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Exploring valence bias as a metric for frontoamygdalar connectivity and depressive symptoms in childhood

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Abstract

Negativity bias is a core feature of depression that is associated with dysfunctional frontoamygdalar connectivity; this pathway is associated with emotion regulation and sensitive to neurobiological change during puberty. We used a valence bias task (ratings of emotional ambiguity) as a potential early indicator of depression risk and differences in frontoamygdalar connectivity. Previous work using this task demonstrated that children normatively have a negative bias that attenuates with maturation. Here, we test the hypothesis that persistence of this negativity bias as maturation ensues may reveal differences in emotion regulation development, and may be associated with increased risk for depression. In children aged 6–13 years, we tested the moderating role of puberty on relationships between valence bias, depressive symptoms, and frontoamygdalar connectivity. A negative bias was associated with increased depressive symptoms for those at more advanced pubertal stages (within this sample) and less regulatory frontoamygdalar connectivity, whereas a more positive bias was associated with more regulatory connectivity patterns. These data suggest that with maturation, individual differences in positivity biases and associated emotion regulation circuitry confer a differential risk for depression. Longitudinal work is necessary to determine the directionality of these effects and explore the influence of early life events.

KEYWORDS
amygdala, emotion, medial prefrontal cortex, negativity bias, puberty

1 | INTRODUCTION

Individual differences in internalizing problems, like depression, are associated with amygdala–prefrontal cortex (PFC) circuitry (Gee, Gabard-Durnam, et al., 2013; Pezawas et al., 2005; Wang et al., 2009), and have been shown to emerge during the transition from childhood to adulthood (Emslie et al., 2005; Hankin et al., 1998; Kessler et al., 2001). Notably, a number of studies have linked the emergence of these individual differences to neurobiological changes during pubertal development (Andersen & Teicher, 2008; Angold & Costello, 2006; Paus et al., 2008). In particular, the medial prefrontal cortex (mPFC) strengthens connections with the amygdala during the years of puberty (Tottenham & Gabard-Durnam, 2017), a change that is intimately tied to the release of gonadal hormones (Lebron-Milad & Milad, 2012; van Wingen et al., 2011). These brain changes accompany profound changes in emotional behavior during this period of development that support functional social behavior (Denham, 1998; Eisenberg et al., 1993; John & Gross, 2004; Saarni, 1984).

In adulthood, connections between amygdala and a network of subregions in the PFC are understood to underpin emotion regulation mechanisms (Banks et al., 2007; Phillips et al., 2008; Wager et al., 2008) vis-a-vis downregulation of amygdala activity during emotional processing (Hare et al., 2008; Hariri et al., 2003; Pezawas

et al., 2005). In particular, the mPFC and amygdala, in addition to sharing numerous structural connections (Ghashghaei et al., 2007), show inverse functional connectivity during explicit emotion regulation (Urry, 2006) that is suggestive of a downregulation of amygdala (Gee, Humphreys, et al., 2013). Further, adults compared to children show greater inverse amygdala–mPFC connectivity (Gabard-Durnam et al., 2014; Gee, Humphreys, et al., 2013; Perlman & Pelphrey, 2011) in addition to relatively decreased amygdala activation (Guyer et al., 2008; Hare et al., 2008; Monk et al., 2003; Swartz et al., 2014; but see Moore et al., 2012) in response to negative emotional information. Indeed, younger children show a non-regulatory positive amygdala–mPFC connectivity pattern, but older children and adolescents show an inverse regulatory connectivity (Gee, Humphreys, et al., 2013). Moreover in adults, this more positive amygdala–mPFC connectivity has been implicated in the development of mental health disorders (Das et al., 2007; Gee, Gabard-Durnam, et al., 2013; Phillips et al., 2008). Taken together, this work suggests that although emotion regulation relies on a broad network of regions, the connections between the mPFC and the amygdala lie at the core of emotion regulation abilities in adulthood.

One notable feature of internalizing symptoms is a negativity bias, or an enhanced attention to and memory for negative information (Browning et al., 2010; Roy et al., 2008; Vasey et al., 1995), which is central to a variety of mood and anxiety disorders (e.g., depression; Beck, 1976; Williams et al., 2007). Interestingly, negativity bias is associated with more positive amygdala–mPFC connectivity (i.e., a non-regulatory pattern) (Etkin et al., 2009; Roy et al., 2013; see also Kim et al., 2011). Given that this same circuitry is sensitive to pubertal changes (Blakemore et al., 2010; Goddings et al., 2014; Herting et al., 2014; Mills et al., 2014; Vijayakumar et al., 2018, 2019) and is related to mental health disorders which emerge during puberty (Burghy et al., 2012; Hulvershorn et al., 2011; Kessler et al., 2005; Lee et al., 2014; Roy et al., 2013), understanding how this circuitry is associated with individual differences in negativity bias across puberty is essential to understanding the development of depression.

Because the release of gonadal hormones which drive neurobiological changes can begin as early as 8 years (Blakemore et al., 2010; Dorn et al., 2006), whereas depression tends to onset at around 14 years of age (Burke, 1991; Lewinsohn et al., 1994), the construction of this system may begin in relatively early pubertal stages prior to the onset of internalizing symptoms. That is, pubertal transitions may act as a developmental "prism", revealing individual differences in emotion regulation behaviors. In particular, the period from early to middle puberty is met with structural (Blanton et al., 2012; Goddings et al., 2014; Hu et al., 2013; Pfefferbaum et al., 2016) and functional (Clark & Beck, 2010; Forbes et al., 2011; Moore et al., 2012; Pfeifer et al., 2013; Vijayakumar et al., 2018, 2019) changes within both the amygdala and mPFC, as well as in their connectivity (Asato et al., 2010; Herting et al., 2014; Menzies et al., 2015; see also Gee, Humphreys, et al., 2013). This evidence is consistent with detailed animal models which find that the onset of puberty triggers reorganization within both the mPFC and its white matter fibers shared with the amygdala (Juraska & Willing, 2017; Zimmermann et al., 2019). The neurobiological processes associated with these relatively early pubertal stages may produce measureable individual differences in frontoamygdalar function critical to mental health outcomes.

Reliably measuring emotional biases in children during these early pubertal stages poses a methodological challege. For example, extant literature on negativity bias, which includes subclinical symptomology (Pagliaccio et al., 2014), tends to measure emotional biases using stimuli that rely on developmentally advanced cognitive/linguistic abilities not ideally suited for younger children. An emerging alternative approach has measured emotional biases using valence ratings of facial expressions, which are reliably identified in early childhood (Bruce et al., 2000; Widen & Russell, 2008). Although some expressions (e.g., happy or angry) signal clear valence information about the emotions and intentions of others, other expressions (e.g., surprise) are ambiguous because they signal both positive (e.g., an unexpected gift) and negative events (e.g., witnessing an accident). Notably, children compared to adults tend to rate surprised expressions as having a more negative meaning (i.e., more negative valence bias; Tottenham et al., 2013). Given that surprised expressions may be reliably identified across all ages and their ratings track developmental changes in emotional behavior, the ambiguity conveyed through surprised expressions is ideally suited to probe differences in negativity bias at early pubertal stages.

