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# Developmental Sex Differences in Negative Emotion Decision-Making Dynamics: Computational Evidence and Amygdala-Prefrontal Pathways

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## Abstract

Sex differences in human emotion and related decision-making behaviors are recognized, which can be traced back early in development. However, our understanding of their underlying neurodevelopmental mechanisms remains elusive. Using developmental functional magnetic resonance imaging and computational approach, we investigated developmental sex differences in latent decision-making dynamics during negative emotion processing and related neurocognitive pathways in 243 school-aged children and 78 young adults. Behaviorally, girls exhibit higher response caution and more effective evidence accumulation, whereas boys show more impulsive response to negative facial expression stimuli. These effects parallel sex differences in emotion-related brain maturity linking to evidence accumulation, along with age-related decrease in emotional response in the basolateral amygdala and medial prefrontal cortex (MPFC) in girls and an increase in the centromedial amygdala (CMA) in boys. Moreover, girls exhibit age-related decreases in BLA–MPFC coupling linked to evidence accumulation, but boys exhibit increases in CMA–insula coupling associated with response caution. Our findings highlight the neurocomputational accounts for developmental sex differences in emotion and emotion-related behaviors and provide important implications into the neurodevelopmental mechanisms of sex differences in latent emotional decision-making dynamics. This informs the emergence of sex differences in typical and atypical neurodevelopment of children's emotion and related functions.

**Key words:** children, development, emotion, sex dimorphism, task fMRI

## Introduction

Sex differences in emotion and related functions are recognized across multiple disciplines including psychology, psychiatry, and neuroscience. Women, for instance, are twice more likely to be diagnosed with depression or anxiety than men (Kessler et al. 2005; McCarthy et al. 2012). In healthy conditions, women are more likely to internalize emotions, which typically results in withdrawal and loneliness (Eaton et al. 2012). Men, on the other hand, are more likely to externalize emotions, which leads to impulsive and coercive behaviors (Eaton et al. 2012). In theory, many sex differences in adulthood are thought to be traced their origins back early in development (Zahn-Waxler et al. 2008). During childhood, in particular, the brain undergoes rapid development and children begin to build up gender schema of their own to guide emotion-related behaviors (Martin and Halverson 1981). Sex differences in affective functions become more pronounced and stabilized as the brain matures, but our understanding of the underlying neurodevelopmental mechanisms is still in its infancy. Sex differences in emotional facial expression recognition have been well characterized at a behavioral level (Olderbak et al. 2019), making this domain an ideal paradigm for studying the potential neural mechanisms of sex differences from childhood to adulthood.

The social–emotional development models posit that children acquire their sex-specific roles and gender identity through learning and socialization experiences, through which sex differences in affective information processing unfold over development (Liben et al. 2002; Chaplin and Aldao 2013). For instance, girls compared with boys are more likely to internalize emotions (Carter et al. 2003) and advantage for self-reported emotional feelings, more sympathy, and higher accuracy to recognize other's emotions (Zahn-Waxler et al. 2008). Such sex differences appear to become more pronounced as children grow up (Chaplin and Aldao 2013), which agrees with the social–emotional development views suggesting that children's recognition, experience and expression of emotions can be modulated by gender-related socialization, expectancies, and social status as they grow up (Zahn-Waxler et al. 2008; Brody and Hall 2010). From a developmental perspective, the neurobiological models posit an organizational hypothesis, suggesting that gonadal hormones early in development are to organize or program permanent sex differences in neural circuits across life span. And this organized substrate is activated by the sex-specific hormonal milieu of adulthood to express sex-related behaviors (Zahn-Waxler et al. 2015). Specifically, testicular hormones organize male agonistic, aggressive, and anxiety-like behaviors, whereas ovarian hormones organize female maternal behaviors from adolescent to adulthood (Peper et al. 2009; Schulz and Sisk 2016; Sisk 2016). Moreover, the biological factors cause sex differences in brain circuits that may in turn lead to different interactions with the environment including early life stress, social expectancies, and a combination of socialization by parents or caregivers and peers (Knickmeyer et al. 2005; Chaplin and Aldao 2013; Bale and Epperson 2015).

People tend to recognize other's emotions with a decision response based on effective information they perceive and accumulate over time (Busemeyer et al. 2007; Forstmann et al. 2016). According to the sequential-sampling theory, emotional perception is analogous to perceptual decision-making, which can be modeled as a continuous process of moment-to-moment evidence accumulation (White et al. 2009; Ratcliff et al. 2016). The drift-diffusion model (DDM) is most commonly used to estimate dynamic evidence accumulation and infer latent cognitive computations by modeling trial-by-trial reaction times (RTs) with several free parameters: "drift rate" referring to the speed of accumulating evidence, "decision threshold" reflecting the amount of effective evidence accumulated to reach a decision response (Ratcliff et al. 2016), "nondecision time" referring to nondecision process like sensory encoding and motor execution. This approach has been used to investigate latent dynamic cognitive computations involved in perceptual decision-making, recognition, emotion in both children (Warren et al. 2020) and adults (White et al. 2010). However, few studies to date have addressed developmental sex differences in latent dynamic computations during emotion processing.

Sex differences in emotion-related brain systems in adulthood have been widely studied (Vuilleumier and Armony 2013), but the underlying neurodevelopmental origins remain elusive. Previous adult studies reported that men showed higher activation in the amygdala and prefrontal regions than women when viewing emotional faces (Fusar-Poli et al. 2009). Mixed findings, however, were reported for age-related changes in task-invoked activation in the amygdala and prefrontal cortex (PFC), with both positive and negative correlations in men but not in women (Andreano et al. 2014; Hardee et al. 2017). Moreover, functional organization of the amygdala and PFC plays a critical role in emotional processing (Hariri et al. 2003; Kim et al. 2003; Pezawas et al. 2005; Hare et al. 2008). The amygdala functional connectivity with medial prefrontal cortex (MPFC) appears to show a "developmental shift" from positive to negative from childhood to adulthood (Gee et al. 2013). The amygdala encompasses several subdivisions, including the basolateral amygdala (BLA) and centromedial amygdala (CMA) as 2 major subregions, with distinct neuroanatomical connections and functions (LeDoux 2000). The BLA is critical in perception and evaluation of emotional stimuli via its direct projections to distributed cortical regions, whereas the CMA is critical for regulation of emotional expression and related physiological responses via projections to subcortical structures including the insula (LeDoux 2000; Davis and Whalen 2001). However, no investigations to date address how sex differences in BLA and CMA connectivity in emotional processing begin to emerge over development.

To address above questions, we leverage computational modeling and functional magnetic resonance imaging (fMRI) to investigate developmental sex differences in emotion-related latent dynamic computations and underlying neural substrates in 243 typically developing children and 78 young healthy adults. Participants underwent fMRI while they were performing an negative emotional face matching task with 2 alternative decision choices adapted from previous studies (Hariri 2002; Hariri et al. 2003) with negative facial expressions as stimuli (Fig. 1A). The hierarchical Bayesian estimation of drift-diffusion model (HDDM) (Wiecki et al. 2013) was implemented to assess latent emotional decision-making dynamics during negative emotion processing, including speed of evidence accumulation and decision threshold. A set of univariate activation, multivariate pattern similarity, and task-dependent functional connectivity were employed to identify developmental sex differences in emotion-related brain maturity, functional activation, and connectivity. According to the socio-emotional development and the organizational hypotheses with empirical observations, we predicted that girls would show more effective evidence accumulation than males, whereas boys would be more impulsive to trigger an executive choice during negative

**Table 1** Participant demographics and sex distributions

| | Children | | Adults | |
|---|---|---|---|---|
| | Girls | Boys | Females | Males |
| Counts | 117 | 126 | 43 | 35 |
| Age range | 7.25 ~ 11.75 | 7.24 ~ 12.26 | 19.95 ~ 25.33 | 19.65 ~ 25.27 |
| Age: mean ± standard deviation | 9.25 ± 1.33 | 9.17 ± 1.30 | 22.78 ± 1.44 | 22.07 ± 1.80 |
| Ethnics | Chinese Han | | | |

emotion processing. We further predicted that sex differences in emotion-related brain systems and connectivity among BLA, CMA, and prefrontal circuits would begin to arise during childhood and would undergo developmental changes from childhood to adulthood.

