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Brain network integration underpins differential susceptibility of adolescent anxiety

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Abstract

Background. Parenting is a common and potent environmental factor influencing adolescent anxiety. Yet, the underlying neurobiological susceptibility signatures remain elusive. Here, we used a longitudinal twin neuroimaging study to investigate the brain network integration and its heritable relation to underpin the neural differential susceptibility of adolescent anxiety to parenting environments.

Methods. 216 twins from the Beijing Twin Study completed the parenting and anxiety assessments and fMRI scanning. We first identified the brain network integration involved in the influences of parenting at age 12 on anxiety symptoms at age 15. We then estimated to what extent heritable sensitive factors are responsible for the susceptibility of brain network integration.

Results. Consistent with the differential susceptibility theory, the results showed that hypo-connectivity within the central executive network amplified the impact of maternal hostility on anxiety symptoms. A high anti-correlation between the anterior salience and default mode networks played a similar modulatory role in the susceptibility of adolescent anxiety to paternal hostility. Genetic influences (21.18%) were observed for the connectivity pattern in the central executive network.

Conclusions. Brain network integration served as a promising neurobiological signature of the differential susceptibility to adolescent anxiety. Our findings deepen the understanding of the neural sensitivity in the developing brain and can inform early identification and personalized interventions for adolescents at risk of anxiety disorders.

Introduction

Adolescence is recognized as a 'sensitive window' during which neural circuit-level formation is highly responsive to ever-changing environmental demands, and hence a series of stress-related psychiatric disorders peak in this period (Meyer & Lee, 2019; Sisk & Gee, 2022). Anxiety disorders are common among adolescents, with a prevalence of 4.7–9.1% (Li et al., 2022; Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). Sub-clinical anxiety symptoms emerge early and predict persistent adolescent and even adult anxiety disorders (Nivard et al., 2015; Reef, van Meurs, Verhulst, & van der Ende, 2010). Therefore, it is of great significance to investigate the neurobiological susceptibility of adolescent sub-clinical anxiety, as it could provide early signs for characterizing the risk of future anxiety disorders.

Parenting is defined as a constellation of attitudes toward child, which creates an emotional climate wherein parents' behaviors are expressed (Darling & Steinberg, 1993). Parenting is a common and potent environmental factor in predicting adolescent anxiety (Apsley & Padilla-Walker, 2020). However, a striking variation is generally observed among individuals exposed to similar negative or positive parenting. Neurobiological characteristics, particularly those within the central nervous system, could account for the substantial behavioral variation in response to the environment (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011). Adolescents with neural susceptibility are proposed to be responsive to both good and bad environments, with a pattern according to predictions from the differential susceptibility theory (DST; Belsky & Pluess, 2009; Ellis et al., 2011; Homberg & Jagiellowicz, 2022). Nonetheless, the brain susceptibility process, that is, the neural signatures of differential susceptibility, is not well-understood. To the best of our knowledge, only three studies have investigated neuroimaging measures that could serve as indicators of differential susceptibility. Individuals with a higher amygdala reactivity (Liu, Oshri, Kogan, Wickrama, & Sweet, 2021),

larger hippocampal volume (Whittle et al., 2011), and lesser thinning of frontal regions (Deane et al., 2020) have better socioemotional adjustments (e.g. depression and well-being) than their counterparts in conditions of supportive rearing, but they perform worse in conditions of unfavorable rearing. Although these studies have made important contributions to our knowledge on neural sensitivity, the roles of further brain areas and neural circuitry should be examined, particularly in the etiology of adolescent anxiety (Zugman, Winkler, & Pine, 2021).

The intrinsic functional architecture of large-scale brain networks has been recently proposed to be an endophenotype that underlies the vulnerability and resilience of psychiatry related to differential susceptibility (Homberg & Jagiellowicz, 2022); however, this assumption has not been proven. fMRI studies have shown that the anxiety susceptibility could be explained by the altered intrinsic functional connectivity of, and the interaction between, the central executive, anterior salience, and default mode networks, as individuals with anxiety disorders and those prone to anxiety usually exhibit irregular connection patterns within and between these networks (Burghy et al., 2012; Dennis, Gotlib, Thompson, & Thomason, 2011; Geng, Li, Chen, Li, & Gu, 2015; Strawn, Lu, Peris, Levine, & Walkup, 2021; Xu et al., 2019). In terms of brain function, the central executive, anterior salience, and the default mode networks support crucial socioemotional processes, such as emotional regulation (Gagnepain, Hulbert, & Anderson, 2017; Turner et al., 2019; Wessing, Rehbein, Postert, Fürniss, & Junghöfer, 2013), salience monitoring (Seeley et al., 2007), and self-referencing (Raichle, 2015). As such, they could fundamentally be involved in the cognitive and emotional responses to the daily parental interactions. When the activity in these networks is aberrant, individuals are unable to successfully regulate unpleasant thoughts and frustrated emotions that may be elicited by negative parenting experiences (hitting, shouting, or insufficient support from a more hostile or less warm mother/father). Nevertheless, this neural bias is thought to be 'permissive' to the influence of positive cues, enabling beneficial outcomes in more positive context (Homberg & Jagiellowicz, 2022). For example, individuals with neural sensitivity have been shown to perform better in supportive rearing environments (Deane et al., 2020; Liu et al., 2021; Whittle et al., 2011). Thus, the atypical brain network patterns likely constitute the neural differential sensitivity that amplifies both the negative impact of unfavorable parenting and the positive impact of favorable parenting on adolescent anxiety.

