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Association between stressful life events and grey matter volume in the medial prefrontal cortex: A 2-year longitudinal study

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Abstract

Stressful life events (SLEs) in adulthood are a risk factor for various disorders such as depression, cancer or infections. Part of this risk is mediated through pathways altering brain physiology and structure. There is a lack of longitudinal studies examining associations between SLEs and brain structural changes. High-resolution structural magnetic resonance imaging data of 212 healthy subjects were acquired at baseline and after 2 years. Voxel-based morphometry was used to identify associations between SLEs using the Life Events Questionnaire and grey matter volume (GMV) changes during the 2-year period in an ROI approach. Furthermore, we assessed adverse childhood experiences as a possible moderator of SLEs-GMV change associations. SLEs were negatively associated with GMV changes in the left medial prefrontal cortex. This association was stronger when subjects had experienced adverse childhood experiences. The medial prefrontal cortex has previously been associated with stress-related disorders. The present findings represent a potential neural basis of the diathesis-stress model of various disorders.

KEYWORDS
adverse childhood experiences, grey matter volume, magnetic resonance imaging, medial prefrontal cortex, stressful life events, voxel-based morphometry

1 | INTRODUCTION

Stressful life events (SLEs) in adulthood are proximal predictors for negative health outcomes such as depression, cancer or infections (Cohen et al., 2019). Understanding how SLEs affect the brain, the key organ of self-regulation, will give us important, new insight into the stress-related pathogenesis of such disorders.

Research linking stressors in adulthood to alterations in the brain mainly stems from animal models with experimentally induced stress (for example [Liston et al., 2006]). In these models, stress has resulted in structural medial prefrontal cortex (mPFC) alterations (Arnsten, 2009; McEwen & Morrison, 2013). The question remains whether this also applies to humans (Shanks et al., 2009). Cross-sectional studies in adult, healthy subjects have associated SLEs in the recent past with structural magnetic resonance imaging measures. Studies in larger samples ($N > 100$) found negative correlations between the number of recent SLEs in adulthood and grey matter volume (GMV) in the mPFC and insula (Ansell et al., 2012). Further, negative correlations between the subjective impact recent SLEs and GMV in the medial orbitofrontal cortex (mOFC) were found (Ringwald et al., 2021). However, due to the cross-sectional design of these studies, they cannot disentangle cause and effect. The associations could arise because structural features are associated with a different appraisal of SLEs, or with traits that lead to the experience of more SLEs, or because SLEs reduce GMV.

In contrast, longitudinal designs in adult humans can identify GMV changes across time. Up to now, only one study has investigated associations between changes in GMV and recent SLEs in adulthood longitudinally (Papagni et al., 2011). They found associations in the anterior cingulate, hippocampus and parahippocampal gyrus. However, the sample size was small ($N = 26$) and the authors could therefore not control for multiple testing, bearing the danger of false positives.

A meta-analysis shows that adverse childhood experiences (ACEs) are important risk factors for poor health outcomes in adulthood (e.g., depression, cancer, infections) (Hughes et al., 2017). The diathesis-stress model (Ingram & Luxton, 2005) predicts that recent SLEs are more likely to lead to poor health outcomes if subjects are more vulnerable, for example due to ACEs. SLEs in adulthood might therefore have a stronger influence on local GMV changes if subjects have experienced ACEs.

In a large longitudinal healthy sample, we correlated the impact of recent SLEs on one's life with GMV changes during a 2-year period. Healthy subjects, as opposed to patients with mental disorders, have the advantage of being free of potentially confounding factors associated with SLEs, such as treatment or illness per se. We expected a negative correlation between SLEs and GMV changes in the insula, mOFC and mPFC because well-powered cross-sectional studies found correlations in these areas (Ansell et al., 2012; Ringwald et al., 2021). Furthermore, we hypothesized that ACEs (i.e., diathesis) would moderate this association, such that SLEs would have a stronger impact on GMV if a subject had experienced more ACEs.

2 | MATERIALS AND METHODS

2.1 | Sample

Data of $N = 212$ subjects with T1-weighted MRI scans at baseline and follow-up and complete data on SLEs drawn from the ongoing FOR2107 cohort study (Kircher et al., 2019) were examined. For sample descriptives see Table 1. Subjects were assessed at two time points. The follow-up assessment took place about 2 years after the baseline assessment (mean = 2.2 years, range: 1.9 years–3.4 years). Both, baseline and follow-up measurements took place at the same site (University of Marburg, University of Münster, Germany) for each subject, respectively. At baseline subjects were 18–65 years old. Exclusion criteria were current or history of psychiatric illness established with the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (Wittchen et al., 1997), severe traumatic brain injury, stroke, neuro-inflammatory diseases, epilepsy, history of severe medical disorders (e.g., cancer), verbal intelligence quotient (IQ) < 80 (Lehrl, 2005), and general MRI contraindications (e.g., heart pacemaker). All study protocols were approved by the ethics committees of the medical faculties, University of Marburg (AZ: 07/14) and University of Münster (AZ: 2014-422-b-S) in accordance with the latest Declaration of Helsinki. Participants provided written informed consent and received financial compensation.

