10%), with the remaining 5% including adoptive parents and guardians.

2.2.6. Hormones

Dehydroepiandrosterone (DHEA), testosterone, and estradiol (available for girls only) were measured from a single saliva sample collected in the lab with the passive drool method and assayed in duplicate by Salimetrics (see Herting et al. 2021 for ABCD biospecimen methods) at baseline and again at 2-year follow-up.

We followed the decision tree in Herting et al. (2021) for quality checking of the hormone data and calculating final hormone levels. In addition, hormone levels were corrected for confounds by regressing the hormone level on all confounds and extracting the residuals for use in outcome modeling. We used multivariate fractional polynomial regression (Royston and Altman, 1994) in R (v3.6.3)'s mfp package (v1.5.2) (Heinze et al., 2022) for this purpose. Variable selection and identification of the best fractional polynomial transformation for each variable were evaluated at significance levels of 0.05 and done for both baseline and 2-year follow up data. We included the following confounds: time between waking and start of collection, collection duration (a proxy for flow rate), caffeine use (yes/no) and exercise (yes/no) in the 12 hours prior to collection, and glucocorticoid medication and oral contraceptives use in the past 2 weeks. Nonsensical values on the time of waking, start of collection and collection duration were set to missing (i.e. negative collection duration or collection longer than 1 hour, starting in-lab collection less than 30 min after waking, waking before 5 am or after 2 pm, starting sample before 7 am or after 9 pm). Medication was categorized using the Medical Subject Headings pharmacological actions (MeSHPA) codes and we focused on glucocorticoids and contraceptives because of their known relevance to the assessed hormones (Salek et al., 2002). Estradiol levels were additionally corrected for cycle regularity and menstrual cycle phase. Menstrual cycle phase was calculated from the starting day of the last period as reported by the participant, methods adapted from Schmalenberger et al. (2021). Binary variables (1=yes, 0=no) were then created for each menstrual cycle phase and for irregular cycling (either self-reported or if the last period was over 36 days ago), which were added to the models for estradiol described above. Hormone values were log-transformed prior to analysis. Code for cleaning and correcting hormone levels is available at https://github.com/marjolein15/Cleaning-ABCD-hormone-data/ (DOI: 0.5281/zenodo.10693410).

2.2.7. Covariates

We first set up all models without any covariates, based on recommendations in Dick et al. (2021). Then, we added age in months as a continuous, time-varying covariate, since this is an important variable for the interpretation of pubertal effects (Vijayakumar et al., 2018). Finally, as a secondary analysis we incorporated additional demographic variables: race/ethnicity, parental education level, marital status, and household income. Race/ethnicity and indicators of socioeconomic status are related to pubertal development and hormone levels (Herting et al., 2021). For race/ethnicity, we used ABCD's derived 'race_ethnicity' variable, which summarizes race and ethnicity into 5 categories: White, Black, Hispanic, Asian, and Other. Parental education level is divided into 5 categories (less than high school (HS) diploma, HS Diploma/GED, Some college or associate degree, Bachelor, Post-graduate degree) and highest level across parents/caregivers was taken if data for both were available. Categories for marital status included married, widowed, divorced, separated, never married or living with a partner. Household income was categorized as <50 K, between 50 K and 100 K, >100 K, and Don't Know/Refused. Of note, we explored log-income-to-needs-ratio (i.e. household income divided by the poverty threshold for a family of that size) as an alternative to income, but the two were highly correlated (r=0.85), so we used income itself. All demographic covariates were modeled as categorical variables and time-varying where applicable.

2.3. Neuroimaging data processing

We used the processed and ROI-extracted neuroimaging data available on the National Institutes of Health Data Archive. These data have been run through the abcd-hcp-pipeline (Hagler Jr et al., 2019), created by the ABCD Data Analysis and Informatics Center. The preprocessing pipeline includes correction of B0 distortions, gradient nonlinearity distortions, and head motion, and alignment to standard space using standard approaches (Glasser et al., 2013; Hagler Jr et al., 2019). First-level modeling used the general linear model and included nuisance regressors to model baseline, quadratic trend, and motion, as well as predictors for anticipation of large, small, and no rewards and feedback for large, small, and no rewards for wins and losses (events modeled as instantaneous). Time points with framewise displacement > 0.9 mm were censored.

Contrasts we focused on were: large or small reward anticipation (large or small win cues vs. no money cue), and reward feedback (win feedback vs no-win feedback). GLM coefficients and t-statistics were sampled onto the cortical surface and projected 1 mm into cortical gray matter along the surface normal vector. Beta coefficients from the following ROIs were used: NAcc and caudate based on FreeSurfer's automated segmentation (Fischl et al., 2002), as well as rostral anterior cingulate cortex (rACC; to capture the vmPFC), medial orbitofrontal cortex (mOFC), superior frontal gyrus (SFG; to capture the dmPFC), and posterior cingulate cortex (PCC) based on the Desikan atlas-based classification (Desikan, et al., 2006). Activation in the left and right hemisphere were averaged for each ROI before entering them in statistical models.