Genetic factors are thought to convey the susceptibility to psychopathology by promoting the individuals' neurobiological responsiveness to stress (Drabant et al., 2012; Homberg & Jagiellowicz, 2022; Notaras & van den Buuse, 2020). For example, a series of gene markers (i.e. *BDNF*, *5-HTT*, and *COMT*) were associated with the differential susceptibility to stress or family rearing context (Chen, Yu, Liu, Zhang, & Zhang, 2015; Li, Berk, & Lee, 2013; Starr, Hammen, Brennan, & Najman, 2013; Stocker et al., 2017; Taylor et al., 2006; Zhang, Cao, Wang, Ji, & Cao, 2016b; Zhang et al., 2016a, 2016b). They have also been shown to be closely related to brain function (Drabant et al., 2012; Mier, Kirsch, & Meyer-Lindenberg, 2010; Notaras & van den Buuse, 2020). Additionally, genetically informed research has demonstrated that genes account for a considerable portion of variances in the connectivity in adolescent brain networks (Fu et al., 2015; Teeuw et al., 2019; Yang et al., 2016). Nevertheless, it remains unclear to what extent heritable sensitive factors are responsible for the susceptible brain networks.

In this study, we conducted a longitudinal twin fMRI study to delineate the neurobiological signature underpinning the differential susceptibility in adolescent anxiety to parenting environments and to clarify its genetic basis. We hypothesized that brain network connectivity pattern could act as an indicator of differential susceptibility and that this was possibly due to genes. First, we tested whether and how intrinsic brain network integration could moderate the influence of the parenting environment in early adolescence on anxiety symptoms in middle adolescence. We then estimated the heritability of the brain network integration identified as a modulator.

Methods

Participants

We recruited 216 same-sex twins from the Beijing Twin Study to perform a two-wave data collection. They were traced from early adolescence (wave 1; mean age = 12.68 years) to middle adolescence (3-year follow-up; wave 2; mean age = 15.72 years). In wave 1, we telephoned twins' parents first to obtain their oral consent. Twins whose parental consents were obtained were gathered in classrooms after school. After describing the study's purposes and explaining the procedures and obtaining twins' consent, trained research staff distributed questionnaires. The adolescents completed the questionnaires independently and were asked to provide a saliva sample for DNA extraction using Oragene's DNA sample collection kit (DNA Genotek Inc., Kanata, ON, Canada). Questionnaires and informed consent letter for parents were taken home by the children and then mailed back to our laboratory after completion. All the adolescents are typically developing and the parents in our study denied their children had a psychiatric history. In wave 2, all 216 twins were invited to our laboratory. They were asked to undergo psychological assessments and fMRI scanning. All procedures were approved by the relevant institutional review board.

Twenty pairs of twins were excluded from subsequent analyses because of excessive movement during scanning (19 pairs) and failure to complete all assessments (one pair; Fig. 1*a*). The zygosity of the twins was determined using DNA analysis (Chen et al., 2010). The final analytical sample included 176 twins (49 monozygotic and 39 dizygotic pairs; 94 female twins).

Parenting and adolescent anxiety measures

In wave 1, twins reported the maternal and paternal warmth and hostility experienced in the past 12 months, using the warmth and hostility subscales of the Parenting Style Scale (Ge, Best, Conger, & Simons, 1996). Warmth and hostility are considered two critical but distinct dimensions of parenting environments. Hostility refers to parental angry, intimidating, and antisocial behavior in their daily interactions with their children, whereas warmth refers to that parent treats their children with love, affection, interest, and positivity. The warmth subscale comprises seven items (e.g. expression of warmth and support), and the hostility subscale comprises six items (e.g. yelling, insulting, and being angry). Higher scores on these 5-point scales indicated warmer or more hostile environmental exposure from their mothers and fathers. These scales have good psychometric properties when used in Chinese adolescents (Chen et al., 2015; Zhang et al., 2016a, 2016b). In the current study, the Cronbach's α of the scale was

