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Age-typical changes in neural reward response are moderated by maternal anhedonia

Katherine R. Luking[1] | **Zachary P. Infantolino**[1] | **Brady D. Nelson**[1] | **Greg Hajcak**[2]

[1]Department of Psychology, Stony Brook University, Stony Brook, New York

[2]Department of Psychology, Florida State University, Tallahassee, Florida

Correspondence
Katherine R. Luking, Department of Psychology, Stony Brook University, Stony Brook, NY, 11794.
Email: katherine.luking@gmail.com

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Abstract

Reward response and mood disorders both increase during adolescence. Here, we investigate whether age and gonadal hormone levels relate to neural response to win and loss feedback in 9- to 14-year-old girls and whether such relations are moderated by maternal anhedonia, a factor linked to psychopathology risk and reward response. Psychiatrically healthy daughters of mothers who did not meet criteria for any current DSM-5 disorder or past anxiety/depression diagnosis ($N = 69$) completed a monetary fMRI guessing task and provided saliva samples for gonadal hormone assay. Voxelwise regressions revealed unique quadratic effects of age and linear effects of gonadal hormones; neither effect was explained by reported puberty. Striatal/insular responses to win/loss feedback peaked between 12 and 13 years, whereas estradiol predicted greater response to wins versus losses within the medial prefrontal cortex, concurrently. Maternal anhedonia specifically moderated the quadratic effect of age within dorsolateral striatum and insula. Daughters of mothers reporting greater anhedonia showed an earlier peak in striatal/insular response to reward and loss feedback. As such, maternal anhedonia predicted blunted striatal/insular response to feedback only in older daughters. A similar pattern was observed for daughters of mothers with lifetime depression in exploratory analyses. These cross-sectional findings suggest that familial anhedonia may relate to altered trajectories of reward responding during adolescence and that these effects are specific to age.

KEYWORDS

adolescence, anhedonia, depression risk, development, hormones, reward

1 | INTRODUCTION

Adolescence is typically a time of heightened responsiveness to reward, relative to childhood and adulthood. This quadratic effect of age, with an adolescent peak in reward response, is well documented across species (Spear, 2011) and assessment modalities, for example, self-report (Pagliaccio et al., 2016), behavior (Cauffman et al., 2010), and neuroimaging (Galvan et al., 2006; Van Leijenhorst, Gunther Moor et al., 2010). Such conservation has been interpreted in terms of the functional role of enhanced reward responding in achieving specific goals and characteristics of adolescence—especially increased exploration, separation from the family unit, and formation of peer bonds and romantic relationships (Somerville, Jones, & Casey, 2010). The network of regions engaged during reward processing (e.g., striatum, insula, cingulate cortex, and middle frontal cortex) is generally conserved across development (Silverman, Jedd, & Luciana, 2015); however, the heightened responsiveness of reward-related regions (most notably the striatum) during adolescence, relative to childhood and adulthood, is a key component of theories regarding

the neural basis of adolescent behavior, for example, dual-system (Steinberg, 2010), triadic (Ernst, Pine, & Hardin, 2006), and imbalance models (Casey, Getz, & Galvan, 2008).

Although adolescent hyper-responsiveness to the receipt of reward feedback, relative to children and adults, is well established, it is less clear what factors drive adolescent changes in striatal response to reward. As puberty, the physical process of sexual maturation, also occurs during adolescence, some have hypothesized that gonadal hormones may play a role in changing striatal function, particularly with relevance to social reorientation (Nelson, Leibenluft, McClure, & Pine, 2005; Smith, Chein, & Steinberg, 2013). In fact, increased levels of testosterone and estradiol predict increased response to win versus loss feedback in adolescent groups (Braams, van Duijvenvoorde, Peper, & Crone, 2015; Op de Macks et al., 2011). However, animal work demonstrates that adolescent increases in both reward-related behavior (Varlinskaya, Vetter-O'Hagen, & Spear, 2013) and dopamine receptor expression (Andersen, Thompson, Krenzel, & Teicher, 2002) are observed even in gonadectomized rodents. As such, it is unclear whether relations between age and striatal reward response remain when controlling for gonadal hormone levels.

