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Abnormalities in brain structure following childhood unpredictability: a mechanism underlying depressive and anxiety symptoms

Zhengxinyue Wang[1,2,*], Xinyu Cao[1,2,*], Xiaoyu Zheng[1,2], Yuanyuan Chen[2,3] and Jianjun Zhu[2,3]

[1]Center for Cognition and Brain Disorders of Affiliated Hospital, Hangzhou Normal University, Hangzhou, China; [2]Center for Early Environment and Brain Development, School of Education, Guangzhou University, Guangzhou, China and [3]Department of Psychology, Guangzhou University, Guangzhou, China

Original Article

*These authors contributed equally to this work.

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Corresponding author:
Jianjun Zhu;
Email: jianjunzhu722@gmail.com

Co-corresponding author:
Yuanyuan Chen;
Email: cyy0765@163.com

Abstract

Background. Childhood adversity is associated with abnormalities in brain structure, but this association has not been tested for childhood unpredictability, one form of adversity. We studied whether abnormalities in gray matter volume (GMV) could be a mechanism linking childhood unpredictability and psychopathology, over and above the effect of childhood trauma.
Methods. Participants were 158 right-handed healthy young adults (aged 17–28 years, M = 22.07, S.D. = 2.08; 66.46% female) who underwent structural magnetic resonance imaging measurements and provided retrospective reports of childhood unpredictability. The anxiety and depression subscales of the self-report Brief Symptom Inventory-53 were used to index psychopathology.
Results. Whole-brain voxel-based morphometric analyses showed that after controlling for the effect of childhood trauma, childhood unpredictability was correlated with greater GMV in bilateral frontal pole, bilateral precuneus, bilateral postcentral gyrus, right hemisphere of fusiform, and lingual gyrus, and left hemisphere of ventrolateral prefrontal cortex as well as occipital gyrus. Greater GMV in bilateral frontal pole, bilateral precuneus, and bilateral postcentral gyrus mediated associations between unpredictability and symptoms of depression and anxiety.
Conclusions. The findings suggest that childhood unpredictability could exact unique effects on neural development, over and above the effect of childhood trauma. These findings are relevant for understanding the occurrence of psychopathology following childhood unpredictability and have implications for intervention.

Introduction

Childhood adversity is common worldwide. Approximately half of youth reported that they had been exposed to at least one form of adversity (e.g. abuse, neglect, parental loss, or poverty) (McLaughlin, Weissman, & Bitrán, 2019). More than 30% of the cases of psychological disorders in the general population are thought to be attributable to childhood adversity (Green et al., 2010; McLaughlin et al., 2019; Teicher, Samson, Anderson, & Ohashi, 2016). Childhood unpredictability is a new conceptualization of a type of childhood adversity due to frequent fluctuation of family conditions across space and time (Ellis, Figueredo, Brumbach, & Schlomer, 2009). Unpredictability is due to factors such as living in a chaotic household and frequent changes in residence or parents' occupation (Ellis et al., 2009). Increasing evidence indicates that childhood unpredictability is associated with a greater risk of depression, anxiety, and suicidal ideation in adulthood (Baram et al., 2012; Glynn et al., 2019; Martinez et al., 2022). Moreover, it may have independent effects on psychopathology beyond the impact of childhood trauma (Spadoni et al., 2022). Childhood unpredictability is a key risk factor for psychopathology (Teicher et al., 2016). However, the underlying neural process by which the experience of unpredictability triggers vulnerability for psychological problems is not clearly understood.

Childhood unpredictability could shape the structure and function of brain regions underpinning important emotional and cognitive abilities. The effects of unpredictable patterns of sensory signals from the mother have been tested extensively in animal models of simulated early-life adversity. Fragmented or unpredictable maternal signals appear to alter the maturation of developing brain in rats by disrupting the synaptic growth and persistence in visual, somatosensory, and stress-responsive hypothalamic circuits (Baram et al., 2012; Lages, Rossi, Krahe, & Landeira-Fernandez, 2021). Indeed, early exposure to unpredictable maternal signals may be a common biological parameter leading to pervasive and long-lasting impairments of hippocampus-dependent memory circuit across species (Davis et al., 2017). Rats exposed to

unpredictable environments in early life also show lower abilities in memory and emotional perception than those raised in a stable environment (Bolton et al., 2018; Molet et al., 2016).