Neuroimaging work suggests that normative developmental shifts in emotional biases might reveal how pubertal changes correlate with variability in the neurobiology of depression. For instance, in adults, positive ratings of surprised faces depend upon slower and more deliberate processing (Kaffenberger et al., 2010; Neta et al., 2011; Neta & Tong, 2016), and appear to rely on emotion regulation mechanisms (Kim et al., 2003; Petro et al., 2018). This work suggests that the development of a more positive valence bias and a more mature (inverse) amygdala–mPFC connectivity during puberty can powerfully impact the emergence of internalizing symptoms during this developmentally sensitive period. For example, maintaining a negative valence bias and a more immature (positive) amygdala–mPFC connectivity into adulthood may be a risk factor for the onset of depression. However, no study has yet used neuroimaging to explore valence bias in youth populations. Thus, measuring normative shifts in valence bias and its associated amygdala–mPFC connectivity is an innovative approach that could reveal how pubertal changes correlate with variability in the neurobiology of depression.

Using a cross-sectional design, we explored the relationships between valence bias, depressive symptoms, and emotion regulation circuitry within an age range demonstrated to show a more negative valence bias (ages 6–13 years; Tottenham et al., 2013), a developing regulatory circuitry (Gabard-Durnam et al., 2014; Gee, Humphreys, et al., 2013; Perlman & Pelphrey, 2011; Silvers et al., 2017), and prior to the typical emergence of depression (age 14 years; Burke, 1991; Lewinsohn et al., 1994). This methodological choice enabled us to explore how relatively early pubertal changes contribute to the emergence of internalizing problems

in depression. We examined functional brain connectivity while viewing facial expressions during magnetic resonance imaging (MRI). We used pubertal scores as our proxy for maturity because (a) puberty is more closely tied than age to neurobiological changes in brain structure and function (Blakemore et al., 2010; Goddings et al., 2012) and especially amygdala–mPFC circuitry (Gabard-Durnam et al., 2014; Gee, Humphreys, et al., 2013; Herting et al., 2014; Perlman & Pelphrey, 2011; Silvers et al., 2017), and (b) age represents a different stage in maturation for males and females (Schuiling & Likis, 2016). For our exploratory analysis, we predict that with increasing maturation (within this relatively immature sample), a more negative valence bias and a more immature amygdala–mPFC connectivity pattern may pose an increased risk for depression.

2 | MATERIALS AND METHODS

2.1 | Participants

We collected data from 61 participants (29 female; ages 6–13 years, mean(*SD*) age = 9.18(2.13)). All participants and their parent reported that the participant had no history of neurological or psychiatric disorders, nor were any taking psychotropic medications. All protocols were approved by the University of Nebraska Committee for the Protection of Human Subjects. The participants and their parent were informed of all procedures prior to the child's participation, and a parent of each participant gave written informed consent prior to testing in accordance with the Declaration of Helsinki.

Six participants did not complete the neuroimaging portion of the task. An additional fourteen participants were excluded for failing to accurately rate the clearly valenced angry ($N = 4$) and happy ($N = 10$) expressions on at least 60% of trials, an accuracy threshold used for adult participants (Brown et al., 2017; Neta et al., 2009, 2013, 2018; Neta & Tong, 2016). The exclusion criteria for accuracy is particularly important because, if participants are not accurately rating angry faces as negative and happy faces as positive, then it is difficult to discern the specific valence interpretations of emotional ambiguity (i.e., valence bias). The final sample consisted of 41 participants (23 female; ages 6–13 years, mean(*SD*) age = 9.46(2.12)) that did not differ in age from those excluded ($t_{59} = 1.44$, $p = .16$, $d = 0.38$; range = 6–13; mean(*SD*) age = 8.60(2.06)), and who identified as either Caucasian ($N = 38$), Black/African-American ($N = 1$), Asian ($N = 1$), or Unknown ($N = 1$).

Albeit relatively small given the analysis of individual differences (Dubois & Adolphs, 2016), this sample size allowed us to explore the potential relationship between pubertal development, depressive symptoms, valence bias, and amygdala–mPFC functional connectivity. Further, given that no study has combined this valence bias task with neuroimaging in childhood, this exploration aims to serve as a first step in developing a testable model of the development of depressive symptoms and emotion regulation circuitry as measured by the valence bias task.

2.1.1 | Individual difference measures

We assessed puberty using the Petersen Puberty Development Scale (PDS; Petersen et al., 1988), and calculated scores as the average of each of the five items assessing physical development (out of the items numbered 1–7, where the five items included varied based on the participant's sex; each with a possible response of 1–4), as described by Petersen and colleagues (possible range = 1–4). Because PDS scores tend to deviate from 1 only after the age of 8 (Hu et al., 2013), all participants under the age of 8 were assigned the lowest score of 1 (i.e., prior to the onset of puberty). The data for each of these variables were submitted to a Shapiro–Wilk test to determine normality. The PDS score (Shapiro–Wilk: $W = 0.90$, $p = .001$), age (Shapiro–Wilk: $W = 0.94$, $p = .03$), and depressive symptoms (see below; Shapiro–Wilk: $W = 0.78$, $p < .001$) were non-normally distributed and valence bias trended toward a non-normal distribution ($W = 0.95$, $p = .07$). Because of the non-normality of these distributions, robust regression was used for all analyses of these variables.

As expected, given our targeted age range, the current sample subtended to relatively low PDS scores (range = 1–2.8, mean(*SD*) = 1.67(0.56), skewness(*SD*) = 0.71(0.37), kurtosis(*SD*) = −0.54(0.72)) rather than representing the full spectrum of possible scores. This questionnaire was completed by the child with instruction from the experimenter and is comprised of questions related to secondary sex characteristics (e.g., growth of body hair, deepening of voice), the appearance of which are a marker of gonadal hormone release during gonadarche (Susman & Rogol, 2013). The PDS score was not related to sex (Figure 1a; $t_{39} = 0.16$, $p = .87$, $d = 0.05$), but was positively corelated with age (Figure 1b; $t_{39} = 6.68$, $p < .001$, $d = 2.14$). The average full-scale intelligence quotient of the sample was within normal range as assessed by the two subset Wechsler Abbreviated Scale of Intelligence (WASI; range = 88–142; mean(*SD*) = 114.18(14.53), however there were missing data for one participant; Wechsler, 1999), and was not related to age ($t_{38} = -0.92$, $p = .36$, $d = -0.30$) or PDS score ($t_{38} = -0.66$, $p = .52$, $d = -0.21$).