Adolescence is also a time of increased onset of psychopathology (Kessler et al., 2005), which often involves reward-processing dysfunction. For example, the reduced striatal response to reward observed in adolescents with major depressive disorder (MDD) or in psychiatrically healthy adolescents at increased risk for MDD, based on maternal depressive features, stands in stark contrast to the robust response to reward observed in typically developing peers (Sharp et al., 2014). Few studies have investigated effects of depression risk over adolescent development. However, there is emerging evidence that the blunted response to reward, particularly within the striatum, observed for both familial and environmental depression risk, emerges or strengthens in adolescence relative to childhood (Goff et al., 2013; Hanson, Hariri, & Williamson, 2015; Luking, Pagliaccio, Luby, & Barch, 2016). This suggests that familial features related to blunted reward function and increased depression risk (Weinberg, Huiting, Hajcak, & Shankman, 2015), for example, maternal low positive affect or anhedonia, may moderate the age-typical pattern of increased response to reward observed during adolescence. However, this hypothesis has not been directly tested, and it is unclear whether an adolescent peak in striatal reward response is simply absent or occurs at an earlier age in groups with greater familial liability for reward dysfunction. As such, the aim of the current study is to first investigate how age and gonadal hormones relate to neural responses to winning and losing feedback within psychiatrically healthy girls during early adolescence and then, in exploratory analyses, also investigate whether maternal anhedonia moderates such relations.

2 | METHOD

2.1 | Participants

One hundred ninety-eight female adolescents participated in the neuroimaging component of a larger, longitudinal study investigating relations between pubertal development, neural correlates of reward, and emerging symptoms of depression in female youth (see Speed, Nelson, Auerbach, Klein, & Hajcak, 2016, for recruitment and assessment methods). Participants were excluded from the current study if fMRI data were of insufficient quality (excessive motion, $n = 5$; scanner sequence or other mechanical error, $n = 16$), the father was the parental participant ($n = 16$), or gonadal hormone data were incomplete ($n = 4$). Further, to focus on development and psychopathology risk, rather than history of psychopathology, adolescents meeting DSM-IV criteria for any mood or externalizing disorder, past or present, were also excluded ($n = 52$), assessed via the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997). Further, analyses in the main text focus on daughters of mothers without any current diagnoses or past diagnosis of depression or anxiety. However, daughters of mothers with lifetime depression ($n = 10$), anxiety ($n = 20$), or both ($n = 6$) are included in exploratory analyses, reported in online supporting information Appendix S1, investigating the independent effects of these two diagnoses.

The final sample ($N = 69$) was aged 9–14 years ($M = 12.95$, $SD = 1.54$) and was 88.4% Caucasian, 4.3% African American, 1.4% Hispanic, 2.9% identified as other, 2.9% chose not to respond. Informed assent and consent were obtained from the participant and their parent, respectively, prior to participation. The Stony Brook University Institution Review Board approved the research protocol.

2.2 | Measures

2.2.1 | Gonadal hormones

Participants provided two saliva samples on the day of the scan; the timing of sample collection varied across participants, with some samples collected in the morning and some in the afternoon. Saliva samples were not collected at a specific point in menstrual cycle. Hormone levels were highly correlated across samples (all rs > 0.98), thus mean values across samples were used in analyses. All samples were assayed for salivary estradiol, progesterone, testosterone, and DHEA (dehydroepiandrosterone, which was not analyzed in the current study) using an enzyme immunoassay kit (Salimetrics, State College, PA); see supporting information Appendix S1 for test detection limits and Figure S1 for a scatter plot of hormone levels.

2.2.2 | Reported puberty

Daughters and mothers both completed the Pubertal Development Scale (PDS; Petersen, Crockett, Richards, & Boxer, 1988) to assess the daughter's pubertal development. This measure focuses on external signs of puberty including spurt in height, pubic hair, skin change, breast development, and menarche. Each item is rated from 1 to 4 with higher scores on the PDS indicating more advanced puberty. Daughter and mother reports of daughters' pubertal development were highly correlated ($r = 0.90$), thus the mean of daughter and mother report on the PDS are used in all analyses. Thirty-seven of the 69 girls had begun menstruation.

2.2.3 | Depressive symptom severity

Mothers and daughters completed the Child Depression Inventory (CDI), parent-report (PR) and self-report (SR) versions, respectively, to assess the daughter's depressive symptom severity (Kovacs, 1995, 1997). The CDI-SR consists of 27 items rated 0–2 and CDI-PR consists of 17 items rated 0–3. In both versions, a higher score indicates greater depressive symptom severity.