## Materials and Methods

### Participants

A total of 243 typically developing children (7–12 years old) and 78 young healthy adults (20–25 years old) were participated in this study (Table 1 for demographics). Neuroimaging and behavioral data were obtained from Children School Functions and Brain Development Project (CBD, Beijing Cohort). Written informed consent form was obtained from every participant or one of their parents for children. Children were recruited by handing out the booklets to several homogeneous elementary schools in Beijing. Adults were recruited by local communities in Beijing. The study procedures were approved by local ethics in accordance with the standards of the Declaration of Helsinki. Participants had no obstacle in vision and reported no history of neurological or psychiatric disorders, and no current use of any medication or recreational drugs. Children aged between 11.5 and 12.4 were grouped with aged between 10.5 and 11.4 for small sample size. Participants with excessive head motions (max. frame displacement >0.5 mm) were excluded from further analyses.

### Negative Emotion Matching Task

Participants were asked to perform an emotional face-matching task with negative facial expressions as stimuli (Fig. 1A) during fMRI scanning. The task consisted of 10 blocks, with 6 trios of images in each block. Each block started with a cue for 5 s indicating either emotional or control condition and followed by 6 trios of images with 5 s each. For emotional block, participants viewed each trio and selected which one of 2 negative facial expressions in the bottom that expressed the same emotion as the target expression on the top. Similar to previous studies (Thomas et al. 2001; Canli 2002; Ewbank et al. 2009), only negative facial expressions (i.e., fear, anger) were included and there were obtained from a standardized dataset (Wang and Luo 2005). For sensorimotor control, participants viewed 6 trios of scrambled shapes and selected which one of 2 shapes in the bottom that displayed the same orientation as the target shape. Participants were instructed to make a response as quickly and accurately as possible. Only negative facial expressions were included in the present study for the following reasons. First, we opted for a blocked-design task by using only negative emotional facial expressions to localize the amygdala and related systems according to previous studies (Thomas et al. 2001; Canli 2002; Ewbank et al. 2009). Second, we collapsed fearful and angry facial expressions into emotional condition to increase the statistical power and sensitivity to the neural response in the amygdala and related systems. This strategy also allowed us to investigate developmental sex differences in the amygdala-prefrontal pathways in response to negative emotion processing in general, rather than dissociate neural substrates of specific emotions.

### Behavioral Analyses

Participant's demographic data and behavioral measures were analyzed in SPSS (version 22.0; platform: Windows 10, https://www.ibm.com/analytics/spss-statistics-software). Accuracy and reaction times (RTs) were obtained separately for emotional and control conditions after the following steps: 1) Trials with RTs shorter than 200 ms or longer than 5 s were removed; 2) participants with accuracy in the control condition less than 50% were considered unable to understand the task and removed from further analyses. Mean accuracy and RTs in the 2 conditions were submitted to repeated-measures analyses of variance (ANOVAs) with Condition (Emotional vs. Control) as within-subject factor and Sex (Male vs. Female) and Group (Children vs. Adults) as between-subject factors. The confidence intervals (CIs) were computed to assess the differences in independent Pearson's correlations using Zou's method (Zou 2007). The basic structure of Zou's method does not require Fisher's z be used because Fisher's z could lead to inflated false positive rates when sampling from non-normal distributions and the population correlation differs from zero. Zou's method also takes into account the dependency between correlations and works well in small to moderate sample sizes.

### Drift-Diffusion Model

The DDM has been extensively used to estimate 2-choice decision-making processes (Ratcliff and McKoon 2008) and has been widely used to assess latent dynamic decision processes involved in perception and decision-making (Ratcliff et al. 2016). It conceptualizes decisions as noisy evidence accumulation processes to fit reaction times and accuracy in terms of parameters decision threshold (a), drift rate (v), and nondecision time (T) (Fig. 2A). The drift rate provided the estimation of the speed during evidence accumulation. Decision threshold reflected the response caution of a decision to be made. The nondecision time refers the sensory processes and response execution, which is not included in the decision processes. The HDDM was implemented to model trial-by-trial RTs across participants during the emotional decision-making task; it has been proven to be effective and robust in estimating model parameters when less data are available in certain circumstances such as pediatric and clinical populations (Wiecki et al. 2013). The Bayesian estimation generates the joint posterior distributions of all model parameters, given the

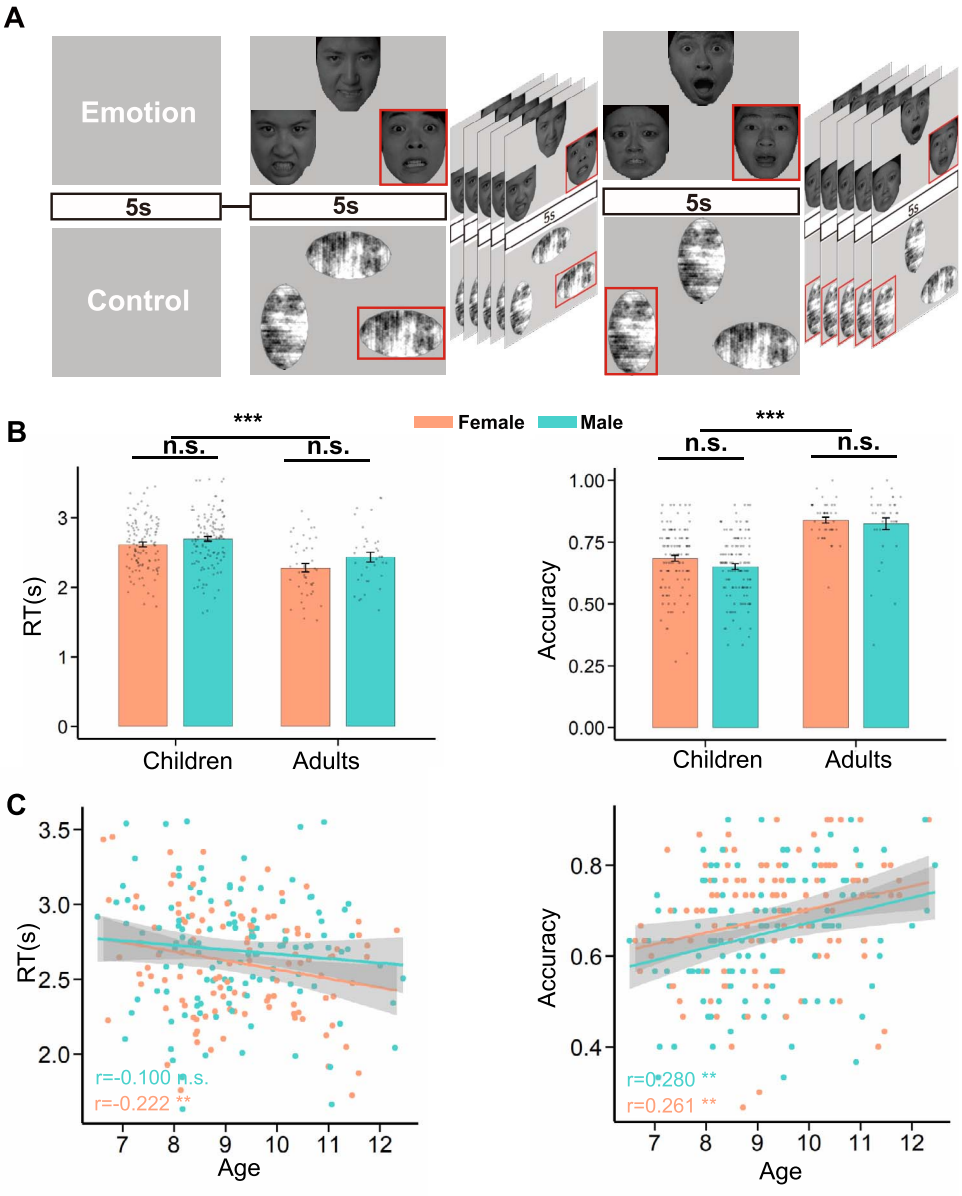


**Figure 1.** Developmental sex differences in behavioral performance in negative emotional face-matching task. (*A*) An illustration of example trials of emotional perception task with anger and fear facial expressions. Participants viewed each trio of facial expressions (or mosaic scrambled ones as control condition) and were instructed to select which one item in the bottom expressed the same emotion type (i.e., anger or fear) as the target face on the top. (*B*) Bar graphs depict mean accuracy and reaction times (RTs) in the emotional perception task, with relatively inferior performance for both emotional and control conditions in children than adults. (*C*) Scatterplots depict the correlations of accuracy (and RTs) with age from 7 to 12 years old in boys and girls. $^{**}P < 0.01$; $^{***}P < 0.001$; n.s., not significant.