Several studies have explored the negative effect of childhood adversity on brain structure (Teicher et al., 2016). For instance, exposure to physical abuse in childhood was shown to be associated with reduced volume of frontal cortex and amygdala–hippocampus complex in adults with psychotic symptoms (Salokangas et al., 2021). Larger precuneus volumes have been documented in individuals with increases in accumulative severity of childhood adversity including interpersonal loss, family instability, and abuse of the child and/or mother (Jensen et al., 2015). However, most previous imaging studies have focused on childhood abuse or neglect. The dimensional model of adversity and psychopathology proposes that distinct dimensions of childhood adversity can affect neural structure in varying ways (McLaughlin, Sheridan, & Lambert, 2014). For instance, exposure to threat-related stressors, like physical abuse, has been linked to alterations in brain regions responsible for regulating emotions, while exposure to deprivation-related stressors, such as neglect, has been associated with changes in brain regions involved in cognitive control and attention (McLaughlin, Colich, Rodman, & Weissman, 2020; McLaughlin et al., 2019). Although previous studies have explored the relationship between particular forms of childhood adversity and brain structure, our study is the first to investigate the association between childhood unpredictability and brain structure in humans.

Previous research using structural magnetic resonance imaging (sMRI) has delineated direct associations between abnormal gray matter volume (GMV) and psychopathology. Depressive adolescents have also been shown to have larger GMV in the dorsolateral prefrontal cortex and in the hippocampus compared to healthy controls (Straub et al., 2019). Anxiety has been shown to be positively associated with hippocampal and media prefrontal GMV (Gorka, Hanson, Radtke, & Hariri, 2014). There is also evidence that abnormal GMV mediates the association between childhood adversity and psychopathology (Busso et al., 2017; Gorka et al., 2014; Opel et al., 2019; Rao et al., 2010). For example, a longitudinal study showed that early exposure to adversity exacted an indirect effect on adolescent depression through reduced hippocampal volume (Rao et al., 2010). Gorka et al. (2014) also observed that prefrontal and hippocampal GMV mediated the association between childhood trauma and trait anxiety among young adults. Further studies are needed to understand whether and how abnormal GMV mediates the link between early exposure to unpredictability, as a type of adversity, and psychopathology.

Hence, using whole-brain voxel-based morphometric (VBM) analysis based on T1-weighted MRI sequences in a sample of 158 young adults, the current study examined (i) the association between childhood unpredictability and altered GMV; (ii) the association between unpredictability-related gray matter abnormalities with depressive symptoms and anxiety symptoms; and (iii) the mediating effect of changes in GMV in the association between childhood unpredictability and psychopathology.

Methods

Participants

This neuroimaging study included 158 right-handed young adults [age range, 17–28 years; mean (s.d.) age, 22.07 (2.08) years; 66.46% female]. Participants were recruited from Hangzhou, China through flyers and social media. Before sMRI scanning, a screening interview was performed to exclude participants who reported any current or past diagnosis of psychiatric, personality, or neurological disorders. No participants had to be excluded for this reason. The protocol employed in the current study was approved by the research ethics committee of our institution and written informed consent was obtained from all participants prior to participation in accordance with the Declaration of Helsinki.

Materials and measures

Childhood unpredictability

Exposure to childhood unpredictability was assessed by eight self-report items (Young, Griskevicius, Simpson, Waters, & Mittal, 2018). Participants were instructed, 'Think back to your life when you were younger than 18'. Then they were asked to indicate the level of exposure to unpredictability in their childhood environment through these items (i.e. 'My family life was generally inconsistent and unpredictable from day-to-day'; 'My parent(s) frequently had arguments or fights with each other or other people in my childhood'; 'People often moved in and out of my house on a pretty random basis'; 'My parents had a difficult divorce or separation during this time'; 'When I woke up, I often didn't know what could happen in my house that day'; 'My family environment was often tense and on edge'; 'Things were often chaotic in my house'; 'I had a hard time knowing what my parent(s) or other people in my house were going to say'). Items were rated on a 7-point scale ranging in frequency from 1 (did not apply to me at all) to 7 (applied to me very much of the time). The combined index of childhood unpredictability consisted of the average of all item scores, with higher scores indicating higher exposure to childhood unpredictability. The reliability of this measure was good, with a Cronbach's alpha of 0.87 in our sample. This measure of childhood unpredictability has been shown to have good reliability and validity in previous studies (Dinh, Haselton, & Gangestad, 2022; Maranges, Hasty, Maner, & Conway, 2021; Mittal, Griskevicius, Simpson, Sung, & Young, 2015; Young et al., 2018).

Psychopathology

Depressive symptoms and anxiety symptoms were assessed using the anxiety and depression subscales of the Brief Symptom Inventory-53 (Derogatis & Melisaratos, 1983), which is a widely used measure with high internal consistency and test–retest reliability. Participants were asked to assess their anxiety symptoms (e.g. 'nervousness or shakiness', 'feeling tense or keyed up') and depressive symptoms (e.g. 'thoughts of ending my life', 'feeling no interest') during the past week. Items were rated on a 5-point scale ranging in intensity from 0 (never) to 4 (serious). Two final scores were calculated by summing across the six items for depressive symptoms and the six items for anxiety symptoms, separately, with higher scores indicating higher symptoms. The Cronbach's alpha in our sample was 0.85 for the depressive subscale and 0.86 for the anxiety subscale.