Quality control information was available alongside the processed data. We used ABCD's recommended inclusion criteria for the MID task fMRI, which includes: no serious MR findings (i.e. possible neurological problems), MID task fMRI series and T1-weighted series passed rawQC (this includes e.g. inspection for ghosting and dental artifacts and automated calculation of framewise displacement and temporal SNR), acceptable performance on the task (all trial types must yield at least 4 events for both positive and negative feedback), MID degrees of freedom

> 200, fMRI B0 Unwarp available, FreeSurferQC not failed (review of cortical surface reconstruction for motion, intensity inhomogeneity, white matter underestimation, pial overestimation, and magnetic susceptibility artifact), fMRI Manual Post-Processing QC not failed (e.g. B0 warping and registration of fMRI to T1w, done on only about 10% of subjects), fMRI registration to T1w automated score less than 19, fMRI Maximum dorsal cutoff score less than 65, and fMRI Maximum ventral cutoff score less than 60.

2.4. Statistical analyses

Linear mixed effect modeling was the main analytic approach and was conducted using R Statistical Computing Software v4.2.2. Longitudinal data from baseline and 2-year follow up were included in order to capture ages 9–13 marking the early adolescent period and thus more variance in pubertal development. A linear mixed modeling approach across time points provides stronger evidence of developmental effects than analysis within time points (e.g. Gadassi Polack et al., 2023). The ABCD sample also contains a substantial number of siblings and twins and data were collected across 21 sites, on 28 MRI scanners. Therefore, random intercepts by participant, family ID and MRI scanner serial number were included in all models to account for within participant, family and scanner correlation. MRI scanner serial number was chosen rather than site because a few sites used multiple scanners and scanner effects are a known source of variance in neural activation data (Marek et al., 2019).

We anticipated missingness in the data due to COVID-19 restrictions on in-person data collection. However, we did not expect this missingness to be related to our outcomes, i.e. we expected missingness to be completely at random. Considering the size of the sample, we did not expect the missingness to lead to statistical power problems. Therefore, we did not impute missing data nor conduct sensitivity analyses. We used all available data including participants with data at only one time point as this missingness can be accommodated in our linear mixed effects modeling strategy.

For all models, we examined residuals to assess model assumptions. In Table 1, we define the statistical model(s) fitted to address each research question for our primary analyses. If interactions were not statistically significant, they were removed and the model refitted without the interaction. We repeated these models with age and then other demographic variables as covariates (see "Covariates"). Demographic variables other than age did not influence the significance of the main predictors, thus, for brevity, we only report models without those demographic variables. For research questions considering different ROIs, each ROI was examined separately. We applied a Bonferroni correction to determine statistical significance across the six ROIs evaluated within each research question, leading to a significance threshold of 0.0083 (with two-sided testing) for these questions. As a measure of effect size, we calculated marginal R-squared values of each model.

3. Results

3.1. Descriptive information

The final sample included baseline data for 9291 participants and 2-year follow-up for 6553 participants, including 5397 participants providing data at both time points. See Table 2 for detailed descriptive information by time point and Supplemental Fig. 1 for correlations between relevant variables. Effects of MID task condition showed the expected pattern: on average, participants responded on-time to 47.2% of neutral trials, 56.3% of small reward trials, and 62.5% of large reward trials.

Table 1
Statistical models by research question.

Research question	Models
1.1	• accuracy difference = reward_size + sex + sex*reward_size + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID) • total earnings = sex + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID)
1.2	Activation in ROI[reward anticipation versus neutral cue] = reward_size + sex + sex*reward_size + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID)
1.3	Activation in ROI[win feedback vs no-win feedback] = sex + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID)
2.1	• accuracy difference = reward size + pub_stage + pub_stage*reward_size + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID) • accuracy difference = reward size + pub_stage + sex + pub_stage*reward_size + pub_stage*sex + sex*reward_size + pub_stage*sex*reward_size + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID) • total earnings = pub_stage + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID) • total earnings = pub_stage + sex + pub_stage*sex + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID)
2.2	• accuracy difference = reward size + testosterone + testosterone*reward_size + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID) • accuracy difference = reward size + testosterone + sex + testosterone*reward_size + testosterone*sex + sex*reward_size + testosterone*sex*reward_size + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID) • total earnings = testosterone + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID) • total earnings = testosterone + sex + testosterone*sex + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID)
2.3	• accuracy difference = reward size + DHEA + DHEA*reward_size + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID) • accuracy difference = reward size + DHEA + sex + DHEA*reward_size + DHEA*sex + sex*reward_size + DHEA*sex*reward_size + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID) • total earnings = DHEA + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID) • total earnings = DHEA + sex + DHEA*sex + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID)
2.4	• accuracy difference = reward size + estradiol + estradiol*reward_size + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID) • total earnings = estradiol + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID)
3.1	• Activation in ROI[reward anticipation versus neutral cue] = reward size + pub_stage + pub_stage*reward_size + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID) • Activation in ROI[reward anticipation versus neutral cue] = reward size + pub_stage + sex + pub_stage*reward_size + pub_stage*sex + sex*reward_size + pub_stage*sex*reward_size + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID)
3.2	• Activation in ROI[reward anticipation versus neutral cue] = reward size + testosterone + testosterone*reward_size + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID) • Activation in ROI[reward anticipation versus neutral cue] = reward size + testosterone + sex + testosterone*reward_size + testosterone*sex + sex*reward_size + testosterone*sex*reward_size + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID)
3.3	• Activation in ROI[reward anticipation versus neutral cue] = reward size + DHEA + DHEA*reward_size + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID) • Activation in ROI[reward anticipation versus neutral cue] = reward size + DHEA + sex + DHEA*reward_size + DHEA*sex + sex*reward_size + DHEA*sex*reward_size + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID)
3.4	• Activation in ROI[reward anticipation versus neutral cue] = reward size + estradiol + estradiol*reward_size + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID)