Depressive symptoms were quantified using the major depression subscale of the *Revised Child Anxiety and Depression Scale* (RCADS; Chorpita et al., 2000) administered to the child's parent to maintain consistency across the sample given the young ages. The non-normality of these data (range = 0–12, possible range = 0–30, mean(*SD*) = 2.20(2.40), skewness(*SD*) = 2.06(0.37), kurtosis(*SD*) = 5.95(0.72)) was characterized by a skewness toward to the lower end of the RCADS scale. This scale has been validated in ages as young as 3 years (Ebesutani et al., 2015). However, because our age range (6–13 years) extends below the minimum of standardized T scores (grades 3–12), raw scores of the major depression subscale were used in the analyses, consistent with a recent study (Vantieghem et al., 2017). One participant reported a major depression score of 12 which, while the age of this participant (7 years) was below the range included in the published T scores, was associated with a T score in the youngest standardized sample (3rd grade) of 74, exceeding the cut-off associated with clinical diagnoses (T = 70;

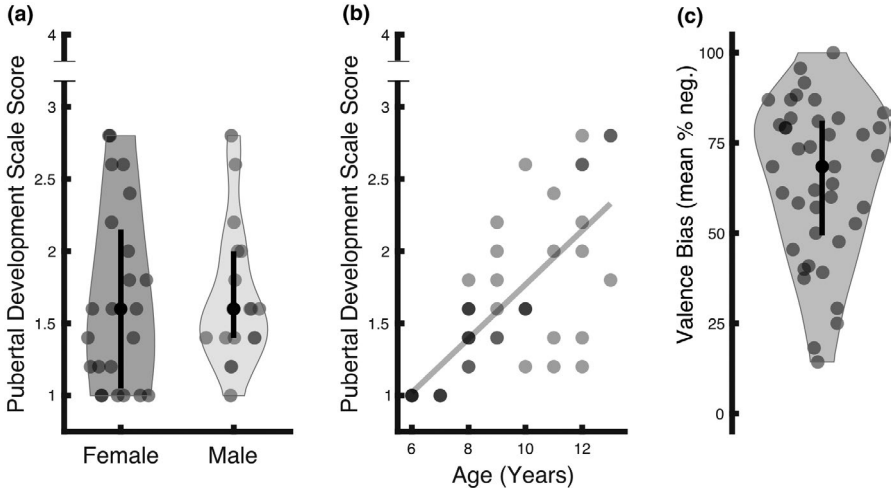

FIGURE 1 Descriptive illustration of measures. (a) The sample's PDS scores ranged from 1 to 2.8, out of a highest possible score of 4. These scores subtend to a low range (mean(*SD*) = 1.67(0.56), skewness(*SD*) = 0.71(0.37), kurtosis(*SD*) = −0.54(0.72)), consistent with the fact that the age range (6–13 years) of the sample subtended to relatively low PDS scores. Females ($N = 23$) and males ($N = 18$) did not differ as a function of PDS score ($t_{39} = 0.16$, $p = .87$). In each violin plot, the black circle indicates the median (females = 1.60, males = 1.60), and the lower and upper ends of the black line indicate the first (females = 1.05, males = 1.40) and third (females = 2.15, males = 2.00) quartile cut-off, respectively. (b) Age was positively related to PDS score ($t_{39} = 6.68$, $p < .001$). Darker dots represent an overlap of participants with identical age/PDS values. (c) Valence bias scores, computed as the percent of negative ratings of surprised expressions, ranged from 14.29% to 100% with a mean of 64.66%. The black circle indicates the median (68.42%), and the lower and upper ends of the black line indicate the first (49.41%) and third (81.12%) quartile cut-offs, respectively

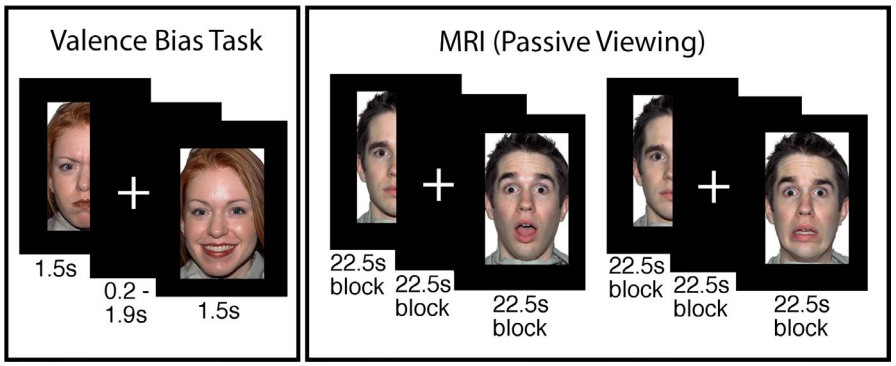

FIGURE 2 Depiction of procedure. In the valence bias task, participants viewed happy, angry, and surprised faces, and indicated whether each image "felt good or felt bad." In the MRI, participants passively viewed new faces (i.e., not overlapping with the valence bias task) during two runs with blocks of surprised and neutral faces. Two runs with blocks of fearful and neutral faces followed, but were not included in the present analysis. Faces shown here are from the NimStim Set of Facial Expressions (Tottenham et al., 2009)

Chorpita et al., 2000). However, the inclusion of this participant did not qualitatively affect the reported results (see Sections 3.1.2 And 3.2.1).

2.2 | Procedure

2.2.1 | Session 1: behavioral

All experimental stimuli were presented on E-Prime software (version 2.0.10; Psychology Software Tools, Pittsburgh, PA). In Session 1 (Figure 2), participants performed a task to assess their baseline valence bias in which they viewed positive (e.g., happy), negative (e.g., angry), and ambiguous (e.g., surprised) images on a black background. For each image, participants were asked to make a two-alternative, forced-choice decision (via keyboard press) as quickly and as accurately as possible, indicating whether each image "felt good or felt bad"; this language and stimuli have been in previous work within similar age groups (Kestenbaum, 1992; Tottenham et al., 2013). This included a set of 48 faces, 24 with an ambiguous valence (surprised expression), and 24 with a clear valence (12 angry and 12 happy expressions). Of the 48 faces, 34 discrete face identities were used (17 males, 17 females) posing angry, happy, and surprised expressions. Fourteen identities (seven females, ages 21–30 years) were taken from

the NimStim Set of Facial Expressions (Tottenham et al., 2009) and 20 (10 female, age 20–30 years) from the Karolinska Directed Emotional Faces database (Goeleven et al., 2008). All identities were European/European American. In separate but alternating blocks, scenes from the International Affective Picture System (IAPS; Lang et al., 1997) were presented, consisting of 24 scenes with an ambiguous valence and 24 with a clear valence (12 negative and 12 positive). The purpose of rating the IAPS scenes was outside the scope of the current report, and did not contribute to the valence bias score nor were they included in any analysis. All blocks of stimuli included 24 images (12 ambiguous, six positive, and six negative) presented in a pseudorandom order (see Figure 2 for a depiction of tasks). Each stimulus was presented for 1,500 ms followed by a fixation cross for either 200 or 1,900 ms.