Covariates

To test the unique effect of childhood unpredictability on brain structure in the VBM analysis, we used the Chinese version of the Maltreatment and Abuse Chronology of Exposure (MACE) scale to measure the total severity of childhood trauma as a

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covariate in the analysis. The MACE scale retrospectively evaluates the severity of exposure to various types of childhood maltreatment across 18 years of childhood, including sexual abuse, verbal abuse, emotional abuse, physical abuse, witnessing violence, bullying, and neglect, through 58 items. The scale has been shown to have good to excellent reliability at each type of maltreatment as well as excellent overall reliability (Chen, Wang, Zheng, Wu, & Zhu, 2022). However, it should be noted that the MACE scale evaluates a wide range of childhood adversities and was not specifically designed to assess childhood unpredictability, which was the focus of our study.

Other covariates were age, subjective socioeconomic status (SSES), and total intracranial volume (TIV) across the analyses. Age was a continuous measure based on the respondent's age. SSES was assessed using the nationally referenced MacArthur Scale of Subjective Social Status (Adler, Epel, Castellazzo, & Ickovics, 2000). This scale assesses the respondent's view of their social standing relative to 10 steps of the 'social' ladder illustrated on the questionnaire. TIV values extracted from the MRI T1-weighted images were estimated. There were significant positive correlations between childhood unpredictability and childhood trauma ($r = 0.53$, $p < 0.001$), and significant negative correlations between childhood unpredictability and SSES scores ($r = -0.21$, $p < 0.01$). No significant associations were found between childhood unpredictability and age or TIV. In the analyses where depressive and anxiety symptoms were the dependent variable, we included aggression and suicidal behavior as additional covariates.

While there was a significant correlation between childhood unpredictability and childhood trauma, with a correlation coefficient of $r = 0.53$, this value did not exceed the threshold for multicollinearity concerns (i.e. $r > 0.8$). We also performed a variance inflation factor (VIF) analysis to evaluate potential multicollinearity. Our analysis included MACE and childhood predictability as predictor variables and GMV from various brain regions as dependent variables. The results of this analysis showed that all VIF values were below the conservative threshold of 2.5, indicating that there were no significant multicollinearity issues.

MRI data acquisition and data processing

T1-weighted high-resolution anatomical images were acquired for all participants on a 3.0T scanner (Siemens Magnetom Trio, A Tim System) equipped with a 12-channel phased-array head coil. Individual high-resolution three-dimensional structural images were acquired using a T1-weighted MPRAGE (magnetization prepared rapid acquisition gradient echo) sequence with the following parameters: repetition time (TR) = 2678 ms, echo time (TE) = 2.98 ms, flip angle = 7, field of view (FOV) = 256 × 256, voxel size = 1 mm^3 (192 slices). During the scanning, participants were asked to relax, close their eyes, and remain awake.

The VBM analyses of the structural data were conducted by using the default preprocessing pipeline of the computational anatomy toolbox (CAT12, http://www.neuro.uni-jena.de/cat/index.html), which is implemented in Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm). Default settings are detailed in the toolbox manual (http://dbm.neuro.uni-jena.de/cat12/CAT12-Manual.pdf). All T1 images were spatially registered to the SPM12 tissue probability maps (TPMs). After correction for bias, these images were segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF). The Diffeomorphic Anatomic Registration Through Exponentiated Lie (DARTEL) algebra algorithm was used to normalize the segmented components in Montreal Neurological Institute (MNI) space. After preprocessing and visual checks for artifacts, all scans passed an automated quality check protocol. The remaining modulated and normalized GM images were further smoothed with an 8 mm full-width half-maximum Gaussian smoothing kernel. We conducted a visual quality check of all images by a trained neuroimaging expert to ensure that the data were of high quality and free from artifacts or other issues that could affect our analyses.

Statistical analysis

To explore the associations between childhood unpredictability and brain structure, we used linear regression in SPM12, with gender, subjective social economic status, childhood trauma (i.e. childhood abuse and neglect), and TIV as covariates. To control for multiple comparisons, whole brain analysis using a voxel-wise statistical threshold of a false-discovery rate (FDR) rate of $p < 0.05$ was performed. Only clusters of $k > 50$ contiguous voxels that survived the voxel-wise FDR correction are reported. We extracted the average GMV within the brain regions identified by the regression analysis from each participant and used it in subsequent analyses. Specifically, we conducted exploratory analyses to examine the relationship between the identified GMV and both anxiety and depressive symptoms. We also performed mediation modeling, which tested the indirect effect of the identified GMV, using the R package lavaan (Rosseel, 2012). We used the bootstrapping method, an approach for implementing statistical tests and constructing confidence intervals without the use of the traditional statistical assumption of normality, to calculate estimators. When the confidence interval does not contain zero, the indirect effect is deemed to be statistically significant. To account for multiple comparisons in our regression and mediation analyses, we applied the FDR correction method as proposed by Benjamini and Hochberg (1995). In the data analysis, we identified outliers based on the criterion of three standard deviations from the mean. After identifying outliers, we removed them from the dataset and then conducted the analysis using the updated data.