(continued on next page)

Table 1 (*continued*)

Research question	Models
4.1	• Activation in ROI[win feedback vs no-win feedback] = pub_stage + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID) • Activation in ROI[win feedback vs no-win feedback] = pub_stage + sex + pub_stage*sex + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID)
4.2	• Activation in ROI[win feedback vs no-win feedback] = testosterone + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID) • Activation in ROI[win feedback vs no-win feedback] = testosterone + sex + testosterone*sex + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID)
4.3	• Activation in ROI[win feedback vs no-win feedback] = DHEA + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID) • Activation in ROI[win feedback vs no-win feedback] = DHEA + sex + DHEA*sex + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID)
4.4	Activation in ROI[win feedback vs no-win feedback] = estradiol + (1|scanner) + (1|scanner:family) + (1|scanner:family:ID)

3.2. RQ1: Sex differences in reward motivation behavior and neural activation during reward anticipation and reward feedback

Girls showed a smaller accuracy difference between reward trials and neutral trials than boys, which was consistent across the small and large reward conditions (i.e. there was a main effect of Sex at $p<0.001$ but no interaction between Sex and Reward Size; see Fig. 2 and Supplementary Table 1). A main effect of sex on task earnings was found. Girls earned, on average, $1.44 less on the task than boys ($p<0.001$, see Fig. 1 and Supplementary Table 2). These sex differences remained significant when correcting for age.

A main effect of reward size was found for neural activation during anticipation of rewards; specifically, activation was higher in the NAcc, caudate, rACC/vmPFC, SFG/dmPFC and PCC, but not in the mOFC, when a large reward could be won compared to a small reward (see Supplementary Tables 3–8). A sex difference in activation was found in rACC/vmPFC only ($p<0.001$, see Supplementary Tables 3–8). Girls showed higher activation when anticipating rewards, regardless of size, than boys in this region.

A sex difference in neural activation was found during reward feedback (i.e. win vs. no-win feedback on reward trials), indicating lower activation for girls than boys in the NAcc, caudate, rACC/vmPFC, mOFC, SFG/dmPFC and PCC (p's between <0.001 and.002, see Fig. 3 and Supplementary Tables 9–14). Although the sex differences were significant, the models explained only a small proportion of the variance (marginal R2 between 0.001 and 0.006). These differences remained significant after controlling for age.

3.3. RQ2: Relation between pubertal development and reward motivation behavior

A main effect of pubertal stage was found for task earnings. Participants at a more advanced pubertal stage earned more on the task, with an increase of $0.56 for every pubertal stage after accounting for sex ($p<0.001$, see Fig. 1 and Supplementary Table 15). However, pubertal stage was not related to the accuracy difference between neutral and reward trials ($p=.08$, see Fig. 2 and Supplementary Table 16). For both outcomes, there was no interaction with sex. After accounting for age, there were significant *negative* associations between pubertal stage and earnings ($p<0.001$, Supplementary Table 17) as well as between pubertal stage and the accuracy difference ($p<0.001$, Supplementary Table 18). That is, more advanced pubertal stage *for one's age* was related to lower earnings and a smaller difference in accuracy between neutral and reward trials.

Higher testosterone levels were associated with more earnings and a

Table 2
Demographic information and descriptives of behavior on the Monetary Incentive Delay (MID) task by time point.

