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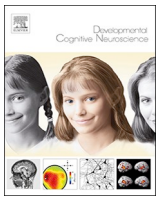

Pubertal influences on neural activation during risky decision-making in youth with ADHD and disruptive behavior disorders

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ABSTRACT

Objective: Risk-taking during adolescence is a leading cause of mortality; Neuroscience research examining pubertal effects on decision-making is needed to better inform interventions, particularly among youth with attention-deficit/hyperactivity (ADHD) and disruptive behavior disorders (DBD), who are particularly prone to risky decision-making. We examined effects of pubertal development on risky decision-making and neural activation during decision-making among youth with ADHD/DBDs.

Method: Forty-six 11–12-year-olds (29.4% girls; 54.9% white; Tanner *M(SD)* = 2.08(1.32)) who met DSM-5 criteria for ADHD/DBD completed the Balloon Analog Risk Task (BART) during fMRI scanning. We examined effects of Tanner stage, sex, and age on risky decision-making (mean wager at which individuals stopped balloon inflation) and neural activation in the middle frontal gyrus and the ventral striatum during the choice and outcome phases of decision-making.

Results: Those in earlier pubertal stages made riskier decisions during the BART compared to those in later Tanner stages ($\beta = -0.62$, $p = .02$). Later pubertal stage was associated with greater activation in the left middle frontal gyrus ($\beta = 0.61$, $p = .03$) during the choice phase and in the right ventral striatum in response to rewards ($\beta = 0.59$, $p = .03$).

Conclusion: Youth with ADHD/DBD in later stages of puberty, regardless of age, show greater ventral striatal activation in response to rewards.

1. Introduction

Adolescence is a developmental period marked by a number of biological and social changes, including increased opportunities for decision-making under risk. Although a normative part of development, adolescents are notoriously vulnerable to engaging in risky decision-making (e.g., substance use, risky sexual behavior), which is a major public health concern, as it greatly influences adolescent morbidity and mortality (Blakemore and Robbins, 2012; Hartley and Somerville, 2015). Developmental changes in decision-making during adolescence are likely driven by changes in neural substrates (Blakemore and Robbins, 2012; Hartley and Somerville, 2015; Crone and Dahl, 2012) and research has highlighted the influence of pubertal development on the neurobiology of decision-making; however, the majority of this research has focused on typically-developing youth (Crone and Dahl, 2012). Youth with attention-deficit/hyperactivity disorder (ADHD) and/or disruptive behavior disorders (DBDs; oppositional defiant disorder and conduct disorder) are also important to consider, as they engage in more risky decision-making and risk-taking compared to typically-developing youth (Humphreys and Lee, 2011; Dekkers et al., 2016). For instance, rates of substance use, risky driving, sexual risk-taking, and unintentional injury are higher among youth with ADHD and DBDs compared to healthy youth (Flory et al., 2006; Lee et al., 2011; Thompson et al., 2007). Despite the costly consequences of risky decision-making in these youth, the prevalence of these disorders in the general population (7% ADHD, 6% DBD) (Polanczyk et al., 2007; NRC and IOM, 2009), and the high comorbidity among these disorders (up to 50% of youth with ADHD have comorbid disruptive behavior disorder) (Children's Health Survey, 2016), little is known about the effects of pubertal changes on decision-making in this population. The current study seeks to further understand pubertal effects on neural mechanisms underlying adolescent decision-making in a sample of 11–12 year-olds with ADHD and DBDs; findings could inform the development of novel intervention and prevention strategies targeted at these highest risk youth.

