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Special Issue Article

Identifying structural brain markers of resilience to adversity in young people using voxel-based morphometry

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Abstract

There is increasing evidence that resilience in youth may have a neurobiological basis. However, the existing literature lacks a consistent way of operationalizing resilience, often relying on arbitrary judgments or narrow definitions (e.g., not developing PTSD) to classify individuals as resilient. Therefore, this study used data-driven, continuous resilience scores based on adversity and psychopathology to investigate associations between resilience and brain structure in youth. Structural MRI data from 298 youth aged 9–18 years (M_{age} = 13.51; 51% female) who participated in the European multisite FemNAT-CD study were preprocessed using SPM12 and analyzed using voxel-based morphometry. Resilience scores were derived by regressing data on adversity exposure against current/lifetime psychopathology and quantifying each individual's distance from the regression line. General linear models tested for associations between resilience and gray matter volume (GMV) and examined whether associations between resilience and GMV differed by sex. Resilience was positively correlated with GMV in the right inferior frontal and medial frontal gyri. Sex-by-resilience interactions were observed in the middle temporal and middle frontal gyri. These findings demonstrate that resilience in youth is associated with volume in brain regions implicated in executive functioning, emotion regulation, and attention. Our results also provide evidence for sex differences in the neurobiology of resilience.

Keywords: Resilience; brain structure; youth; voxel-based morphometry; adversity

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Introduction

Epidemiological surveys conducted across 21 countries estimate that more than one third of the population have been exposed to at least one adverse childhood experience such as maltreatment or parental loss (Green et al., 2010; Kessler et al., 2010). Although there are well-documented associations between childhood adversity and poor mental health, many young people who experience adversity do not go on to develop mental health problems (Collishaw et al., 2007). In fact, many young people show resilience which, broadly speaking, means that they remain free of or recover quickly from mental health problems following exposure to adversity (Kalisch et al., 2017, 2021). There have been calls for resilience research to take a multilevel approach to elucidate mechanisms that give rise to resilience versus vulnerability following adversity exposure (Southwick et al., 2014). It is well established that adolescence is a period characterized not only by increased stress exposure but also greater neural plasticity (Leal & Silvers, 2021). Therefore, it is critical that we understand the neurobiological processes of resilience operating in this developmental phase, as this research could inform resilience-promoting interventions and prevention programs that reduce the negative impact of childhood adversity across the life span (Gee, 2021).

To our knowledge, just six neuroimaging studies have investigated the structural brain basis of resilience in young people to date, and these studies were based on just four independent data sets (see Eaton et al., 2022 for a review). Definitions of resilience varied markedly between studies, making

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it difficult to compare them. For example, one study did not explicitly define resilience but instead investigated whether psychopathology mediated the relationship between childhood maltreatment and brain development (Whittle et al., 2013). The authors found that young people who remained resilient during the follow-up period (by virtue of remaining free of psychopathology despite maltreatment) showed accelerated hippocampal, but slower amygdala, growth. Furthermore, three studies from the Healthy Childhood Brain Development Program defined resilience as the absence of posttraumatic stress disorder (PTSD) following childhood maltreatment. All three studies compared an overlapping sample of maltreated youth with PTSD, maltreated youth without PTSD (i.e., resilient youth), and non-maltreated controls. The first two studies found that resilience was associated with larger cerebral and cerebellar gray matter volumes (GMV; De Bellis et al., 2015) and greater left amygdala and right hippocampal volumes (Morey et al., 2016). The third study examined structural networks in the brain and found that the resilient group exhibited greater centrality in the left anterior cingulate and right frontal pole than the PTSD or control groups (Sun et al., 2018). Higher centrality is thought to indicate that a cortical region is of high importance within its respective network.

Another study defined resilience as being low in mood and anxiety disorder symptoms despite exposure to traumatic stress and found that resilient youth showed smaller total brain volumes than those classified as susceptible (stress-exposed youth with elevated anxiety/depressive symptoms; Barzilay et al., 2020). Similar effects were observed in the basal ganglia and parietal cortex (resilient youth showed lower volumes in these regions). Finally, research from the European multisite IMAGEN study found that resilient adolescents (defined as being high in "competence" despite adversity) had increased GMV in the right middle frontal and right superior frontal gyri compared to individuals low in adversity exposure and those high in adversity exposure but low in competence (Burt et al., 2016). Competence was defined based on being low in internalizing symptoms, but also showing intact or superior academic and social functioning. Overall, these studies suggest that youth resilience is related to greater GMV in the prefrontal cortex, hippocampus, and amygdala, although existing findings are mixed or even contradictory. These brain regions are implicated in executive functions and emotion processing and regulation.

Although it is important to understand the structural brain basis of resilience in young people, resilience research is characterized by several limitations and conceptual challenges. The overarching issue is that different researchers and studies have defined, measured, and operationalized resilience in different ways (Kalisch et al., 2017). Firstly, many studies rely on narrow definitions of resilience, such as not developing PTSD following trauma exposure or childhood maltreatment. However, individuals may not reach formal thresholds for a diagnosis of PTSD but may have developed other forms of psychopathology and/or functional impairment. As it is well established that adversity increases risk for multiple classes of psychopathology, rather than just PTSD or internalizing symptoms specifically (Bauer et al., 2022; Green et al., 2010; Kessler et al., 2010), it is important to take a broad perspective in measuring resilient outcomes, capturing many different forms of psychopathology rather than just one categorical disorder or class of symptoms.

Secondly, in studies that have taken a broader approach to resilience, different cutoffs are used to define who in a sample is deemed resilient versus vulnerable, which renders comparisons between studies challenging. For example, two separate studies based on the IMAGEN cohort used different cutoffs for significant adversity exposure (four versus six negative life events) and assessed these in relation to different outcomes (low risk of mental disorders versus low levels of internalizing symptoms and competence across multiple life domains) to classify participants as resilient (Burt et al., 2016; Galinowski et al., 2015). As a consequence of the challenges arising from the use of different definitions and ways of operationalizing resilience, it has been suggested that researchers should move away from using categorical measures of resilience and instead use quantitative, continuous measures (Kalisch et al., 2015).