Results

Childhood unpredictability and psychopathology

Demographic information and questionnaire results are provided in Table 1.

Linear regressions were performed to test childhood unpredictability's associations with depressive symptoms and anxiety symptoms, adjusting for the covariates (i.e. gender, SSES, and total severity of childhood trauma). Results showed that exposure to higher childhood unpredictability was associated with higher depressive symptoms ($\beta = 0.19$, $p_{FDR} = 0.041$) and anxiety symptoms ($\beta = 0.23$, $p_{FDR} = 0.014$).

Childhood unpredictability and brain structure

As seen in Table 2, Fig. 1, and online Supplementary Fig. S1, the whole-brain VBM analyses revealed that childhood unpredictability was positively correlated with GMV in the bilateral frontal pole, bilateral precuneus, bilateral postcentral gyrus, right hemisphere of fusiform and lingual gyrus, and left hemisphere of

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Table 1. Sample characteristics

Characteristic	Total sample ($n = 158$)
Sex (M/F)	53/105
Age (years)	22.07 ± 2.08
SSES	4.50 ± 1.32
Total intracranial volume	1460.54 ± 122.74
Childhood trauma	20.28 ± 12.57
Childhood unpredictability	1.93 ± 1.13
Depressive symptoms	3.06 ± 3.7
Anxiety symptoms	2.86 ± 3.3

SSES, subjective socioeconomic status.

ventrolateral prefrontal cortex (vlPFC), as well as inferior, superior, and middle parts of occipital gyrus, after controlling for TIV, gender, SSES, and total severity of childhood trauma. Childhood unpredictability was not associated with lower volume in any region.

Brain structure and psychopathology

Further, we tested whether symptoms of psychopathology were associated with GMV in regions that were found in the regression analyses to be significantly related to childhood unpredictability. Left and right regions were combined for frontal pole, precuneus, and postcentral gyrus in subsequent analyses. As seen in Table 3, after FDR correction, depressive symptoms were significantly associated with higher volumes in the bilateral frontal pole, bilateral precuneus, bilateral postcentral gyrus, bilateral inferior temporal gyrus, and left middle occipital gyrus. Increased left vlPFC volume was marginally associated with higher depressive symptoms. After FDR correction, anxiety symptoms were significantly associated with higher volumes in bilateral precuneus, bilateral postcentral gyrus, and bilateral inferior temporal gyrus.

Mediation effect of structural changes

Given the significant correlations among childhood unpredictability, GMV alterations, and psychopathological symptoms, we next conducted mediation analyses (Fig. 2 and online Supplementary Fig. S2). The mediation models showed that the association between childhood unpredictability and depressive symptoms was positively and significantly mediated by higher volume in bilateral frontal pole, bilateral precuneus, bilateral postcentral gyrus, bilateral inferior temporal gyrus, and left middle occipital gyrus. The association between childhood unpredictability and anxiety symptoms was positively and significantly mediated by high volume in bilateral precuneus, bilateral postcentral gyrus, and bilateral inferior temporal gyrus. All indirect effects remained significant after FDR correction.

Supplementary analyses

To better capture the distinction between childhood unpredictability and childhood trauma, we further examined the association of childhood trauma and GMV estimates extracted from regions that were hypertrophic in relation to unpredictability. Results showed that total severity of childhood trauma was associated with decreased volumes in left vlPFC ($\beta = -0.29$, $p_{FDR} < 0.001$), left precuneus ($\beta = -0.23$, $p_{FDR} < 0.01$), right precuneus ($\beta = -0.26$, $p_{FDR} < 0.01$), right fusiform ($\beta = -0.19$, $p_{FDR} < 0.05$), left superior occipital gyrus ($\beta = -0.23$, $p_{FDR} < 0.05$), left middle occipital gyrus ($\beta = -0.20$, $p_{FDR} < 0.01$), right lingual gyrus ($\beta = -0.17$, $p_{FDR} < 0.05$), left inferior temporal gyrus ($\beta = -0.17$, $p_{FDR} < 0.05$), and right inferior temporal gyrus ($\beta = -0.21$, $p_{FDR} < 0.05$), when TIV, gender, SSES, and childhood unpredictability were included as covariates. It appears that both