We calculated the valence bias for each participant as the percentage of times that a participant indicated that a particular surprised face felt bad (e.g., a valence bias was 100% if that participant rated surprised faces as bad on all trials). Note that only the ratings of the surprised faces were used to calculate each valence bias score. Indeed, ratings of angry and happy faces serve primarily as anchors that support the validity of the valence bias measure. For this reason, we excluded participants whose ratings of angry and happy faces were below 60% accuracy. Thus, the variability in ratings for angry and happy faces is necessarily restricted and would not be a useful measure to include when calculating valence bias. Perhaps more importantly, ratings of surprised faces are the best representation of one's tendency to interpret dual-valence ambiguity as having a positive or negative meaning, which is indeed what the valence bias measure is intended to capture. Participants and parents then completed surveys (see above) and participants completed a mock scan (see below).

2.2.2 | Session 2: MRI

Session 2 followed Session 1 by approximately 9 days (mean(*SD*) days = 9.34(6.69), range 1–46 days; Table 1). Days between sessions was unrelated to the behavioral (see Section 3.1.2) and neuroimaging results (see Section 3.2.1). Participants viewed a new set of European/European American faces from the Umeå University Database of Facial Expressions (Samuelsson et al., 2012) across four experimental runs while positioned in a MRI scanner (Figure 2). Prior to entering the MRI, all participants underwent a mock scanning session to acclimate to the environment and practice instructions to remain still during scanning. Padding was used to secure the participants' head in a comfortable, static position. The experimenters provided feedback and reminders to remain still throughout the session.

Each experimental run consisted of four blocks of 15 image presentations. Faces were presented for 500 ms and separated by a fixed interstimulus interval of 1,000 ms. The first two runs consisted of two blocks of surprised faces and two blocks of neutral faces. Then, two additional runs followed which contained fearful instead of surprised faces, but their analysis was outside the scope of the present report. For the purpose of monitoring participants' attention to the stimuli, participants were instructed to make a button response each time a flower appeared (instead of a face) on the screen; within each block, three images of flowers were pseudo-randomly presented amid the presentation of 12 face stimuli. All stimuli during this session were 500 × 750 pixels with a black background. Note that, consistent with extant work measuring valence bias, we used angry and happy faces in the behavioral task because they are clearly negative and positive and also perceptually distinct from surprised faces. However, for the MRI session, we used fearful and surprised faces because both recruit a similar dorsal region of the amygdala due to their increased uncertainty (Whalen, 2007) and because fearful faces are commonly used in studies measuring amygdala reactivity in development (Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013; Perlman & Pelphrey, 2011). However the scope of the current report is focused on the neural responses to surprised faces given their dual-valence ambiguity and use in the valence bias task.

TABLE 1 Descriptive statistics for behavioral variables

Variables	Mean (*SD*)	Min	Max	Min possible	Max possible
Valence bias (mean % negative)	64.66% (21.76%)	14.29%	100%	0%	100%
Depressive Symptoms (RCADS – Major Depression; Chorpita et al., 2000)	2.20 (2.40)	0	12	0	30
Petersen Pubertal Development Scale (PDS) score (Petersen et al., 1988)	1.67 (0.56)	1	2.8	1	4
Days between sessions	9.34 (6.69)	1	46	—	—

2.3 | MRI Parameters

2.3.1 | MRI data acquisition parameters

The MRI data were collected at the University of Nebraska-Lincoln, Center for Brain, Biology, & Behavior, on a Siemens 3T Skyra scanner using a 32-channel head coil. Structural images were acquired using a T1-weighted MPRAGE sequence (TR = 2.20 s, TE = 3.37 ms, slices = 192 interleaved, voxel size = 1.0 × 1.0 × 1.0 mm matrix = 256 × 256, FOV = 256 mm, flip angle = 7°, total acquisition time = 5:07). Blood oxygen level-dependent (BOLD) activity was measured using an EPI scanning sequence (TR = 2.50 s, TE = 30 ms, slides = 42 interleaved, voxel size = 2.50 × 2.50 × 2.80 mm, matrix = 88 × 88 mm, FOV = 220 mm, flip angle = 80°, total acquisition time = 3:14 per block) in which slices were acquired parallel to the intercommissural plane and the volume positioned to cover the extent of the entire brain.

2.3.2 | Preprocessing

Preprocessing of MR images was conducted using the Analysis of Functional Neuroimages (AFNI) program suite (Cox, 1996). The first four TRs of each run were excluded to allow for scanner stabilization. Voxel time-series were first despiked by removing values with outlying data in each separate voxel's time-series. Then, slice timing correction was accomplished by re-referencing each scan to the first slice. These slice time corrected volumes were realigned to the minimum outlier image. Each volume was then aligned to the anatomical image before being warped to the Talairach template atlas (Talairach & Tournoux, 1988) provided by AFNI. Functional volumes were then spatially smoothed using a 6 mm^3 full width at half maximum kernel. The BOLD time-series, in each voxel separately, was normalized by dividing each time point by its average across all time points and then multiplying each time point by 100. Any images containing movements >0.9 mm^3, as determined by the motion parameters calculated during spatial realignment, were censored frame-wise from further analysis. No participants showed excessive movements in more than 16% of their scans (mean(*SD*) = 2.47%(4.37%)), consistent with previous work (Gee, Humphreys, et al., 2013). The number of censored scans did not differ between surprise and neutral trials ($t_{40} = 0.74$, $p = .46$, $d = 0.23$), and was not related to participant age ($t_{39} = -1.50$, $p = .14$, $d = -0.48$).

2.4 | Statistical analysis

2.4.1 | Behavioral

See Table 1 for descriptive information of analyzed behavioral variables. Although this study aimed to explore a puberty-moderated link between valence bias and both depressive symptoms and amygdala–mPFC connectivity, the cross-sectional design limited the possibility of inferring directional associations between these variables (e.g., valence bias impacts depressive symptoms or depressive symptoms impacts valence bias). We conducted two separate moderation analyses, first within the behavioral data, and second related to the MRI data (see section 2.4.4).

First, to determine whether a more negative valence bias was related to higher depressive symptoms, the two measures were submitted to a robust bivariate regression (calculated using the *fitlm* command in Matlab) in which valence bias was a predictor of depression. Then, the moderating effect of pubertal score on the relationship between valence bias and depressive symptoms was tested in a robust regression with valence bias as the outcome variable; this model had a constant term and four predictors: (a) depressive symptoms, (b) PDS score, (c) the interaction between depressive symptoms × PDS score, and (d) age, which was included in the model as a covariate. The interaction term coefficient represented the moderation effect. Importantly, the covariate of age was included to assess the effect of maturity as measured by PDS score, above and beyond the effect of age (Wierenga et al., 2014).