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Decision-making is conceptualized as a two-phase process: the decision/choice phase as well as the outcome phase, or one's response to reward/loss (Ernst and Paulus, 2005). In the decision phase, individuals assess and weigh potential choices of action (e.g., consider potential positive or negative outcomes of different choices) and actively complete choice-related actions, which may also be based on their motivation to avoid loss or motivation to seek reward); in the outcome phase, individuals learn and process the outcome of their choices (e.g., process whether the outcome was expected or unexpected and favorable or unfavorable and potentially use this information for further decision-making) (Reyna and Rivers, 2008). Extensive research has examined risk-taking differences across children, adolescents, and adults (Defoe et al., 2015). Meta-analytic results from studies examining laboratory measures of risk-taking found that children and adolescents typically engage in equal levels of risk-taking; however, context matters. Specifically, when adolescents are forced to choose between options with differing levels of expected reward, adolescents engage in riskier decision-making (Defoe et al., 2015). Evidence for differences in risk-taking across adolescents and adults is more consistent: Adolescents are more likely to base decisions on more proximal versus distal outcomes, less likely to consider negative consequences of potential rewards, and more motivated by reward over punishment compared to adults (Byrnes, 2002). Recent research has highlighted that these changes in decision-making and differences across developmental stages are likely associated with pubertal development. (Blakemore and Robbins, 2012; Hartley and Somerville, 2015; Crone and Dahl, 2012; Braams et al., 2015), Increases in testosterone during pubertal development have organizing and activating effects on brain function in regions thought to be involved in decision-making, and thus, may underlie these changes (Hartley and Somerville, 2015; Crone and Dahl, 2012; Sisk and Zehr, 2005; Peper et al., 2013; Goddings et al., 2014). In general, among typically-developing youth, the magnitude of risky decision-making increases with pubertal development, as evidenced by studies measuring laboratory-based and real-world decision-making (van Duijvenvoorde et al., 2016; Galvan et al., 2007; Carlson et al., 2000). Although it is understood that youth with ADHD/DBD engage in riskier decision-making compared to healthy youth, changes in risky decision-making across pubertal development among this population are unknown (Humphreys and Lee, 2011; Carlson et al., 2000). Nonetheless, there is evidence that pubertal-related hormonal changes may influence ADHD symptomatology (Nussbaum, 2012), as well as findings showing a remittance or decline in hyperactive/impulsive symptoms from childhood to early adolescence (Franke et al., 2018); this evidence suggests that there may also be pubertal effects on risk-taking and decision-making among those with ADHD/DBD.

Neuroimaging studies on risky decision-making in healthy youth have found regions uniquely associated with the choice and outcome phases of decision-making (Hartley and Somerville, 2015; Crone and Dahl, 2012). In particular, the lateral prefrontal cortex and the ventral striatum are the two regions which have most consistently been reported in the decision-making literature (Op de Macks et al., 2011; Galvan et al., 2006; Bjork et al., 2004; Forbes et al., 2010); each has also been shown to undergo changes during pubertal development (Braams et al., 2015; Casey et al., 2000; Herting and Sowell, 2017) and have been associated with ADHD/DBD symptoms (Bush et al., 2005; Sagvolden et al., 2005). The lateral prefrontal cortex, which is comprised of the middle frontal gyrus, has been reported to play a role in the choice phase of decision-making (Eshel et al., 2007; Van Leijenhorst et al., 2010) and is involved in dynamic cognitive control processes integrating cognitive and emotional information to inform decision-making (Gray et al., 2002; Mathalon et al., 2003; Ridderinkhof et al., 2004). Several studies suggest that activation in this region is particularly mutable across adolescent development (Casey et al., 2000). There is also evidence that pubertal-related changes are seen during activation specific to decision-making. For example, in a sample of healthy adults aged 20–40 (n = 16) and adolescents aged 9–17 (n = 18), adults showed greater activation in the ventrolateral prefrontal cortex when making risky selections during a monetary decision-making task, suggesting changes across development in the role of the lateral prefrontal cortex in decision-making (Eshel et al., 2007). Still, another study comparing children (8–11 years, n = 23), adolescents (16–19, n = 25), and adults (25–34, n = 24) found that all groups showed similar patterns of lateral prefrontal activation during the choice phase of a risky decision-making task (van Duijvenvoorde et al., 2015). Less research has examined changes in lateral prefrontal cortex activation during the choice phase of decision-making more specifically across pubertal stage (Van Leijenhorst et al., 2010). Further, while imaging studies have shown unique middle frontal gyrus activation during reward processing and response inhibition in youth with ADHD; (Rubia et al., 2007; Schulz et al., 2005) pubertal effects on activation are unknown. Given evidence for pubertal effects on other structural and functional changes in this area (Herting and Sowell, 2017), we hypothesize there are also pubertally-driven changes in activation during decision-making among youth with ADHD/DBD.

The ventral striatum has been associated with the outcome phase of decision-making and is important in reward processing and forming preferences (Galvan et al., 2006; Ernst et al., 2005; Pagnoni et al., 2002). Imaging studies have supported the notion that the ventral striatum is particularly central to pubertal changes, and in general, show that ventral striatum activity increases across pubertal development (Galvan et al., 2006; Urošević et al., 2012; Silverman et al., 2015). More advanced pubertal stages, as measured by testosterone levels, were associated with increased ventral striatal activity following receipt of reward among a sample of healthy 10–16 year-olds (n = 50) (Op de Macks et al., 2011), as well as in anticipation of reward in a sample of healthy 10–13 year-olds (n = 77) (Forbes et al., 2010). Similarly, in a sample of typically-developing 8–25 year-olds (n = 255), those in later pubertal stages showed greater activation in the ventral striatum in response to rewards (Braams et al., 2015). While other studies have failed to find differences across children and adolescents in striatal activity (May et al., 2004), this may be due to the heterogeneity in pubertal status across children and adolescents and speaks to the need to more specifically examine pubertal status as a marker of development as opposed to age. Further, although imaging studies have examined ventral striatal activity during reward anticipation and reward processing among adolescents and adults with ADHD (Scheres et al., 2008; Plichta and Scheres, 2014),studies on younger adolescents with ADHD, and moreover, potential pubertal effects on ventral striatal activation during decision-making among youth with ADHD/DBD are lacking.

