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Negative Parenting Affects Adolescent Internalizing Symptoms Through Alterations in Amygdala-Prefrontal Circuitry: A Longitudinal Twin Study

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ABSTRACT

BACKGROUND: The synergic interaction of risk genes and environmental factors has been thought to play a critical role in mediating emotion-related brain circuitry function and dysfunction in depression and anxiety disorders. Little, however, is known regarding neurodevelopmental bases underlying how maternal negative parenting affects emotion-related brain circuitry linking to adolescent internalizing symptoms and whether this neurobehavioral association is heritable during adolescence.

METHODS: The effects of maternal parenting on amygdala-based emotional circuitry and internalizing symptoms were examined by using longitudinal functional magnetic resonance imaging among 100 monozygotic twins and 78 dizygotic twins from early adolescence (age 13 years) to mid-adolescence (age 16 years). The mediation effects among variables of interest and their heritability were assessed by structural equation modeling and quantitative genetic analysis, respectively.

RESULTS: Exposure to maternal negative parenting was positively predictive of stronger functional connectivity of the amygdala with the ventrolateral prefrontal cortex. This neural pathway mediated the association between negative parenting and adolescent depressive symptoms and exhibited moderate heritability (21%).

CONCLUSIONS: These findings highlight that maternal negative parenting in early adolescence is associated with the development of atypical amygdala-prefrontal connectivity in relation to internalizing depressive symptoms in mid-adolescence. Such abnormality of emotion-related brain circuitry is heritable to a moderate degree.

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Internalizing symptoms, such as depression and anxiety, emerge and develop rapidly during adolescence (1–3). Empirical research indicates that negative parenting plays an important role in the etiology of adolescent internalizing issues (4,5). It has long been believed that the association between negative parenting and depression or anxiety symptoms is associated with dysfunction of emotion-related brain circuitry and networks, which involves multiple genetic and environmental sources (6–8). Recent efforts have examined how the synergic interaction among risk environmental factors and genes affects the risk of emotional health problems (9,10).

Negative parenting may affect adolescent internalizing symptoms, at least in part, through its influence on emotion-related brain circuitry (11–13). The amygdala, as a key structure within this circuitry, encompasses multiple subregions with distinct anatomical connectivity with other brain regions, including the prefrontal cortex (PFC) (14,15). During adolescence, the brain undergoes a developmental leap from relative immaturity to a more mature state, with dynamically strengthening and weakening connections among limbic and prefrontal regions critical for affective and cognitive functions (16–23). In particular, adolescent brain development, characterized by rapid maturation of limbic regions but relative immaturity of PFC, is highly vulnerable and sensitive to harmful environmental exposure (24–28). For example, adolescents reporting negative family relationships are more likely to show longitudinal increases in risk-taking behavior through higher ventrolateral PFC (vlPFC) activation during cognitive control (29). Individuals exposed to high childhood family stress exhibit reduced amygdala reactivity and a positive correlation between amygdala and vlPFC activation in response to emotional stimuli (30). Thus, negative parenting may affect the maturation of amygdala-vlPFC circuitry during adolescence. However, no studies to date have investigated this assumption.

Dysconnectivity of the amygdala and prefrontal circuitry has been consistently reported among individuals with depression and anxiety symptoms (31,32). Recent evidence suggests that increased functional connectivity between the amygdala and vlPFC may be a characteristic of brain circuitry for internalizing symptoms among young adults (33). Notably, a longitudinal study demonstrated that increased amygdala-prefrontal intrinsic functional connectivity mediates the association between early-life stress in childhood and internalizing

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depressive symptoms in adolescence (34). Furthermore, a recent study demonstrated that functional interactions among amygdala, vlPFC, and medial PFC (mPFC) are responsible for age-related developmental improvement in cognitive regulation of emotion throughout childhood and adolescence (19). Many recent studies also demonstrated that functional coordination among amygdala, vlPFC, and other regions is critical for emotion perception and appraisal as well as cognitive regulation of emotion in both healthy and psychiatric conditions (35–38). These findings indicate that the amygdala-vlPFC circuitry may serve as a candidate neural pathway underlying the adverse effects of negative parenting exposure on internalizing symptoms during adolescence.

Both depression and anxiety are thought to result from a consequence of the synergic interaction of risk genes and environmental factors (8,39,40). As risk genes are considered to shape brain structure and function at the molecular and cellular levels (41), neuroimaging genetic studies usually take neural phenotypes as a function of genotype (6). In fact, the neural phenotypes of depression and anxiety disorders involving the amygdala and the PFC are influenced by the interactions among genetic and environmental factors (8,42). Twin neuroimaging designs are useful approaches that offer a unique opportunity to disentangle genetic and environmental effects on brain structure and function. Recent twin studies report significant genetic influences on resting-state brain networks in both children (43) and adults (44,45). However, little information is available regarding whether intrinsic functional organization of the amygdala with other brain regions, especially those relevant to the etiology of internalizing symptoms, are heritable.