observed data. The posterior parameter distribution provides not only a point estimate, but also uncertainty of the estimate, and can be straightforwardly applied for Bayesian inference (Gelman and Meng 2005). Here we used HDDM to generate each parameter on individual level. Markov Chain Monte Carlo simulations were used to generate 120 000 samples from the joint posterior parameter distributions (Gamerman and Lopes 2006). The first 50 000 samples were discarded as burn-in (see Wiecki et al. 2013 for a more detailed description of the procedure), and we used a thinning factor of 10, with outliers specified at 5%. Convergence was assessed by visually inspecting Markov chains and computing R-hat Gelman–Rubin statistic where successful convergence is indicated by the values less than 1.1 (Krypotos et al. 2015). The best model was determined by comparing the deviance information criterion (DIC) of each model, which evaluates the goodness of fit of model with lower DIC values indicating better model fit (Spiegelhalter et al. 2002).

## Image Data Acquisition

Whole-brain images were acquired from Siemens 3.0 T scanner (Magnetom Prisma syngo MR D13D, Germany) using a 64-channel head coil with a $T_2$*-sensitive echo-planar imaging (EPI) sequence based on blood oxygenation level–dependent contrast with 33 slices (3.5 mm thickness, 0.7 mm skip) parallel to the anterior and posterior commissure line and covering the whole

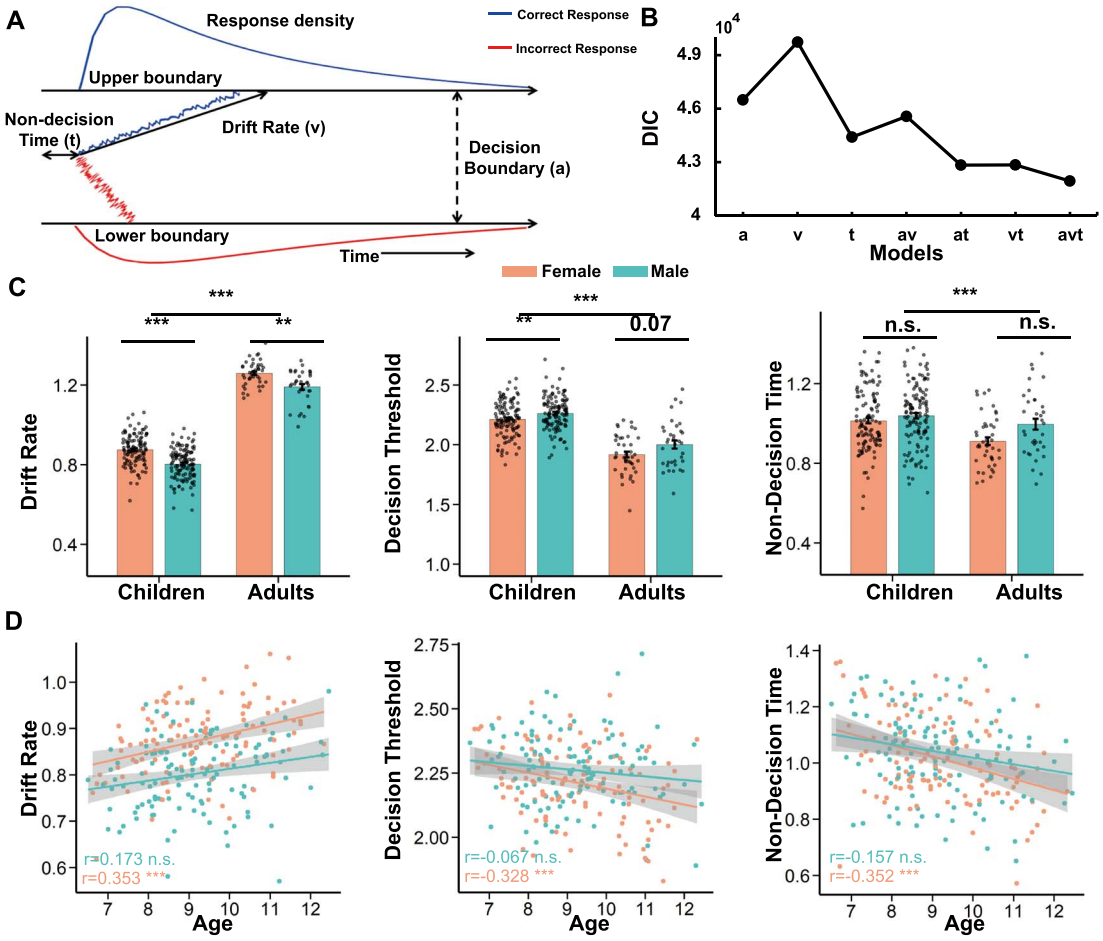


**Figure 2.** Developmental sex differences in latent decision-making dynamics during negative emotion processing. (*A*) An illustrate of latent parameters for HDDM. In this model, evidence information representing by the sample paths with added Gaussian noise is accumulated until a certain decision threshold (or boundary) is reached to make a choice response. The drift rates for emotional and control conditions are depicted as lines with high and low color saturation, respectively. (*B*) The DIC differences between the best-fit model and the other model variants. The best model consists of the boundary (a), drift rate (v), and nondecision time (t) varying across emotional and control conditions. (*C*) Bar graphs depict parameters of boundary, drift rate, and nondecision time in emotional and control conditions as a function of males (boys) and females (girls) in children and adults, with better performance in females than males in both adults and children. (*D*) Scatterplots depict developmental trajectories of latent dynamic computations during emotional processing from 7 to 12 years old in boys and girls, with a prominent improvement in boundary, drift rate, and nondecision time as age increases in girls but not in boys. ***$P < 0.001$.

brain were imaged with the following parameters: repetition time (TR) 2000 ms, echo time (TE) 30 ms, flip angle (FA) 90°; voxel size 3.5 × 3.5 × 3.5 mm3, field of view (FOV) 224 × 224 $mm^2$, the emotional face-matching task lasted 358 s, or 179 volumes. Each participant's high-resolution anatomical images were acquired through 3D sagittal $T_1$-weighted magnetization-prepared rapid gradient echo (MPRGE) with the following parameters: 192 slices, TR 2530 ms, TE 2.98 ms, FA 7°, inversion time 1100 ms, voxel size 0.5 × 0.5 × 1.0 $mm^3$, acquisition matrix 256 × 224, FOV 256 × 224 $mm^2$, Bandwidth (BW) 240 Hz/Px, slice thickness 1 mm.

## Image Data Preprocessing

Brain images were preprocessed using statistical parametric mapping (SPM12) based on MATLAB platform (version 8.1). The first 4 volumes of functional images were discarded for signal equilibrium and participants' adaptation to scanning noise. Remaining images were corrected for slice acquisition timing and realigned for head motion correction. Subsequently, functional images were co-registered to each participant's gray matter image segmented from corresponding high-resolution $T_1$-weighted image, then spatially normalized into a common stereotactic MNI space and resampled into 2-mm isotropic voxels. Finally, images were smoothed by an isotropic 3D-gaussian kernel with 6-mm full-width half-maximum.