Mothers completed the Beck Depression Inventory (BDI) to assess current maternal depressive symptom severity (Beck, Steer, & Brown, 1996). The BDI consists of 21 items rated from 0–3 with a higher total score indicating greater depressive symptom severity. Four items from the BDI address anhedonic symptoms (loss of pleasure, loss of interest, loss of energy, loss of interest in sex). The sum of responses on these four items was used to quantify maternal anhedonia.

2.2.4 | Anxiety symptom severity

Mothers and daughters completed the Screen for Child Anxiety-Related Disorders (SCARED), parent-report and self-report versions, respectively, to assess the daughter's anxiety symptom severity at scan (Birmaher et al., 1999). Both versions consist of 41 items rated 0–2 with higher scores indicating greater symptom severity.

Mothers did not complete a report of current maternal anxiety symptoms.

2.3 | fMRI procedure

2.3.1 | Task design

Details regarding the doors task, a monetary guessing task, including patterns of activation and internal consistency, have been published previously for a larger overlapping sample (Luking, Nelson, Infantolino, Sauder, & Hajcak, 2017). See Figure S2 for a schematic of the doors task timing. Briefly, in the doors task, participants are instructed to select via button press one of two doors (door cue) and told that they could either win \$0.50 or lose \$0.25 on each trial depending on their selection. Unbeknownst to participants, subsequent win and loss feedback is then delivered in a fixed pseudorandom order such that all participants received exactly 50% win and loss feedback events (30 of each type) and thus "earned" the same amount of money. Feedback was delivered trial by trial (i.e., there was no running total).

2.3.2 | fMRI data processing

All functional images were preprocessed using Statistical Parametric Mapping (SPM8; Penny, Friston, Ashburner, Kiebel, & Nichols, 2011). The initial six volumes were discarded for spin saturation. The ArtRepair toolbox (P. Mazaika, Whitfield-Gabrieli, Reiss, & Glover, 2007; P. K. Mazaika, Hoeft, Glover, & Reiss, 2009) was used to correct motion artifacts by replacing affected volumes with a volume interpolated from the nearest unaffected volumes. Volumes with rapid movement above 1 voxel (2 mm) were identified and excluded. Participants were excluded from analyses if over 20% of data were discarded ($n = 6$). This motion correction strategy had been used in our previous work (Infantolino, Luking, Sauder, Curtin, & Hajcak, 2018; Luking et al., 2017). On average, 1.05% of volumes were interpolated ($SD = 2.41$). As is common for this age range, the number of interpolated volumes decreased linearly with age ($r = -0.22$; $p = 0.03$).

For each participant, the motion-corrected data were spatially realigned to the first volume. The T1-weighted structural image was coregistered to the mean functional image averaged across the realigned data, and segmented into maps of gray matter, white matter, and cerebrospinal fluid, thereby generating the realignment parameters needed to normalize to the Montreal Neurological Institute (MNI) EPI (echo-planar imaging) brain template. The same normalization parameters were then applied to the realigned functional data to warp the images to MNI space. Finally, the functional data were spatially smoothed with an isotropic Gaussian kernel of full-width half-maximum (FWHM) of 8 mm.

Event-related fixed-effects general linear models (GLMs) were created for each participant. Onset of door cue, win feedback, and loss feedback were modeled separately. The implicit baseline included between-trial fixation events. T contrasts were created from each participant's GLMs to examine activation to the difference between win and loss (i.e., win > loss) and general feedback (combined win and loss). Second-level mixed effects for each event type were created to examine between-subject effects.

2.3.3 | fMRI analyses

All fMRI analyses were conducted using SPM 8. Voxelwise regressions were conducted predicting the main effect of feedback (i.e., all win and loss feedback > baseline) and the difference

between win and loss feedback (i.e., win > loss). Predictors were entered in a hierarchical fashion. The first step of regressions was designed to investigate whether the quadratic effect of age explains a significant amount of variance in neural response to reward and whether maternal anhedonia moderates this effect.

As such, predictors in the first step of regressions included linear and quadratic effects of age, maternal anhedonia, and interactions between maternal anhedonia and age^2.[1] The second step of regressions was designed to investigate whether effects of age^2 would remain significant when controlling for gonadal hormone levels, whether gonadal hormone levels explain additional variance in neural response to wins/losses beyond effects of age, and whether maternal anhedonia moderates effects of gonadal hormones. As such, levels of gonadal hormones (estradiol, progesterone, testosterone) and their interactions with maternal anhedonia were included as additional predictors in the second step of regressions. All dependent variables and predictors were assessed on the same day, thus statistical predictions from regression analyses reflect concurrent rather than longitudinal relationships.