Therefore, in the broader resilience field, researchers have begun to operationalize resilience by regressing different types of adversity exposure (e.g., bullying, socioeconomic disadvantage) against outcomes of interest (e.g., emotional difficulties, psychopathological symptoms) and calculating how much each individual deviates from the expected positive relationship between adversity and psychopathology (e.g., Bowes et al., 2010; Miller-Lewis et al., 2013; van Harmelen et al., 2017). This "residuals" approach allows researchers to derive data-driven, dimensional resilience scores for each participant in their sample and allows even those with diagnosable disorders to be considered resilient; for example, if an individual has had experienced very high levels of adversity, yet only just meets the threshold for a psychiatric diagnosis. However, to our knowledge, this approach is yet to be applied when studying the neurobiology of resilience. Therefore, in the present study, we generated continuous resilience scores for the participants in our sample and, for the first time, used them to perform a structural MRI data analysis.

There have also been calls to investigate whether there are sex differences in the neurobiological basis of resilience (Moreno-López et al., 2020). It has long been recognized that many forms of childhood psychopathology are more prevalent in one sex than the other (Eme, 1979). For example, early-onset neurodevelopmental conditions (e.g., autism spectrum conditions and externalizing disorders) are more prevalent in males, whereas adolescent-onset mood and anxiety disorders are more prevalent in females (Martel, 2013; Rutter et al., 2003). Furthermore, previous research has identified sex differences in the neurobiological basis of psychiatric disorders (e.g., Helpman et al., 2017; Smaragdi et al., 2017). However, to our knowledge, no studies have investigated sex differences in the neurobiology of resilience in young people.

Thus, our primary aim was to derive continuous, multidimensional resilience scores using a data-driven approach that captures many different forms of adversity (from relatively normative to extreme) and multiple classes of psychopathology (both internalizing and externalizing, and current and lifetime symptoms). Our secondary aim was to examine whether these resilience scores were related to brain structure using voxel-based morphometry, an unbiased approach that tests for alterations in GMV across the entire brain. We also investigated whether the relationship between resilience and GMV differs by sex. As we were applying a novel approach to defining resilience to investigate relationships between resilience and brain structure, we initially ran exploratory, whole-brain analyses. We then conducted region-of-interest (ROI) analyses, defining the amygdala, hippocampus, anterior cingulate, and key prefrontal regions as ROIs based on a recent systematic review (Eaton et al., 2022). We predicted that resilience scores would be positively correlated with GMV in the amygdala and hippocampus, middle frontal and superior frontal regions, and the orbitofrontal and anterior cingulate cortices and frontal pole.

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We did not have any predictions about sex differences in the relationship between resilience and GMV; this was an exploratory analysis, as no previous neuroimaging studies have tested for sex-by-resilience interactions.

Methods

The FemNAT-CD study

This study utilized secondary data from 298 participants who took part in the neuroimaging substudy of a large European multisite project (Freitag et al., 2018). The aim of the original FemNAT-CD study was to investigate sex differences in conduct disorder (CD) in children and adolescents aged 9–18 years. Therefore, over half of the full sample had a current diagnosis of CD as assessed using the Kiddie-Schedule for Affective Disorders and Schizophrenia – Present and Lifetime version (K-SADS-PL; Kaufman et al., 1997), which in the majority of cases was completed with a parent/caregiver as well as the participant themselves. Participants with CD were also allowed to have other current or lifetime DSM-IV disorders such as attention-deficit/hyperactivity disorder (ADHD). The remaining participants were healthy controls (HCs) and were free of current DSM-IV disorders. A further exclusion criterion for this group was having a lifetime diagnosis of CD, oppositional defiant disorder (ODD) or ADHD, as assessed using the K-SADS-PL. However, it should be noted that the healthy controls could have subthreshold levels of psychopathology (e.g., mild symptoms of depression or anxiety). Exclusion criteria for both groups were IQ < 70, and the presence of genetic syndromes, autism spectrum conditions, bipolar disorder/mania, schizophrenia, and neurological disorders. Participants were recruited from five sites across three European countries (Table S1), with neuroimaging data, including structural magnetic resonance imaging (MRI) data, collected within a single scanning session lasting around one hour.

Details regarding the recruitment strategy and clinical assessments, as well as inclusion and exclusion criteria, for the full FemNAT-CD study were reported in a previous paper (Konrad et al., 2022). Briefly, participants were recruited from the community (e.g., schools) and clinical and forensic settings (e.g., mental health clinics and youth offending services). Once their eligibility to take part in the study was confirmed, participants took part in three separate data collection sessions. During these sessions, multilevel data (e.g., phenotypic, neuropsychological, neuroimaging, and genetic data) were collected from participants. Measures relevant to this substudy are described in more detail below.

Ethical approval

The current study was granted ethical approval by the University of Bath Psychology Research Ethics Committee (Ref: 18–322). All participants and their parents/caregivers gave written informed consent and/or informed assent to take part in the FemNAT-CD study, which was approved by the European Commission and local ethics committees at each site.

Participants

The current study included 298 young people aged 9–18 years ($M_{age} = 13.51$, $SD_{age} = 2.57$; 51% females; 39% of the 767 participants who had undergone a structural MRI scan). All of those included had usable structural MRI data and a resilience score. The remaining participants (61%) who had undergone a structural MRI scan were excluded from the current study due to either missing and/or incomplete data for many of the key exposure and psychopathology measures required to derive the resilience scores, poor-quality structural MRI data, or missing demographic data. A flowchart detailing the full sample selection process can be found in Figure S1. Table S2 shows the demographic and clinical characteristics of participants included ($n = 298$) versus excluded ($n = 454$) from the analysis. Participants included in the present analysis were significantly younger, had higher estimated IQs, had experienced fewer traumatic events, and had fewer current CD symptoms than the excluded participants.

As the FemNAT-CD study's original aim was to investigate the neurobiology of CD, of the 298 participants included, 78 (26%) had a diagnosis of CD, while the other 220 (74%) were free of current DSM-IV disorders and past disruptive behavior disorders.

Measures

Demographic and clinical data were also collected as part of the FemNAT-CD study. Sex was self-reported; no information was collected regarding gender identity. IQ was estimated using the vocabulary and matrix reasoning subscales of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) at the UK sites, or the Wechsler Intelligence Scale for Children-IV (Wechsler, 2003) at the other sites. Pubertal development was measured using the Pubertal Development Scale (PDS; Petersen et al., 1988). Supplement 1 describes the methods used to impute missing data on measures relevant to the current study.