## Univariate General Linear Model (GLM)

To assess task-invoked neural response to emotional stimuli, the emotional and control conditions were modeled as 2 separate boxcar regressors and convolved with the canonical hemodynamic response function (HRF) built in SPM12. Additionally, 6 head motion parameters were included to regress out the variability related to head movement. We used high-pass filtering

with a cutoff of 1/128 Hz, and corrections for serial correlations using a first-order autoregressive model AR (1) in the GLM framework. Relevant contrast parameter estimate images were initially generated at the individual-subject level, then submitted to a group-level analyses for treating participants as a random variable. Significant clusters were determined at a voxel-level threshold of false discovery rate corrected $q < 0.05$ on the whole brain. Given our priori hypotheses regarding the MPFC, this region was additionally investigated with a reduced search region (i.e., small volume correction) consisting of an unbiased mask derived from the Neurosynth for family-wise error correction for multiple comparisons, with a height threshold of $P < 0.001$ and an extent threshold $P < 0.05$ corrected using 3dClustSim in AFNI (Nichols and Hayasaka 2003). Parameter estimates from each cluster were extracted by using MarsBar to characterize developmental differences in brain activation patterns between children and adults.

### Multivariate Maturation Index

We implemented multivariate pattern similarity analysis to compute an overall maturation index of brain systems involved in emotional matching. Multivoxel neural activity patterns were extracted from the whole-brain mask associated with the contrast of emotional with control condition in adult females and males separately as well as their average, with age and sex as covariates of no interest. We then computed the similarity of multivoxel neural activity patterns in each child with corresponding multivoxel pattern of adult females and males separately as well as their average, with age and sex as covariates of no interest. Pearson correlation coefficients were Fisher's z-transformed and submitted to further analyses to assess developmental sex differences in negative emotional processing of both sexes. This index assessed the degree of multivoxel neural activity pattern in each child as relative to the averaged neural activity pattern across adults as well as the same-sex adults.

### Mediation Analysis

Mediation analysis was performed both on boys and girls with drift rate as dependent variable, age as independent variable, and maturation index as mediator. A total of 5000 bootstrap resamples were used to generate 95% CIs that estimated the size and significance of the effects. All $P$ values $< 0.05$ were considered statistically significant and all reported $P$ values are 2-tailed.

### Moderated Mediation Analysis

Moderated mediation model was constructed to examine the moderation effect of sex on the mediatory roles of maturation index in the associations between age and drift rate. The moderated mediation analysis and several mediation analyses were performed using PROCESS macro (version 2.16), a mediation package executed on SPSS (version 20.0, IBM Corporation, Armonk, NY) that is based on the regression analyses. The schematic illustration of moderated mediation analyses was shown in Figure 3G. The dependent variable (drift rate), independent variable (age), the mediator variable (maturation index), and moderator (sex) were included in the moderated mediation model. A total of 5000 bootstrap resamples were used to generate 95% CIs that estimated the size and significance of the effects. All $P$ values $< 0.05$ were considered statistically significant and all reported $P$ values are 2-tailed.

### Task-Dependent Functional Connectivity Analysis

Task-dependent functional connectivity was examined using psychophysiological interaction (PPI) analysis (Friston et al. 1997). This analysis examined condition-specific modulation of functional connectivity of a specific region of interest (ROI) with the rest of the brain, after removing overall task activation and common driving inputs. To accommodate more than 2 experimental conditions within the same model, we employed a generalized form of task-dependent PPI (Friston et al. 1997) by following procedures. First, mean time series of each seed were extracted and then deconvolved to uncover neural activity (i.e., physiological variable). Next, the resultant neural activities from each seed were multiplied with the task design vectors corresponding emotional and control conditions (i.e., a binary psychological variable) to form 2 PPI vectors. These vectors were further convolved with a canonical HRF to form 2 PPI regressors of interest. The psychological variables representing the emotional and control conditions, as well as mean-corrected time series of each seed, were also included in the GLM to remove overall task-related activation and the effects of common driving inputs on brain connectivity. Brain regions showing significant PPI effects were determined by testing for a positive slope of the PPI regressor. Contrast images of PPI at an individual level were then submitted to a second-level group analysis for 4 seed regions separately. Significant clusters were determined by using the same thresholding criteria for the GLM analyses above. To illustrate developmental sex differences in functional connectivity of the BLA (or CMA) with its target regions, we extracted data from significant clusters and plotted correlations for visualization purposes only.

### Definitions of Amygdala Subregions

Two major amygdala subregions were separately created by using observer-dependent cytoarchitectonic probabilistic maps of the amygdala nuclei implemented in the Anatomy toolbox including the BLA and the CMA. Maximum probability maps were used to create these anatomical masks using the Anatomy toolbox (Eickhoff et al. 2005). To avoid potential partial volume effects of small ROIs like CMA with the limited spatial resolution, voxels were included in the maximum probability maps only if the probability of their assignment to either one of 3 subdivisions was higher than any other nearby structures with greater than 40% likelihood. Specifically, we used 40% probabilistic masks of the left and right CMA according to the Juelich histological atlas implemented in FSL with the same resolution in our present study. These probabilistic maps have proven to have high reliability and accuracy for segmenting the CMA and BLA in young children (Kim et al. 2010) and have also been successfully implemented in analyses of human fMRI data with a low spatial resolution in adults (Etkin et al. 2009; Roy et al. 2009; Michely et al. 2020), adolescents (Barbour et al. 2010; Roy et al. 2013; Callaghan et al. 2017), and children (Qin et al. 2012; Davis et al. 2018). Given the relatively small size for CMA, we also opted to use the bilaterally combined CMA mask as a seed of interest.

## Results

### Developmental Sex Differences in Negative Emotion-Related Latent Decision-Making Dynamics

We first investigated developmental sex differences in behavioral performance and latent decision-making dynamics during emotional perception. Separate 2-by-2 repeated ANOVAs were