Previous studies have shown that differences in relative pubertal timing, or the relative individual differences in pubertal score at each age, are related to differences in emotion regulation and mental health outcomes (Gee, Gabard-Durnam, et al., 2013; Vantieghem et al., 2017). One possibility is that a moderation effect including valence bias and puberty could reflect a difference in relative pubertal timing, such that those who have a more negative valence bias are those who are either more or less developmentally mature than is typical for that age. To test for this possibility, the relative pubertal timing scores were submitted to a robust regression with valence bias.

2.4.2 | BOLD reactivity

To identify brain regions in which BOLD activity related to each stimulus condition, the BOLD data were submitted to a general linear model (GLM) in which surprise, fear, and neutral blocks were modeled separately for the four runs of the experiment. These regressors included a boxcar function modeling the onset and duration of each block that was convolved with the hemodynamic response function. Each run included a constant term and nuisance regressors: six motion parameters (three rotational and three translational vectors) calculated during realignment, and both a linear and cubic polynomial trend model to control for BOLD signal drifts, consistent with AFNI guidelines given each runs' 172.5 s duration.

2.4.3 | BOLD context-dependent connectivity

To assess the functional connectivity between the amygdala and the rest of the brain specific to each condition, a context-dependent connectivity analysis (i.e., psychophysiological interaction or PPI) was conducted using AFNI commands. Given that previous research has shown that a dorsal region of the amygdala—which is not typically captured in a structural amygdala region of interest—is

particularly sensitive to the ambiguity conveyed by surprised faces (Kim, Somerville, McLean, et al., 2003; Whalen et al., 2009), a functional, rather than structural, amygdala region was used as the seed. This functional amygdala seed region was defined as the voxels showing activation while viewing surprised expressions compared to baseline (the fixation period between blocks). This contrast was used to identify all voxels functionally related to the surprised expressions. The resulting amygdala clusters were considered significant if exceeding a corrected threshold (FWE: $p < .05$) based on Gaussian Random Field theory (Friston et al., 1994; Hayasaka & Nichols, 2003) that avoids the spatial autocorrelation issue raised by Eklund and colleagues (Eklund et al., 2016). This threshold consisted of both a cluster-forming ($p < .001$) and cluster-extent ($k > 21$) threshold. One voxel cluster, which thus served as the seed region in the context-dependent connectivity analysis, showed peak activation in the right basal forebrain (peak-$t_{40} = 7.01$, $p < .001$, $d = 2.22$; $k = 86$; x = 16, y = −4, z = −11) and extended into the dorsal amygdala (Figure 3a). Highlighting the importance of using this functionally defined amygdala region, this seed region overlapped in only 10 voxels with a structural amygdala region in an atlas from Faria et al. (2012).

To model the face-evoked BOLD activity in this amygdala region, the BOLD activity from this dorsal amygdala region was first deconvolved with a hemodynamic response function, and then multiplied with boxcar functions modeling stimulus onsets and durations separately for each condition, resulting in four condition-specific models of amygdala activity. Lastly, these condition-specific amygdala regressors were convolved with a hemodynamic response function. These regressors entered a GLM with a constant term, task onset regressors, and a model of the amygdala activity across the whole duration of the experiment. Thus, the beta values associated with the condition-specific amygdala regressors reflect changes in amygdala connectivity evoked by the blocked stimulus presentation. As in the previously described analysis of BOLD reactivity, nuisance regressors consisted of the six motion models to control for movement artifacts and, because the BOLD activity was analyzed across all runs continuously (690 s), five polynomial trends to control for BOLD signal drifts, consistent with AFNI guidelines.

2.4.4 | mPFC–amygdala BOLD connectivity and valence bias

Connectivity between the amygdala and mPFC during emotional processing changes across development, such that there is a shift toward more inverse connectivity around age 10 years, thought to support age-related changes in emotion regulatory behaviors (Gee, Humphreys, et al., 2013). The amygdala seed region used in this connectivity analysis was defined as voxels showing significant activation for surprise relative to baseline, a criterion chosen in order to include as many voxels sensitive to the surprised face expressions as possible. For comparison with valence bias and puberty, the connectivity beta differences for surprise *relative to neutral* were used in order to isolate amygdala connectivity specific to the ambiguity conveyed through the surprised expressions rather than a general response to facial expressions. Thus, these surprise > neutral connectivity beta differences for each participant were submitted to a robust multiple regression (calculated using the *fitlm* command in Matlab), separately at each voxel, with a constant term and four predictors: (a) valence bias, (b) PDS score, (c) the interaction between valence bias × PDS score, and (d) age, which was included in the model as a covariate. To determine whether puberty moderated the

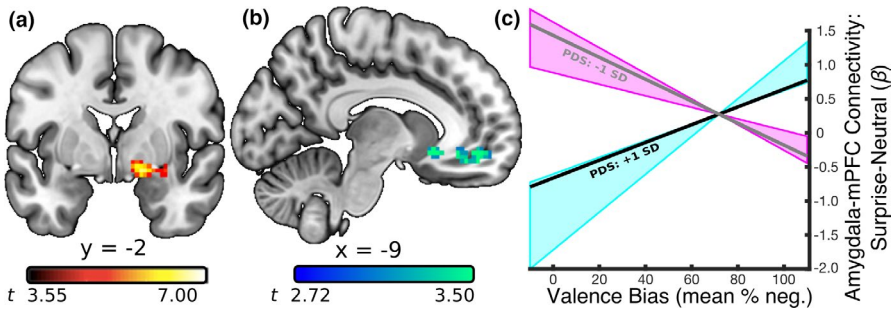

FIGURE 3 Relationship between amygdala–mPFC connectivity and negative valence bias as a function of PDS score. (a) A seed region in the right amygdala was defined using the contrast of surprised facial expressions versus baseline ($p < .0005$). The dorsal position of this cluster within the amygdala is consistent with previous work demonstrating that content conveying ambiguous valence recruits the amygdala/substantia innominata in particular (Kim, Somerville, McLean, et al., 2003; Whalen et al., 2009). (b) A PPI analysis based on surprise > neutral activity in the amygdala seed revealed a relationship between amygdala connectivity and valence bias that was moderated by PDS score in the mPFC (peak-$t_{36} = 4.50$, $p = .00007$). (c) The estimated regression slopes between valence bias and the surprise > neutral amygdala–mPFC connectivity betas, at a lower (gray line; 1 standard deviation below the mean PDS score; $t_{36} = -4.89$, $p = .00002$) and relatively higher (black line; 1 standard deviation above the mean PDS score; $t_{36} = 3.52$, $p = .001$) PDS scores. More mature children (within this relatively immature sample) that have a mature (inverse) connectivity pattern were more likely to have a positive valence bias while those that have the less mature (positive) connectivity pattern were more likely to show a negative valence bias; this relationship reached significance for PDS scores between 2.0 and 2.8 (blue shaded area). Lower PDS scores predicted the *opposite* relationship between valence bias and amygdala–mPFC connectivity; this relationship reached significance for PDS scores between 1.0 and 1.4 (pink shaded area)

relationship between valence bias and amygdala connectivity in any mPFC region, the interaction term coefficients, computed at each voxel separately, were passed through a cluster-forming ($p < .01$) and -extent threshold ($k > 75$) according to Guassian Random Field theory guidelines for multiple comparison correction (Friston et al., 1994; Hayasaka & Nichols, 2003).