Resilience scores

The resilience scores used in this study were calculated using the "residuals" approach (Miller-Lewis et al., 2013). Briefly, we calculated our resilience scores using a range of self- and parent-report measures of exposure to adversity and traumatic experiences and psychopathology. We selected a subset of the most relevant adversity exposure and psychopathology variables, partly because data were missing for many participants due to parents not completing questionnaires or ethical constraints which meant that we were not allowed to collect data on maltreatment exposure from participants aged below 16 years (i.e., the Childhood Trauma Questionnaire; (Bernstein et al., 2003)) at the UK sites, or because there was considerable overlap between measures in terms of item content.

A total of 45 variables measuring *exposure to adversity and traumatic experiences*, such as childhood maltreatment, exposure to violent crimes, and dysfunctional relationships with parents, were retained. They were collected using a parent-report interview (the Children's Bad Experiences interview; Arseneault et al., 2011), a self-report questionnaire (the Childhood Experience of Care and Abuse; Bifulco et al., 2005), and the PTSD trauma screening subsection of the K-SADS-PL (completed by both informants). It should be noted that the variables measured the *occurrence* of adversity and traumatic experiences rather than their severity or perceived impact.

Additionally, a total of 130 psychopathology variables measuring *current and lifetime psychopathology* were retained. They were measured using the other sections of the K-SADS-PL and a parent-report questionnaire assessing dimensional psychopathology (the Child Behaviour Checklist; Achenbach, 1991). These measures assessed a broad range of internalizing and externalizing symptoms covering depression and anxiety disorders and CD, ADHD, and ODD (among other disorders). Rather than

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using data on categorical diagnoses, symptom-level data from the K-SADS-PL were used. Furthermore, parent and child responses for all K-SADS-PL data were integrated to create a composite score for each K-SADS-PL variable such that the highest score was taken (i.e., a symptom was considered present if endorsed at threshold by either informant).

Additional steps were then taken to ensure that the data were suitable for conducting a factor analysis. For example, ensuring the data matrix was full rank, identifying which columns were linearly dependent and making sure the correlation matrix was positive definite. This meant ensuring that we did not have any columns that could have been derived from a combination of others (e.g., a composite score from item level data), as if this was the case, the matrix would be rank deficient (as opposed to full rank), and we may still have had missing data.

Next, two exploratory factor analyses based on principal axis factoring with direct oblimin rotation were run. An exploratory factor analysis was deemed more suitable than a confirmatory factor analysis as there were no a priori hypotheses regarding the latent dimensions that would be identified by this procedure (Field, 2013). We chose to use principal axis factoring as it is the most commonly used factor analysis approach in social and behavioral science research (Warner, 2013). Given that childhood adversities (McLaughlin et al., 2012), and different forms of psychopathology (Kessler et al., 2005) often co-occur, we chose to use the direct oblimin rotation method which allows factors to be correlated (Field, 2013).

Based on Field's (2013) recommendations, as our sample size exceeded 250, it was deemed appropriate to use Kaiser's criterion and retain all factors with eigenvalues greater than 1. In order to ensure additional robustness in the number of factors selected, a parallel analysis (O'Connor, 2000) was also run to determine the number of factors to retain (Goldberg & Velicer, 2006). Once the final set of exposure to adversity (Table S3) and psychopathology (Table S4) factors were extracted, factor scores were then calculated using the regression method (recommended by Tabachnick & Fidell, 2007). To aid understanding and interpretation, some factors were inverted such that higher scores for all factors represented higher exposure to adversity/trauma and more severe levels of psychopathology.

To derive a resilience score for each participant, factor scores were weighted by variance explained, normalized individually using robust scaling between the 1st and 99th percentile and then aggregated (separately for exposure to adversity and psychopathology factors) using the median operator to reduce the influence of outliers. Six psychopathology factors which are thought to have a stronger genetic basis (and which therefore may be less under environmental influence, that is, those related to neurodevelopmental disorders and psychosis (Carroll & Owen, 2009)), were removed (Supplement 2). We then derived a resilience score for each participant by regressing their aggregated adversity exposure score against their aggregated psychopathology score and calculating the individual distance from the regression line along the psychopathology dimension. The positive relationship between exposure to adversity and psychopathology was fitted to linear, cubic, and quadratic models, comparing model appropriateness using Akaike's information criterion (AIC; Bozdogan, 1987). The best model (i.e., lowest AIC) was linear (Figure S2). Participants who were lower than expected in psychopathology based on their level of adversity exposure had higher resilience scores, whereas participants who were higher in psychopathology than expected given their level of adversity exposure had lower resilience scores. Resilience scores could range from 1 to -1, with higher scores indicating higher resilience.

MRI data acquisition and preprocessing

Structural MRI data were obtained at each site using Siemens 3T (Tim-Trio and Prisma) or Philips 3T (Achieva) scanners. T1-weighted scans were collected using a magnetization-prepared-rapid-acquisition gradient-echo (MP-RAGE) sequence. Details regarding site qualification procedures and acquisition parameters are reported in Supplement 3 and Table S5. An MRI operator assessed the T1-weighted image quality after the scan and repeated scans as necessary.

Prior to preprocessing and analysis, we visually inspected the quality of all images in MRIcron (https://www.nitrc.org/projects/mricron/) following a published protocol (Supplement 4; (Backhausen et al., 2016). In total, 16 scans were excluded due to poor image quality or gross neuroanatomical abnormalities, leaving a final sample of 298 youth.

Statistical Parametric Mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm/) was used to preprocess and analyze the data. We rechecked the quality and orientation of each T1-weighted scan in SPM12, and reoriented images where necessary to aid normalization. T1-weighted images were segmented into gray matter (GM), white matter, and cerebrospinal fluid and the resulting GM tissue class images were used to construct a study-specific DARTEL template. We then normalized the template to MNI space and warped and smoothed the modulated GM images using an isotropic Gaussian kernel of 6-mm full-width-at-half-maximum (Ashburner & Friston, 2000). Finally, we used the proportional scaling method with total intracranial volume values to control for individual differences in global brain size.