Table 2. Brain regions where GMV was associated with childhood unpredictability

Region	Hemisphere	Peak MNI coordinate			Peak *T* score	*k* (no. of voxels)
		x	*y*	*z*		
Frontal pole	R	40.5	51	−12	4.86	639
Frontal pole	L	−18	70.5	−12	4.12	139
vlPFC	L	−9	33	52.5	4.58	981
Precuneus	R	7.5	−63	33	4	345
Precuneus	L	−1.5	−51	46.5	4.63	677
Postcentral gyrus	R	48	−24	60	3.7	123
Postcentral gyrus	L	−34.5	−33	67.5	3.94	242
Fusiform	R	28.5	−70.5	−9	4.37	59
Inferior temporal gyrus	L	−66	−60	−7.5	3.61	89
Inferior temporal gyrus	R	51	−55.5	−16.5	4.67	229
Inferior occipital gyrus	L	−34.5	−70.5	−6	4.67	54
Middle occipital gyrus	L	−34.5	−96	0	5.12	219
Superior occipital gyrus	L	−13.5	−102	18	3.79	93
Lingual gyrus	R	9	−72	−7.5	4.4	504

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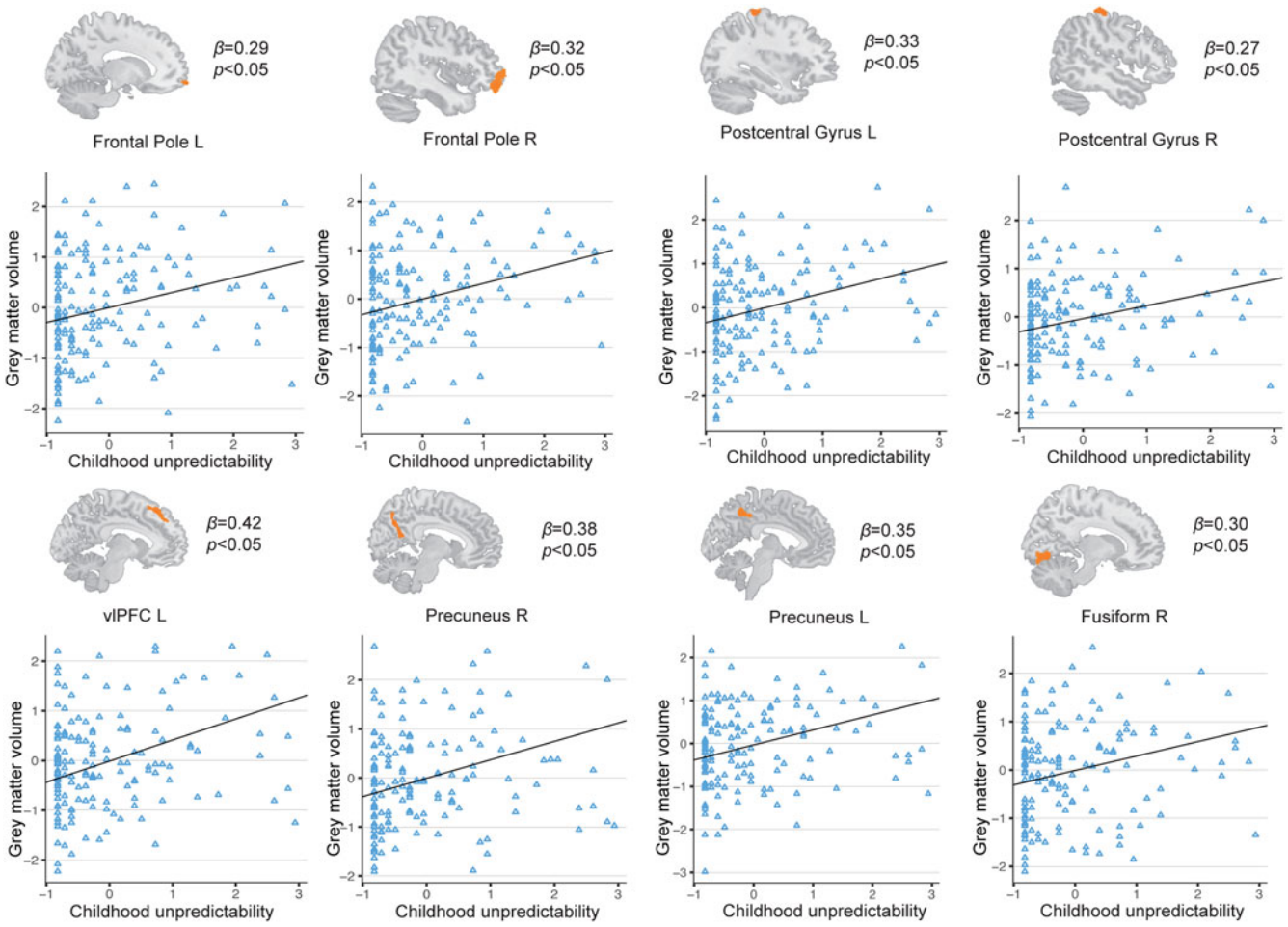

Figure 1. Relationship between childhood unpredictability and GMV in frontal pole, vlPFC, postcentral gyrus, precuneus, and fusiform. Standardized scores of mean values were used for both the *X* and *Y* axes, with the *X* axis representing the index of childhood unpredictability and the *Y* axis representing the mean GMV in specific brain regions.