There is increasing evidence to show that risk environmental factors such as maternal parenting and genes work together to influence brain development during adolescence, which in turn leads to heightened internalizing symptoms (9,42,45–47). However, studies deciphering the underlying neurodevelopmental pathways of these environmental and genetic interactions are rare. Here we conducted a longitudinal twin study of 108 pairs of same-sex adolescent twins, which extends our prior behavioral studies on interactions between gene and stressful life events in predicting adolescent internalizing symptoms (48,49). Maternal parenting was assessed in early adolescence, resting-state functional magnetic resonance imaging (fMRI) was obtained in mid-adolescence, and persistent internalizing symptoms were assessed during mid-adolescence. We implemented intrinsic functional connectivity analysis of resting-state fMRI data to investigate the influence of negative maternal parenting on large-scale functional connectivity of the amygdala. Next, structural equation modeling was conducted to assess whether amygdala-based functional circuits mediated the association between maternal parenting and persistent depressive and anxiety symptoms. Finally, genetic modeling was performed to estimate the heritability of amygdala-based functional circuits. Based on previous findings of adverse experiences and amygdala-prefrontal development in adolescents, we hypothesized that exposure to maternal negative parenting would be associated with increased intrinsic functional connectivity of the amygdala-prefrontal circuitry. This neural pathway would account for the effect of maternal negative parenting on adolescent internalizing symptoms, which would be heritable according to genetic modeling of environmental and genetic interactions.

METHODS AND MATERIALS

Participants

Data were obtained from BeTwiSt (Beijing Twin Study), a longitudinal research project designed to investigate how genes, the environment, and their interplay influence mental health among a representative sample of Beijing adolescents 10–18 years of age (50). A subsample of 108 pairs of same-sex twins of Han ethnicity who underwent fMRI scanning was included in this study. Two waves of data collection were performed. In wave 1 assessment, when all the twins entered early adolescence, participants were asked to report their maternal parenting and stressful life events. Depression symptoms and anxiety were assessed in wave 2 when all the participants entered mid-adolescence. fMRI was conducted in wave 2. Twins' zygosity was determined by DNA analyses with 9 short tandem repeat loci. An overall accuracy of zygosity determination was estimated to be 99.99%. All participants were typically developing and reported no history of craniocerebral trauma or neurological or psychiatric disorders. There were 19 pairs of twins excluded from further analyses owing to either incomplete neuropsychological assessment or excessive head motion during scanning. Hence the final sample included 50 monozygotic pairs (25 male pairs) and 39 dizygotic pairs (17 male pairs) with good-quality fMRI and behavioral data. Mean (SD) age of these 89 pairs of twins was 12.67 (0.86) years in wave 1 and 16.03 (0.86) years in wave 2. All adolescents and their parents signed informed consent forms. The Ethics Committee of the Institute of Psychology at the Chinese Academy of Sciences approved all study procedures.

Neuropsychological Assessments

In wave 1, adolescents rated their maternal parenting behavior during the past 12 months on a 5-point scale ranging from 1 (never) to 5 (always) that assessed two dimensions of negative parenting, harshness (e.g., hit you, 3 items) and hostility (e.g., swear at you, 6 items), and two dimensions of positive parenting, inductive reasoning (e.g., ask you what you think before making a decision about you, 5 items) and warmth (e.g., act loving and affectionate toward you, 8 items) (51–53). Items of maternal negative parenting and positive parenting were summed separately, so that higher scores on the negative parenting subscale indicated more negative and/or stressful environmental exposure, while higher scores on the positive parenting subscale indicate more positive environmental exposure. Our previous study proved that these scales have good psychometric properties when used in Chinese adolescent samples (49). Participants also reported stressful life events (SLEs) that occurred in their daily life during the past 12 months with a modified version of the Life Events Checklist (54). The number of SLEs was summed, and scores ranged from 0 to >6 to indicate adolescent life stress. In wave 2, adolescents reported their depressive symptoms with the Children's Depression Inventory (55,56). Their susceptibility to experiencing anxious thoughts was measured with the Trait

subscale of Form Y of the State-Trait Anxiety Inventory (57,58), which has been used in multiple studies to investigate anxious characteristics in nonclinical samples (59). Both the Children's Depression Inventory and the State-Trait Anxiety Inventory Trait subscale of Form Y were applied twice, at the same time as fMRI scanning and 1.5 years before fMRI scanning. Average scores of both scales were used to ensure a stable and persistent measurement of participants' internalizing symptoms during their mid-adolescence (60), with higher scores indicating more serious symptoms.