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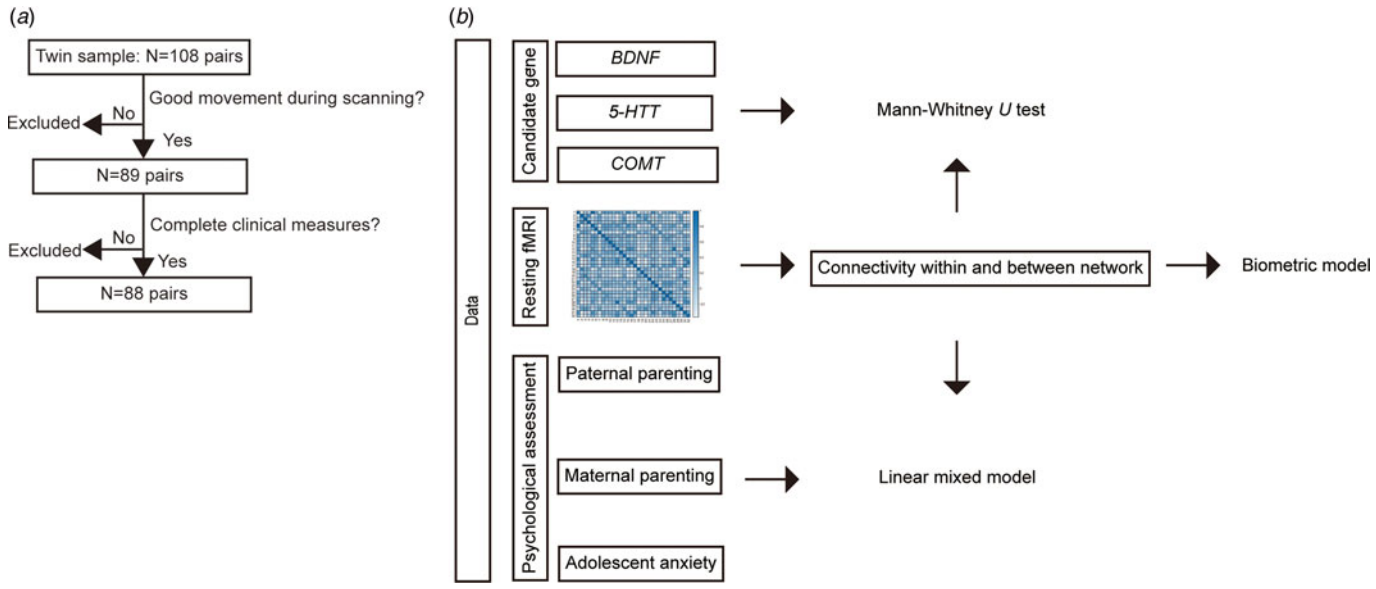

Figure 1. Participant selection and data analysis.

0.87 for maternal warmth, 0.89 for paternal warmth, 0.87 for maternal hostility, and 0.88 for paternal hostility.

In wave 2, anxiety levels were assessed using the trait subscale of Form Y of the State-Trait Anxiety Inventory (TAI subscale; Shek, 1993). This subscale comprises 20 items, two representative items of which were 'I feel nervous and restless' and 'I worry too much.' Twins were asked to choose the statement that most closely described their mood or thoughts in their daily lives on a 4-point Likert scale (1 = almost never to 4 = almost always). The scores were averaged to indicate the anxiety severity, with higher average scores in a possible range from 1 to 4 indicating more symptoms. This scale has been used in multiple studies to investigate anxious characteristics in nonclinical samples (Ding, Bi, Zhou, Bai, & Li, 2021; Jiang et al., 2021). In the current study, the Cronbach's α was 0.88.

Covariates

Twins reported their age, birth order, and sex. Stressful life events that occurred in their daily life within the past 12 months were assessed using a modified version of the Life Events Checklist (Johnson & McCutcheon, 1980). This scale comprises 39 items. Each item was scored 1 or 0 if the specific event had or had not occurred, respectively. The scores were averaged to indicate life stress, with higher scores in a possible range from 0 to 1 indicating more stress. Because of the significant familial transmission of anxiety (Ding et al., 2021), we also controlled for parental anxiety symptoms, which was assessed using the TAI subscale completed by both parents, in the moderation analysis. All the covariates were obtained in wave 1.

Image acquisition, preprocessing and network analysis

In wave 2, the twins underwent resting-state fMRI using a 3-Tesla Trio Trim scanner (Siemens Healthineers AG, Erlangen, Germany) at the Beijing MRI Center for Brain Research. fMRI data were preprocessed using the Functional Connectivity Toolbox (CONN), version 18a in SPM12 (Whitfield-Gabrieli & Nieto-Castanon, 2012). Regions-of-interest (ROIs) for the central executive network, anterior salience network, and default mode network were defined based on meta-analytic research and publicly available atlases (online Supplementary Table S1; Anderson, Ferguson, Lopez-Larson, & Yurgelun-Todd, 2011; Kohn et al., 2014; Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012). Within-network and between-network resting-state functional connectivity were quantified using Pearson's correlation of the first eigenvariate between ROIs. The details for image acquisition, preprocessing and network analysis are provided in the online Supplementary.