While these neuroimaging studies offer important insights into the effects of puberty on neural development, they solely focus on typically-developing, healthy youth. Despite evidence for effects of pubertal development on neural mechanisms related to certain ADHD symptoms, such as motor symptoms/hyperactivity (Andersen and Teicher, 2000), no such studies have examined pubertal effects on risky decision-making or neural correlates of decision-making. For example, ADHD has been characterized by delays in fronto-cortical maturation; (Shaw et al., 2007) however, whether those delays are associated with pubertal development or influence associations between pubertal development and neural activation underlying decision-making is unknown. Understanding effects of pubertal development on risky decision-making among this high-risk group could better inform preventive interventions for risk-taking behaviors, given that this population is at high risk for risky decision-making.

The current study seeks to fill these gaps in the literature by examining a sample of 11–12 year-olds with comorbid ADHD and DBDs in order to examine how prefrontal and striatal neural activity during risky decision-making is related to pubertal development, independent of age. To assess decision-making, we utilized the balloon analog risk task (BART) (Lejuez et al., 2007), which allows for examination of both the choice and outcome phases of decision-making, during fMRI scanning. Based on findings from typically-developed youth, we hypothesized that those in later pubertal stages would similarly exhibit riskier and more frequent risky decision-making behavior on the BART. We also hypothesized that pubertal development would be positively associated with middle frontal gyrus activation while making risky decisions and ventral striatal activation upon reward outcomes, such that

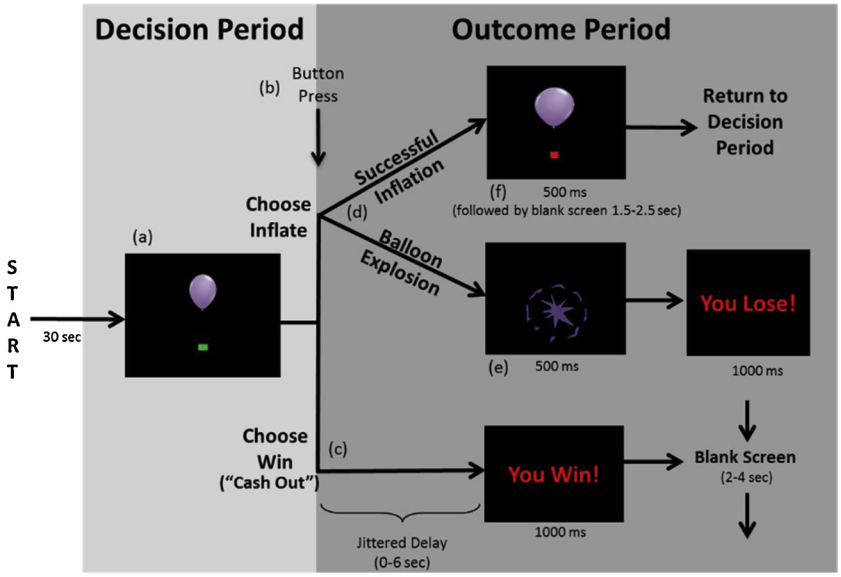

Fig. 1. Illustration of the Balloon Analog Risk Task (BART). At the start of each trial, a balloon is displayed on the screen along with a green decision cue indicating a button can be pressed (a). Participants then choose to inflate the balloon (Choose Inflate) or take the accumulated wager (Choose Win, i.e., "cash out") via button pressing (b). The time between decision and outcome phases of each trial is randomly jittered (0–6 seconds) to enable differentiation of decision-making and feedback-related processes. Following Choose Win trials, participants view a screen that says "You Win!" for 1000 ms followed by a fixation screen for 2–4 seconds before starting a new balloon trial (c). Following Choose Inflate trials, the balloon either explodes or inflates (d). For explosions, participants view an exploding balloon for 1500 ms (e) and then the fixation screen, while inflate trials show an inflated balloon for 1500 −2500 ms before permitting another choice (f). For each balloon, explosions are possible at any inflation choice except the first, with the likelihood of explosion increasing as the balloon size increases. A maximum of 12 inflations are possible for each balloon (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

those in later pubertal stages would show greater activation in these areas while making a risky choice and in response to a reward, given previous studies in typically-developing adolescents (Bjork et al., 2004; Forbes et al., 2010; Eshel et al., 2007).