To focus analyses on regions typically engaged during reward processing/decision-making tasks, maps for individual predictors were masked to include only voxels within the striatum, insula, anterior cingulate, and middle frontal gyrus, which includes the dorsolateral prefrontal cortex (DLPFC; mask created using the automatic anatomical labeling atlas—Figure S3). Voxels within the mask were then thresholded at $p < 0.001$ prior to applying a small volume correction to yield cluster-level statistics corrected for multiple comparisons. Clusters with a familywise error (FWE)-corrected $p < 0.05$ were considered significant. Individual participants' responses to feedback were then extracted from significant clusters (i.e., regions of interest, ROIs) via the MarsBar toolbox (Brett, Anton, Valabregue, & Poline, 2002) and used in post hoc analyses. Post hoc regressions were conducted using SPSS 22 and investigated whether reported puberty (PDS) explained effects of age/hormones and whether current child symptom levels (CDI-SR/PR, SCARED-SR/PR) explained effects of maternal anhedonia.

3 | RESULTS

3.1 | Relations between age, reported puberty, gonadal hormones, and symptom severities

See Table 1 for descriptive statistics of individual difference measures. Age and reported puberty were strongly positively correlated, and levels of gonadal hormones were moderately positively correlated (Table 2). Neither age nor reported puberty related significantly to gonadal hormones, and hormone levels did not significantly differ based on menarche (all *p*s > 0.10). Maternal anhedonia did not relate significantly to developmental factors or to daughter depressive/anxious symptom severity.

TABLE 1 Descriptive statistics for measures of development and symptom severity

	Mean	*SD*	Min	Max
Age in years	12.92	1.54	9.05	14.99
PDS-SR	2.66	0.79	1.00	3.80
PDS-PR	2.70	0.78	1.20	4.00
CDI-SR	4.59	4.05	0	17
CDI-PR	0.27	0.22	0.00	0.80
SCARED-SR	0.45	0.24	0.00	1.05
SCARED-PR	0.18	0.14	0.00	0.58
Maternal BDI	3.34	3.98	0	20
Maternal anhedonia	0.99	1.24	0	4
Estradiol	1.95	0.90	0.51	5.21
Progesterone	94.34	65.61	9.34	312.49
Testosterone	49.33	20.54	13.28	99.57
Mean RT (ms)	786	237	393	1763

Note. Hormone levels are presented in ng/mL. SR = self-report; PR = parent-report; PDS = Pubertal Development Scale; CDI = Child Depression Inventory; SCARED = Screen for Child Anxiety-Related Disorders; BDI = Beck's Depression Inventory; RT = reaction time.

3.2 | Age and neural response to feedback

Age^2 significantly negatively predicted the general response to feedback within the left striatum/insula (Table 3, Figure 1a) with predicted quadratic relations between feedback response and age increasing through age ~12 and then decreasing after age ~13 (Figure 1b). No regions showed only a linear effect of age. Age^2 remained a significant predictor of feedback response when controlling for reported puberty in post hoc regressions (Table S1) and in analogous exploratory voxelwise regressions using PDS instead of age; neither PDS nor PDS^2 significantly predicted response to either feedback or win-loss. Further, age^2 significantly negatively predicted feedback response within a similar striatal/insular region in the voxelwise regression including gonadal hormone levels (Table 4). As such, the quadratic relation between age and response to feedback within the striatum and insula is specific to age, not reported puberty, and are not explained by reported puberty or current gonadal hormone levels. To test whether this effect was specific to feedback, an additional exploratory

[1]Exploratory regressions including additional participants (i.e., daughters of mothers with lifetime anxiety/depression diagnoses) were conducted to investigate effects of maternal lifetime anxiety and maternal lifetime depression diagnoses instead of dimensional maternal anhedonia. These analyses are presented in the supporting information Appendix S1.