2.4.5 | Individual differences between BOLD, age, and puberty

Lastly, we examined the direct relationship between the BOLD measures (amygdala activation and connectivity with mPFC) and age and puberty. Specifically, we calculated the average betas values, separately for each participant, for (a) the surprise > neutral BOLD activation for all voxels in the amygdala seed (see Section 2.4.3) and (b) the surprise > neutral amygdala connectivity for all voxels in the mPFC (see Section 3.2.1). These average beta values were submitted to a robust regression with both age and PDS score, yielding four separate beta coefficients.

3 | RESULTS

3.1 | Behavioral

3.1.1 | Valence ratings – Characterizing valence bias

Participants rated angry faces as negative (mean(*SD*) % negative = 85.91(11.75); range = 62–100), and happy faces as positive (mean(*SD*) % negative = 10.18(9.10); range = 0–30). In contrast, ratings of surprised faces showed greater variability (Figure 1c; mean(*SD*) % negative = 64.66(21.75); range = 14.29–100), and represented the valence bias for each individual, such that higher scores indicated a more negative bias. Within this age range, which subtended to relatively low PDS scores, valence bias was not significantly related to age ($t_{39} = -0.48$, $p = .63$, $d = -0.15$) or PDS score ($t_{39} = -0.42$, $p = .68$, $d = -0.14$).

3.1.2 | Depressive symptoms and valence bias moderated by puberty

Table 1 lists the descriptive statistics for the behavioral variables. A bivariate robust regression revealed that valence bias was positively related to depressive symptoms ($t_{39} = 2.29$, $p = .03$, $d = 0.73$), such that those with a more negative bias had higher depressive symptoms. For the moderation analysis, the interaction between depressive symptoms and PDS score was significant ($t_{36} = 2.48$, $p = .02$, $d = 0.83$; Figure 4) indicating that puberty, when controlling for age, moderated the relationship between depression and valence bias. As an additional means to address the concern of sample size in this model, we also conducted the moderation analyses in Bayesian models and found moderate support for the hypothesis that puberty moderates the relationship between depression and valence bias compared to the null hypothesis of no moderation (see Supporting Information).

To explore this moderation, the relationship between valence bias and depressive symptoms was calculated for each PDS score. This relationship became significant between a PDS score of 1.6 and 2.8 (out of the sample's range of 1.0–2.8; Figure 4, blue shaded area). To test for potential confounding effects, we ran similar moderation analyses that included sex (male or female), or number of days between sessions 1 and 2, or excluded the participant with a supra-threshold clinical major depression score, or excluded participants who did not identify as Caucasian. Notably, the effects were qualitatively the same with each of these modifications, suggesting these variables did not impact the reported findings.

As an additional analysis we tested whether a difference in relative pubertal timing is associated with valence bias, which may potentially confound the moderation effects reported above. Relative

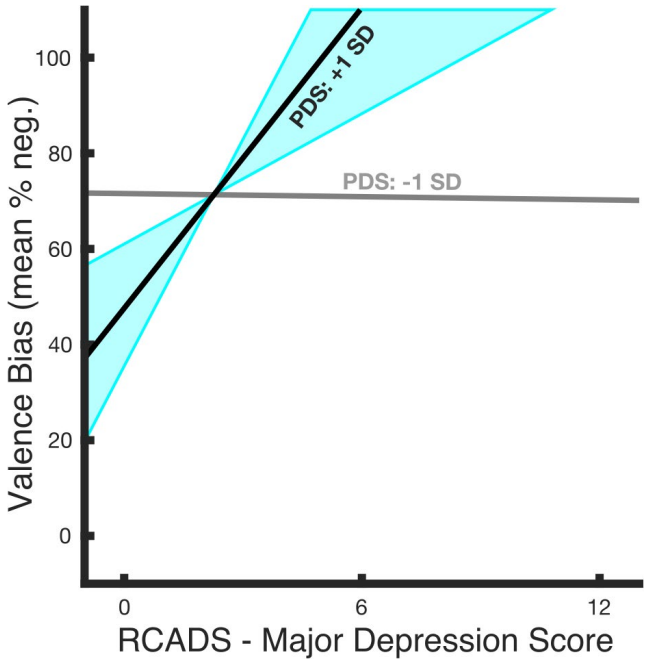

FIGURE 4 Relationship between valence bias and depressive symptoms as a function of PDS score. The relationship between depressive symptoms and valence bias was moderated by PDS score ($t_{36} = 2.48$, $p = .02$) such that valence bias and depressive symptoms shared a stronger positive relationship at relatively higher PDS scores. The estimated regression slopes for the relationship between valence bias and depressive symptoms at different PDS scores illustrate that a lower PDS score (gray line; 1 standard deviation below the mean PDS score; $t_{36} = -0.06$, $p = .95$) predicted no relationship, whereas a higher PDS score (black line; 1 standard deviation above the mean pubertal score; $t_{36} = 2.63$, $p = .01$) predicted a positive relationship; this relationship reached significance for PDS scores between 1.6 and 2.8 (blue shaded area). At no point did lower PDS scores predict a significant relationship between valence bias and depressive symptoms, therefore no shaded area (region of significance) is illustrated around the −1 *SD* line

pubertal timing was operationalized as the residuals of the relationship between PDS score and age. These relative pubertal timing scores were not related to valence bias across all participants ($t_{39} = -0.17$, $p = .86$, $d = -0.05$).

3.2 | MRI

3.2.1 | Context-dependent amygdala–mPFC connectivity and valence bias

The relationship between surprise > neutral amygdala connectivity and valence bias, when controlling for age, was moderated by puberty in two clusters (Table 2). In other words, those with a higher PDS score (within this relatively immature sample) showed an effect whereby a more positive valence bias was associated with a more inverse (mature, i.e., suggestive of emotion regulation) connectivity in these regions. The first cluster showed peak activation in the right subcollosal gyrus (peak-$t_{36} = 5.52$, $p = .000003$, $d = 1.84$; $k = 170$; Talaraich (x, y, z) coordinates: 11, 11, −14) and extended into the right rectal gyrus and right anterior cingulate. The second cluster showed peak activation in the left medial frontal gyrus (Figure 3b; peak-$t_{36} = 4.50$, $p = .00007$, $d = 1.50$; $k = 92$; Talaraich (x, y, z) coordinates: −11, 49, −11) and extended into the left anterior cingulate, consistent with reports of amygdala connectivity with the mPFC (Kim, Somerville, Johnstone, et al., 2003). Again, as an additional means to address the concern of sample size in this model, we conducted the moderation analyses in Bayesian models and found strong support for the hypothesis that puberty moderates the relationship between valence bias and amygdala–mPFC connectivity compared to the null hypothesis of no moderation (see Supporting Information).