Image Data Acquisition

In wave 2, brain imaging data were acquired on a 3.0T MRI scanner (Siemens Healthineers AG, Erlangen, Germany) in the Beijing MRI Center for Brain Research. Whole-brain resting-state functional images were collected in 32 axial slices using an echo-planar imaging sequence (repetition time 2000 ms, echo time 30 ms, flip angle 90°, matrix 64 × 64, field of view 22 cm, voxel size 3.5 × 3.5 × 4 mm, slice thickness 3 mm, slice gap 1 mm, 180 volumes for 24 pairs of twins and 225 volumes for 84 pairs of twins), aligned along the anterior commissure–posterior commissure line. Scan duration was 6 minutes for 24 pairs of twins and 7.5 minutes for 84 pairs of twins. During the scanning procedure, participants were explicitly instructed to remain still and awake with their eyes closed. High-resolution structural images were acquired axially using a three-dimensional gradient recalled sequence (repetition time 2530 ms, echo time 3.37 ms, flip angle 7°, matrix 256 × 192, slice thickness 1.33 mm).

Image Data Preprocessing

Data preprocessing was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The first and last 5 volumes were discarded to account for magnetic field stabilization. The functional images were realigned to correct for head motion. Nineteen twin pairs were excluded because root mean squared head motion exceeded a voxel's width during MRI scanning (61). Subsequently, realigned volumes were slice-timing corrected, normalized into a standard stereotaxic anatomical Montreal Neurological Institute space, and resampled into 2-mm isotropic voxels. Functional images were spatially smoothed using an isotropic Gaussian filter of 6 mm full width at half maximum. Linear detrend and filtering (0.008–0.1 Hz) were applied.

Intrinsic Functional Connectivity Analysis

The region of interest masks for the amygdala were defined by the automated anatomical labeling atlas (62). The left and right amygdala were separately selected as two seed regions. The Eigen time series within each seed was extracted from bandpass-filtered images, then submitted into an individual-level fixed-effects analysis under the framework of the general linear model to assess each seed-based intrinsic functional connectivity. Six motion parameters and white matter and cerebrospinal fluid signals were included as nuisance covariates to account for physiological and movement-related artifacts. Additional control analyses with extensive steps were conducted to account for potential effects related to micromotion and physiological artifacts, involving 24 head motion parameters (i.e., 6 head motion parameters, 6 head motion parameters one time point before, and the 12 corresponding squared items) and white matter and cerebrospinal fluid signals (63–68).

To examine whether maternal parenting in wave 1 predicted intrinsic functional connectivity of the left and right amygdala, a connectivity map of each seed region was submitted into a second-level multiple regression analysis, with maternal negative and positive parenting score as the covariate separately, by controlling sex, wave 2 age, and SLEs as covariates of no interest. Only clusters significant at a height threshold of $p < .001$ and an extent threshold of $p < .05$ with 3dClustSim correction for multiple comparisons are reported. Parallel analyses were also conducted for each amygdala subregion, including the basolateral, centromedial, and superficial amygdala in the left and right hemispheres (see Supplement).

Mediation Analysis

Before mediation analysis, average values representing connectivity strength were extracted from 7 significant clusters identified in the above regression analyses to examine the correlation of these connectivity measures with internalizing symptoms. To control false-positives, we used the number of regions identified from the amygdala connectivity analyses for Bonferroni correction ($p < .05/9 = .005$). Only significant clusters in the vlPFC remained significant after correction. Structural equation modeling was then constructed to examine the mediating effect of amygdala-vlPFC connectivity on the relationship between maternal parenting and internalizing symptoms using Mplus 7.0 (69), with sex, wave 2 age, and SLEs as covariates. Overall model fit indices were considered acceptable if they had a nonsignificant χ^2 value, a root mean square error of approximation below 0.08 to 0.10, a comparative fit index at 0.93 or above, and a standardized root mean square residual at <0.08 (70). Moreover, both direct and indirect effects of maternal parenting on adolescent internalizing symptoms were estimated using bias-corrected bootstrapping resampling method with 1000 resamples and relevant 95% confidence interval (71).

Quantitative Genetic Analysis

The heritability of average connectivity values that served as a significant mediator was computed using a univariate ACE model in the OpenMx package for R (R Foundation for Statistical Computing, Vienna, Austria) (72,73). According to the assumption of behavioral genetics, each phenotype difference between twins can be decomposed into additive genetic (A), shared environmental (C), and nonshared environmental (E) effects (74,75). Shared environment refers to a nongenetic influence that results in the similarity within twin pairs, while nonshared environment results in the differences within twin pairs, which also includes a measurement error. A full ACE model, which contained all the A, C, and E factors, was examined initially, and then submodels (AE, CE, and E models) were nested within the full model. Statistical inference was obtained by comparing χ^2 differences between the full model and a submodel. A nonsignificant χ^2 difference and the smallest Akaike information criterion was chosen as the optimal model (76).