	Baseline (N=9291)	Two-year follow-up (N=6553)	Total (N=15844)
Sex (n; %)			
Boys	4755 (51%)	3528 (54%)	8283 (52%)
Girls	4536 (49%)	3025 (46%)	7561 (48%)
Age (years)*			
Mean (SD)	9.93 (0.63)	11.95 (0.65)	10.76 (1.18)
Median (Q1, Q3)	9.92 (9.33, 10.5)	11.92 (11.42, 12.5)	10.75 (9.75, 11.67)
Range	8.92–11.08	10.58–13.75	8.92–13.75
Annual Household Income (USD; combined across parents/caregivers; n; %)			
[>=100 K]	3752 (43.9%)	2948 (48.7%)	6700 (45.9%)
[>=50 K & <100 K]	2424 (28.3%)	1700 (28.1%)	4124 (28.2%)
[<50 K]	2375 (27.8%)	1411 (23.3%)	3786 (25.9%)
N-Missing	740	494	1234
Highest Education of parents (n; %)			
Post Graduate Degree	3315 (35.7%)	2207 (33.8%)	5522 (34.9%)
Bachelor	2424 (26.1%)	1437 (22.0%)	3861 (24.4%)
Some College	2333 (25.1%)	2082 (31.8%)	4415 (27.9%)
HS Diploma/GED	793 (8.5%)	539 (8.2%)	1332 (8.4%)
< HS Diploma	416 (4.5%)	273 (4.2%)	689 (4.4%)
N-Missing	10	15	25
Race/Ethnicity at Baseline (n; %)			
Asian	197 (2.1%)	132 (2.0%)	329 (2.1%)
Black	1213 (13.1%)	715 (10.9%)	1928 (12.2%)
White	5003 (53.8%)	3766 (57.5%)	8769 (55.3%)
Hispanic	1906 (20.5%)	1280 (19.5%)	3186 (20.1%)
Other	972 (10.5%)	660 (10.1%)	1632 (10.3%)
Marital status of parents			
Divorced	826 (9.0%)	629 (9.7%)	1455 (9.2%)
Living with partner	509 (5.5%)	422 (6.5%)	931 (5.9%)
Married	6439 (69.8%)	4544 (69.8%)	10983 (69.8%)
Never married	1022 (11.1%)	616 (9.5%)	1638 (10.4%)
Separated	355 (3.8%)	232 (3.6%)	587 (3.7%)
Widowed	75 (0.8%)	65 (1.0%)	140 (0.9%)
N-Missing	65	45	110
Pubertal Stage (Tanner stages)			
Mean (SD)	1.84 (0.80)	2.68 (1.18)	2.19 (1.06)
Median (Q1, Q3)	1.50 (1.00, 2.00)	2.50 (1.50, 3.50)	2.00 (1.50, 3.00)
Range	1–5	1–5	1–5
N-Missing	666	464	1130
Testosterone Levels (uncorrected, pg/ml)**			
Mean (SD)	34.01 (19.47)	53.63 (28.80)	39.42 (24.08)
Median (Q1, Q3)	30.77 (21.50, 42.50)	48.33 (35.20, 66.00)	34.84 (23.98, 49.43)
Range	0.66–548.06	1.20–480.29	0.66–548.06
N-Missing	884	3357	4241
DHEA Levels (uncorrected, pg/ml)**			
Mean (SD)	63.04 (48.97)	82.02 (65.95)	68.28 (54.85)
Median (Q1, Q3)	51.28 (29.20, 83.00)	67.57 (38.30, 108.00)	55.27 (31.16, 90.26)
Range	0.00–648.62	0.00–940.74	0.00–940.74
N-Missing	926	3362	4288
Estradiol Levels (uncorrected, pg/ml)**			
Mean (SD)	1.02 (0.52)	1.05 (0.62)	1.03 (0.55)
Median (Q1, Q3)	0.98 (0.67, 1.33)	1.00 (0.64, 1.37)	0.99 (0.66, 1.34)
Range	0.00–6.42	0.00–5.29	0.00–6.42
N-Missing (incl all boys)	5198	5060	10258
Earnings on the MID task ($)			
Mean (SD)	20.76 (14.2)	23.93 (12.81)	22.07 (13.37)
Median (Q1, Q3)	20.8 (11.20, 30.20)	25.4 (15.8, 30.8)	21.20 (15.40, 30.40)
Range	-103.8–60	-103.6–59.6	-103.80–60.00
Accuracy neutral trials of the MID task (proportion on-time responses)			
Mean (SD)	0.47 (0.14)	0.47 (0.14)	0.47 (0.14)
Median (Q1, Q3)	0.50 (0.40, 0.55)	0.50 (0.40, 0.55)	0.50 (0.40, 0.55)
Range	0–0.9	0–0.95	0–0.95
Accuracy small reward trials of the MID task (proportion on-time responses)			
Mean (SD)	0.56 (0.10)	0.57 (0.10)	0.56 (0.10)

(*continued on next page*)

Table 2 (*continued*)

	Baseline (N=9291)	Two-year follow-up (N=6553)	Total (N=15844)
Median (Q1, Q3)	0.55 (0.50, 0.65)	0.55 (0.50, 0.65)	0.55 (0.50, 0.65)
Range	0–0.95	0–0.9	0–0.95
Accuracy large reward trials of the MID task (proportion on-time responses)			
Mean (SD)	0.62 (0.10)	0.63 (0.10)	0.62 (0.10)
Median (Q1, Q3)	0.60 (0.55, 0.70)	0.65 (0.55, 0.70)	0.65 (0.55, 0.70)
Range	0–0.95	0–0.95	0–0.95

Note: *Age was analyzed in months, but reported in this table in years for ease of interpretation. **Hormone levels were analyzed in corrected, log-transformed format, but the raw values are reported here for ease of interpretation. For descriptives of task behavior by sex, see Supplementary Table 76.

bigger accuracy difference between neutral and reward trials in both sexes ($p<0.001$ and $p=.006$ respectively, see Figs. 1 and 2 and Supplementary Tables 19–20). However, these associations were no longer significant when controlling for age ($p=.23$ and $p=.42$, Supplementary Tables 21–22). Higher DHEA levels were associated with more earnings after accounting for sex ($p=.02$, Supplementary Table 23), but this association disappeared when controlling for age ($p=.60$, see Fig. 2 and Supplementary Tables 24). DHEA was not related to the accuracy difference between neutral and reward trials ($p=.62$, Supplementary Table 25). Estradiol levels in girls were not related to reward motivation behavior ($p=.57$ and $p=.87$, see Supplementary Tables 26–27).