Linear mixed model

The analysis plan is shown in Fig. 1*b*. As the twins were nested within families, we used a linear mixed model with a random intercept parameter to test the moderation hypothesis using the lme4 package in R version 3.5.3 (Bates, Mächler, Bolker, & Walker, 2015). Each model included parenting environment, brain network integration of interest and the interaction of these two terms as predictors, and adolescent anxiety as an outcome. Age, sex, birth order, stressful life events, and parental anxiety were considered as covariates of no interest.

DST pattern determination

As suggested by the DST determination approaches (Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2007; Del Giudice, 2017; Roisman et al., 2012), we conducted a simple slope analysis and used three metrics, namely the crossover point, the Proportion of Interaction (PoI) and the Proportion Affected (PA), as rigorous examinations of our hypothesis that the brain network integration determines adolescent neurobiological differential sensitivity, for better and for worse, to rearing environments. The DST was supported only if (1) the association between parenting environments and anxiety symptoms were statistically significant at relatively high or relatively low levels of the functional connectivity index, or both, (2) the crossover

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point fell near the average range of the observed parenting score, (3) the PoI ranged from 20% to 80%, and 4) the PA ranged from 16% to 84% (Del Giudice, 2017; Roisman et al., 2012; Widaman et al., 2012).

Biometric model

A univariate biometric model was utilized to compute the genetic and environmental contribution to the differential susceptibility-related brain network integration using the Openmx package (Neale et al., 2016). In this model, each phenotype difference could be decomposed into additive genetic (A; genetic similarity between twins), shared environmental (C; environmental similarity between twins), and unique environmental (E; environmental differences) effects. The ACE model was estimated as an initial full model, and then the nested AE, CE, and E models were estimated. From a series of models, the model with the lowest Akaike information criterion (AIC) was considered the best.

Results

The effects of negative and positive parenting on adolescent anxiety

Descriptive statistics of demographic information and psychological measures are presented in Table 1. Adolescent and parental anxiety mean scores are well below the cut-off value (2.7/2.75) for anxiety disorders (Kvaal, Ulstein, Nordhus, & Engedal, 2005). Bivariate Pearson's correlation coefficients revealed that parental warmth and hostility in early adolescence were all significantly associated with anxiety symptoms in middle adolescence (Table 2). No significant correlation, however, was found for the average resting-state functional connectivity (within or between networks) with parenting measures or with anxiety.

Brain network integration linked to differential susceptibility of adolescent anxiety

The results for all interactions between parenting environments and intrinsic brain network connectivity are shown in online Supplementary Table S2. Figure 2 summarizes the significant interactions between network integration and parenting environments that influence adolescent anxiety, all of which survive the Benjamini–Hochberg false discovery rate (FDR) correction (Benjamini, 2010). We found that connectivity within the central executive network nodes moderated the effect of maternal hostility on anxiety symptoms (Fig. 2*a*). For paternal hostility, a significant moderating role was found for the connectivity between the anterior salience network and the default mode network (Fig. 2*b*). There was a significant interaction between paternal hostility and the anterior salience network, yet it did not survive FDR correction, and thus we did not interpret this further. No significant moderation effects were found for either maternal warmth or paternal warmth.

We used standard procedures to plot outcomes at different observed values of intrinsic network connectivity distributions (i.e. − 2 S.D., − 1 S.D., mean, + 1 S.D.). For maternal hostility, the slopes for the connectivity index in the central executive network from mean to + 1 S.D. were non-significant, ranging from $\beta = 0.06$ (95% CI −0.02 to 0.14; $p = 0.16$) to $\beta = -0.03$ (95% CI −0.13 to 0.07; $p = 0.58$). The slopes for the connectivity index from − 1 S.D. to − 2 S.D. were significant, ranging from $\beta = 0.14$ (95% CI 0.04 to 0.25; $p = 0.009$) to $\beta = 0.23$ (95% CI 0.08 to 0.39; $p = 0.005$; Fig. 3*a*). The crossover point fell close to the middle range of maternal hostility scores. The index of the PoI and the PA all met the quantitative criteria for the DST pattern (Fig. 3*b*). These results indicated that the effect of maternal hostility on anxiety was amplified by the lower connectivity in the central executive network. Specifically, among adolescents with hypo-connectivity in this network, high maternal hostility was

Table 1. Descriptive statistics of demographic information and psychological measures

Characteristic	Minimum	Maximum	Mean	S.D.
Age, y				
wave 1	10.83	15.17	12.70	0.95
wave 2	14.00	17.00	15.79	0.93
Sex, number and %				
Female	94	53.41%		
Male	82	46.59%		
Psychological measures				
Maternal hostility in wave 1	1.00	4.50	2.51	0.80
Maternal warmth in wave 1	1.25	5.00	3.67	0.86
Paternal hostility in wave 1	1.00	4.50	2.35	0.80
Paternal warmth in wave 1	1.00	5.00	3.43	0.98
Stressful life events in wave 1	0.00	0.21	0.07	0.05
Maternal anxiety in wave 1	1.00	2.75	1.88	0.37
Paternal anxiety in wave 1	1.05	2.80	1.84	0.41
Adolescent anxiety in wave 2	1.00	2.95	1.95	0.41

The anxiety scores possibly ranges from 1 to 4 on average. The stressful life events score possibly ranges from 0 to 1 on average.