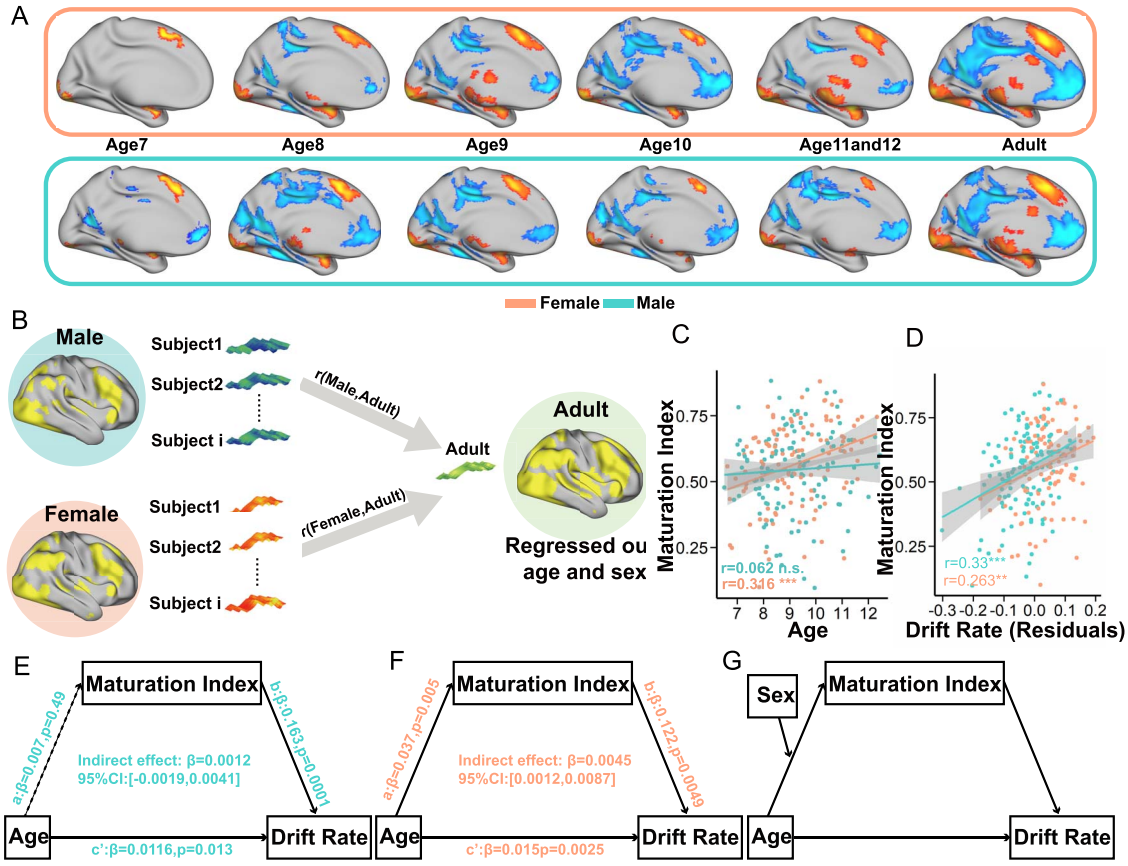


**Figure 3.** Sex differences in the maturation of emotion-related brain systems. (*A*) An overview of brain activation patterns involved in emotional processing in males (boys) and females (girls) from childhood to adulthood. (*B*) A schematic illustration of emotion-related brain maturity index, by computing the multivariate pattern similarity of task-involved neural activity during emotional processing in boys (or girls) as relative to the averaged mature activity pattern in adults without sex and age-related effects. (*C*) Scatterplots depict maturational trajectories of brain activity involved in emotional processing from 7 to 12 years old, with the positive correlation with age in girls but not boys. (*D*) Scatterplots depict maturational trajectories of emotion-related brain maturity was positively correlated with drift rate both in girls and boys irrespective age. (*E* and *F*) Separate mediation models in boys and girls with maturation index as a mediator. (*G*) A schematic illustration of moderated mediation analyses with sex as moderator. ***$P < 0.001$.

conducted for the accuracy and RTs with the emotional conditions as within-subject factor, with Sex and Group as between-subject factors. These analyses revealed the main effects of Group ($F_{1,317} = 34.70$, $P < 0.001$) and Sex ($F_{1,317} = 5.56$, $P = 0.02$) for RTs but only main effects of Group for accuracy ($F_{1,317} = 99.92$, $P < 0.001$, Fig. 1B), but not on interaction effects (both $F_{1,317} < 0.32$, $P > 0.57$). Follow-up *t*-tests revealed a significant developmental improvement in accuracy (both $t_{159} > 6.75$, $P < 0.001$) and RTs (both $t_{159} < -3.46$, $P < 0.001$). We then conducted separate correlation analyses to examine age-related changes in accuracy and RTs. These analyses revealed a positive correlation between accuracy and age in girls ($r = 0.26$, $P = 0.005$) and boys ($r = 0.28$, $P = 0.002$) and a negative correlation between RTs and age in girls ($r = -0.22$, $P = 0.02$) and but not in boys ($r = -0.10$, $P = 0.267$) (Fig. 1C), indicating prominent age-related improvement in behavioral performance during childhood.

Importantly, we investigated developmental sex differences in latent decision-making dynamics during negative emotion processing by implementing the HDDM (Fig. 2). The DIC was used to identify which of the 7 plausible models fit the data best (Fig. 2B). We then conducted 2 (Sex)-by-2 (Group) ANOVAs for drift rate (v), decision threshold (a), and nondecision time (*T*). These analyses revealed the main effects of Sex for v and a (both $F_{1,317} > 18.11$, $P < 0.001$) and Group for v, *a*, *T* (all $F_{1,317} = 13.814$, $P < 0.001$) and a marginally significant Sex-by-Group interaction effect for v ($F_{1,317} = 3.61$, $P = 0.058$). Follow-up *t*-tests revealed that females showed lower decision threshold ($t_{319} = 2.54$, $P = 0.01$) and higher drift rate ($t_{319} = -4.48$, $P < 0.001$). During childhood, we observed prominent age-related changes in decision threshold, drift rate, and nondecision time (Fig. 2D), with significant developmental sex differences in decision threshold (Zou's test 95% CI = 0.0175 ~ 0.4943, see Methods from Zou 2007). These results indicate developmental sex differences in latent decision-making dynamics during negative emotion processing from childhood to adulthood.

## Developmental Sex Differences in Brain Maturation Involved in Negative Emotion Processing

Next, we investigated sex-related developmental differences in emotional brain maturation from 7 to 12 years old during childhood and both compared with the adults without age and sex effects and same-sex adults. Each child's emotion-related brain activity pattern was extracted from a whole-brain mask, with a focus on the contrast of emotion with control condition. We then computed an adult-like emotional brain maturity index representing by the similarity of each child's activity pattern as relative to an averaged pattern across either all of

**Table 2** Bootstrap results for regression model parameters

| | Drift rate | | | | Maturation index | | | |
|---|---|---|---|---|---|---|---|---|
| | $\beta$ | BootMean | BootSE | CI | $\beta$ | BootMean | BootSE | CI |
| Constant | 0.6232 | 0.6230 | 0.0349 | 0.556 ~ 0.693 | 0.7313 | 0.7307 | 0.1857 | 0.370 ~ 1.090 |
| Age | 0.0135 | 0.0136 | 0.0039 | 0.006 ~ 0.021 | −0.0225 | −0.0225 | 0.0202 | −0.062 ~ 0.017 |
| Sex | | | | | −0.2533 | −0.2520 | 0.1232 | −0.487 ~ −0.013 |
| Age × Sex | | | | | 0.0298 | 0.0297 | 0.0132 | 0.004 ~ 0.055 |
| Maturation index | 0.1610 | 0.1605 | 0.0349 | 0.093 ~ 0.230 | | | | |

adults (Fig. 3B) or the same-sex adults (Supplementary Fig. S3B). Further analyses for the same-sex emotional brain maturity indices of revealed a prominent increase from 7 to 12 years old in girls ($r = 0.329$, $P < 0.001$), but not in boys ($r = 0.06$, $P = 0.51$), with significantly higher positive correlation in girls than boys (Zou's test 95% CI = 0.0253 ~ 0.5021) (Supplementary Fig. S3C). Similar results were again observed when the whole-brain mask was defined across female and male adults, with a prominent increase from 7 to 12 years old in girls ($r = 0.316$, $P < 0.001$) but not boys ($r = 0.062$, $P = 0.49$). Girls exhibited significantly higher positive correlation than boys (Zou's test 95% CI = 0.0095 ~ 0.4883) (Fig. 3C).

We then investigated the relations between emotional brain maturity indices and latent decision-making dynamics. Separate correlational analyses for both sexes revealed positive correlations between drift rate and the maturity indices in girls ($r = 0.263$, $P = 0.004$ uncorrected, $P = 0.012$ Bonferroni corrected) and boys ($r = 0.33$, $P < 0.001$ uncorrected, $P = 0.012$ Bonferroni corrected) (Fig. 3D). Partial correlation analysis was applied to compute the correlation between drift rate and the maturity indices with age and sex as covariates of no interest. This analysis revealed a positive correlation in general regardless of sex and age ($r = 0.252$, $P < 0.001$, Bonferroni corrected) (Supplementary Fig. S3E).

To further investigate the role of maturation index on the behavioral performance in both girls and boys, we conducted moderated mediation analysis and mediation analysis. Moderated mediational analysis revealed a significant moderating effect for sex on the link between age and maturation index ($\beta = 0.0048$, BootSE = 0.0025, 95%CI = [0.0005, 0.0103]). We then implemented separate mediation analyses to test the mediatory effect of maturation index on the age effect of drift rate. These analyses showed that maturation index mediated the association between age and drift rate only in girls (indirect estimates = 0.0045, 95%CI [0.0012, 0.0087]) but not boys (indirect estimates = 0.0012, 95%CI [−0.0019, 0.0041]) (Fig. 3E–G, Table 2). These results indicate prominent sex differences in emotion-related brain maturity, with girls reaching an adult-like level earlier than boys, and this maturity is predictive of more effective evidence accumulation during emotion perception.

## Developmental Sex Differences in Amygdala Subregional and Prefrontal Engagement

To further identify developmental sex differences in emotion-related brain systems from childhood to adulthood, we conducted whole-brain ANOVA with Sex and Group for the contrast of emotion with control condition. This analysis revealed the main effect of Group, and the Sex-by-Group interaction effect in limbic structures and frontal cortex (Supplementary Table S1). For Sex-by-Group interaction effect, we observed greater activation in girls than boys, mainly in the amygdala (Supplementary Fig. S4A–C) and MPFC (Fig. 4B). Critically, we observed an opposite sex pattern in these regions during adulthood—that is, weaker activation in females than males in these regions (Fig. 4A,B).