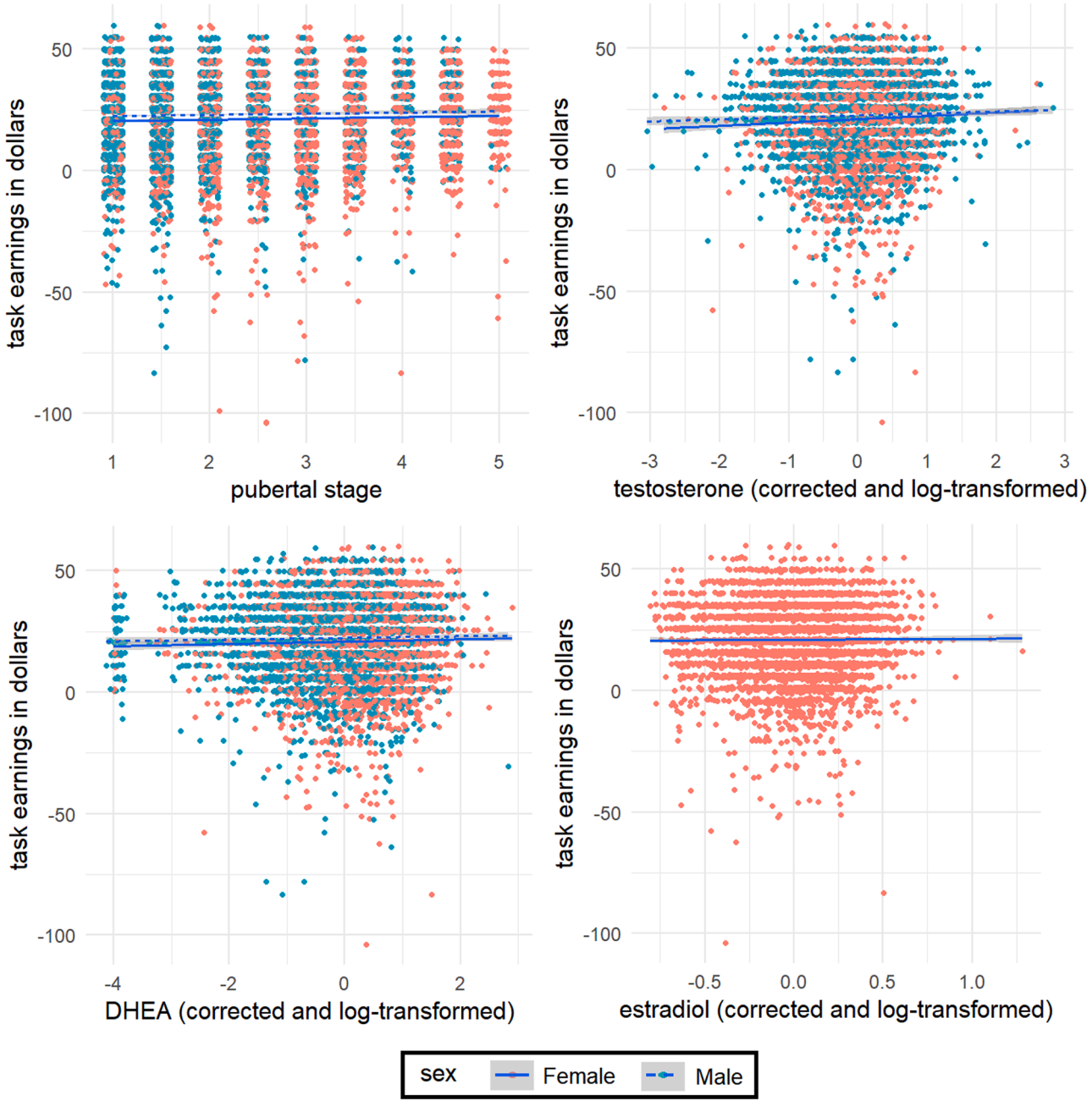

Fig. 1. Scatterplots of the association between pubertal variables and earnings on the reward task by sex. Points on the pubertal stage plot are jittered (i.e. scattered around their actual stage or half-stage) for visualization purposes. Girls depicted in red; boys depicted in blue.