To explore the moderation within this latter mPFC cluster, the conditional effects of puberty were calculated from the intercept and slope of the relationship between valence bias and the voxel averaged amygdala–mPFC connectivity beta values; this was done separately at each PDS score in this sample (range = 1.0–2.8). These conditional effects (Figure 3c) indicated that for those with a relatively higher PDS score (2.0–2.8; i.e., the highest scores in this sample), the relationship between valence bias and amygdala–mPFC connectivity was more positive (Figure 3c, blue shaded area). In other words, children with both a higher PDS score and a less mature (positive) connectivity pattern had a more negative valence bias. In contrast, children with both a higher PDS score and a more mature (inverse) connectivity pattern had a more positive valence bias. The opposite effect (i.e., a more negative valence bias predicted more inverse amygdala–mPFC connectivity) was significant at PDS scores 1.0–1.4 (Figure 3c, pink shaded area).

TABLE 2 Clusters of significant BOLD surprise > neutral amygdala connectivity whose relationship with valence bias was moderated by pubertal score

Region	x	y	z	Peak-t	k
R Subcollosal Gyrus	11	11	−14	5.52	170
L Medial Frontal Gyrus	−11	49	−11	4.50	92

As with the behavioral results (see Section 3.1.2), we tested for potential confounding effects by rerunning the moderation analyses and including sex, or number of days between sessions 1 and 2, or excluding the participant with a supra-threshold clinical major depression score, or excluding participants who did not identify as Caucasian. In addition, although surprise > neutral amygdala activation was not related to amygdala connectivity ($t_{39} = -1.10$, $p = .28$), we ran another moderation which included amygdala activation as a covariate to test whether the connectivity moderation effect was confounded by the level of BOLD activation. Notably, the effects were qualitatively the same with each of these modifications, suggesting these variables did not impact the reported findings.

It is also important to note that the BOLD signal within the amygdala is sensitive to signal dropout (Krasnow et al., 2003). Because the PPI analysis consists of correlations between BOLD signals in different brain regions, the diminished signal may lead to false-positive or false-negative correlations related to noise. To rule out the possibility that the current results were driven by signal dropout, we performed the same PPI and moderation analysis, but applied an intensity-based mask, calculated as described by Peer et al. (2016) and implemented using these authors' Matlab code as provided on their webpage (Computational Neuropsychiatry Lab - Intensity Based Masking (IBM) Tool, n.d.) to remove amygdala voxels with low signal in each individual participant. The results of this analysis were qualitatively identical to the moderation analysis reported above.

3.2.2 | Individual differences between BOLD, age, and puberty

To describe the basic relationship between the BOLD measures and age and puberty, the surprise > neutral amygdala BOLD activation betas and the amygdala–mPFC connectivity betas were submitted to a robust regression with age and PDS score. Neither amygdala activation nor connectivity were related to age (activation: $t_{39} = 0.68$, $p = .50$, $d = 0.22$; connectivity: $t_{39} = -0.19$, $p = .85$, $d = -0.06$) or PDS score (activation: $t_{39} = 0.08$, $p = .94$, $d = 0.03$; connectivity: $t_{39} = -0.37$, $p = .72$, $d = -0.12$).

Finally, we used a Cox test (Greene, 2003) to compare the fit of the model that measures the moderating effect of puberty (see section 3.2.1) with a second model in which puberty is replaced by age as the moderating variable. This analysis found that the model including puberty compared to the model including age explained more variance in amygdala–mPFC connectivity ($z = -3.72$, $p = .0002$; but note that both models explained significant variance in depression symptomology). In other words, as expected, brain activity was more sensitive to the biological changes that occur during puberty,

as there does appear to be a unique role for pubertal variability in moderating these overarching effects.

4 | DISCUSSION

Within this relatively pubertally immature sample, higher PDS scores coupled with a more negative valence bias were associated with more depressive symptoms and less inverse amygdala–mPFC connectivity (suggestive of weaker emotion regulation). Broadly, this pattern of exploratory results is consistent with the notion that internalizing problems, such as depression, arise from dysfunctional emotion regulation circuitry (Banks et al., 2007; Phillips et al., 2008) and, more specifically, that this link arises from developmental differences (Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013; Hare et al., 2008; Perlman & Pelphrey, 2011).

Given that this amygdala–mPFC circuit is intimately tied to biological changes during puberty (Andersen & Teicher, 2008; Angold & Costello, 2006; Paus et al., 2008), the early pubertal period explored in this study may be critical in the construction of healthy emotion regulation mechanisms. These exploratory results support a model for future research which predicts that, while negative valence bias in early childhood is normative, negative bias in later development is putatively *maintained* by the failure to develop a more mature, regulatory frontoamygdalar circuitry, which may *increase the risk* for depression.

These findings are consistent with our "initial negativity hypothesis" that posits that the initial or default interpretation of surprise is more negative (Neta et al., 2011; Neta & Tong, 2016; Neta & Whalen, 2010). In contrast, positive ratings depend upon slower and more elaborate emotion regulation processes which override the initial negativity and putatively downregulate the amygdala response (Kaffenberger et al., 2010; Kim, Somerville, Johnstone, et al., 2003; Neta et al., 2011; Neta & Tong, 2016; Neta & Whalen, 2010; Petro et al., 2018), processes that are likely compromised in depression and anxiety (Beck, 1976; Reef et al., 2011; Williams et al., 2007). Indeed, age-related differences in this emotion regulation circuity (i.e., amygdala–mPFC connectivity; Gee, Humphreys, et al., 2013) are associated with mental health risk factors in adults (Hare et al., 2008). The current results extend this "initial negativity hypothesis" by suggesting that individual differences in valence bias may originate during pubertal development, alongside the development of this emotion regulatory circuitry that putatively overrides the default, or initial negativity.

The utility of surprised faces in tracking individual differences in negativity bias and emotion regulation brain circuits is broadly consistent with a functional—contextual account of facial displays (Crivelli & Fridlund, 2018), which predicts that an expression's emotional value depends on its social, environmental, and/or cultural context (Barrett & Kensinger, 2010). Whereas happy and angry expressions signal predominantly positive or negative social outcomes, respectively, surprised faces signal multiple possible outcomes spanning positive and negative valence (i.e., dual-valence ambiguity). Thus, the valence assigned to surprised expressions presented without context is more pliable to interpretation. The use of stimuli with dual-valence ambiguity represents a methodological advance in conceptualizing negativity bias in that it side-steps limitations present in extant literature. For instance, negativity bias is often measured via either an attentional bias toward clearly negative *or* away from clearly positive stimuli (see Fales et al., 2008) or by examining responses to ambiguous stimuli with alternate meanings that could be either negative or neutral, but not positive (e.g., "lie"; Mathews et al., 1989). These findings not only rely on cognitive/linguistic abilities not developmentally appropriate for children, but by not examining responses to stimuli with a dual-valence representation (i.e., negative *and* positive possible interpretations), these earlier findings are skewed toward the extremes of the valence spectrum. As such, this earlier work is limited in its ability to identify individual differences in responses to emotional stimuli during sensitive periods of development, and thus has more limited findings regarding the developmental origins of negativity bias. Future work will benefit from incorporating our valence bias task to examine individual differences in emotion reactivity and regulation, particularly in young ages.