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Table 2. Bivariate correlations of major study variables

Variables	1	2	3	4	5	6	7	8	9	10	11
1. Maternal hostility	–										
2. Paternal hostility	0.39***	–									
3. Maternal warmth	−0.45***	−0.20*	–								
4. Paternal warmth	−0.26***	−0.38***	0.54***	–							
5. CEN rsFC	0.05	−0.03	−0.06	−0.03	–						
6. aSN rsFC	−0.07	−0.03	−0.03	0.05	0.23**	–					
7. DMN rsFC	0.07	−0.03	−0.10	−0.05	0.11	0.28***	–				
8. CENaSN rsFC	0.07	0.13	0.02	−0.06	−0.15*	−0.36***	−0.30***	–			
9. CENDMN rsFC	0.05	−0.14	−0.10	0.01	0.43***	0.22**	0.43***	−0.46***	–		
10. aSNDMN rsFC	−0.03	0.07	0.02	−0.14	−0.07	−0.60***	−0.53***	0.62***	−0.30***	–	
11. Adolescent anxiety	0.16*	0.22**	−0.16*	−0.18**	0.11	−0.01	−0.03	−0.02	−0.05	0.07	–

CEN, central executive network; rsFC, resting-state functional connectivity; aSN, anterior salience network; DMN, default mode network; CENaSN, the interaction between the central executive network and anterior salience network; CENDMN, the interaction between the central executive network and default mode network; aSNDMN, the interaction between the anterior salience network and default mode network.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

associated with higher-than-average levels of anxiety, whereas low maternal hostility was associated with lower-than-average levels of anxiety.

For paternal hostility, the slopes for the connectivity between the anterior salience network and the default mode network from the mean to + 1 s.d. were non-significant, ranging from $\beta = 0.01$ (95% CI −0.08 to 0.08; $p = 0.91$) to $\beta = -0.09$ (95% CI −0.20 to 0.02; $p = 0.12$). Furthermore, the slopes ranged from a marginally significant $\beta = 0.10$ (95% CI −0.00 to 0.20; $p = 0.05$) of − 1 s.d. to a significant $\beta = 0.19$ (95% CI 0.04 to 0.34; $p = 0.01$) of − 2 s.d. (Fig. 3*c*). The crossover point was calculated close to the middle range of paternal hostility scores. The index of the PoI and PA met the quantitative criteria for the DST pattern (Fig. 3*d*). As the intrinsic connectivity between the anterior salience network and default mode network in adolescent brain is generally negative, these results indicated that the effect of paternal hostility on anxiety symptoms was amplified by the higher anti-correlation between these two networks. Specifically, among adolescents with high anti-correlation, high paternal hostility was associated with higher-than-average levels of anxiety, whereas low paternal hostility was associated with lower-than-average levels of anxiety.

Genetic and environmental contribution to differential susceptibility-related brain network integration

Monozygotic twins exhibited a significant within-pair association for the connectivity in the central executive network ($r = 0.29$; 95% CI 0.01 to 0.50), but the association in dizygotic twins was not significant ($r = -0.12$; 95% CI −0.39 to 0.16), implying genetic effects. Biometric model revealed that the AE model was the optimal model, as indicated by its lowest AIC (online Supplementary Table S3). Specifically, additive genetic effects accounted for 21.18% (95% CI 0.000 to 44.83%) of the variance, suggesting moderate genetic effects, whereas unique environmental effects accounted for 78.82% (95% CI 55.17% to 100%) of the variance. For the interaction between the anterior salience network and the default mode network, there were non-significant within-pair associations both in monozygotic ($r = 0.13$; 95% CI −0.12 to 0.35) and dizygotic ($r = 0.10$; 95% CI −0.14 to 0.35) twins. Genetic analysis revealed that the E model was the optimal, suggesting non-genetic effects.

To determine whether genetic and neural differential susceptibility were correlated, we performed a supplemental analysis to examine if the well-established gene markers (i.e. *BDNF*, *5-HTT*, and *COMT*) of differential susceptibility had an effect on the brain network integration. Results showed significant differences for *BDNF* variants in the connectivity of the central executive network ($U = 1270.00$, $p = 0.007$). The polygenic susceptibility score derived from these three genes was significantly related to the central executive network connectivity ($\beta = -0.183$, $p < 0.05$). The detailed analysis and results can be found in the online Supplementary Material.