Table 3. Linear regression of depressive symptoms and anxiety symptoms on alterations in GMV

	Depressive symptoms[a]			Anxiety symptoms[a]		
Region	β	p	p_{FDR}	β	p	p_{FDR}
Bilateral frontal pole	0.207	0.003	**0.007**	0.129	0.047	0.104
Left vlPFC	0.142	0.052	0.087^{+}	0.134	0.052	0.104
Bilateral precuneus	0.258	0.001	**0.005**	0.225	0.002	**0.008**
Bilateral postcentral gyrus	0.228	0.001	**0.005**	0.210	0.001	**0.008**
Right fusiform	0.124	0.094	0.104	0.121	0.085	0.122
Bilateral inferior temporal gyrus	0.208	0.008	**0.015**	0.186	0.012	**0.041**
Left inferior occipital gyrus	0.120	0.089	0.104	0.099	0.137	0.171
Left middle occipital gyrus	0.227	0.003	**0.007**	0.125	0.083	0.122
Left superior occipital gyrus	0.074	0.278	0.278	0.070	0.285	0.285
Right lingual gyrus	0.134	0.087	0.104	0.086	0.243	0.269

Note: Significant p values are bolded.
[a]Gender, SSES, childhood trauma, and TIV were included as covariates across the analyses.
$^{+}p < 0.09$.

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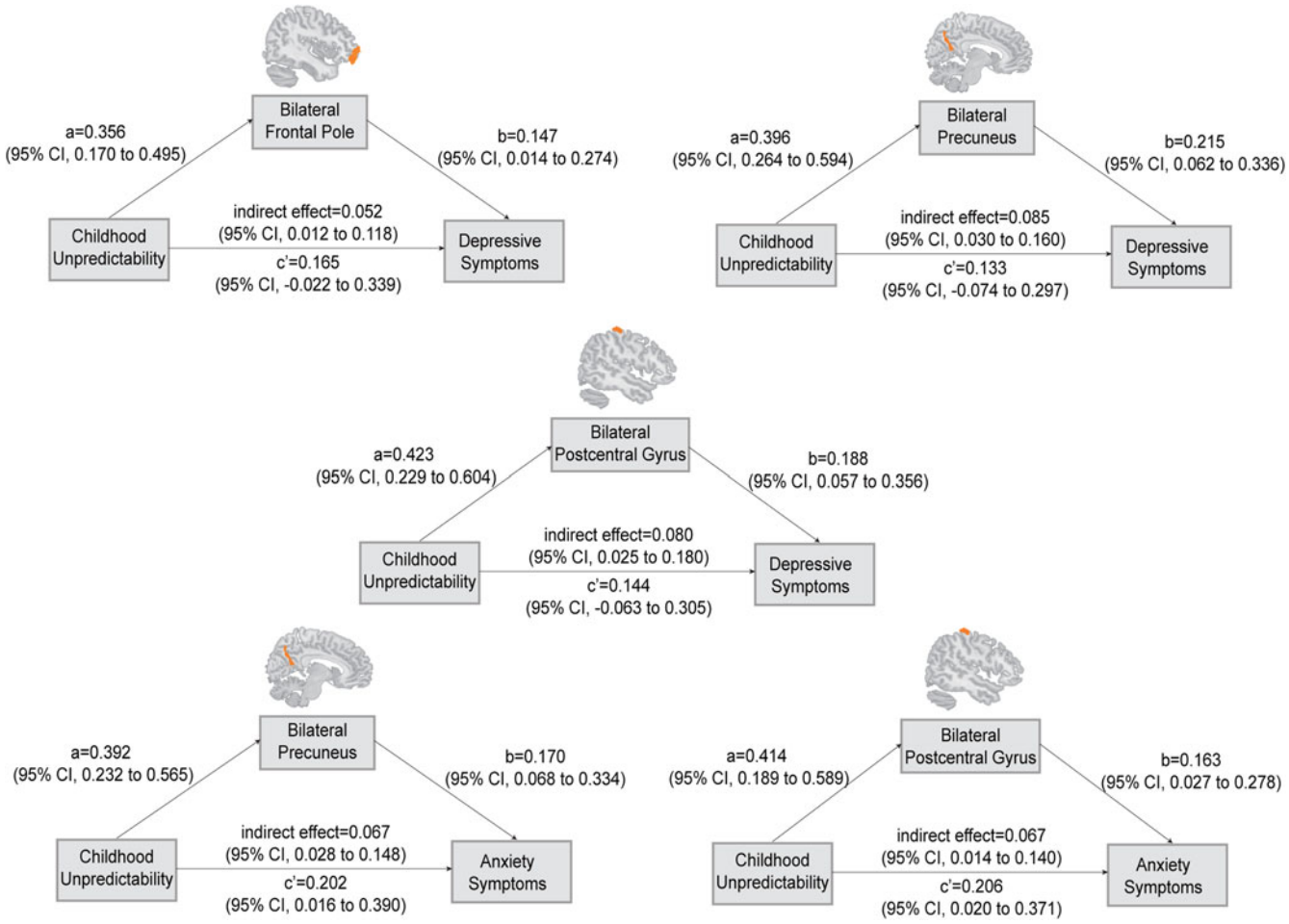