Table 1. Statistics and Bivariate Correlations of Study Variables

Variables	Variables 1	2	3	4	5	6	7	Mean (SD)	Range
1. Maternal Negative Parenting[a]	–	–	–	–	–	–	–	19.51 (6.55)	9–41
2. Maternal Positive Parenting[a]	−0.44[b]	–	–	–	–	–	–	47.95 (10.91)	21–65
3. Depressive Symptoms[c]	0.32[b]	−0.29[b]	–	–	–	–	–	37.81 (6.18)	27–54.50
4. Trait Anxiety[c]	0.27[b]	−0.26[b]	0.85[b]	–	–	–	–	39.62 (8.23)	21–64.5
5. SLEs[a]	0.20[d]	−0.06	0.36[b]	0.36[b]	–	–	–	3.12 (2.77)	0–14
6. Sex	−0.06	−0.12	0.12	0.12	0.61	–	–	–	–
7. Wave 2 Age	−0.08	0.04	−0.15	−0.08	−0.12	0.11	–	16.03 (0.86)	14–17
8. Mean FD	−0.10	0.04	0.04	0.01	0.02	−0.20[d]	−0.07	0.15 (0.05)	0.06–0.31

FD, framewise displacement; SLEs, stressful life events.
[a]Data collected in wave 1.
[b]$p < .001$.
[c]Data collected in wave 2.
[d]$p < .01$.

RESULTS

Participant Demographics and Behavioral Association

Table 1 presents behavioral measurements and statistics for the final sample of 89 twins. Bivariate Pearson's r (2-tailed) correlation coefficients among behavioral variables revealed that negative parenting was positively correlated with SLEs and internalizing symptoms (both $r \geq .20$, $p < .01$). Depressive symptoms were positively correlated with trait anxiety. The mean framewise displacement during scanning was not significantly correlated with maternal parenting or adolescent internalizing symptoms (Table 1).

Maternal Parenting in Early Adolescence Predicts Amygdala Intrinsic Functional Connectivity in Mid-adolescence

First, we analyzed how maternal negative parenting modulates amygdala intrinsic functional connectivity patterns. Seed-based intrinsic functional connectivity analysis for the left and right amygdala as separate seeds revealed very robust functional connectivity of the amygdala with a widely distributed network of regions (Figures S1 and S2). We conducted separate multiple regression analyses for each amygdala-seeded functional connectivity pattern with maternal negative parenting as a covariate of interest, by controlling for sex, age, and SLEs. This analysis revealed that maternal negative parenting significantly predicted intrinsic connectivity of the left amygdala with distributed regions in the left inferior frontal gyrus (located at the anterior portion of the vlPFC), left middle temporal gyrus, and bilateral middle cingulate cortex as well as intrinsic functional connectivity of the right amygdala seed with regions in the left inferior frontal gyrus and right precentral gyrus (Table 2; Figures 1 and 2). Parallel control analyses with extensive steps were conducted to ensure that motion artifact did not contaminate the data (Table S1). These analyses replicated a very similar pattern of amygdala connectivity target regions predicted by maternal negative parenting (Figure 1; Table S1; Figure S3). There was no reliable effect pertaining to maternal positive parenting. These results indicate that maternal negative parenting in early adolescence predicts amygdala-based intrinsic functional connectivity later in mid-adolescence.

Negative Parenting Predicts Adolescent Internalizing Symptoms via Amygdala-vlPFC Connectivity

We investigated the relationships between negative parenting, internalizing symptoms, and amygdala intrinsic functional connectivity. Among target regions of the amygdala connectivity predicted by maternal negative parenting, only connectivity between the left amygdala and the left vlPFC ($r = .26$, $p = .001$) significantly correlated with adolescent depressive symptoms after correction for multiple comparisons ($p = .009$, Bonferroni corrected) when covariation of trait anxiety was considered. No other amygdala connectivity target regions retained a significant correlation with trait anxiety when covariation of adolescent depressive symptoms was considered (Table S2).

We further investigated the association of maternal negative parenting with internalizing symptoms, considering a potential

Table 2. Amygdala Intrinsic Functional Connectivity Predicted by Maternal Negative Parenting

Seed	Regions	R/L	t Value	MNI (x y z)	Voxels
L Amygdala	IFGtri/vlPFC	L	4.20	−28 34 14	80
	MTG	L	−3.98	−46 −52 14	88
	MCC	R	−4.86	10 −14 36	84
		L	−3.97	−14 −6 40	89
	MOG	R	−3.91	40 −78 6	40
R Amygdala	ORBinf	L	−4.18	−40 22 −8	144
	PreCG	L	−3.80	−54 −12 38	66
		R	−4.31	46 −8 40	232
	STG	R	−4.10	44 −40 6	43

Significant clusters are determined by a height threshold of $p < .001$ and an extent threshold of $p < .05$ corrected for multiple comparisons.

IFGtri, inferior frontal gyrus triangular part; L, left; MCC, middle cingulate cortex; MNI, Montreal Neurological Institute; MOG, middle occipital gyrus; MTG, middle temporal gyrus; ORBinf, inferior frontal gyrus orbital part; PreCG, precentral gyrus; R, right; STG, superior temporal gyrus; vlPFC, ventrolateral prefrontal cortex.