VBM analysis

The final statistical analyses were performed using general linear models in SPM12. We first explored associations between resilience and regional GMV. For completeness, we also tested for sex differences in GMV. We also computed a sex-by-resilience interaction term by multiplying demeaned resilience scores by the dichotomous sex variable and included the resulting variable in the model to explore whether resilience–GMV relationships differed by sex. Diagnostic group (CD vs. healthy controls), sex, age, and scanner site were included as covariates of no interest (the latter using the "one-hot encoding" approach which involves creating a different regressor for each site; Hancock & Khoshgoftaar, 2020).

We used two approaches in our analysis: an exploratory whole-brain approach and a ROI approach. Given the exploratory nature of our study, in the former, we report findings at a threshold of $p \leq .001$, with a cluster extent threshold of $k = 41$ voxels that was empirically determined according to random field theory (Hayasaka & Nichols, 2004; Worsley et al., 1996). For our ROI approach, we used the automated anatomical labeling atlas, version 3 (Rolls et al., 2022). We analyzed the left and right hemispheres separately for all regions (the amygdala, hippocampus, anterior cingulate, middle frontal and superior frontal gyri, and orbitofrontal cortex) except the frontal pole. For our ROI analysis, only clusters that survived family-wise error (FWE) correction at $p < .05$ for multiple comparisons in small volumes (i.e., small-volume correction, SVC) are reported (Friston, 1997). In our sensitivity analyses, we report findings at a threshold of $p \leq .001$ and only report clusters that met the relevant cluster extent threshold. Finally, parameter estimates were exported from SPM12

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Table 1. Demographic and clinical characteristics of the participants included in the voxel-based morphometry analysis (N = 298)

Variable	
Female/Male, *n* (%)	151 (51%) / 147 (49%)
CD/HC, *n* (%)	78 (26%) / 220 (74%)
Age (years), mean (SD)	13.51 (2.57)
Resilience Score, mean (SD)	0.00 (0.12)
Estimated IQ, mean (SD)	103.63 (11.97)
Number of Traumatic Events, mean (SD)	1.25 (1.34)
Number of Current CD Symptoms, mean (SD)	1.13 (2.14)

Number of Traumatic Events and Number of Current CD Symptoms are measured by the Kiddie-Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version (K-SADS-PL); CD = conduct disorder; HC = healthy controls; IQ = intelligent quotient; SD = standard deviation.

and correlated (using a Spearman correlation) with resilience scores in IBM SPSS Statistics 26 to provide an estimate of the strength of the correlations (https://www.ibm.com/support/pages/ibm-spss-statistics-26-documentation), although all inferential statistics assessing for associations between resilience scores and GMV or sex-by-resilience interactions were performed in SPM12 using GLMs. It should be noted that these Spearman correlations were run using parameter estimates extracted from the local cluster maxima rather than an independently defined ROI image, which is not consistent with best practice in MRI data analysis as outlined in the COBIDAS report (Nichols et al., 2017).

Results

Demographic and clinical characteristics

Table 1 shows the demographic and clinical characteristics of participants included in the VBM analysis. The participants' resilience scores ranged from –0.59 to 0.22 (where higher values indicate higher resilience). Figure S3 in the Supplement shows the distribution of resilience scores in females and males. Of the four groups included in the study, male healthy controls had the highest resilience scores, although there was substantial variance in resilience scores in all four groups. The number of current CD symptoms ranged from 0 to 11 (out of a possible 15), reflecting the inclusion of both healthy controls and participants with CD diagnoses. Comparisons between the CD and healthy control groups are reported in Table S6 for completeness.

Factor analysis

Factor analysis assumptions were tested and are reported in Supplement 5. When comparing each eigenvalue from both factor analyses to the corresponding 95th percentile of the distribution for that eigenvalue generated by the parallel analysis, it was found that none of the factors from the adversity exposure or psychopathology factor analyses were random. However, a final decision was made to retain 11 factors from the adversity exposure factor analysis and 36 factors from the psychopathology factor analysis based on Kaiser's criterion (although six psychopathology factors were removed prior to computing the resilience scores - see above for further details). All the factors retained made sense theoretically (i.e., they indexed normative and severe adversities or various common forms of psychopathology) and cumulatively explained > 60% of the total variance in each factor analysis. Based on recommendations from Osborne and colleagues (2011), only factor loadings > .3 were interpreted.

Whole-brain analyses

We then tested for associations between resilience scores and GMV using VBM, with diagnostic group, sex, age, and scanner site included as covariates of no interest. To reiterate, as there were significant sex differences in total intracranial volume (Females $M_{TIV} = 1.33$, Males $M_{TIV} = 1.45$, $p < .001$), we used the proportional scaling method to control for individual differences in global brain size.

Correlations between resilience and GMV

We observed positive correlations between resilience scores and GMV in the right inferior frontal gyrus (IFG) and right medial frontal gyrus (Fig. 1), as well as the right superior parietal lobule, right postcentral, right precentral, and bilateral paracentral gyri (Table 2). No negative correlations between resilience scores and GMV were observed.

Main effects of sex

Main effects of sex were observed in several cortical and subcortical regions (Table S7). Males had higher GMV in the fusiform, inferior occipital and inferior temporal gyri compared to females, whereas females had higher caudate nucleus and hippocampal GMV.

Sex-by-resilience interactions

We identified three areas where the relationship between resilience scores and GMV differed significantly between male and female youth. Firstly, resilience scores were positively correlated with GMV in the left middle temporal gyrus in males, but negatively correlated with GMV in this area in females (Table 2 and Fig. 2a). In contrast, resilience scores were positively correlated with GMV in the right middle frontal gyrus (Fig. 2b) and bilateral cerebellar tonsil in females, but negatively correlated with GMV in these regions in males.

ROI analysis

We identified positive and negative correlations between resilience scores and GMV in several ROIs, although none survived FWE small-volume correction. In line with our whole-brain analyses, a sex-by-resilience interaction was detected in the right middle frontal gyrus ($p < .05$, FWE SVC), driven by a positive correlation between resilience and GMV in females, but a negative correlation in males.