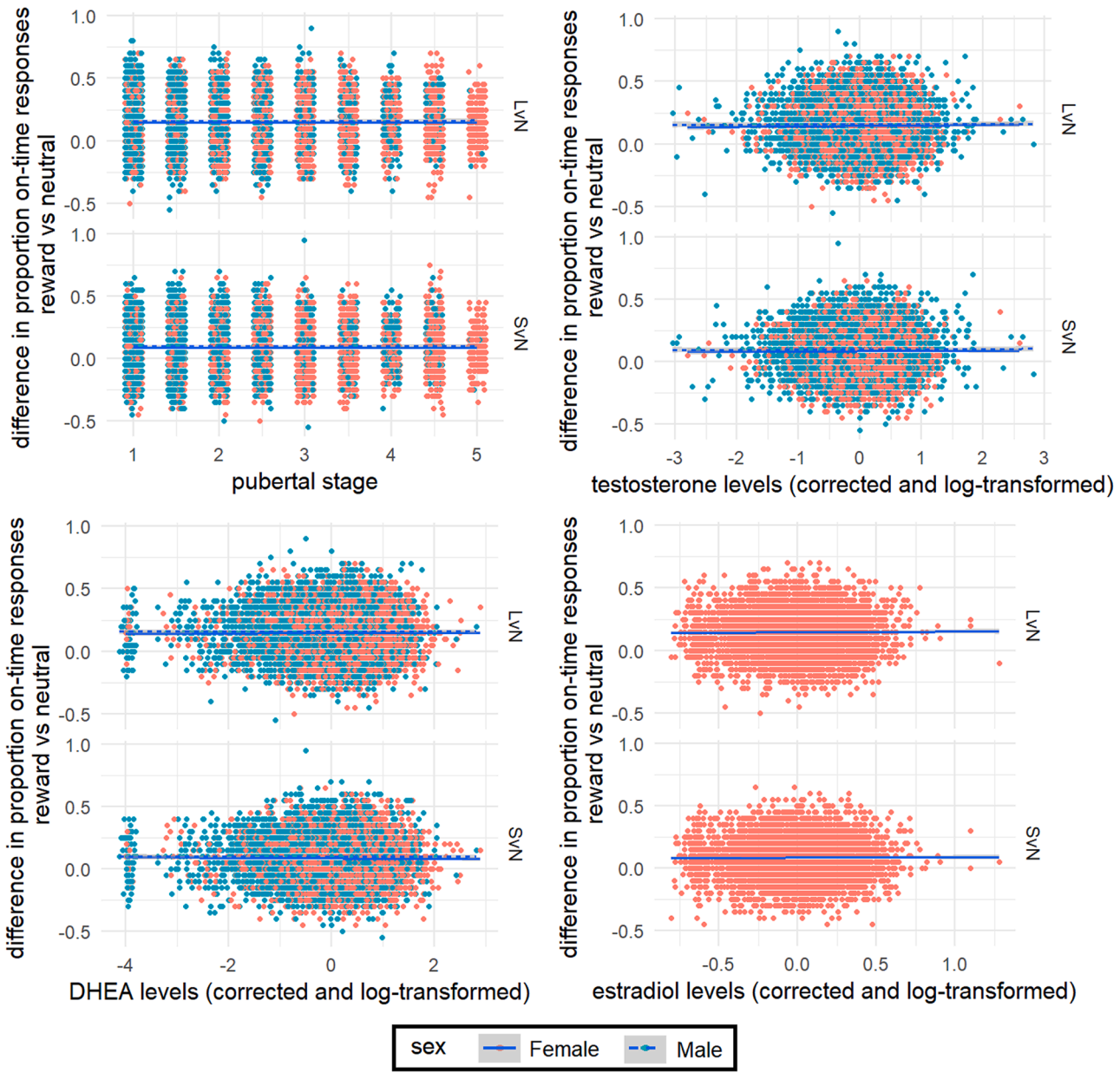

Fig. 2. Scatterplots of the association between pubertal variables and accuracy on the reward task by sex. Points on the pubertal stage plot jittered for visualization purposes. LvN=Large reward versus neutral; SvN=Small reward versus neutral. Girls depicted in red; boys depicted in blue.

3.4. RQ3: Relation between pubertal development and neural activation during reward anticipation

Pubertal stage was not related to neural activation during reward anticipation in any of the ROIs, and there were no interactions with sex or reward size. Testosterone and DHEA levels were not related to neural activation during reward anticipation in any of the ROIs in either sex. Estradiol levels in girls were not related to neural activation during reward anticipation in any of the ROIs (all p's>05, see Supplementary Tables 28 - 51). These findings remained the same after adding the age covariate.

3.5. RQ4: Relation between pubertal development and neural activation during reward feedback

Pubertal stage was not related to neural activation during reward feedback in any of the ROIs after accounting for sex, nor in interaction with sex. Testosterone and DHEA levels were not related to neural activation during reward feedback in any of the ROIs in either sex. Estradiol levels in girls were not related to neural activation during reward feedback in any of the ROIs (all p's>05, see Supplementary Tables 52 - 75).

4. Discussion

The current study sought to characterize differences related to sex and pubertal markers in reward-related behaviors and neural processing in a large community sample of early adolescents. In doing so, we aimed to document developmental patterns in reward-related brain function and behavior in the general population, which in turn can help us more fully understand risk for mental health problems characterized by features of low sensitivity to reward (e.g. anhedonia).

As hypothesized, sex differences in reward motivation behavior indicated boys had higher reward sensitivity than girls, manifested as