TABLE 2 Correlations between measures of development and depressive/anxious symptom severity

	1	2	3	4	5	6	7	8	9	10
1. Age										
2. PDS – Mean	0.73**									
3. CDI–SR	0.11	0.29*								
4. CDI–PR	0.06	0.15	0.34**							
5. SCARED–SR	0.13	0.28*	0.64**	0.41**						
6. SCARED–PR	−0.01	−0.04	0.36**	0.55**	0.34**					
7. BDI - total	−0.03	−0.10	0.20	0.33**	0.23	0.38**				
8. BDI - anhedonia	−0.15	−0.22	0.10	0.22	0.02	0.23	0.75**			
9. Estradiol	0.17	0.17	0.15	0.09	0.01	0.16	0.05	0.03		
10. Progesterone	0.05	0.17	0.28*	0.39**	0.17	0.24	0.10	<0.01	0.53**	
11. Testosterone	0.28*	0.23	0.01	−0.14	0.01	−0.01	−0.08	−0.15	0.62**	0.40**

Note. Hormone levels are presented in ng/mL. SR = self-report; PR = parent-report; PDS = Pubertal Development Scale; CDI = Child Depression Inventory; SCARED = Screen for Child Anxiety-Related Disorders; BDI = Beck's Depression Inventory (maternal SR).
*$p < 0.05$ **$p < 0.01$.

voxelwise regression predicting response to the door cue was conducted. No regions showed a significant linear or quadratic effect of age on response to the door cue.

No regions showed significant relations between win-loss response and either linear or quadratic effects of age, indicating that responses to winning and losing feedback showed similar relations with age.

3.3 | Gonadal hormones and neural response to feedback

Estradiol significantly positively predicted the response to win > loss within a region of the medial frontal gyrus/anterior cingulate (Table 4, Figure 2), above and beyond other gonadal hormone levels and age. Estradiol continued to significantly predict win versus loss response within the medial PFC (beta = 0.61, $p < 0.001$) when menarche (yes/no) was entered into the model in a post hoc within-ROI regression. Further, menarche did not significantly predict win > loss response (beta = −0.06, $p = 0.65$).

The remaining gonadal hormone levels did not significantly predict the response to win > loss feedback. No regions showed a significant relation between gonadal hormone levels and the general response to feedback.

3.4 | Moderation of developmental trends by maternal anhedonia

Maternal anhedonia moderated the effect of age^2 on the response to feedback within the striatum/insula (Table 3, Figure 1). Within both regions, daughters of mothers reporting greater anhedonia showed an earlier peak in response to feedback relative to daughters of mothers reporting lower anhedonia (Figure 1; Seeley et al., 2007). A similar pattern was observed for daughters of mothers with a lifetime depression within regions showing functional connections to the salience network (ventral striatum, anterior insula) and regions functionally connected to the executive control network (dorsal striatum, dorsal anterior insula, DLPFC; Table S4, Figures S4, S5; Seeley et al., 2007).

Maternal anhedonia remained a significant moderator of the quadratic effect of age when daughter depressive and anxious symptom severities, both maternal and daughter report, and interactions between symptoms and age^2 were entered as additional predictors in post hoc analyses (dorsal striatum/insula [20,14,17] beta = −2.21, $p < 0.001$). Further, daughter anxiety/depression symptoms, and their interactions with age, did not significantly predict response to feedback (all ps > 0.10). This suggests that current daughter symptoms do not explain moderating effects of maternal anhedonia on developmental trends. No significant relationships were observed when predicting win > loss response.

Maternal anhedonia did not moderate effects of gonadal hormones for either the response to feedback or the response to win-loss feedback.

4 | DISCUSSION

Adolescence is a dynamic time of increasing response to reward and increasing liability for psychopathology, particularly for girls (Weissman et al., 2016). In the current study, we examined relations between developmental factors (i.e., age, reported puberty, gonadal hormones) and neural response to win and loss feedback. Further, we examined whether maternal anhedonia, a feature of depression related to blunted reward responding (Der-Avakian & Markou,

TABLE 3 Regions from voxelwise age regression investigating linear/quadratic effects of age and the moderation of such effects by maternal anhedonia

Contrast	Region	BA	MNI coordinates			*k*	*T*	*Z*	*p*(FWE)
			x	*y*	*z*				
Age^2: negatively predicting FB response	Putamen		−22	7	3	586	5.68	5.11	<0.001
	Insula	13	−38	−5	13		4.31	4.03	
	Insula	13	−31	2	17		4.26	3.99	
	Insula	13	−34	0	13		4.26	3.99	
	Putamen		−36	−19	−1		4.12	3.88	
	Insula	13	−38	2	6		4.02	3.79	
	Insula	13	−43	−12	6		3.98	3.75	
	Insula	13	−41	−9	10		3.97	3.75	
	Lateral globus Pallidus		−29	−19	−1		3.94	3.72	
	Insula	13	−34	9	−1		3.81	3.61	
	Caudate body	0	−10	14	13		3.70	3.52	
	Lateral globus Pallidus	0	−24	−12	−5		3.49	3.33	
	Insula	13	−45	−9	3		3.25	3.12	
	Putamen		25	12	−8	65	4.17	3.91	0.052
	Caudate body		15	16	10		3.50	3.34	
	Caudate body		18	21	3		3.43	3.28	
	Putamen		20	9	6		3.34	3.20	
Age^2 × maternal anhedonia: negatively predicting FB response	Caudate body		20	14	17	150	4.60	4.27	0.005
	Insula	13	39	9	6		4.28	4.00	
	Putamen		29	9	6		3.96	3.74	

Note. FB = feedback (mean win and loss); BA = Brodmann area; FEW = familywise error corrected.