2. Method

We recruited right-handed, English-speaking, 11–12 year-old participants as part of an ongoing longitudinal study. After consent and assent, diagnoses were determined at the first visit utilizing the K-SADS-PL (Kaufman et al., 1997). Individuals who met DSM-5 criteria for a diagnosis of ADHD and DBD were eligible. Individuals with a history of current or past psychotic symptoms, autism spectrum disorder, current depression or mania, substance use, neurological problems, or debilitating medical conditions were excluded, given the possible influence of those conditions on brain activation. Other exclusionary criteria included estimated Full-Scale IQ < 80; (Wechsler, 1999) routine MRI contraindications; and use of any psychopharmacologic medications, apart from psychostimulants, within the last two weeks. Any psychostimulant medications were held on the days of participation. All procedures were conducted in accordance with Indiana University Institutional Review Board.

2.1. Measures

2.1.1. Pubertal development

Parents completed checklists for pubertal development utilizing Tanner scale pictures with possible Tanner scores from 1 to 5 (1 = prepubertal, 5 = pubertal development complete) (Marshall and Tanner, 1968). If parents were unsure of their child's development, their ratings were not included in analyses (n = 3 excluded). Tanner staging has been shown to be a valid measure of pubertal staging and used in previous studies measuring differences across pubertal development (Braams et al., 2015; Goddings et al., 2014). Further, parent reports of Tanner stages among pre-adolescents have been shown to correlate with physicians' ratings of Tanner stages based on physical examination (Rasmussen et al., 2015; Terry et al., 2016), suggesting this is an accurate measure of pubertal status. For analyses, we mean-centered Tanner scores within each sex, based on research for sex differences in timing of pubertal development (i.e., females initiate pubertal development at an earlier age than males) (Marshall and Tanner, 1968).

2.1.2. Balloon analog risk task (BART)

The BART was administered to participants in the scanner (Lejuez et al., 2007). The BART is a decision-making task in which participants virtually inflate a balloon and choose whether to risk cash rewards that increase with each balloon inflation or bank the amount and start a new balloon. Participants were told that they would win more money for larger unexploded balloons, and actual earnings were paid in cash following the scan. Participants completed as many trials as possible over three eight-minute runs. At the start of each trial, a balloon is displayed on the screen along with a green decision cue indicating a button can be pressed. Participants then choose to inflate the balloon (*choose inflate*) or take the accumulated wager (*choose win*, i.e., "cash out") via button pressing. Following *choose inflate* trials, the balloon either explodes (*outcome explode*) or inflates (*outcome inflate*). If the balloon explodes, participants start a new balloon trial. If the balloon inflates, participants decide whether to again continue to inflate the balloon (*choose inflate*) or take the accumulated wager (*choose win*). For each balloon, explosions are possible at any inflation choice except the first, with the likelihood of explosion increasing as the balloon size increases. A maximum of 12 inflations are possible for each balloon (see Fig. 1 for illustration).

We quantified risky decision-making with the mean stop wager, or the mean amount at which individuals chose to bank the money and stop inflating the balloon (Hulvershorn et al., 2015). Because chance for explosion increases with each wager increase, higher mean stop wagers denote riskier decisions.

2.2. Procedure

2.2.1. Imaging procedures

Before the scanning session, participants completed mock scanning, urine drug screening, pregnancy testing, and BART learning trials. We used a 3-Tesla Siemens Prisma MRI scanner with a 32-channel head coil. A high-resolution 3D magnetization-prepared rapid gradient echo (MPRAGE; 160 sagittal slices; 1.05 × 1.05 × 1.2 mm voxel dimension) scan was used for co-registration and normalization of functional image volumes to Talairach space. BART runs were acquired using a T2*-weighted gradient echo-planar imaging (EPI) sequence (54 axial slices; voxel size 2.5 × 2.5 × 2.5 mm; TR/TE 1200/29 ms, flip angle 65°; Field-of-view:220 × 220 mm, Matrix:88 × 88).

2.3. Statistical analyses

To assess decision-making behavior on the BART, we conducted a

Table 1
Sample Characteristics.