Given the MPFC and amygdala nuclei implicated into emotional processing, we conducted further analyses and focused on the ROIs defined independently. These analyses again revealed significant Sex-by-Group interaction in the MPFC ($F_{1,317} > 13.30$, $P < 0.001$), the bilateral amygdala (both $F_{1,317} > 6.51$, $P < 0.01$), as well as its subregional nuclei including the BLA and CMA ($F_{1,317} > 5.41$, $P < 0.02$). Follow-up $t$-tests significantly higher activation in the amygdala nuclei ($t_{158} = 2.23$, $P = 0.02$) and the MPFC ($t_{158} = 3.23$, $P = 0.001$) in girls as relative to adult females, but not pronounced in boys relative to adult males (all $t_{159} > -1.42$, $P > 0.05$). These results indicate less pronounced and even opposite sex-related differences in emotion-related activation in the amygdala nuclei and MFPC during childhood than adulthood.

To investigate brain systems associated with computational measures of emotional decision-making dynamics, we conducted separate 2-sample $t$-tests for emotion-related brain reactivity map with decision threshold as covariates of interest by regressing out the age. This analysis revealed a significant cluster in the MPFC (voxel-wise $P < 0.001$, cluster-level $P < 0.01$ corrected, Supplementary Table S6). Further ROI analysis revealed a positive correlation with decision threshold in girls ($r = 0.28$, $P = 0.002$ uncorrected, $P = 0.006$ Bonferroni corrected) but an opposite pattern in boys ($r = -0.18$, $P = 0.044$ uncorrected, $P = 0.132$ Bonferroni corrected), with higher correlation in girls than boys (Zou's test 95% CI = −0.6886 ~ −0.2118) (Fig. 4D).

Further ROI analyses were conducted to examine the correlations between emotional response in the amygdala nuclei and latent emotional decision-making dynamics. We observed a positive correlation of decision threshold with emotional response in the CMA in girls ($r = 0.27$, $P = 0.004$ uncorrected, $P = 0.024$ Bonferroni corrected) but not in boys ($r = -0.03$, $P = 0.72$ uncorrected, $P = 1$ Bonferroni corrected), with higher correlation in girls than boys (Zou's test 95% CI = −0.5366 ~ −0.0506) (Fig. 4C). These results indicate developmental sex differences in the relationship between decision threshold and emotional response in the MPFC and CMA during childhood.

## Developmental Sex Differences in Emotion-Related Amygdala-Prefrontal Functional Circuitry

To investigate developmental sex-related differences in emotion-related amygdala-prefrontal functional circuitry, we implemented task-dependent PPI analysis to assess functional connectivity of the BLA and CMA. Separate 2 (Group)-by-2

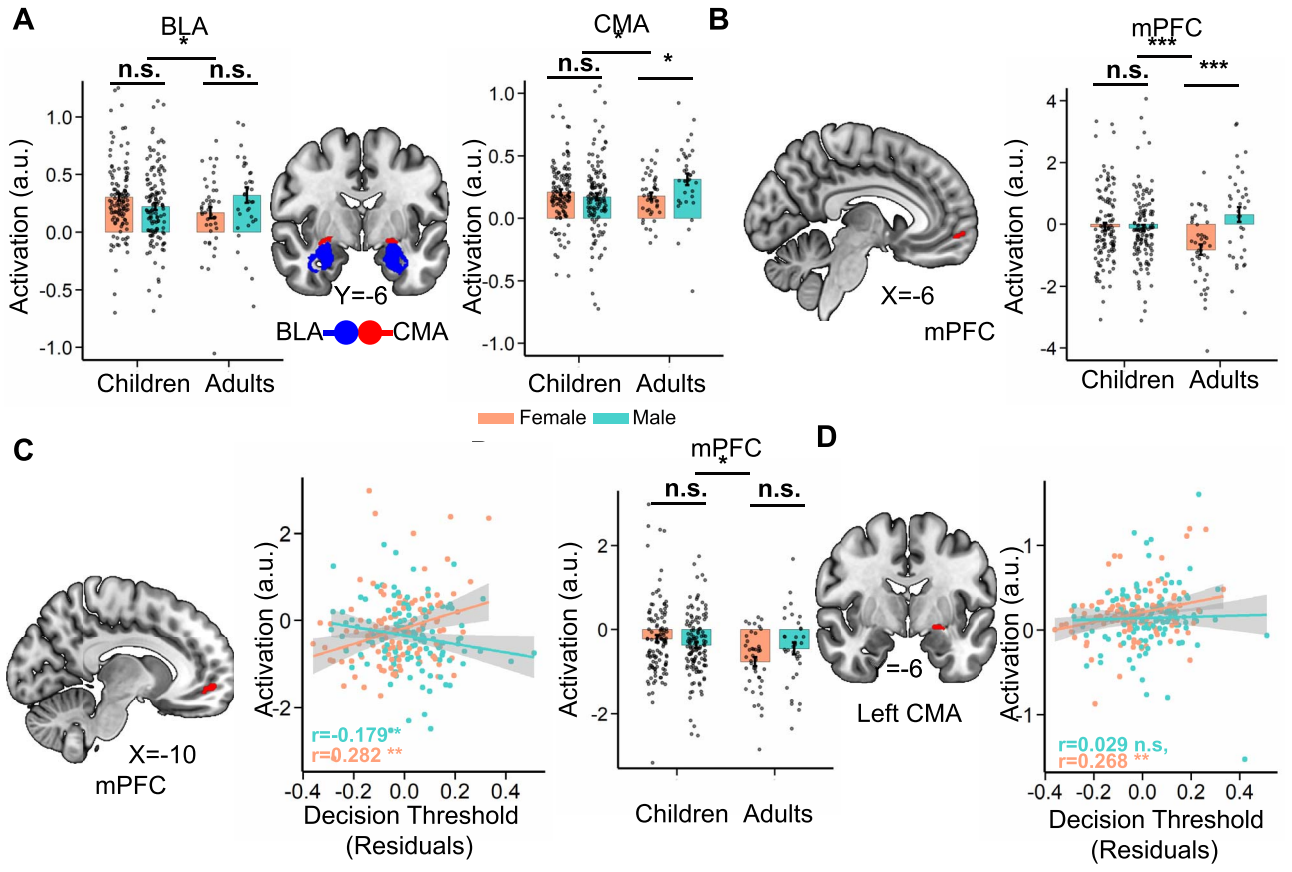


**Figure 4.** Developmental sex differences in emotion-related brain systems from childhood to adulthood. (*A*) A coronal view of the BLA and CMA nuclei showing Sex-by-Group interaction effects. Bar graphs represent beta estimates from corresponding clusters, with prominent sex differences in adults but less pronounced in children. (*B*) A sagittal view of the MPFC showing Sex-by-Group interaction effect. Bar graphs depict parameter estimates from corresponding cluster, with prominent sex differences in adults but not in children. (*C*) A sagittal view of significant cluster in the MPFC and corresponding scatterplot depicting a significantly positive correlation between task-invoked neural activity and decision threshold in girls but not in boys. Bar graphs depict parameter estimates from corresponding cluster, with prominent developmental sex differences from childhood to adulthood. (*D*) A coronal view of significant cluster in the left CMA and corresponding scatterplot depicting a significantly positive correlation between task-invoked neural activity and decision threshold in girls but not in boys. $^{*}P < 0.05$; $^{***}P < 0.001$.