Sensitivity analyses

To ensure that we were not overcontrolling for diagnostic group by including data related to psychopathology when deriving our resilience scores as well as including diagnostic group as a regressor in the VBM analysis, we ran a sensitivity analysis including just the healthy controls ($n = 220$). The results remained broadly similar in terms of showing positive associations between resilience and GMV (Table S8), although most of the significant clusters were now in the left hemisphere. There was also an additional positive correlation with resilience in the left precuneus, and a negative correlation with resilience in the left precentral gyrus. Further, in the sex-by-resilience interaction analysis, resilience scores were positively correlated with GMV in males, but negatively correlated with GMV in females, in the left angular gyrus, left insula, and right inferior parietal lobule. An additional interaction was observed in the left

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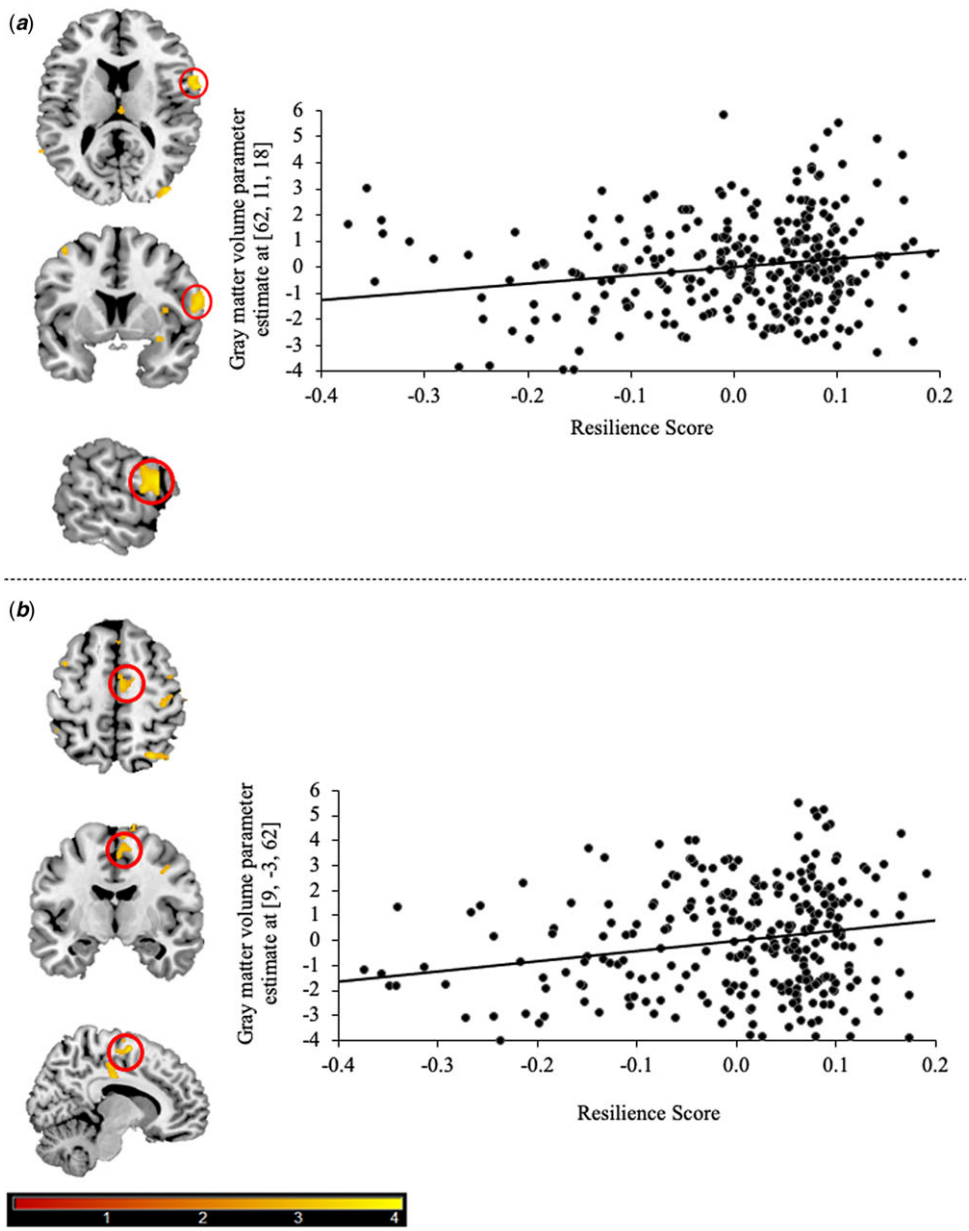

Figure 1. Positive correlations between resilience scores and gray matter volume in (a) the right inferior frontal gyrus (r_s = .15) and (b) the right medial frontal gyrus (r_s = .15) in the whole-brain analysis.

Notes. Color bar represents the T values. The images are thresholded at p < .005, uncorrected, for display purposes only. Red circles highlight the relevant regions.

superior temporal gyrus (positive correlation between resilience scores and GMV in females, but a negative correlation in males).

Furthermore, to focus on a more developmentally homogenous subsample, we ran an additional sensitivity analysis where only those classified as mid-, late-, or postpubertal on the PDS ($n = 225$) were included. Again, the results were broadly similar to those obtained with the entire sample (Table S9). However, additional negative correlations between resilience scores and GMV in bilateral dorsal caudate nucleus (extending into the ventral caudate; Figure S4) and left pars orbitalis were observed in this case.

Discussion

To our knowledge, this is the first study to use data-driven, continuous resilience scores to investigate the brain structural correlates of resilience in young people. We hypothesized that resilience would be positively associated with GMV in the orbitofrontal gyrus, middle and superior frontal regions, frontal pole, anterior cingulate, amygdala, and hippocampus. We found that, across the whole sample, higher levels of resilience were associated with greater GMV in frontal and parietal areas of the brain, including the inferior and medial frontal gyri, mainly in the right hemisphere. Furthermore, and contrary to our hypotheses, resilience was not associated with GMV in the frontal pole, anterior cingulate, amygdala or hippocampus.