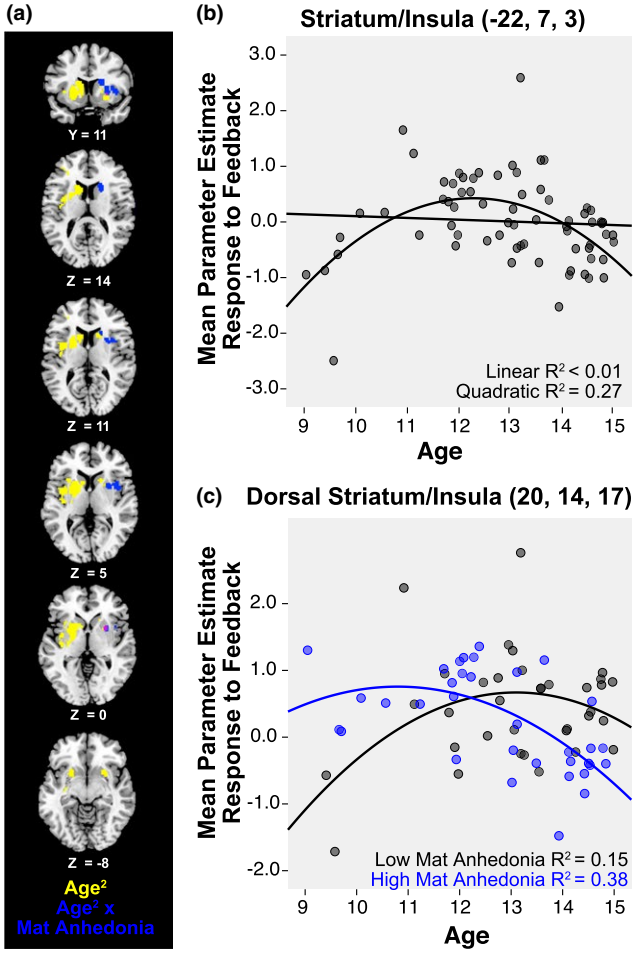

FIGURE 1 (a) Regions where feedback response showed a quadratic relation with age (yellow) or maternal anhedonia (Beck Depression Inventory anhedonia subscale) moderated the quadratic effect of age (blue); overlap presented in magenta. (b) Scatter plot showing the quadratic relation between age and feedback response within the putamen/insula. (c) Scatter plot showing the moderation of the quadratic relation between age and feedback response within the dorsal striatum/insula by maternal anhedonia (Mat Anhedonia)

2012), moderated relations between developmental factors and response to winning/losing. We found that age^2 and estradiol were unique predictors of reward response and that maternal anhedonia moderated the relation between age^2 and reward response within limbic regions.

Striatal response to feedback versus baseline peaked between 12 and 13 years, adding to the large body of neuroimaging work documenting peak striatal response to the receipt of winning feedback, typically versus neutral or loss feedback, in adolescence (for review, see Richards, Plate, & Ernst, 2013; Silverman et al., 2015). Further, this pattern was observed in regions beyond the ventral striatum, including more dorsal and lateral components of the striatum as well as within the insula. Although many studies have focused exclusively on the ventral striatum, there is also evidence of enhanced caudate response to both the receipt of gain feedback (Van Leijenhorst, Gunther Moor et al., 2010) and the receipt of aversive liquids (Galvan & McGlennen, 2013) during adolescence. Adolescents also show greater reactivity than adults within the posterior insula to appetitive liquids (Galvan & McGlennen, 2013) and greater reactivity than children and adults within the anterior insula to reward cues (Van Leijenhorst, Zanolie et al., 2010). Collectively, this evidence suggests that adolescence is a time of increased reactivity to the receipt of salient feedback/stimuli more broadly and within a more distributed set of regions that fall largely within the salience network (Seeley et al., 2007).