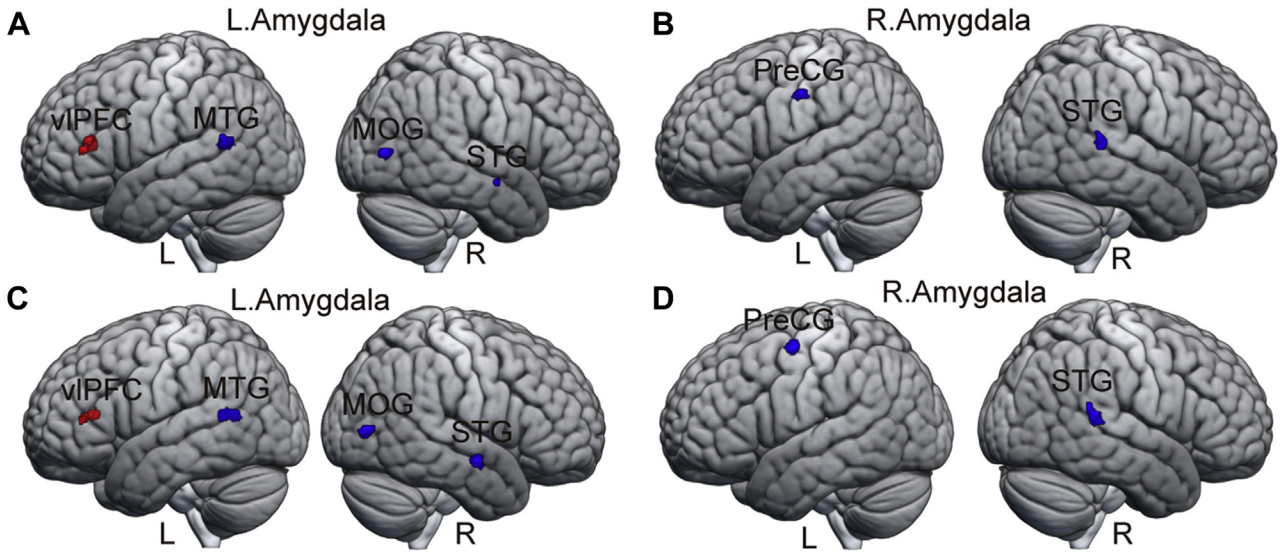

Figure 1. Amygdala intrinsic functional connectivity in mid-adolescence predicted by negative parenting in early adolescence. **(A, B)** Lateral views of significant clusters in distributed brain regions whose connectivity with the left and right amygdala seeds was positively (red) and negatively (blue) predicted by maternal negative parenting. Target regions include the left inferior frontal gyrus—anterior portion of the ventrolateral prefrontal cortex (vlPFC), left middle temporal gyrus (MTG), right superior temporal gyrus (STG), right middle occipital gyrus (MOG), and left precentral gyrus (PreCG). **(C, D)** Lateral views of significant clusters in distributed brain regions from control analyses with extensive steps (see Methods and Materials) to mitigate motion-related artifacts. L, left; R, right.

mediating effect of amygdala connectivity with the left vlPFC identified above (Figure 3). Thus, we tested an indirect pathway in which maternal negative parenting predicted adolescent depression via amygdala connectivity with the left vlPFC with sex, wave 2 age, SLEs, and trait anxiety as covariates of no interest (Figure 3). The model accounted for 75.3% of the variance in adolescent depressive symptoms when trait anxiety was included and revealed a significant mediating effect of amygdala connectivity with the left vlPFC (indirect effect = 0.03; bootstrapped 95% confidence interval = 0.009–0.054). Additionally, given that data collecting time of internalizing symptoms and neuroimaging overlapped, another mediation model was constructed with the positions of depressive symptoms and brain connectivity reversed. This model fit was poor, and the indirect effect was not significant (indirect effect = 0.01; bootstrapped 95% confidence interval = −0.003 to 0.032) (Figure S2). Parallel mediation analysis was also conducted for amygdala-vlPFC connectivity after controlling motion-related artifacts with the Friston 24-parameter model. This analysis again replicated the mediation effect of amygdala-vlPFC connectivity on the association between negative parenting and adolescent internalizing depressive symptoms (Figure 4; Table S3; Figure S5).

Genetic Basis of Variation of Amygdala-vlPFC Connectivity

After we regressed out the effects of sex and age on amygdala-vlPFC connectivity, standardized residuals were used for subsequent genetic analyses according to a traditional method named the ACE model (77). Monozygotic twins exhibited significant within-pair correlation for amygdala functional connectivity with the left vlPFC (r = .29, p = .043), but dizygotic twins showed no reliable within-pair correlation (r = −.13, p = .440). These results indicated a genetic influence on connectivity between the left amygdala and left vlPFC. The univariate model-fitting analyses revealed that the AE model best fit the data; 21% variation of this amygdala-vlPFC connectivity pathway was explained by genetic factors, while another 79% was attributed to nonshared environment effects (Table 3). A parallel ACE model was also conducted for amygdala-vlPFC connectivity after controlling motion-related artifacts with the Friston 24-parameter model, which revealed that the heritability of amygdala-vlPFC connectivity was 22% (Table S4).