Discussion

Herein, we used a longitudinal twin neuroimaging study to investigate whether and how the developing brain networks served as moderators of the relationship between parenting and adolescent anxiety symptoms, and to explore the genetic correlates of the susceptible network integration. The hypo-connectivity within the central executive network and the high anti-correlation

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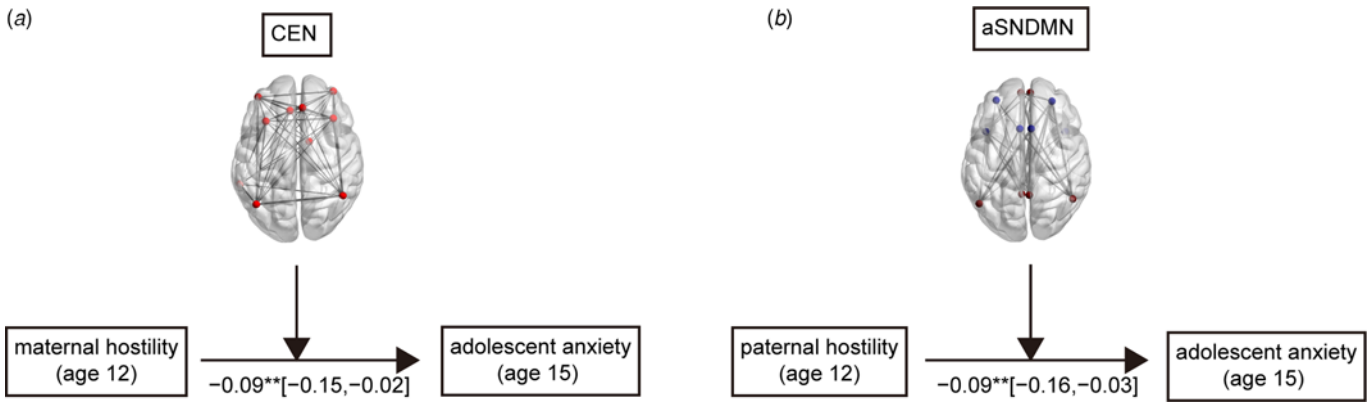

Figure 2. Parameter estimates for significant moderation models (*a*) Connectivity within the central executive network significantly moderated the influence of maternal hostility on anxiety. (*b*) Connectivity between the anterior salience network and default mode network significantly moderated the influence of paternal hostility on anxiety. $^{**}p < 0.01$.

between the anterior salience network and default mode network emerged as key differential susceptibility signatures for distinguishing the influences of maternal and paternal hostility in early adolescence on anxiety in middle adolescence, respectively. Moreover, the connectivity within the central executive network exhibited moderate heritability. Our findings provide insight into the brain network integration underpinning the differential susceptibility to adolescent anxiety and the underlying gene-brain correlation.

The connectivity patterns in the central executive network and between the anterior salience network and default mode network appear to play distinct roles in response to maternal and paternal