We also examined whether the relationship between resilience and brain structure differed by sex. We identified three areas where this was the case: the left middle temporal and right middle frontal gyri, and bilateral cerebellar tonsil. Resilience was positively associated with GMV in the right middle frontal gyrus and

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Table 2. Coordinates and cluster sizes for the correlations between resilience scores and gray matter volume, and sex-by-resilience score interactions in the whole-brain analysis (N = 298)

Contrast	Region	BA	Hemisphere	T-value	Cluster size (*k*)	MNI Coordinates		
						x	y	z
Correlations with resilience score								
Positive correlations								
	Postcentral gyrus	3	Right	3.91	148	56	−18	54
	Postcentral gyrus	3	Right	3.20	Same as above	44	−20	53
	Superior parietal lobule	7	Right	3.86	51	27	−66	59
	Paracentral lobule	31	Left	3.84	80	−8	−20	50
	Medial frontal gyrus	6	Right	3.78	51	9	−3	62
	Medial frontal gyrus	6	Right	3.27	Same as above	5	−11	57
	Inferior frontal gyrus	45	Right	3.70	194	62	11	18
	Precentral gyrus	6	Right	3.61	Same as above	66	3	12
	Paracentral lobule	31	Right	3.42	66	5	−18	47
Sex-by-resilience score interactions								
Males positive, females negative								
	Middle temporal gyrus	21	Left	4.25	60	−48	−53	2
Females positive, males negative								
	Cerebellar tonsil	–	Left	4.05	132	−26	−53	−45
	Middle frontal gyrus	9	Right	3.91	49	33	18	35
	Cerebellar tonsil	–	Right	3.73	147	14	−45	−53

All correlations and sex-by resilience score interactions were significant at a threshold of $p \leq .001$, with a cluster extent threshold of $k = 41$ voxels. BA = Brodmann's area; MNI = Montreal Neurological Institute.

cerebellar tonsil in females, but negatively associated with GMV in males. In contrast, resilience scores were positively correlated with GMV in the left middle temporal gyrus in males, whereas a correlation in the opposite direction was observed in females. Overall, our findings provide preliminary evidence for sex differences in the relationship between resilience and brain structure in young people and suggest that future studies should also test for sex-specific associations between resilience and brain structure.

Correlations between resilience and GMV

As mentioned above, higher levels of resilience were associated with greater GMV in the right IFG, an area implicated in executive functions, such as response inhibition and attentional control (Hampshire et al., 2010), and emotion regulation (Dixon et al., 2017). Interestingly, Luby et al. (2017) found that early adversity was linked to reduced IFG volume in childhood, and that smaller IFG volumes mediated the association between early adversity and depression severity in adolescence. In a subsequent study, Barch et al. (2018) found that early adversity was related to connectivity between the IFG region observed in the previous study and several other brain regions (e.g., premotor cortex, posterior parietal cortex, and cerebellum). Further to this, IFG connectivity with these brain regions also predicted externalizing disorder symptom severity in childhood and early adolescence. Although previous *structural* MRI studies of resilience have not identified this region, a longitudinal *functional* MRI study found that young people who remained resilient during the follow-up period (by remaining free of psychopathology despite being at high familial risk for mood disorders) showed lower right IFG activation when processing fearful faces compared to individuals at high familial risk who did develop psychopathology (Nimarko et al., 2019). Taken together, these findings suggest that the IFG may play an important role in resilience.

Our data also support the proposal that emotion regulation is a key psychological resilience factor (Kalisch et al., 2019), although it should be noted that the right IFG region we identified is also implicated in the coordination of attention to external stimuli. Hartwigsen et al. (2019) revealed five functional clusters within the right IFG; the functional cluster that corresponds to the location of our IFG cluster ("cluster 5") is in a relatively posterior part of the IFG (y = 11; Brodmann's Area 44) and interestingly is functionally connected to the other regions that we found were positively associated with resilience: the right superior parietal lobule, the right middle frontal gyrus and the right precentral gyrus. This cluster is part of the dorsal attention network, which is implicated in spatial attention, memory encoding, attentional control, and action execution, and therefore plays a key role in the coordination of attention to external stimuli. The other regions we identified, such as the right precentral and postcentral gyri and paracentral lobule, are implicated in motor and sensory functions (particularly hand movements). These findings could be interpreted as evidence that resilient youth do not show the decreases in volume in sensory and motor regions that are observed in maltreated individuals or those exposed to significant adversity (Teicher et al., 2016). We also found that resilience was positively associated with GMV in the medial frontal gyrus and superior parietal lobule. The medial frontal gyrus is implicated in cognitive processes such as decision-making (Talati & Hirsch, 2005), while the superior parietal lobule

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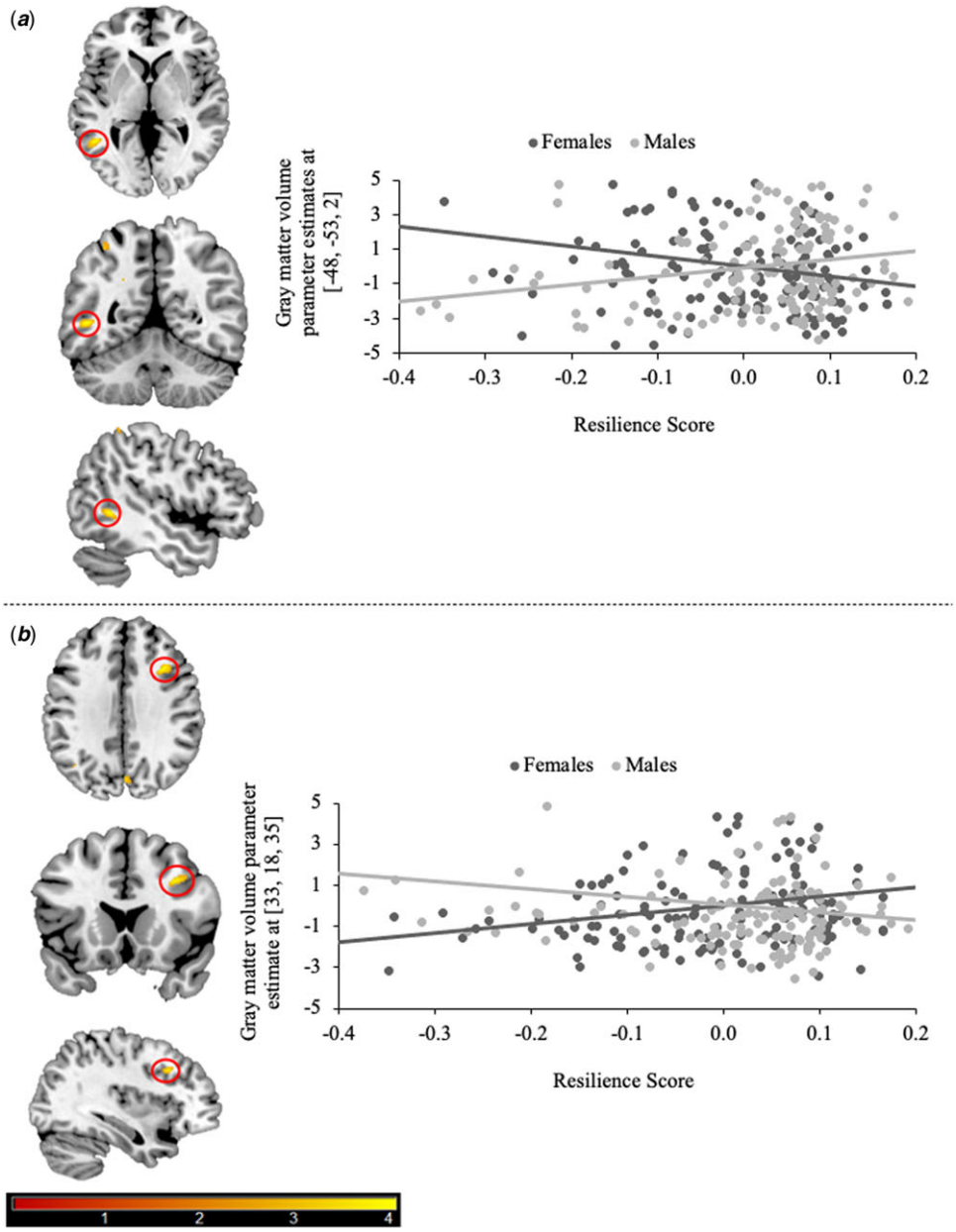