DISCUSSION

This study investigated the effects of maternal negative parenting in early adolescence on amygdala-prefrontal circuitry and longitudinal outcomes on internalizing symptoms later in mid-adolescence within a framework linking the synergic interaction of risk genetic and environmental factors to amygdala dysconnectivity and adolescent depression symptoms. Negative parenting in early adolescence was positively predictive of amygdala-vlPFC connectivity and subsequent internalizing symptoms. Specifically, adolescents who were exposed to more negative parenting showed stronger intrinsic functional connectivity between the left amygdala and left vlPFC, and this amygdala-prefrontal connectivity in turn mediated higher depressive symptoms later in mid-adolescence. We also observed that amygdala-vlPFC connectivity exhibited moderate genetic heritability (21%–22%). Our findings suggest that maternal negative parenting and genetic factors in early adolescence may increase the risk of

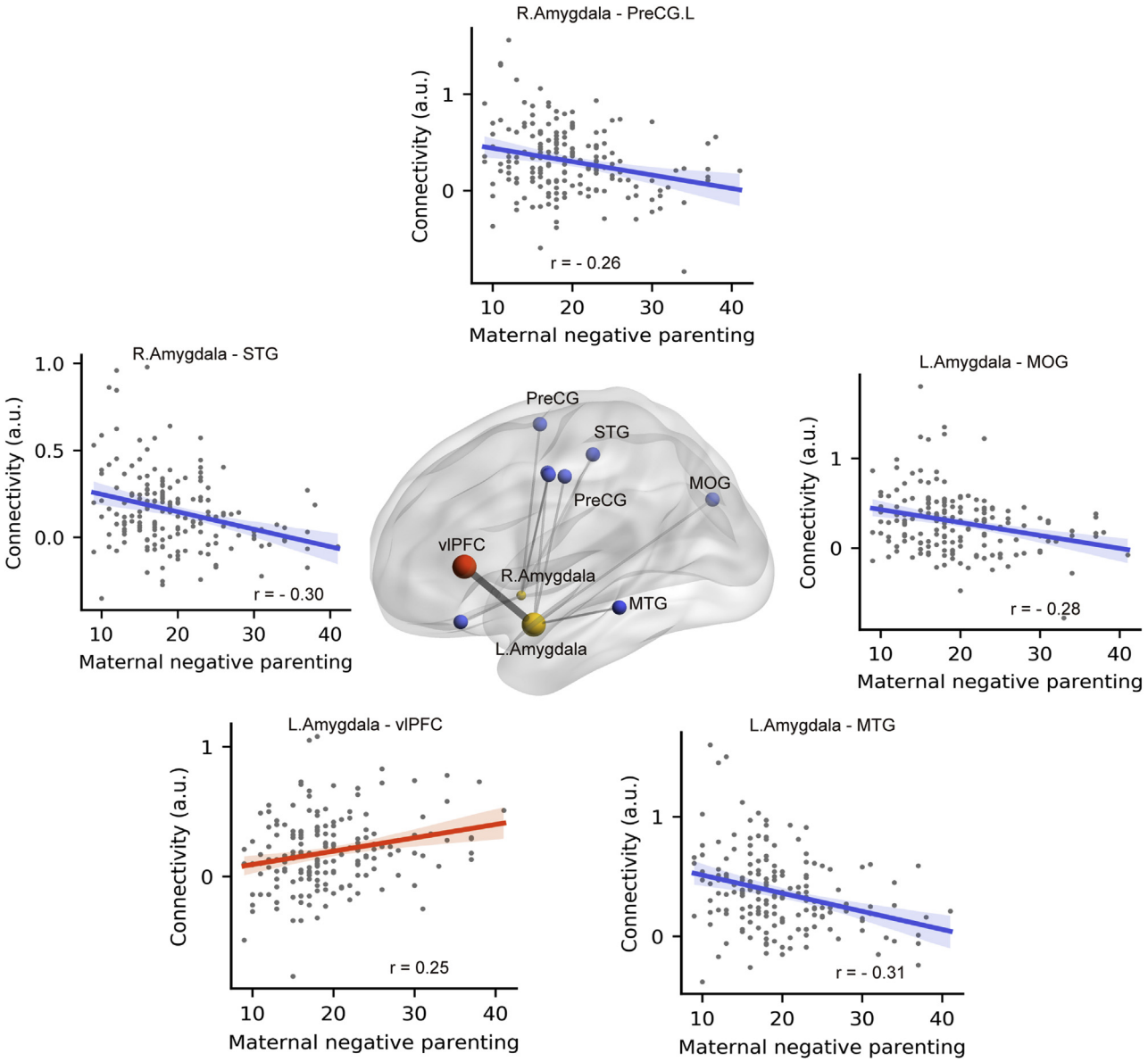

Figure 2. A schematic illustration of the effects of maternal negative parenting on amygdala-based intrinsic functional connectivity. Representative brain regions showing significantly positive (red) or negative (blue) correlations between maternal negative parenting and intrinsic functional connectivity with the left and right amygdala seeds separately. Target regions include the left ventrolateral prefrontal cortex (vlPFC), left middle temporal gyrus (MTG), right superior temporal gyrus (STG), right middle occipital gyrus (MOG), and bilateral precentral gyrus (PreCG). Scatter plots depict correlations between maternal negative parenting (x-axis) and connectivity strength of the left and right amygdala seeds with corresponding target regions (y-axis). Note that this figure displays only brain regions reproducible from additional control analyses using the Friston 24-parameter model. a.u., arbitrary units; L, left; R, right.

development of depressive symptoms through their synergic effects on amygdala-vlPFC circuitry.