These findings make a meaningful first step toward establishing the developmental origins of negativity bias. One caveat is the relatively small sample size with somewhat limited variance in depressive symptoms, and that the PDS was only administered to children ages 8 years and older. Future work should replicate our exploratory findings in larger samples with a wider range of depressive symptoms and also determine the extent to which these findings, which use parent-reported subclinical depression (see; Muris et al., 2003), generalize to those with clinically diagnosed or self-reported depression. Further, future work should also explore the extent to which the effects generalize to the range of mental health disorders in which internalizing problems manifest. Finally, although there was no explicit emotion regulation task, a more inverse frontoamygdalar connectivity is thought to represent emotion regulation (Gee, Humphreys, et al., 2013; Ochsner et al., 2004). Indeed, the connectivity in these children spanned both positive and negative values, consistent with previous studies (Gee, Humphreys, et al., 2013; Hare et al., 2008) which suggest that *inverse* connectivity (rather than a *lack of positivity connectivity*) may be associated with a more adult-like regulatory circuitry. While this study treated connectivity as a continuous measure in order to test its relationship to valence bias and puberty, future work with larger sample sizes in normative adults should aim to identify the point at which negative frontoamygdalar connectivity defines an emotion regulatory process.

Whether or not long-term mental health trajectories are impacted by environmental factors may also be explored in future research. For instance, early life stress is a risk factor for mental health disorders (Tottenham et al., 2011) and is associated with developmental differences in regulatory circuitry (Cohodes et al., 2020; Heim & Binder, 2012; Lupien et al., 2009). Recent work suggests that positive affect (Sewart et al., 2019) and even more specifically, an earlier developmental shift toward a more positive valence bias (Gee, Gabard-Durnam, et al., 2013; Vantieghem et al., 2017) may

serve as a buffer from the development of depressive symptoms. This suggests that resiliency, or the ability to find a positive outlook in potentially negative situations (Gross & John, 2003), may implicate the same emotion regulation mechanism explored in this study (Tugade & Fredrickson, 2004).

The moderating role of puberty on the relationship between valence bias and depressive symptoms occurred earlier in maturation (starting at a PDS score of 1.6 and up to the highest score in this sample of 2.8) than the relationship between valence bias and brain connectivity (starting at a PDS score of 2 and up to the highest score in this sample of 2.8). Although cross-sectional, these findings provide preliminary evidence that a change toward a more positive valence bias and away from depressive symptoms may have downstream effects on developing more adult-like brain connectivity patterns. Future longitudinal work should extend our exploratory work and aim to (a) test the prediction that the *maintenance* of negative valence bias is associated with both an increase in depressive symptoms and a slower development of (inverse) amygdala–mPFC connectivity, and (b) establish the directionality these relationships. The opposite relationship between valence bias and amygdala–mPFC connectivity was also observed at a PDS score of 1.4 and below. However, our predictions about the effects in those at the earliest stages of puberty were less clear, particularly before the point at which puberty moderates the link between valence bias and depressive symptoms (below a PDS score of 1.6) and given the assumed scores in children ages 6–7 years.

Because females and males show different age onsets in puberty (Schuiling & Likis, 2016), maturity was measured via a scale of pubertal development. While sex differences in depression tend to emerge after the age of 13 (i.e., outside of this sample's range; Ferguson et al., 1999; Hankin & Abramson, 2001), other work has shown that there are important sex differences in the emergence of depression (Graber, 2013; Hankin et al., 1998). If negative valence bias is a risk factor for depression, then sex may moderate the relationship between these two variables. Relatedly, early pubertal timing is also a risk factor for depression in females in particular (Hankin & Abramson, 2001). Given that this study was underpowered to test potential sex differences, continued work should explore, in wider ranges of age and PDS, whether sex differences in the relationships between valence bias, depression, and emotion regulation circuitry emerge in older ages. Further, this future work could also explore whether or not normative pubertal timing differences predict differences in valence bias and emotion regulation skills.

Future longitudinal work may also hold broad implications for treating mental health. For instance, the effects reported here may pinpoint developmental periods most sensitive to long-term mental health outcomes. Such information will be critical for informing potential interventions (e.g., mindfulness), which can improve emotion regulation success and decrease negativity bias (Goldin & Gross, 2010; Jazaieri et al., 2014). These types of training may be particularly useful for individuals that putatively maintain a negativity bias beyond a normative developmental stage such that this bias interferes with normal, healthy functioning.

Finally, there are a few limitations worth noting. First, although the face stimuli used here were taken from previous work examining valence bias (Neta et al., 2009) even using a developmental sample (Tottenham et al., 2013), one potential limitation of this work is that the face stimuli were exclusively adult facial expressions. Indeed, previous research has shown better facial identity recognition and memory for own-age faces (Anastasi & Rhodes, 2005; Denkinger & Kinn, 2018). Having said that, children appear to perform equally well at identifying facial expressions (Vetter et al., 2018) of children versus adult faces. In addition, given that the participants range from 6 to 13 years of age, the use of appropriately age-matched actors would introduce a new challenge of providing different stimuli to participants of different ages. Future studies comparing valence bias across child and adult facial expressions in a developmental sample will be useful for identifying the impact of this methodological choice. Second, the present findings did not replicate the age-related decrease in amygdala activity (Gee, Humphreys, et al., 2013; Guyer et al., 2008; Hare et al., 2008). This discrepancy may have arisen because the current sample was aged 6–13 years, which is on the low end of pubertal maturation and thus may not capture the full range of biological changes which affect the amygdala (Blakemore et al., 2010; Goddings et al., 2014; Vijayakumar et al., 2019). Indeed, previous work showing an age-related decrease in amygdala activity reported such an effect only after adolescence (Gee, Humphreys, et al., 2013; Hare et al., 2008). Third, we note that the reported effect sizes may be inflated, given recent work showing that lower sample sizes are susceptible to biased and unstable effect sizes (Marek et al., 2020). Lastly, the pattern of results reported here was achieved using two separate moderation analyses and did not directly test the relationship between depression and brain activity, given there was insufficient power to relate these measures in the context of both valence bias and puberty. In other words, additional work may test the degree to which developmental differences in depression are linked with emotion regulation circuitry, and if valence bias is a risk factor for these developmental differences.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data relevant to this manuscript are available on the NIH National Database Archive.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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