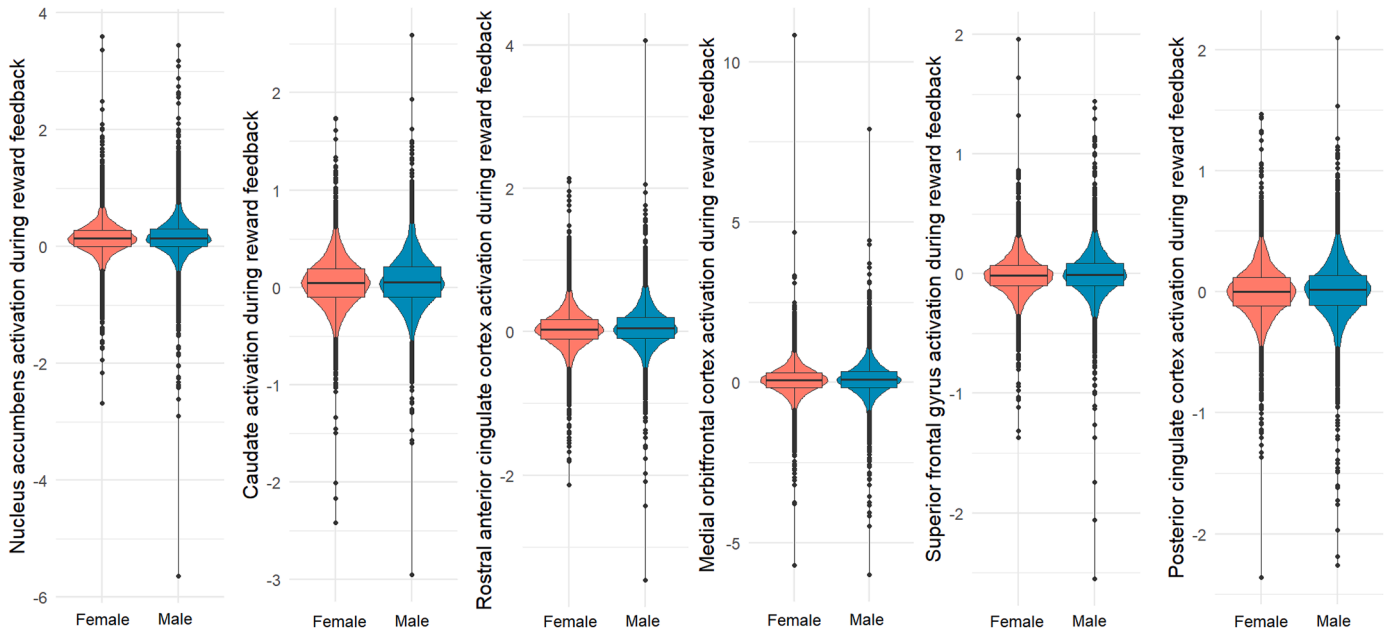

Fig. 3. Neural activation during reward feedback in the regions of interest by sex. Girls depicted in red; boys depicted in blue.

greater accuracy on trials providing rewards relative to no reward. Boys also earned more money on the task. A sex difference in reward motivation behavior is thus already visible in early adolescence. These sex differences in behavior remain significant and of similar size in models that include age and in models with pubertal stage or hormone levels as predictors. This suggests the stronger reward motivation behavior in boys is not accounted for by the pubertal processes as measured in the current study. Of note, the task used in this study focused on monetary rewards. Previous findings suggest reward sensitivity might depend on the type of reward: girls self-reported more sensitivity to social and attachment-related rewards, whereas boys reported higher reward sensitivity when questions related to status and money (Cross et al., 2011). Thus, our findings of sex differences in reward motivation behaviors might not generalize to all rewards.

With regard to sex differences in neural activation, girls showed greater activation than boys in the rACC/vmPFC when anticipating rewards. However, neural activation upon learning whether the reward was obtained or not was lower for girls than boys in the NAcc, caudate, rACC/vmPFC, mOFC, SFG/dmPFC and PCC. Previous research on sex differences in the neural processing of rewards was scarce and based on small, cross-sectional studies, thus we had no directional hypothesis. The rACC/vmPFC is a central part of the valuation system, it responds to both reward anticipation and feedback and is closely connected to the ventral striatum (Bartra et al., 2013; Pujara et al., 2016). The higher activation during reward anticipation but lower activation during reward feedback in girls might indicate a shorter window of activation, or that different psychological processes guide how boys and girls experience different phases of reward processing. Activation in the ventral striatum (including NAcc and caudate) and mOFC are thought to reflect reward value, particularly in the feedback/receipt phase for mOFC (Chaarani et al., 2021; Diekhof et al., 2012; Peters and Büchel, 2010). In that sense, the sex differences in neural activation align with the sex differences in reward motivation behavior. The findings together suggest girls in early adolescence have lower frontostriatal sensitivity to reward feedback. It should be noted that the explained variance was small. Yet, sex differences at the behavioral level were found as well, and small neural activation differences can have behavioral impact. These findings imply that theories of developing changes in reward-related behavior should evolve to theorize about sex differences in neural activation to reward, in both striatal and frontal reward-related areas. For example, based on our finding of girls having lower neural activation during reward feedback than boys in the reward network, the imbalance from the Dual Systems model could be hypothesized to be smaller in females than in males.

Turning to pubertal markers, we found that being at a more advanced pubertal stage was associated with obtaining higher earnings on the task, for both boys and girls. However, we did not find a relation between pubertal stage and the difference in accuracy between neutral and reward trials (p=.08). Earnings are not only influenced by accuracy on neutral and reward trials, but also by loss trials. The link between higher earnings and more advanced pubertal stage might thus, in part, be driven by responses on loss trials (i.e. punishment sensitivity). When age was included in the models as a covariate, the association between pubertal stage and accuracy and earnings went from positive to negative, and there were positive age effects. This suggests the pubertal stage effect before adding age might represent a more general developmental effect. It also suggests pubertal timing (i.e. pubertal stage relative to age) may contribute to the patterns we found.