Variable	Mean (SD) or No. (%)	Range
Sex		
Male	33 (71.7%)	
Female	13 (28.3%)	
Age	11.90 (0.50)	11–12
Tanner stage	2.07 (1.31)	
1	22 (3 F, 19 M)	
2	10 (3 F, 7 M)	
3	7 (3 F, 4 M)	
4	3 (2 F, 1 M)	
5	4 (2 F, 2 M)	
Race		
White	26 (53.1%)	
African American	13 (26.5%)	
Hispanic	1 (2%)	
Multiracial	9 (18.4%)	
IQ	105.57 (15.31)	76–141
ADHD diagnosis		
Other specified ADHD	7 (15.2%)	
Inattentive type	16 (34.8%)	
Hyperactive/Impulsive type	3 (6.5%)	
Combined type	20 (43.5%)	
DBD diagnosis		
Other specified DBD	15 (32.6%)	
Oppositional defiant disorder	27 (58.7%)	
Conduct disorder	4 (8.7%)	
Mean stop wager (in dollars)	0.97 (0.40)	0.33–2.11

Note: N = 46. N = 45 with usable imaging data.

hierarchical multiple regression with mean stop wager as the dependent variable and the following mean-centered independent variables: (1) age, Tanner stage (mean-centered by sex); (2) sex (male = 1); and (3) Tanner by sex interaction term. Tanner was mean-centered within boys and girls, given the small age range of the sample and that girls typically enter puberty at least one year earlier than boys (Marshall and Tanner, 1968).

Image preprocessing of each blood-oxygen level-dependent (BOLD) time-series, using AFNI software (Cox, 1996), consisted of slice-time correction, de-spiking of time series outliers (3dDespike algorithm), motion correction via realignment to a baseline time point, registering the functional image to the structural image, and spatial smoothing with a Gaussian kernel of 6-mm full-width at half-maximum.

For noise reduction, individual time points with high motion (> 0.5 mm total movement from previous time point) and/or noise (> 10% of voxels considered time-series outliers; AFNI command 3dToutcount) were excluded from analyses. Participant runs were excluded if > 10% of time points were excluded based on above criteria, motion exceeded 5 mm from baseline to any time point, or > 10% of reaction times > 5000 ms, signaling inattention.

After preprocessing and noise reduction, runs were concatenated, and a general linear regression model with random effects was created to estimate event-related responses. Six motion parameters, six motion derivatives, and detrending terms to correct for scanner drift were modeled. Regressors were created by convolving the timing of each condition with a haemodynamic-response function to create a model BOLD time series for each condition. Five event regressors encompassed potential decisions (choose inflate, choose win), outcomes (outcome win, outcome inflate, outcome explode), and a nuisance regressor (choice trials with reaction times > 5000 ms).

Choice events were aligned to the time at which the button was pressed for a choice: inflating the balloon (*choose inflate*) or discontinuing inflation and banking the money (*choose win*). Outcome events were modeled as the time point that included balloon explosion (*outcome explode*) or successful inflation (*outcome inflate*). For participant level analyses, *choose win–inflate* and *outcome inflate–explode* contrasts were calculated. Individual activation maps were warped to a standard Talairach atlas for region of interest (ROI) and group analyses.

For whole brain analyses, we conducted permutation testing by randomly shuffling dependent variables and conducting linear regression analysis on a voxelwise level across the entire brain, with individual voxels considered significant at $p < .01$. This process was repeated for 5000 iterations to estimate cluster-size thresholds of significant voxels required for $p < .05$, corrected for multiple comparisons.

Structural ROIs were created using the standard Talairach Daemon atlas and were identified based on previous literature on reward processing and decision-making: right and left middle frontal gyrus for the choice phase, and right and left ventral striatum (nucleus accumbens) for the outcome phase. For these regions, we extracted the mean contrast of interest for each participant. Age, mean-centered Tanner stage (mean-centered within sex), sex, and Tanner by sex interaction variables were used as predictors of mean activity in each ROI with linear regression analyses, across the entire sample.

3. Results

Forty-six participants (29% girls; 55% white; *M*age = 11.9, *SD* = 0.56) completed the protocol with usable data (n = 3 excluded for missing Tanner data; n = 5 were excluded due to unusable scan data); All met criteria for ADHD and DBD (see Table 1 for subtype diagnoses). Most participants were in early pubertal stages (45% in Tanner stage 1; $M = 2.08$, $SD = 1.32$). Girls were in more advanced pubertal stages compared to boys ($t = 2.79$, $p = .01$). There were no differences in pubertal development across race or age ($r = 0.22$, $p = .16$). Neither Tanner stage ($r = 0.23$, $p = .13$) nor risky decision-making as measured by mean stop wager ($r = -0.13$, $p = .40$) were related to framewise displacement.