Figure 2. Mediation models explaining the associations between childhood unpredictability and psychopathology. The numbers are standardized regression coefficients and 95% confidence intervals. Not displayed are paths between controlled variables (e.g. age, SSES, TIV, and childhood trauma) and each of the variables in the model.

childhood unpredictability and childhood trauma were associated with brain structure but in the opposite direction.

Discussion

Earlier studies (Baram et al., 2012; Glynn et al., 2019; Martinez et al., 2022) documented significantly positive associations of childhood unpredictability with depressive and anxiety symptoms, over and above the effect of childhood trauma. In order to understand the underlying neural processes of these associations, the current study provided the first evidence that childhood unpredictability, independent of childhood trauma, is related to enlarged GMV in several regions involved in visual processing, memory retrieval, cognitive control, and emotional regulation. Mediation analysis revealed that structural alterations could be a mechanism by which the experience of childhood unpredictability is associated with depressive and anxiety symptoms in young adults.

Studies of rats and mice have identified effects of exposure to childhood unpredictability on neural circuits implicated in vision processing, memory, and stress responses (Baram et al., 2012; Davis et al., 2017; Lages et al., 2021). Adding to these prior results, our study showed that childhood unpredictability was associated with larger GMV in brain regions including frontal pole, vlPFC, precuneus, postcentral gyrus, fusiform and inferior temporal gyrus, and occipital lobes in young adults. Both frontal pole and vlPFC are critical regions responsible for higher cognitive functions such as response inhibition and emotional regulation (Koechlin, 2011), and it has been proposed that they are parts of the adversity-disrupted circuit in humans (Teicher & Samson, 2016). Stronger vlPFC and frontal pole recruitment could downregulate negative emotions by mitigating the activity of the amygdala. Jenness et al. (2021) found that maltreated youth showed increased activity in the vlPFC during cognitive reappraisal, whereas decreased recruitment was observed in the control group. In an inhibitory control task, youth exposed to childhood trauma showed lower frontal pole activation, related to decreases in adaptive functioning, compared with non-maltreated youth (Demers et al., 2021). Associations between self-reported childhood unpredictability and volume increments in frontal pole and vlPFC were prominent findings in this study. Hypertrophy in GMV of these two regions may elicit damages in emotional regulation and impulsive control.

As a major component of the default mode network, precuneus is involved in recollection and memory, affective responses to pain, self-referential thinking, and self-centered mental imagery (Cavanna & Trimble, 2006). Our findings support those of prior studies that found that larger GMV in the

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precuneus was associated with childhood adversity (Jensen et al., 2015). Similarly, in the current study we found a positive association between increased volume in precuneus and childhood unpredictability. Postcentral gyrus as a part of somatosensory cortex could mediate face emotion recognition, response control, and motor response. We add further evidence to the literature suggesting that structural changes of postcentral gyrus are related to childhood adversity (Everaerd et al., 2016; Lim, Radua, & Rubia, 2014).

Most prior research reported that childhood abuse and neglect were associated with reductions of GMV in frontal pole, vlPFC, precuneus, and postcentral gyrus (Everaerd et al., 2016; Lim et al., 2018; Salokangas et al., 2021), whereas our study observed that childhood unpredictability may stimulate and enlarge the volumes in these regions. These opposite results further support the opinion that different dimensions of adversity could exact unique effects on neural development and through different mechanisms (McLaughlin et al., 2014). Moreover, regression analyses in present study provided evidence that childhood trauma contributes to decreased GMV in the same regions that are hypertrophic following unpredictability. Both increases and decreases in the volume of brain structure in response to childhood adversity may be abnormal outcomes that raise the risk of mental illness through complicated paths (Lee et al., 2018; Tang et al., 2016).