Our examination of testosterone revealed that higher testosterone levels were associated with more earnings and a bigger accuracy difference between neutral and reward trials in both sexes. This aligns with our hypotheses and previous literature (Kurath and Mata, 2018; Laube et al., 2017), suggesting that testosterone plays a significant role in driving reward sensitivity. We also found, however, that the association of testosterone levels with reward motivation behavior disappeared after controlling for age. Age and testosterone were moderately correlated (r=0.42 across time points), and the variance relevant for reward motivation behavior might be that shared between the hormone level and age.

In looking at pubertal markers (stage, hormones) in relation to neural activation, we found no significant associations with neural activation during either reward anticipation or feedback. This pattern is not completely in line with hypotheses: we expected positive associations between testosterone levels and striatum activation, as well as positive associations between estradiol levels and striatum activation during reward anticipation and vmPFC activation during reward feedback. The hypotheses for estradiol were based on animal research (Diekhof, 2018) and experimental research around menopause (Thomas et al., 2014), however, it is plausible that these findings might not translate to human adolescent girls. Earlier, smaller studies on

testosterone were not completely consistent in their findings, but the majority showed a positive association between testosterone levels and striatal activation in adolescents (Alarcón et al., 2017; Braams et al., 2015; Ladouceur et al., 2019; Op de Macks et al., 2011; Poon et al., 2019). They used varying, sometimes very broad, age ranges. Publication bias might have had an effect here, or the previously reported positive association may not become visible until later in adolescence. It will be important to repeat the current study when time points covering all of adolescence are available.

4.1. Limitations

The current work is the largest longitudinal study to date on sex and pubertal development in relation to neural and behavioral reward processing. Yet, our study has to be considered in light of several limitations. First, there is missing data at the two-year follow up, and this is believed to be largely due to COVID-19 restrictions. Sites might have differed in how they handled these restrictions, or as a function of local laws. We took into account the scanner as a grouping variable, which is very similar to the site (only a few sites have multiple scanners). Second, there might be practice effects on task behavior. Practice effects tend to be more present in cohort study designs (like the ABCD study) than in accelerated longitudinal designs (McCormick, 2021). The impact of these practice effects is largest when you compare behavior by time point, and smaller with our predictor variables (pubertal stage and hormone levels) as there is substantial variation between participants within a time point on these variables as well as variation between participants in change over time. Still, it would be relevant to know if our findings would hold in a large accelerated longitudinal study. Third, we used parent-reported PDS because of the high level of missingness of self-reported PDS data, especially in the baseline assessment of the study. Since parent-reported PDS becomes less accurate as adolescents get older (Dorn et al., 1990), this could potentially have reduced our ability to detect associations between PDS and neural function. Also, most parent-reports were from biological mothers. It is unknown if there are differences in accuracy between biological mothers and fathers and non-biological parents. However, inclusion criteria required the reporting parent to be a main caregiver who lives in the same house as the child most of the time. Therefore, the reporting parent is closely involved in the child's life. Finally, controlling for short-term variations in the hormone data was difficult, as only one sample was collected per assessment time point and a large proportion of the girls were pre-menarche or had irregular cycles. We corrected the hormone levels for time of day and monthly cycle stage as best as possible with the available information (described in the Methods), but these short-term variations may account for residual noise in the data. For a more extensive discussion of the opportunities and limitations of pubertal indices in the ABCD study, we refer to Cheng et al., (2021).

4.2. Conclusion

We aimed to characterize the role of sex and pubertal development in reward motivation behavior and neural processing in a large longitudinal sample of early adolescents. We found that boys had higher reward motivation than girls, measured behaviorally, in line with previous research. Neural activation during reward feedback was lower for girls than boys in the NAcc, caudate, rACC/vmPFC, mOFC, SFG/dmPFC, and PCC. Pubertal stage and testosterone levels were positively associated with reward motivation behavior, but these associations were due to overlapping variance with age and thus might represent a more general developmental effect. Unexpectedly, we did not find significant associations between pubertal development and neural activation during reward anticipation or feedback. Earlier, smaller studies might have overestimated these associations, or they might not become visible until later in adolescence. Therefore, associations between hormone levels and neural activation during reward anticipation or feedback should be examined again when time points covering all of adolescence are available. Nonetheless, the present study was rigorous and well-powered, providing novel evidence of sex differences in reward motivation behavior and neural activation in the frontostriatal system to reward feedback. This enhances our understanding of the neurobehavioral underpinnings of reward processing in early adolescence. It can help explain the development of sex differences in prevalence of disorders involving anhedonia or low motivation, such as depression, that emerge during adolescence, coupled with future research that examines how the sex differences in reward processing interact with the neural and other developmental changes underlying the increased risk for reward-related disorders during adolescence.

CRediT authorship contribution statement

MEAB: Conceptualization, Methodology, Data curation, Writing – original draft, Visualization, Writing - review & editing. JRS: Conceptualization, Funding acquisition, Writing - review & editing. **SLT:** Methodology, Formal analysis, Writing - review & editing, Supervision. **JRF:** Methodology, Formal analysis, Writing - review & editing. **EAS:** Conceptualization, Funding acquisition, Writing - review & editing. **LY:** Writing - review & editing. **SJM:** Writing - review & editing. **LMT:** Conceptualization, Funding acquisition, Supervision, Project administration. **AEG:** Conceptualization, Funding acquisition, Supervision, Project administration, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

This study is a secondary analysis of a publicly available dataset, see Acknowledgements.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2024.101358.

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