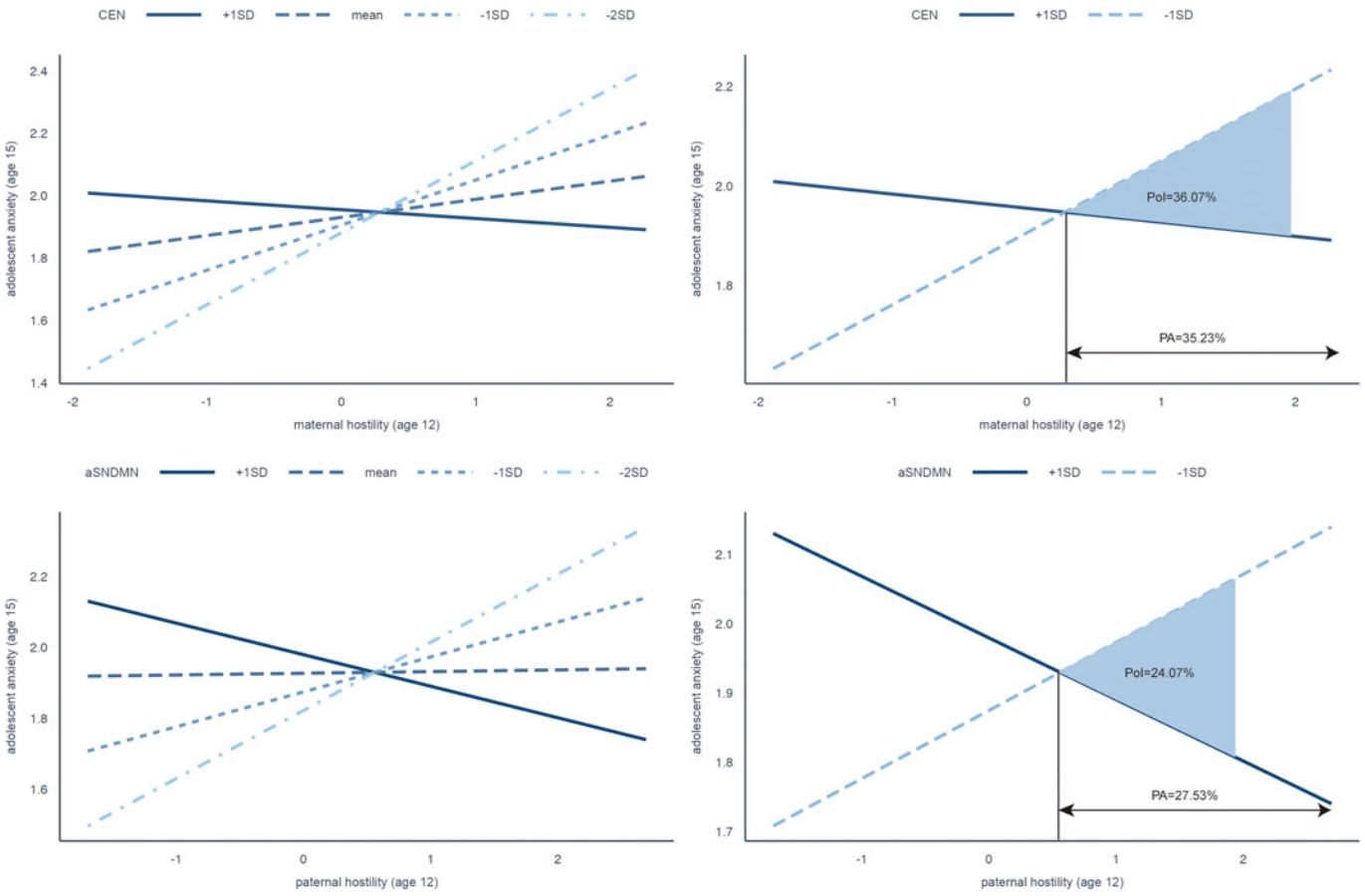

Figure 3. Brain network integration linked to differential susceptibility of adolescent anxiety under maternal and paternal hostility CEN, central executive network; aSNDMN, the interaction between the anterior salience network and default mode network; PoI, proportion of interaction; PA, proportion affected. (*a*) Variation in the effects of maternal hostility on adolescent anxiety according to the degree of CEN connectivity. (*b*) DST determination metrics for the moderating role of CEN. (*c*) Variation in the effects of paternal hostility on adolescent anxiety according to the degree of aSNDMN connectivity. (*d*) DST determination metrics for the moderating role of aSNDMN. Maternal and paternal hostility were also standardized and plotted within the distribution.

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hostility. It is consistent with the recent opinion of DST that differential susceptibility is domain-specific: individuals with certain sensitivities are sensitive to a specific context (Belsky, Zhang, & Sayler, 2022; Markovitch & Knafo-Noam, 2021). Adolescents usually perceive paternal and maternal hostility as two different rearing contexts, likely due to the disparity in the roles of the parents in Chinese family. For instance, mothers generally take more responsibility for rearing their children and show a higher level of sacrifice for children's education than do fathers (Leung & Shek, 2012). Though the mothers in Chinese contexts are usually perceived as more demanding than fathers (Dou, Shek, & Kwok, 2020), these efforts mothers devoted could mitigate the negative influences toward adolescents from the parenting attributes of mothers (Shek, 1998, 2000).

The central executive network is critical for the reappraisal of threatening events (Wessing et al., 2013), suppression of intrusive thoughts (Gagnepain et al., 2017), and self-control (Turner et al., 2019). Exposure to maternal hostility elicits relatively mild stress, the effect of which could be sustained by the developing central executive network in adolescence. Adolescents with high self-regulation strategies can flexibly reappraise maternal hostility as 'tough love' that reflects their mother's intention to help them reach higher potential and achievements (Dou et al., 2020; Katz, 2017). In contrast, low connectivity in the central executive network usually indicates a reduced ability to regulate distress during adversity (Miller et al., 2018), which may lead to a marked increase in the susceptibility to psychological symptoms. This observation agrees with a prior finding that youth with hypo-connectivity in the central executive network are more likely to have cardiometabolic risks in chronic stress, such as living in areas with a high neighborhood murder index (Miller et al., 2018).

In contrast, when communicating with a hostile father, adolescents tend to report more stress and negative feelings (Shek, 1998). The interaction between the anterior salience network and default mode network is largely responsible for appraising acute stress and high emotional arousal (van Oort et al., 2017). High anti-correlation might reflect a failure of top-down regulation from the central executive network during stress, resulting in the anterior salience network feeding more negative information to the default mode network (Homberg & Jagiellowicz, 2022). This atypical connectivity has been observed in adolescents with high levels of anxiety (Burghy et al., 2012; Dennis et al., 2011), and is related to hypervigilance and hyperarousal symptoms (Hart et al., 2018; Zhang et al., 2015). Thus, higher anti-correlation between the anterior salience network and default mode network may confer sensitivity through a process that amplifies the anxious behavioral and physiological responses induced by paternal hostility.