The increased amygdala-vlPFC connectivity in adolescents exposed to maternal negative parenting appears consistent with previous findings on hyperconnectivity of the amygdala with prefrontal regions among individuals with depressive and/or anxious symptoms (28,78–81). One recent study, for instance, found that adults exposed to harsh parenting in childhood displayed a positive correlation between amygdala and vlPFC activation during an emotion-labeling task, reflecting a deficiency in recruiting vlPFC for regulating amygdala reactivity in responses to emotional stimuli (30). By extending this finding among adults, our study further demonstrates that exposure to negative parenting in early adolescence is associated with stronger amygdala-vlPFC intrinsic functional connectivity in the absence of external task demands in mid-adolescence. In contrast to two studies reporting atypical amygdala-mPFC development in children and adolescents

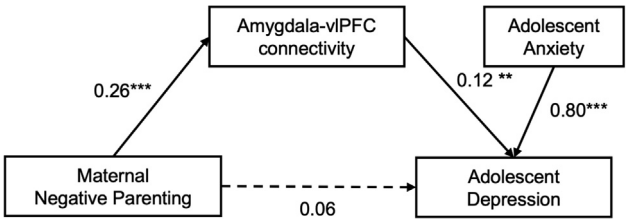

Figure 3. Mediation model depicts the relationships among negative parenting in early adolescence, mid-adolescent depressive symptoms, and amygdala–ventrolateral prefrontal cortex (vlPFC) connectivity. Structural equation modeling demonstrates good fit, with $\chi^2_1 = 0.01$, $p = .92$, root mean square error of approximation = 0 (95% confidence interval = 0–0.07), standardized root mean square residual = 0.01, comparative fit index = 1.00. Indirect effect was significant (indirect effect = 0.03; bootstrapped 95% confidence interval = 0.009–0.054). For clarity of presentation, the diagrams do not show nonsignificant control variables (i.e., sex, wave 2 age, and stressful life events). Paths are marked with standardized coefficients. $^{**}p < .01$. $^{***}p < .001$.

with maternal deprivation and insensitive parenting (28,80), our finding indicates the longitudinal effect of negative parenting on increased amygdala-vlPFC intrinsic connectivity in mid-adolescence. From a perspective of brain maturation and emotional development, the most rapid transformation from relative immaturity to a more mature state occurs during adolescence (17–19). Our finding indicates that negative parenting in early adolescence may lead to suboptimal brain maturation, especially for the development of amygdala-prefrontal circuitry. Although the definitive mechanisms underlying increased amygdala-vlPFC connectivity in our study remain an open question, one possible explanation is that chronic stress related to negative parenting may lead to stress-induced modifications of the hypothalamic-pituitary-adrenal axis activity with excessive cortisol release and thereby affects the maturation process of emotion-related brain circuitry (26,28,82). Future studies are needed to address the neurobiological mechanisms of how adverse environmental factors such as negative parenting in childhood shape amygdala-prefrontal development during adolescence.

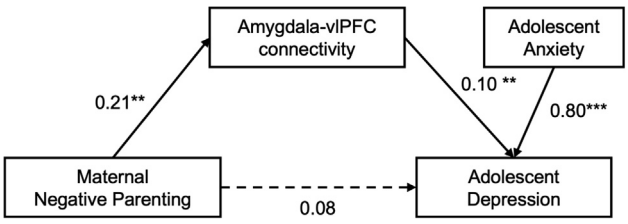

Figure 4. Mediation model depicts the relationships among negative parenting in early adolescence, mid-adolescent depressive symptoms, and amygdala–ventrolateral prefrontal cortex (vlPFC) connectivity using the Friston 24-parameter model. Structural equation modeling demonstrates good fit, with $\chi^2_1 = 1.01$, $p = .32$, root mean square error of approximation = 0.01 (95% confidence interval = 0–0.20), standardized root mean square residual = 0.02, comparative fit index = 1.00. Indirect effect was significant (indirect effect = 0.02; bootstrapped 95% confidence interval = 0.003–0.039). For clarity of presentation, the diagrams do not show nonsignificant control variables (i.e., sex, wave 2 age, and stressful life events). Paths are marked with standardized coefficients. $^{**}p < .01$. $^{***}p < .001$.