Figure 2. Sex-by-resilience score interactions for gray matter volume in (a) the left middle temporal gyrus (Females, $r_s = -.21$; males, $r_s = .21$) and (b) the right middle frontal gyrus (Females, $r_s = .21$; males, $r_s = -.10$) in the whole-brain analysis.

Notes. Regression lines are shown for males and females separately (females = darker gray, males = lighter gray). Color bar represents the T values. The images are thresholded at $p < .005$, uncorrected, for display purposes only. Red circles highlight the relevant regions.

has been implicated in working memory and attention (Wang et al., 2015), as well as tactile perception (Stoeckel et al., 2004). Taken together, these findings suggest that higher GMV in regions implicated in decision-making and working memory is a structural marker of resilience in young people. However, as the superior parietal lobule finding was not predicted, this region should be explored in future studies using a hypothesis-driven approach.

Sex-by-resilience interactions

We also observed sex differences in the relationship between resilience and brain structure. Higher levels of resilience in male youth were associated with increased GMV in the left middle temporal gyrus, whereas female youth showed the opposite relationship. Relevant to this, Samplin et al. (2013) reported sex differences in the effects of childhood emotional abuse on hippocampal volume: while abused males showed reduced hippocampal volume, there was a trend toward larger hippocampal volume in abused females versus non-abused females. It is possible that there are sex differences in vulnerability to adversity-related changes in middle temporal gyrus structure (volume is reduced in maltreated males but increased or no different in maltreated females). Coupled with the idea that resilient individuals might be resistant to adversity's effects on the brain, this potentially gives rise to the sex-by-resilience interaction observed in this region. We recognize this explanation is speculative, but there is evidence for effects of maltreatment on middle temporal gyrus volume (De Brito et al., 2013; Jackowski et al., 2011), sex differences in the effects of maltreatment on volume in adjacent regions such as the hippocampus (Samplin et al., 2013), and the idea that resilience is

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associated with resistance to the effects of maltreatment on brain structure (De Bellis et al., 2015).

Although the middle temporal gyrus has not been implicated in resilience specifically, a meta-analysis found that trauma-exposed adults with PTSD had reduced GMV in the temporal pole/middle temporal gyrus compared to trauma-exposed adults *without* PTSD (i.e., a group that could be considered resilient; Kühn & Gallinat, 2013). The left middle temporal gyrus is implicated in autobiographical memory (Holland et al., 2011) and McCrory et al. (2017) found that maltreated children showed abnormally increased middle temporal gyrus activation during an autobiographical memory test relative to non-maltreated controls. Abuse in childhood is related to autobiographical memory disturbances, such as over-general memory (Puetz et al., 2021; Valentino et al., 2009). These findings suggest that the effects of maltreatment and adversity on this region may differ by sex, and resilience may be characterized by an absence of such maltreatment-related effects on middle temporal gyrus structure or function. Along these lines, it would be interesting to investigate whether resilient individuals are protected from the effects of childhood maltreatment on autobiographical memory specificity. However, as this region has not previously been linked to youth resilience, we recommend that it is included as a ROI in future studies.

In contrast, we found that resilience was positively correlated with GMV in the right middle frontal gyrus in females, whereas males showed a weak correlation in the opposite direction. The right middle frontal gyrus was also included as an *a priori* ROI and a sex-by-resilience interaction in the same direction in this region survived correction for multiple comparisons. The largest study to date with an adolescent sample also found that resilience was associated with greater GMV in the right middle frontal gyrus (Burt et al., 2016), although the authors did not test for sex differences. Previous research has found the middle frontal gyrus to be involved in attentional reorienting (Japee, Holiday, Satyshur, Mukai, & Ungerleider, 2015). Thus, it could be speculated that an important resilience mechanism for female youth is their ability to reorient their attention away from negative stimuli or adverse events toward other more positive aspects of their life. This fits with theory and research on resilience to chronic pain (Goubert & Trompetter, 2017).

Finally, we also observed a sex-by-resilience interaction in the cerebellar tonsil, such that resilience was positively associated with GMV in females, but negatively associated in males. Childhood maltreatment has been linked to reduced cerebellar GM volume (Edmiston et al., 2011). In female adolescents specifically, there was an inverse relationship between childhood trauma and cerebellar volume, as well as other areas involved in emotion regulation. Thus, female youth who do not show trauma-related reductions in cerebellum volume (or even display compensatory increases in this region) may be protected from developing psychopathology as a result. Taken together, these findings suggest that greater cerebellar volume may be a neural marker of resilience in youth exposed to adversity, particularly in females.