3.1. BART performance

In the hierarchical regression, Tanner stage was related to mean stop wager ($\beta = -0.62$, $p = .02$), such that those in earlier Tanner stages had higher mean stop wagers (i.e., made riskier decisions). Further, there was a Tanner by sex interaction ($\beta = .58$, $p = .03$); girls in earlier Tanner stages had significantly higher mean stop wagers (i.e., more risky decisions) than girls in earlier Tanner stages ($b = -0.20$, $p = .02$), while boys had similar mean stop wagers across Tanner stages ($b = 0.03$, $p = .65$; Table 2).

3.2. BART Imaging Results (Fig. 2)

In whole-brain analyses, no significant clusters were associated with regressors of interest after correction for multiple comparisons, for either choice or outcome contrasts. However, significant results were found with a priori ROI analyses.

In the *choose win–inflate* contrast, participants showed relatively greater activation in the middle frontal gyrus during *choose win* trials. Tanner stage was related to activation in the left middle frontal gyrus, such that those in later Tanner stages showed greater activation when choosing win vs. inflate ($\beta = 0.61$, $p = .03$). Sex was related to

Table 2
Regression for Effects of Tanner on Decision-making Behavior on the BART.

	β	*P* value
Age	.05	.75
Tanner stage	−.62	.02
Sex[a]	.11	.48
Tanner x sex interaction	.58	.03

Note: Mean stop wager is the dependent variable. Regression coefficients are standardized. Only final step from hierarchical multiple regression is shown for simplicity. All variables were mean-centered.

[a] 0 = female, 1 = male.

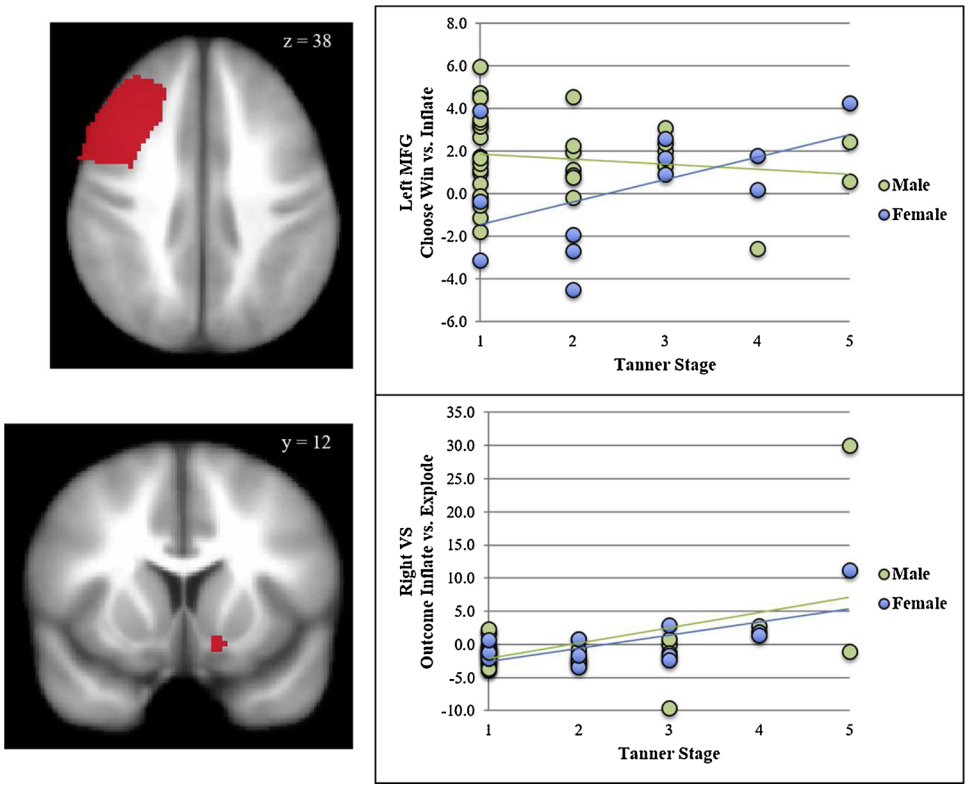

Fig. 2. Significant Effects of Tanner and Sex on Activation during Choice and Outcome Trials. Regions of interest (*left*) are depicted for left middle frontal gyrus (MFG) and right ventral striatum. Scatterplots (*right*) depict mean ROI beta estimates for contrasts of interest showing a significant relationship with Tanner stage (VS) or a Tanner-by-Sex interaction (MFG).

activation in both the right (β = .39, p = .01) and left (β = .30, p = .04) middle frontal gyrus, such that boys showed greater activation when choosing win vs. inflate compared to girls (see Table 3). Further, there was a significant Tanner x sex interaction in the left middle frontal gyrus (β = −0.57, p = .04): girls showed increasing activation during choose win vs. choose inflate trials across later Tanner stages (b = 1.05, p = .04), while boys showed similar activation across Tanner stages (b = −0.24, p = .46).