In conjunction with increased amygdala-vlPFC connectivity, we further observed that this neural pathway mediated the association between negative maternal parenting in early adolescence and higher internalizing depressive symptoms later in mid-adolescence. There is increasing evidence from recent neuroimaging studies suggesting that early adverse experiences can lead to an increased risk for the development of psychopathology, most likely through acting on amygdala-prefrontal circuitry (24,25). For instance, increased amygdala-vmPFC connectivity mediates the association between childhood stress hormone cortisol levels and adolescent internalizing depressive symptoms 14 years later (34). A major discrepancy is that we observed a mediation effect of amygdala-vlPFC connectivity on the association between negative parenting and adolescent depression, while they observed a mediation effect localized to amygdala-vmPFC connectivity pathway. Given that there are large differences in the independent variables and age ranges for participants between the two studies, the effects of childhood stress cortisol and maternal negative parenting in early adolescence on internalizing depressive symptoms may be mediated by different amygdala-prefrontal pathways in middle to late adolescence. Thus, our findings provide ample opportunities for future research, particularly using longitudinal neuroimaging design with multiple sampling points to delineate how longitudinal dynamics in brain maturation, especially for different amygdala-prefrontal pathways, mediate the adverse effects of different early adverse experiences (i.e., stress exposure, negative parenting) on internalizing symptoms later in adolescence. It is worth noting that maternal negative parenting was associated with decreased amygdala connectivity with distributed brain regions other than the vlPFC in our present study. However, none of the connectivity of these regions with the amygdala is related to internalizing symptoms during adolescence at the time of scanning.

Moreover, we observed that the amygdala-vlPFC connectivity pathway displayed moderate heritability. This result is in part consistent with findings from one recent study in which amygdala-prefrontal functional connectivity demonstrated influences of genetics and environment, with substantially larger environmental influences than genetic contributions to this connectivity pathway in 7- to 9-year-old twins (43). This finding together with our observation highlights both genetic and environmental influences on the development of amygdala-prefrontal circuitry and further suggests that environmental influences mostly explain the longitudinal effect of negative parenting on internalizing depressive symptoms later in mid-adolescence. Our previous studies, for instance, demonstrated the interacting effect of *BDNF* Val66Met polymorphism with maternal parenting and stressful life events on adolescent depressive symptoms (48,49). Together, our present and previous findings suggest potential neurodevelopmental mechanisms underlying the synergic effects of risk genes such as *BDNF* Val66Met polymorphism and environmental factors on adolescent internalizing symptoms likely by acting on the amygdala-prefrontal circuitry.

This study is, to our knowledge, the first to suggest a genetically based neurodevelopmental pathway by which negative parenting increases vulnerability for internalizing symptoms during adolescence. Our findings should be

Table 3. Statistics and Parameter Estimates for Univariate Genetic Modeling of Amygdala-vlPFC Connectivity

Model	χ^2	*df*	AIC	$\Delta\chi^2$	Δdf	*p*	A (95% CI)	C (95% CI)	E (95% CI)
ACE	496.36	174	148.36				0.21 (0–0.44)	0 (0–0.28)	0.79 (0.56–1.00)
AE[a]	496.36	175	146.36	0	1	1.00	0.21 (0–0.44)		0.79 (0.56–1.00)
CE	497.81	175	147.81	1.45	1	.23		0.12 (0–0.32)	0.88 (0.69–1.00)
E	499.04	176	147.04	2.65	2	.31			1.00 (1.00–1.00)

A, additive genetic factors; AIC, Akaike information criterion (low and ideally negative values indicate good fit); C, shared environmental factors; CI, confidence interval; E, specific environmental factors; vlPFC, ventrolateral prefrontal cortex.

[a]Best-fitting model.

considered in light of some limitations. First, there were no fMRI data obtained before negative parenting in our study. Thus, we can test only the association between negative parenting and the resting-state fMRI data and cannot come to a causal conclusion. Future studies are required to examine how negative parenting in early childhood affects the development of amygdala-prefrontal circuitry, ideally with multimodal brain imaging techniques at multiple time points spanning childhood and adolescence. Second, behavioral measurements in our present study were based solely on self-reports; more objective physiological and endocrine measures (e.g., autonomic arousal, blood pressure, stress hormones) as well as family interaction experiments, such as an event-planning interaction, are also critical in future studies (83). Third, high-spatial-resolution brain imaging techniques are required to better address amygdala subregion–specific mediation effects.

In conclusion, this study demonstrates that maternal negative parenting in early adolescence leads to internalizing depressive symptoms later during mid-adolescence through increased amygdala-vlPFC connectivity, which is thought to be critical for appraisal and regulation of emotions. The moderate heritability of this amygdala-prefrontal pathway suggests that interplay of genetic and environmental factors plays a critical role in the development of emotion-related brain circuitry and internalizing symptoms from early to middle adolescence. Our findings have the potential to advance our understanding of the neurodevelopmental origins of emotion-related psychopathology following exposure to adverse environmental factors.

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