(Sex) ANOVAs for amygdala subregional connectivity maps revealed significant Sex-by-Group interaction effects on BLA and CMA coupling with the dorsolateral prefrontal cortex (DLPFC) and MPFC, respectively. For CMA–DLPFC coupling, we observed a developmental increase of CMA coupling with the left DLPFC from childhood to adulthood in females ($t_{158} = -3.79$, $P < 0.001$), but opposite pattern in boys than adult males ($t_{159} = 2.47$, $P = 0.01$, Supplementary Fig. S6). For BLA–prefrontal coupling, we observed weaker BLA coupling with the bilateral DLPFC (both $t_{159} < -2.27$, $P < 0.025$) in girls than adult females, but an opposite pattern in boys rather than adult males (both $t_{159} > 2.91$, $P < 0.004$). Likewise, we also observed marginally significant weaker BLA coupling with MPFC in girls than adult females ($t_{158} = -1.76$, $P = 0.08$), but an opposite pattern in boys than adult males ($t_{159} = -1.39$, $P = 0.01$) (Supplementary Fig. S5).

To further characterize developmental sex-related differences in amygdala-prefrontal circuitry from 7 to 12 years old, we conducted separate regression analyses for BLA- and CMA-based connectivity maps in girls and boys with age as covariates of interest (Fig. 5A–D). These analyses revealed a positive correlation of age with CMA–insula coupling in girls ($r = 0.22$, $P = 0.015$), but an opposite pattern in boys ($r = -0.27$, $P = 0.002$), with higher correlation in girls than boys (Zou's test 95% CI = −0.7171 ~ −0.2423). Interestingly, we observed a negative correlation of age with BLA–MPFC coupling in girls ($r = -0.29$, $P = 0.002$) but an opposite pattern in boys ($r = 0.20$, $P = 0.026$) with significant sex difference in correlation (Zou's test 95% CI = 0.2429 ~ 0.7164). These results indicate sex-related developmental shift in BLA–MPFC and CMA–insula connectivity pathways from childhood to adulthood, and the emergence of such sex differences at 7–12 years old during childhood.

Given the CMA–insula and BLA–MPFC circuits are implicated into emotional appraisal and expressive response, we conducted partial correlation analyses to investigate their relations with latent emotional decision-making dynamics with age and sex as covariates of no interest. We observed a negative correlation between drift rate residuals with BLA–MPFC coupling ($r = -0.167$, $P = 0.009$ uncorrected, $P = 0.027$ Bonferroni corrected) and a positive correlation between decision threshold residuals with CMA–insula coupling ($r = 0.151$, $P = 0.018$ uncorrected, $P = 0.054$ Bonferroni corrected). These results indicate that BLA–MPFC and CMA–insula couplings are, respectively, associated with the speed of evidence accumulation and the response caution in emotional perception.

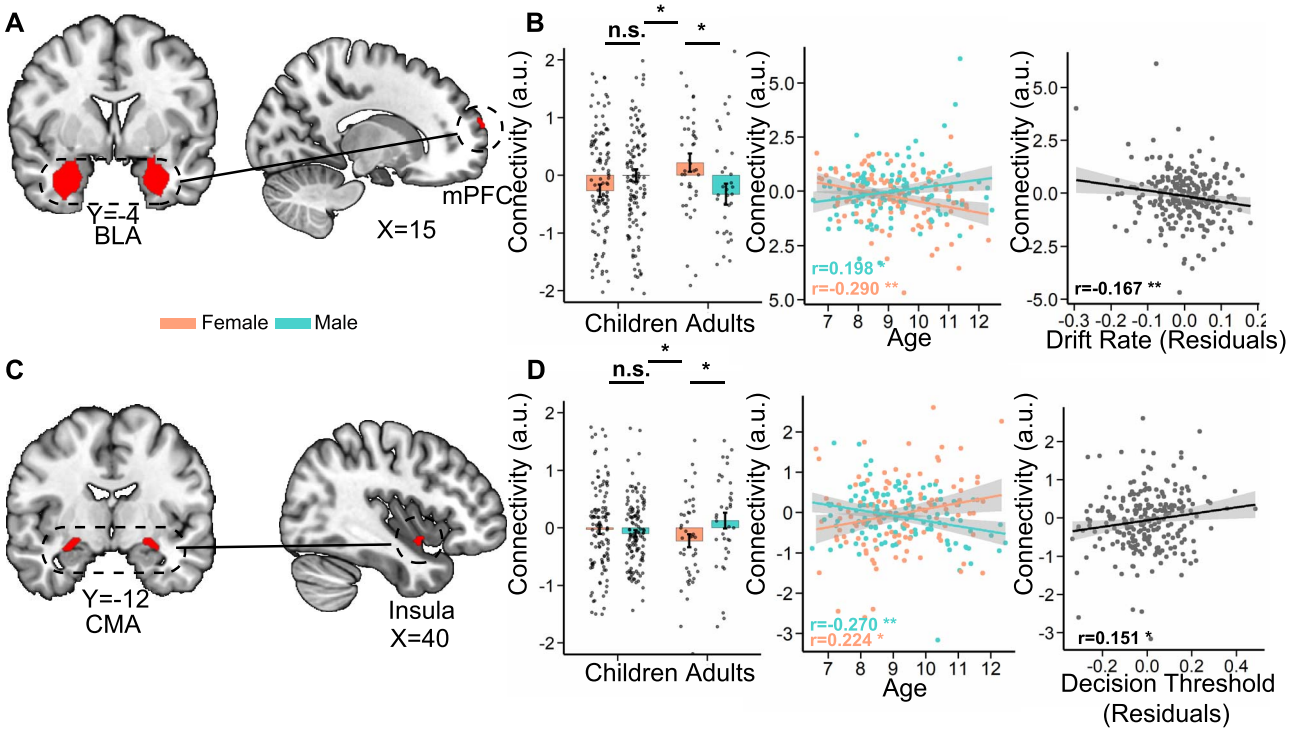


**Figure 5.** Developmental sex differences in amygdala subregional connectivity with the anterior insula and MPFC. (*A*) A coronal view of the bilateral BLA as seed and its functional coupling with the MPFC during negative emotion processing task. (*B*) Bar graphs with scatterplot depict parameter estimates from corresponding clusters showing prominent interaction between sex and groups, with stronger BLA–MPFC coupling in females than males during adulthood but a negative correlation with age in girls but not in boys during childhood. Scatterplot depicts a negative correlation between BLA–MPFC coupling and drift rate irrespective of sex and age. (*C*) A coronal view of the bilateral CMA as seed and its functional coupling with the anterior insula during emotional processing. (*D*) Bar graphs with scatterplot depict parameter estimates from corresponding cluster showing prominent interaction between sex and groups, with weaker CMA–insula coupling in females than males during adulthood, but a positive correlation with age in girls but not in boys during childhood. Scatterplot depicts a positive correlation between CMA–insula coupling and decision threshold, irrespective of sex and age. $^{*}P < 0.05$; $^{**}P < 0.01$.

## Discussion

In this study, we investigated developmental sex-related differences in emotional decision-making dynamics, amygdala-prefrontal systems, and connectivity from 7 to 12 years old during childhood compared with adulthood. Behaviorally, girls showed faster evidence accumulation with lower decision threshold than boys during emotional processing. In parallel, girls exhibited prominent increase in brain maturity from 7 to 12 years old but not in boys, and girls exhibited greater activation in the amygdala nuclei including BLA and CMA than boys, but an opposite pattern in males than females during adulthood. Moreover, girls exhibited a developmental decrease in BLA–MPFC coupling relative to adult females, but boys exhibited a developmental increase in CMA–insula coupling relative to adult males. These findings are discussed under the psychological and neurobiological models of sex differences in emotional development from childhood to adulthood.

Our observed faster RTs and higher drift rate with lower decision threshold in girls than boys suggest the emergence of such sex differences in emotional decision-making dynamics as young as 7–12 years old. According to the DDM, faster drift rate with lower decision threshold may reflect more effective accumulation of evidence information from low-level perceptual inputs, which then supports higher-level appraisal and regulation of emotional responses. This is in line with that girls are more sensitive to recognize others' emotion (Zahn-Waxler et al. 2015) and women superiority in identifying facial affect (Campbell et al. 2002). Social–emotional development theory posits that this superiority is likely resulted from higher social awareness in girls than boys (Zahn-Waxler et al. 2008). Critically, girls also showed a significant improvement with age in latent drift rate involved in emotional processing, along with more conservative threshold to reach a decisive response. In parallel, girls showed an age-related increase in overall brain maturity from 7 to 12 years old, whereas boys did not. Moreover, the increase in overall brain maturity was also positively associated with latent evidence accumulation during emotional perception. This measure has been associated with widespread regions, including frontoparietal network (Mulder et al. 2014), lateral occipital cortex (Philiastides and Sajda 2007), anterior cingulate cortex, and insular cortex (Mulder et al. 2014). In fact, the brain maturation indices incorporate those regions associated with integration of sensory evidence and decision computations, establishing a potential neurobehavioral link to developmental changes in emotional decision-making dynamics. This provides an individualized maturity measure in childhood as relative to the adult matured pattern.