The early adolescent peak in response to feedback versus baseline was not explained by levels of gonadal hormones or reported puberty. This finding is echoed by work in rodent models where adolescent peaks in dopamine receptor expression and reward-related behaviors are observed in the absence of gonadal hormones (Andersen et al., 2002; Varlinskaya et al., 2013). However, this does not mean that puberty and/or gonadal hormones do not play a role in reward processing. In fact, relatively increased estradiol levels linearly predicted greater response to wins versus losses within the medial prefrontal cortex, replicating other work in adolescent females (Op de Macks et al., 2011).[2] Further, studies investigating effects of menstrual cycle phase in adult women suggest that estradiol increases neural response to reward (Diekhof & Ratnayake, 2016; Mulligan et al., 2018). It is important to note that we did not control for menstrual cycle phase in the current study. This is a common practice in early adolescence given that gonadal hormone levels show diurnal and monthly variability prior to menarche (Mitamura et al., 2000; Winter & Faiman, 1973) and that postmenarche monthly variability can take years to stabilize. This variability makes it difficult in adolescent females to translate gonadal hormone levels into a purely developmental measure, independent of cyclic variation. It is also difficult to examine the relative effects of reported puberty and age given that these processes are tightly coupled in adolescence (see Blakemore, Burnett, & Dahl, 2010, for commentary). Keeping in mind such limitations, our findings broadly suggest that early adolescent age, relative to late childhood and midadolescence, is related to a general increase in response to affective stimuli within salience regions, like the anterior insula and striatum, and that current levels of estradiol are related to an increase in response to win versus loss feedback within regions involved in regulation/control of reward signals, like anterior cingulate and medial prefrontal cortices (Nelson et al., 2005; Seeley et al., 2007). Future studies are needed to investigate potential mechanisms (e.g., changes in connectivity, endocannabinoid, or dopaminergic signaling) driving age-related changes in the response to feedback.

[2]Op de Macks et al., 2011, controlled for time of day but not cycle phase when assessing gonadal hormone levels.

TABLE 4 Regions from voxelwise regression investigating effects of both age and gonadal hormone levels

Contrast	Region	BA	MNI coordinates			*k*	*T*	*Z*	*p*(FEW)
			x	*y*	*z*				
Estradiol: positively predicting win > loss response	Medial frontal gyrus	9	−13	42	17	324	4.86	4.46	0.001
	Medial frontal gyrus/ anterior cingulate	10/32	15	44	3		4.16	3.90	
	Anterior cingulate	24/32	6	35	10		3.93	3.70	
	Anterior cingulate	24/32	6	28	13		3.89	3.67	
	Anterior cingulate	24/32	−6	21	24		3.82	3.61	
	Medial frontal gyrus	9/6	13	42	24		3.77	3.56	
	Anterior cingulate	24/32	−3	23	20		3.70	3.50	
	Medial frontal gyrus	9/6	1	35	27		3.64	3.46	
	Anterior cingulate	24/32	13	33	17		3.56	3.39	
	Medial frontal gyrus/ anterior cingulate	9/32	15	35	24		3.55	3.38	
	Anterior cingulate	24/32	−8	16	27		3.53	3.36	
	Anterior cingulate	24/32	−1	44	3		3.50	3.33	
	Medial frontal gyrus	9/10	13	49	10		3.37	3.22	
	Medial frontal gyrus	9/6	4	42	27		3.36	3.21	
Age^2: negatively predicting FB response	Putamen		−22	7	3	254	4.82	4.43	0.001
	Insula	13	−31	2	17		4.06	3.81	
	Insula	13	−43	0	3		3.94	3.71	
	Insula	13	−41	−5	10		3.88	3.66	
	Insula	13	−43	−12	6		3.86	3.64	
	Caudate body		−8	9	17		3.72	3.52	
	Caudate body		−8	14	13		3.72	3.52	
	Insula	13	−41	−12	13		3.71	3.52	
	Insula	13	−45	−9	3		3.70	3.51	
	Lateral globus pallidus		−15	5	−8		3.64	3.45	
	Caudate head		−10	12	−5		3.53	3.36	
	Putamen	2	−27	2	13		3.47	3.31	
	Insula	13	−38	−16	3		3.37	3.22	

Note. FB = feedback (mean win and loss); BA = Brodmann area; FWE = Familywise error corrected.