More work is necessary to identify factors that mediate adversity-related growth or reduction in brain structures. There is evidence that increases or decreases of brain volume may be strongly dependent on the age at which the adversity occurred (Kuo, Kaloupek, & Woodward, 2012; Teicher et al., 2016; Whittle et al., 2013). The developmental timing may determine the differential effects of unpredictability and childhood trauma on brain structure. One possibility is that earlier exposure to childhood trauma impedes synaptic formation, leading to decreased volume, whereas later exposure to unpredictability continuously promotes synaptic production and hinders the process of synaptic pruning, leading to increased volume.

Fusiform, lingual gyrus, inferior temporal gyrus, and occipital lobes are brain regions determining visual and sensory systems that relay adverse experiences. Decreased GMV in fusiform, lingual gyrus, and inferior temporal gyrus, and increased GMV in occipital gyrus, have been found in individuals exposed to adverse childhood experiences (Lim et al., 2014, 2018; Tomoda, Polcari, Anderson, & Teicher, 2012). We found a positive association between childhood unpredictability and increases in right fusiform, right lingual gyrus, bilateral inferior temporal gyrus, and left occipital lobes. Childhood unpredictability may be a specific risk factor for abnormal development of visual and sensory systems that process and interpret adverse sensory inputs, and these effects are independent of those due to childhood trauma. Increased GMV in several regions distributed in frontal, temporal, and occipital lobes in the present study may be a neural maker of impaired stress response that is specific to youth exposed to early unpredictability.

Structural abnormalities in the brain have been linked to mental illness (Yu, Kan, & Kable, 2020). Consistent with prior studies reporting hypertrophic precuneus and postcentral gyrus in patients with major depressive disorder and anxiety disorder (Kang et al., 2020; Peng et al., 2019; Strawn et al., 2013; Wang, Cheng, Luo, Qiu, & Wang, 2018), we found that increased volumes in precuneus and postcentral gyrus were associated with higher levels of anxiety and depressive symptoms. It needs to be pointed out that the positive association in the present study between frontal pole volume and depressive symptoms is somewhat at odds with neuroimaging studies in participants with major depression disorder, in which there was decreased GMV in prefrontal cortex including frontal pole (Bora, Harrison, Davey, Yücel, & Pantelis, 2012; Wise et al., 2017). This discrepancy might be due to the difference in clinical characteristics across samples. Different from participants with documented psychopathology, our sample was recruited in healthy young adults. Furthermore, a novel aspect of the present study is the finding that the hypertrophy of frontal pole, precuneus, and postcentral gyrus could mediate the association between childhood unpredictability and both depressive symptoms and anxiety symptoms. These results add to previous research that structural alterations play a role in accounting for the risk of childhood adversity on psychopathology in youth (Gorka et al., 2014; Rao et al., 2010). It is noteworthy that this is the first study to identify a neural mechanism by which individuals who have experienced unpredictability in childhood develop depressive and anxiety symptoms in adulthood.

While our study focused on the potential negative effects of childhood unpredictability on brain structure and psychopathology, our findings suggest that the smaller GMV observed in certain brain regions in our healthy sample may also indicate potential factors of resilience. Specifically, previous research has found that smaller GMV in the prefrontal cortex, which is associated with cognitive control and emotion regulation, could serve as protective factors against the development of psychopathology following childhood adversity (Moreno-López et al., 2020). Further research is needed to confirm the potential resilience factors and determine the extent to which they can mitigate the effects of childhood unpredictability on psychopathology in both healthy and clinical populations. These results have important implications for interventions aimed at promoting resilience and preventing psychopathology in individuals exposed to childhood unpredictability.

Some limitations of this study should be mentioned. First, childhood unpredictability was assessed using retrospective self-reports, and participants' responses may have been influenced by memory bias. The correlations may be underestimated and possibly produce a type II error. Second, information about the timing of childhood unpredictability was not collected. This hinders the exploration of possible differential effects of unpredictability on brain development based on the timing of exposure. The sensitive period of childhood trauma on alteration of GMV in stress-susceptible regions has been reported in previous studies (Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014; Teicher et al., 2018). Lastly, we conducted this study in a community sample and participants did not meet the criteria for psychiatric diagnoses. Thus, the ecological validity of the results should be evaluated with caution. Future research should verify these results in patient populations.

Conclusions

This study is the first to show that exposure to childhood unpredictability is positively associated with increased GMV in frontal pole, vlPFC, precuneus, postcentral gyrus, fusiform and inferior temporal gyrus, and occipital lobes in young adults, beyond the impact of childhood trauma. These findings support prior suggestions that different dimensions of adversity could exact unique effects on neural development in different ways. Furthermore, we demonstrated that GMV enlargement in stress-susceptible

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regions could serve as a mechanism linking unpredictability in childhood and symptoms of psychopathology in adulthood.

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