In the *outcome inflate–explode* contrast, individuals showed greater activation in the left and right ventral striatum in response to inflation trials. Tanner stage was related to activation in the right ventral striatum (β = .59, p = .03; left ventral striatum β = .37, p = .22), such that later Tanner stage was related to greater right ventral striatum activation in response to inflations vs. explosions. Neither sex nor Tanner by sex interactions were significant (p's > .10; Table 3).

Table 3
Regression Results for Choice and Outcome Contrasts with Effects of Tanner on Brain Activation in the Middle Frontal Gyrus and Ventral Striatum.

	Choose Win – Inflate				Outcome Inflate – Explode			
	Left MFG		Right MFG		Left VS		Right VS	
	β	*P* value	β	*P* value	β	*P* value	β	*P* value
Age	−.23	.13	−.18	.26	.18	.28	.10	.49
Tanner	.61	.03	.27	.34	.37	.22	.59	.03
Sex[a]	.30	.04	.39	.01	−.24	.13	−.07	.65
Tanner x sex	−.57	.04	−.27	.35	−.32	.29	−.14	.60

Note: Results shown are from four separate hierarchical regression equations. To consolidate space only regression results from the final step of the regression with all variables is shown. Values shown are standardized regression coefficients. P values < 0.05 are considered statistically significant. All variables were mean-centered. (Abbreviations: MFG = Middle Frontal Gyrus; VS = Ventral Striatum).

[a] 0 = female, 1 = male.

4. Discussion

We examined how pubertal stage was related to behavior and neural activation during risky decision-making, independent of age, in 11–12 year-olds with comorbid ADHD and DBDs. To our knowledge, this is the first study to examine the relationship between pubertal status and decision-making behavior and neural correlates of decision-making among youth with ADHD and DBDs.

Our primary neuroimaging finding occurred in the outcome phase of decision-making, where, despite a narrow chronological age range, those in later pubertal stages showed greater activity in the ventral striatum in response to rewards (inflations) versus losses (explosions). In other words, compared to those in the pre-pubertal or early pubertal stages, those in middle or later pubertal stages showed more sensitivity to reward as evidenced by greater striatal activation in response to a positive outcome (inflation). As discussed earlier, the ventral striatum is part of the brain's reward circuitry, and present findings are consistent with evidence among typically-developing youth that increases in gonadal hormones at puberty are related to increases in reward sensitivity as evidenced by increases in striatal activity in response to rewards (Op de Macks et al., 2011; Forbes et al., 2010; Peper and Dahl, 2013). Those with ADHD/DBD are already prone to heightened reward sensitivity (Tripp and Alsop, 2001), and these results emphasize how pubertal effects may further exacerbate reward sensitivity, thus increasing vulnerability for risky decision-making during this developmental period.

With respect to neural activation during the choice phase of decision-making, contrary to hypotheses, Tanner stage was not related to activity in the middle frontal gyrus. Given that prefrontal cortex development extends into early adulthood post puberty (Casey et al., 2000), development may be more gradual and there may be fewer significant changes across early pubertal stages. Lack of findings may also be related to delayed cortical maturation seen in youth with ADHD, particularly in areas involved in cognitive control and attention (Shaw et al., 2007). Although the extent of delay and the relationship between delay in cortical maturation and pubertal changes among youth with ADHD is not well studied, results highlight a potentially unique

prefrontal trajectory in youth with ADHD/DBD. There were also gender effects that emerged in the imaging findings, although we interpret them with caution given the small number of girls in our sample. Overall, boys showed greater middle frontal gyrus activation when making less risky decisions (*choose win*) while girls showed greater activity when making more risky decisions (*choose inflate*). Results could be related to unique ADHD symptom profiles across boys and girls; (Yeager et al., 2017) however, additional research is needed to determine potential sex-specific neural mechanisms.