Consistent with DST, the brain network integration revealed by our study presented both costs and benefits depending on the rearing circumstances, indicating that adolescents with susceptible network connectivity patterns are at high risk of anxiety in response to high levels of hostility, while they are also at low risk in the absence of hostility. Previous neuroimaging studies on adolescents also reported that some neural indicators exhibited differential susceptibility to other developmental outcomes in the context of rearing (Deane et al., 2020; Liu et al., 2021; Whittle et al., 2011). Taken together, these results may reveal that neural susceptibility in the developing brain, similar to the differential susceptible role of risky genes, could be adaptive in certain parenting environments.

The significant interactions were only detected in parental hostility, not parental warmth. Some neurobiological indicators not examined in our study may underpin the sensitivity to positive parenting. Previous study, for example, discovered that higher left amygdala reactivity to positive stimuli significantly amplified the effect of parental warmth on adolescent prosocial behavior (Liu et al., 2021). Another possible explanation is that the 'dose' required for a significant interaction in positive parenting is higher than that in negative parenting. Low amounts of negative parenting over short periods of time may cause a substantial interaction, whereas greater dosages over longer periods of time may be required to produce equal effects in positive parenting (Deane et al., 2020).

We observed moderate genetic effects on the connectivity pattern in the central executive network, but no genetic effects on the interaction between the anterior salience network and the default mode network, which aligns with the previous twin neuroimaging study that reported the presence of genetic effects among certain nodes in the central executive network, and the absence of that among nodes between the anterior salience network and the default mode network in adolescence (Teeuw et al., 2019). Our results shed light on the extent to which the genetic and environmental factors contributed to the differential susceptibility-related brain network integration. Regarding specific gene markers, the significant influence of *BDNF* as well as polygenic susceptibility score on the central executive network may suggest that genetic and neural differential susceptibility are potentially correlated in explaining the individual differences in anxiety. Our study is the first to attempt to detect the genetic substrate of neural susceptibility, but we have to admit that the interpretation of this candidate gene finding requires great caution due to the relatively small sample size.

The strengths of the current study include its longitudinal neuroimaging design, which enables a direct examination of how brain network differentiates the long-term influences of parenting on anxiety. Moreover, the twin group allows us to examine a general genetic basis of the neural susceptibility. Our study provides insight into that brain network integration could underpin the neurobiological differential susceptibility of adolescent anxiety and emphasized its genetic correlation. The neural sensitivity markers found in our study can prospectively help clinical researchers identify youth at risk of future anxiety disorders and tailor personalized treatment approaches accordingly. Despite these strengths, our study has several limitations. First, data on parenting and anxiety were collected via adolescent self-report. Though there is plenty of evidence to support the superiority of adolescent self-report (Comer & Kendall, 2004; Lagattuta, Sayfan, & Bamford, 2012), future research should extend our findings with observation data from parents. Second, the relationship between parenting and anxiety can be bi-directional (Allmann, Klein, & Kopala-Sibley, 2022). A further study with multiple waves of parenting and anxiety assessments is required to clarify this issue. Furthermore, sex is considered a confounding factor in adolescent anxiety (Apsley & Padilla-Walker, 2020), however, we are unable to detect its influence in terms of the limited sample. Though it was considered as a covariate in the analysis, future studies should use larger sample size to examine the sex effects. Moreover, it is unclear whether our findings could be generalized to children or adults. Future research should clarify the susceptible network integration in the etiology of anxiety from other developmental periods. Finally, more environmental factors, such as socioeconomic status (Tian et al., 2021), neighborhood disadvantages, and peer victimization (Quinlan et al., 2020), should be examined to offer a more comprehensive

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understanding of whether brain network integration could play a differential susceptibility role in other contexts.

In conclusion, the intrinsic connectivity patterns in the central executive network and between the anterior salience network and default mode network emerge as early neurobiological susceptibility indicators of adolescent anxiety to parenting environments. The differential susceptibility of the central executive network is partly due to genes. These findings provide insight into the distinct brain network integration and its genetic correlation to characterize biological susceptibility to adolescent anxiety symptoms, with critical implications for identifying at-risk youth and informing intervention programs. Future studies could examine the role of brain network integration in other contexts. (*BDNF*: Brain-derived neurotrophic factor gene. A single-nucleotide polymorphism within the *BDNF* causes a valine-to-methionine substitution at codon 66 (Val66Met, rs6265). Molecularly, the Val66Met polymorphism in BDNF affects synaptic plasticity and axonal growth by altering BDNF expression in the brain (Egan et al., 2003). *5-HTT*: Srotonin transporter gene. The srotonin transporter-linked polymorphic region (5-HTTLPR) within the *5-HTT* alter the transcription of the serotonin transporter.

COMT: Catechol-O-methyltransferase gene. A single nucleotide polymorphism (Val158Met) within the *COMT* alters a single amino acid in the enzyme and replaces the amino acid valine with methionine.)

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723002325.

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Competing interests. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The authors assert that ethical approval for publication of this research paper has been provided by their local Ethics Committee.

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