The sex differences identified in the current study support the notion that females and males might become resilient partly via different pathways (Fallon et al., 2020). For example, based on our findings, it could be inferred that avoiding adversity-related impairments in autobiographical memory or dysfunction in the neural substrates of autobiographical memory is an important resilience factor for male youth, whereas an important resilience factor for female youth is their ability to reorient their attention away from adverse/traumatic experiences. Alternatively, it could be that sex differences in adversity exposure and/or risk for psychopathology are driving these differences. For example, depression (Breslau et al., 2017) and experiences of sexual abuse (Briere & Elliott, 2003) are both more common in female youth. Therefore, remaining free of depression is arguably stronger evidence for resilience in female youth than male youth. Overall, based on our exploratory findings, future research should investigate factors that might underpin sex differences in the relationship between resilience and brain structure.

Although not a major focus of the study, the fact that we observed sex differences in brain structure that are consistent with prior findings (i.e., total intracranial volume was ~ 10% higher in males than females, and the amygdala was larger in males, while the caudate nucleus was larger in females, even after accounting for sex differences in total intracranial volume; Eliot et al., 2021) supports the validity of our VBM results. Interestingly, a recent meta-analytic review by Eliot et al. (2021) speculated that increases in caudate nucleus volume in females compared to males might be confined to adolescents as adult-only studies have not reported sex differences in caudate volumes, that is, our study might have been better placed to identify a sex difference in the caudate nucleus than many others, due to the age of the sample ($M_{age} = 13.5$ years) and the fact that girls typically go through puberty earlier than boys, which may cause increases in caudate volume.

Strengths and limitations

Overall, this study had several strengths. Firstly, our resilience scores were data-driven and continuous and were derived based on each participant's exposure to multiple types of adversity, as well as their current and lifetime psychopathology. We also used information about maltreatment and trauma exposure and psychopathology from the participants themselves and their parents or caregivers. This meant that we took a much broader perspective of resilience than many previous studies and were capturing "transdiagnostic" resilience – although current externalizing disorders and past ODD symptoms were the most influential psychopathology factors of those studied, given the original study's focus on CD. These two factors alone (out of 36) accounted for > 20% of the variance in the psychopathology factor analysis.

Secondly, although some of the MRI subsample had to be excluded from the VBM analysis because we were missing data on key adversity measures that fed into the resilience score calculations, our sample was relatively large for a neuroimaging study ($N = 298$). We also included similar numbers of male and female youth which allowed us to investigate sex differences in the relationship between resilience and brain structure. Furthermore, we controlled for several potentially important covariates in our analyses including diagnostic status, age, and scanner site – as well as individual differences in total intracranial volume. We also screened the structural MRI data carefully, using an established quality control pipeline (Backhausen et al., 2016), to ensure that only high-quality images were included. Finally, a limitation of some of the earlier studies in this field is that they have not corrected for multiple comparisons (Eaton et al., 2022). Although in our whole-brain analysis we report findings at a threshold of $p \leq .001$, we only reported clusters that exceeded an extent threshold that was empirically determined based on random field theory (Hayasaka & Nichols, 2004; Worsley et al., 1996).

Despite these strengths, the current study had several limitations. Firstly, different scanners were used to collect the structural MRI data, which may have introduced noise into the

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data. However, this issue should have been partly mitigated by the site qualification procedures that were used and the fact that we controlled for site in our analyses.

Secondly, participants included in the analysis were significantly younger and had higher estimated IQs, experienced fewer traumatic events, and had fewer current CD symptoms compared to those excluded from the analysis. Although these differences indicate that the present sample is not fully representative of the original FemNAT-CD study sample (which was focused on case–control comparisons), it could be argued that the current study sample is more representative of the general population given that participants included in the analysis had experienced significantly lower levels of adversity and had fewer CD symptoms than the excluded participants. Importantly for the purposes of this study, almost the full range of traumatic events (0–7) and CD symptoms (0–11) was observed in the present sample, which meant that it was suitable for addressing research questions related to resilience to adversity.

Additionally, we included participants across a wide age range. However, our sensitivity analysis focusing on a more developmentally homogenous group revealed broadly similar findings, but also negative correlations between resilience and caudate nucleus and pars orbitalis GMV. A systematic review found that sexual abuse and emotional neglect, but not physical or emotional abuse, were related to decreased caudate nucleus volumes (Cassiers et al., 2018). Previous research also found that adolescents' scores on the Childhood Trauma Questionnaire were negatively correlated with GMV in the striatum (Edmiston et al., 2011). Furthermore, our data were cross-sectional rather than longitudinal. This means that we cannot tell whether the observed differences in brain structure reflect post-trauma adaptations in the brain (i.e., resilience effects) or whether they represent preexisting differences that may have buffered the effects of adversity exposure. Future research should adopt longitudinal designs to differentiate between preexisting differences versus post-trauma modifications in brain structure.

A further limitation was that the exposure to adversity and traumatic experiences variables used to derive the resilience scores assessed whether traumatic or negative events had occurred, rather than measuring the severity, or the perceived impact, of these experiences. There are several aspects of adversity and trauma exposure that can influence resilient outcomes, such as whether it is a one-off incident, whether the perpetrator was known to the victim, and whether the traumatic experience was deliberately intended or accidental (Bolger & Patterson, 2003; Diamond et al., 2022; Hyman & Williams, 2001; Marriott et al., 2014). Future research using the residuals approach could incorporate these additional details about participants' exposure to adversity and traumatic experiences, but these data were not systematically collected in the original FemNAT-CD study.

Finally, in terms of our analysis method, a limitation of VBM is that it conflates different cortical properties (i.e., surface area, cortical thickness and folding) that have distinct developmental trajectories and etiologies into one composite measure, namely GMV (Panizzon et al., 2009). Therefore, future research could use surface-based morphometry to determine whether the global volumetric effects observed here are driven by specific cortical properties (e.g., cortical thickness).

Conclusion

Overall, this study suggests that higher levels of resilience in youth are associated with greater GMV in frontal and parietal regions. It also emphasizes the importance of taking sex into account when investigating the brain basis of resilience, as we observed sex differences in the relationship between resilience and brain structure. However, across both males and females, many of the brain areas found to be related to resilience in young people are involved in emotion regulation, executive functions, and attention, which supports the idea that these are key processes involved in resilience that should be targeted in treatment and preventative interventions (Greenberg, 2006).

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0954579423000718.

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