With respect to behavioral patterns of decision-making during the BART, overall there were no differences in risky decision-making across pubertal stage; however, there were differential effects of Tanner stage for boys and girls. Boys showed similar decision-making patterns across pubertal stages, while girls in later Tanner stages made significantly fewer and less risky decisions compared to girls in earlier Tanner stages. Differences could be related to the unique symptom presentation seen among boys and girls with ADHD; boys are more likely to present with more severe impulsive and externalizing symptoms (Plichta and Scheres, 2014) and boys may not "mature out" of disinhibitory symptoms that influence decision-making at the same rate as girls. Further, there is also evidence that puberty-related hormonal changes may influence ADHD symptomatology, and further, that these effects may be sex-specific (Nussbaum, 2012); however, given the small sample of girls as well as the possible restriction of range in pubertal stage among boys in this study, additional research with a larger sample is needed. These findings are inconsistent with research among healthy youth in which more frequent and riskier decision-making was seen in later versus earlier pubertal stages (Peper et al., 2013); thus, future research investigating youth with and without ADHD is needed to determine whether there are unique patterns of risk-taking and decision-making across pubertal development. Nonetheless, our findings offer valuable interim results.

These results offer implications for intervention/prevention in youth with ADHD/DBD. The finding for greater striatal activation in response to rewards among those in more advanced pubertal stages suggests that intervention/prevention strategies that target reward sensitivity may be particularly beneficial for youth who have started puberty. Cognitive training to reduce reward sensitivity as well as increasing awareness of negative outcomes may be beneficial for these youth in the middle stages of pubertal development. These results are consistent with recent research in the area of developmental neuroscience emphasizing the importance of considering developmental stage, including pubertal stage, when developing universal preventive interventions for adolescents (Yeager et al., 2017).

Even beyond the effects of pubertal stage, these results add to other literature on risky decision-making and related neural mechanisms among youth with ADHD/DBD (Humphreys and Lee, 2011; Sonuga-Barke et al., 2016) and underscore the need to develop preventive interventions that target decision-making prior to the onset of problems *resulting* from risky decision-making, such as substance use. For example, there have been recent advances in substance use disorder interventions that also target comorbid psychiatric issues, including ADHD/DBD; (Robinson and Riggs, 2016) however, interventions that are informed by neural mechanisms underlying risky decision-making more generally from a developmental neuroscience perspective and prior to the onset of problems are lacking. This work suggests that future development of preventive interventions to reduce incidence of substance use and other risk-related problems should account for pubertal status, particularly when addressing reward learning.

4.1. Limitations

First, the cross-sectional nature of the study does not allow for a developmental understanding of actual individual-level changes in decision-making due to puberty. Second, the relatively small sample size limited power. Relatedly, the majority of the sample were boys in earlier pubertal stages, and few individuals who had completed puberty were represented; a larger, more heterogeneous sample of boys and girls across pubertal stage is needed for replication. We also relied on parent reports of pubertal status; although parent ratings are shown to correlate with physician ratings of pubertal stage (Rasmussen et al., 2015; Terry et al., 2016), research utilizing a more rigorous measure of pubertal status is warranted. Third, although the goal of the study was to focus on youth with ADHD/DBDs, future research should directly compare youth with and without ADHD and assess real world measures of decision making such as ecological momentary assessment, to determine if these laboratory findings generalize to actual adolescent functioning. Lastly, we did not consider heterogeneity in ADHD symptoms or use a continuous measure of ADHD and DBD symptomatology, which would offer an additional perspective. Nonetheless, our sample was representative of the general population and prevalence estimates of youth with ADHD/DBD: there was a higher prevalence of combined type and predominantly inattentive type ADHD compared to hyperactive type ADHD and higher rates of ODD and other specified DBD compared to conduct disorder, which is consistent with prevalence estimates of ADHD and DBD in the general population (Polanczyk et al., 2007; NRC and IOM, 2009; Children's Health Survey, 2016; Willcutt, 2012), and also consistent with prevalence estimates of comorbid DBDs and ADHD subtypes in the general population (American Psychiatric Association, 2013). Lastly, in our measure of decision-making, it is uncertain whether we are measuring risky decision-making versus reward sensitivity, which is a common limitation in studies of decision-making and reward. Nonetheless, the neuroimaging analysis aimed to separate the processes, since the BART was designed to create temporal separability between the choice and outcome phases.

5. Conclusion

Study findings offer insights into the effects of pubertal development on decision-making and its neural substrates among high-risk youth. The study is particularly important given evidence that not only are youth with ADHD/DBDs more likely to engage in risky decision-making, but the effects of pubertal development also increase adolescents' risk-taking vulnerability. Results highlight the role of pubertal changes in increased sensitivity to rewards, as driven by increasing striatal activation, as well as potential sex-specific patterns in decision-making behavior across pubertal development. The study highlights the importance of a developmental neuroscience perspective, as these mechanisms should inform novel intervention/prevention strategies targeting decision-making and risk-taking among this vulnerable group.

Conflict of Interest

None.

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