In comparison to adults, children's sex differences in emotional response in the amygdala and MPFC were less pronounced. Based on the organizational hypothesis, gonadal hormones early in development are to program sex differences in neural circuits that is activated by the sex-specific hormonal milieu of adulthood to express sex-related behaviors. Considering the social–emotional development models,

emotion-related functions could be influenced by the cultural pressures and display rules for socialization from their caregivers (Brody and Hall 2010). We thus speculate that less pronounced sex differences in the amygdala and MPFC during childhood may result in the immaturity of brain systems that work in concert with the organizational effects of gonadal hormones exposures as well as gender-related socialization experiences. Importantly, girls exhibited higher activation in BLA and MPFC relative to adult females, whereas boys exhibited lower activation in CMA relative to adult males. The BLA is thought to play a crucial role in integration of emotional cues and affective value of the stimulus (Likhtik and Paz 2015). Higher BLA engagement in girls may reflect more effective integration to facilitate rapid detection of facial affects in our present study. The involvement of MPFC has been linked to understanding of other's emotions and regulation of emotional response (Burnett et al. 2009; Orem et al. 2019). Thus, higher MPFC activation in girls may reflect a higher involvement of MPFC in understanding other's facial affect. This also concurs with the social–emotional development models, suggesting a superiority of females in emotional awareness and understanding of other's emotions (Denham et al. 1990).

Critically, higher MPFC and CMA engagement were associated with higher decision threshold in girls but not in boys. Decision threshold is thought to reflect response caution and the amount of information required to reach for a correct decision. The MPFC and anterior cingulate cortex have been implicated into determining the amount of evidence to accumulate (Mulder et al. 2014), whereas the CMA has been linked to emotional response (LeDoux 2000). We infer that girls are prone to recruit higher MPFC in making cautious response, whereas recruit higher CMA in emotional information accumulation (Herz et al. 2016). Together with the developmental differences in MPFC from childhood to adulthood, higher response caution associated with greater level of MPFC activity may reflect the superiority of females in decision-making process already emerged during childhood. For boys, an opposite pattern associated with less response caution may reflect a more impulsive behavior during emotional decision-making.

Beyond regional activation, we found developmental sex differences in amygdala nuclei functional connectivity with prefrontal and insular regions from childhood to adulthood. The CMA–insula coupling appears to play an important role in controlling interoceptive feelings and autonomic reactions to negative emotions ((Bud) Craig 2009). Dysfunction of the CMA–insula pathway is seen in affective disorders, with lower CMA–insula coupling in depression (Wu et al. 2016). Hence, it is possible that lower CMA–insula coupling in females may reflect a tendency to be less effective in controlling interoceptive feelings and reactions to negative expressions than males. Interestingly, we found that CMA–insula coupling is positively correlated with age in girls, but an opposite pattern in boys from 7 to 12 years old. This may implicate that girls are more likely to use a suppression strategy to regulate emotional behavior. CMA–insula coupling was also found to be positively correlated with decision threshold, suggesting that girls tend to set their decision threshold based on the integration of emotion-related interoceptive information. The elevated decision threshold may also reflect more efforts in emotion suppression to postpone response to facilitate emotional behavior like distinguishing facial expressions (Iuculano et al. 2020).

Research in animal studies has recognized that the BLA–MPFC pathway plays a critical role in emotional appraisal and regulation (Rosenkranz and Grace 2001; Quirk et al. 2003; Rosenkranz et al. 2003; Motzkin et al. 2015). We observed a developmental increase in BLA–MPFC coupling in females, but a developmental decrease in males from childhood to adulthood. According to the organizational hypothesis, such sex differences might be resulted from gonadal hormones that act on their organized neural targets with different receptors in females and males. Such actions may lead to expressing sex differences in functional coordination between BLA and the MPFC in emotion processing (Maeng and Milad 2015). Indeed, human neuroimaging studies have shown that progesterone can lead to increased BLA–MPFC coupling, whereas testosterone decreases functional coupling of this pathway (van Wingen et al. 2011).

During childhood, we also found an opposite developmental sex pattern for BLA–MPFC coupling from 7 to 12 years old, with a developmental decrease in girls but an increase with age in boys. According to the neurobiological model, boys secret testosterone at high level and reach its peak at puberty(Alexander 2014), whereas girls reach high-level estradiol within first 2–4 months after delivery (Kurtoglu and Bastug 2014), and the testosterone levels of boys are 10 times higher than girls (Zegher et al. 1992). These gonadal hormones surge have long-lasting effects that have been linked to major depression symptoms between 8 and 11 years old (Lombardo et al. 2012). Our results showed that the from 7 to 9 years old, the BLA–MPFC functional coupling was higher in girls than boys but lower after 9 years old. We speculate that the long-lasting effects of gonadal hormones surge might persist until mid-childhood. Notably, there is evidence from fMRI studies to suggest that a negative amygdala–MPFC connectivity reflects top-down prefrontal regulation of emotional response (Hariri et al. 2003; Kim et al. 2003; Hare et al. 2008). Our observed negative BLA–MPFC connectivity, showing gradually decreased with age, may thus suggest an earlier emergence of top-down prefrontal modulation over emotional response in the BLA in girls than boys in the developing brain. Meanwhile, a negative correlation of drift rate with BLA–MPFC connectivity may reflect a superiority in emotional information accumulation with less efforts of such top-down control. The results are also in line with predictions by the social–emotional development models.

Several limitations should be considered in light of our findings. First, our present study only investigates biological sex differences in school-aged children and adults, but children's recognition, experience, and expression of emotions are also shaped by gender-related socialization, expectancies, and social status, known as gender identity. Second, our emotional task paradigm consisted of only negative facial expressions rather than specific emotion categories. Additionally, developmental differences in emotion-related decision-making dynamics, brain systems, and circuitry were derived from a cross-sectional design rather than a longitudinal cohort, and the age range in children did not sample adolescence. Third, the amygdala nuclei especially CMA were acquired under a limited spatial resolution, which could lead to partial volume effects. We would be cautious that the CMA-related results could be sensitive to EPI spatial resolution and pediatric population here, due to its relatively small size. However, we still feel responsible to report these results, because we found several aspects of results pertaining to CMA activation, task-dependent functional connectivity, and their relations to sex, age, and computational measures. These CMA-related data may inform ample opportunities for future studies with higher spatial-resolution neuroimaging techniques. Finally, the neurobiological

accounts for development sex differences remains speculative, especially for those aspects pertaining to sex hormones. Future studies with a longitudinal design and sex-related hormonal assessments are required to understand the neurobiological underpinnings of our findings. Moreover, the interplay of gender-related socialization experiences of specific negative and positive emotions, organizational effects of sex-related hormones, and brain maturation should be also considered to better understand sex differences in the typical and atypical neurodevelopment of emotions and emotion-related behaviors.

In conclusion, our study demonstrates developmental sex differences in children's emotional decision-making dynamics, emotional brain maturity, and amygdala-prefrontal functional organization. Our findings have important implications into understanding sex differences in the neurodevelopment of children's emotion and emotion-related behaviors. This has the potential to inform the development of brain-inspired metrics that assess sex differences in children's emotion-related brain circuits and guide personalized early detection and intervention for emotional disturbances.

## Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online

## Author Contributions

S.Q., S.T., and Q.D. designed the research; L.H., M.C., M.J., Y.W., D.W., H.W., and T.T. performed research; J.X. and L.H. analyzed data; J.X. and S.Q. wrote the manuscript; all authors commented and edited the manuscript.

## Notes

*Conflict of Interest*: The authors declare no conflict of interests.

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