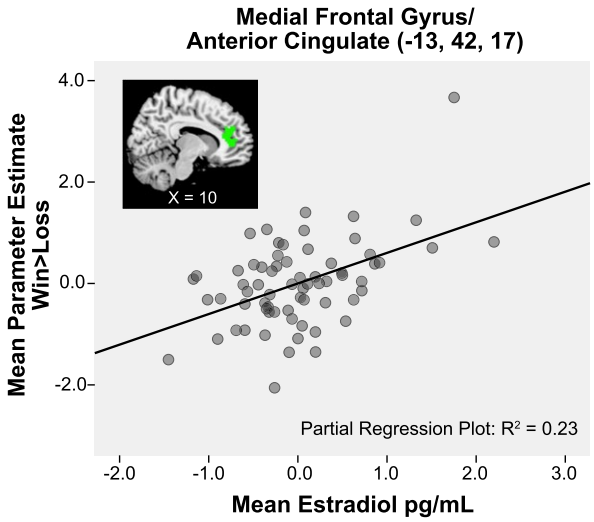

FIGURE 2 Partial plot depicting the relation between estradiol and win > loss response within the medial frontal gyrus/anterior cingulate

Maternal anhedonia moderated relations between the quadratic effect of age and neural response to feedback within the striatum and insula. In exploratory analyses, maternal lifetime depression diagnosis moderated effects of age^2 within a similar, but extended network of regions, largely within components of both the executive control network (bilateral DLPFC, dorsal caudate, dorsal anterior insula) and the salience network (ventral striatum, anterior insula; Seeley et al., 2007). Across regions, daughters of mothers with greater anhedonia, or lifetime depression, showed an earlier "peak" in response to feedback. As such, neural phenotypes associated during adolescence with major depressive disorder (i.e., blunted responses within salience and control regions; Halari et al., 2009; Sharp et al., 2014) were observed only at older ages—meaning that although blunted reactivity to feedback is observed in adolescent depression, in psychiatrically healthy females these neural signatures may emerge over adolescence in the context of familial risk and prior to the onset of elevated depression symptoms. This is consistent with the extant depression risk literature where reported relations between maternal depression and blunted striatal reward response are larger in adolescent than child samples (for review, see Luking et al., 2016) and effects of early emotional neglect/institutional rearing predict altered functional development of ventral striatal reward response with blunted response to reward emerging across adolescence in high-risk groups (Goff et al., 2013; Goff & Tottenham, 2015; Hanson et al., 2015). Future studies are needed to replicate these findings and investigate potential mechanisms (e.g., changes in connectivity, within different neural circuits) mediating the differential effects of anxiety and depression risk on developmental trajectories of feedback response.

This study had several strengths including a focus on multiple developmental factors; however, it is not without limitations. First, the severity of maternal anhedonia was low with a limited range, as mothers were never clinically depressed and was assessed at only one point in time. Although exploratory analyses where a small group of daughters of depressed mothers were compared to the larger sample showed a similar pattern, future studies, enriched for younger ages and wider range of maternal anhedonia, are needed to replicate current findings and to better understand relations between maternal anhedonia and reward-system function over a wider developmental range. Second, the sample was all female; it is possible that paternal and maternal anhedonia relate to development and reward function in different ways and that those patterns differ further for female and male offspring. Third, the current study was cross-sectional. Longitudinal change, not just in age but also in puberty (i.e., pubertal-tempo, Mendle, Harden, Brooks-Gunn, & Graber, 2010), may be particularly important for understanding how relations between psychopathology risk and neurodevelopment unfold over adolescence.

In conclusion, this is the first study to investigate relations between multiple developmental factors and neural response to winning and losing feedback in early adolescence using fMRI, as well as how such relations might differ based on maternal anhedonia. We observed a peak in response to both winning and losing feedback during early adolescence within the striatum and insula, not explained by gonadal hormones or reported puberty, which replicated and expanded upon extant findings. This age-related pattern differed based on maternal anhedonia or lifetime depression such that the blunted neural response to feedback, within salience and executive control regions associated with depression, was observed only at older ages. This suggests that patterns of neural response to reward associated with psychopathology risk may differ while these neural systems are in flux (Goff & Tottenham, 2015). Future work is needed to examine the mechanisms linking altered developmental trajectories of feedback response and maternally defined risk for mood disorder, as well as whether feedback response at different ages or across time are better predictors of functional outcomes.

ORCID

Katherine R. Luking https://orcid.org/0000-0002-8661-2387
Brady D. Nelson https://orcid.org/0000-0003-3214-8977

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1
Tables S1, S2
Figures S1–S5

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