TABLE 1 Sample descriptives

	N = 212
Marburg/Münster	140/72
Male/Female	81/131
Age at baseline	32.8 years (12.3 years)
LEQ total events score	20.9 (13.3)
LEQ positive events score	15.0 (10.6)
LEQ negative events score	5.9 (6.5)
LEQ total number of events	11.3 (6.1)
LEQ number of positive events	8.0 (4.7)
LEQ number of negative events	3.3 (3.0)
ACE score[a]	0.7 (1.0)
Beck Depression Inventory-II sum score baseline/follow-up[b]	3.5 (3.8)/2.4 (3.2)[d]
State–Trait Anxiety Inventory state subscale baseline/follow-up[c]	33.7 (8.2)/31.1 (7.9)[d]

[a]ACE scores were not available for four subjects.
[b]Beck Depression Inventory-II sum score was not available for one subject at baseline and four subjects at follow-up.
[c]The state subscale of the State–Trait Anxiety Inventory was not available for two subjects at follow-up.
[d]Significant difference between baseline and follow-up measurement ($p < .001$, two-tailed Wilcoxon signed rank test).
Notes: Values represent either absolute numbers or mean (standard deviation).
Abbreviations: ACE, adverse childhood experiences; LEQ, life events questionnaire.

2.2 | Assessment of recent SLEs

We assessed recent SLEs that happened between the baseline and 2-year follow-up measurement based on the "adaptation definition" of SLEs (Cohen et al., 2019). According to this definition, an SLE is every event that impacts our life substantially and requires adaptation, no matter if it is subjectively perceived as negative or positive. Since each event adds to the overall burden of change someone has to adapt to, SLEs are cumulative. We used the total events score of the Life Events Questionnaire (LEQ, [Norbeck, 1984]) to assess the cumulative impact of SLEs on life during the 2-year follow-up period. In this questionnaire, subjects were asked to mark life events that happened since the baseline MRI measurements, to indicate whether the experienced events were perceived as positive or negative, and to rate the event's impact on their life on a four-point scale, ranging from "no effect" to "great effect" (scored 0–3). The 82 items of the LEQ fall into 11 categories: health, work, school, residence, love and marriage, family and close friends, parenting, personal and social, financial, crime and legal, and other. Three scores were calculated: the negative events score (the sum of the impact ratings for all items designated as negative by the respondent), the positive events score (the sum of the impact ratings for all items designated as positive by the respondent), and the total events score (the sum of all impact ratings for both negative and positive events).

2.3 | Assessment of adverse childhood experiences

ACEs were assessed using a 10-item ACE questionnaire derived from the Adverse Childhood Experiences (ACE) Study (Felitti et al., 1998). In the questionnaire, subjects were asked which of the following ACEs they experienced before the age of 18: (1) physical, (2) emotional, and (3) sexual abuse; (4) physical and (5) emotional neglect; (6) parental divorce or loss of a parent; (7) violence toward the mother; (8) substance abuse of a household member, (9) mental illness of a household member, or (10) incarceration of a household member. For the analysis, the ACE score was used which is the absolute number of experienced ACEs.

2.4 | MRI acquisition and pre-processing

Subjects were scanned with 3 T MRI scanners using a three-dimensional MP-RAGE sequence with a slice thickness of 1 mm, distance factor of 50%, voxel size of $1 \times 1 \times 1$ mm, and a field of view of 256 mm. Scanners and parameters: Marburg (Tim Trio, 12-channel head matrix Rx-coil, Siemens, Erlangen, Germany): repetition time $(T_R) = 1.9$ s, echo time $(T_E) = 2.26$ ms, inversion time $(T_I) = 900$ ms, flip angle $= 9°$; Münster (Prisma fit, 20-channel head matrix Rx-coil, Siemens, Erlangen, Germany): $T_R = 2.13$ s, $T_E = 2.28$ ms, $T_I = 900$ ms, flip angle $= 8°$ (Vogelbacher et al., 2018).

T1-weighted scans were pre-processed using the longitudinal pre-processing pipeline for large changes of the CAT12 toolbox (Computational Anatomy toolbox, Version 1742, Structural Brain Mapping group, Jena, Germany) building on SPM12 (Statistical Parametric Mapping, Institute of Neurology, London, UK), running under MATLAB (Version R2017a, The MathWorks, USA) with default parameter settings. Images were segmented (grey matter, white matter, and cerebrospinal fluid), spatially normalized using the Geodesic Shooting template, and smoothed with a Gaussian kernel of 8 mm full width at half maximum (FWHM). An absolute grey matter threshold of 0.1 was used. As part of a quality control, outliers were identified by the check homogeneity function as implemented in CAT12 using the segmented images and visually inspected to exclude data with severe artifacts and very atypical brain structure.

2.5 | Analyses

First, to examine whether SLEs in adulthood are associated with longitudinal GMV changes, a flexible factorial design was applied in CAT12. In CAT12, subject and scanning time point (baseline or follow-up) were used as factors and set as main effects. Furthermore, the variance of both factors was set equal in CAT12. Age at follow-up and gender were used as covariates of no interest (i.e., at baseline covariates were set 0 and at follow-up we entered age at follow-up and dummy-coded gender). The covariate age had no linear or non-linear relationship with whole-brain GMV changes (Figure S1). Furthermore, no clusters with an age-dependent effect of SLEs on GMV change were found in a whole-brain analysis in CAT12 (i.e., clusters with a significant interaction between the LEQ total events score and age). Nevertheless, to account for potential regional associations of GMV changes and age, we controlled for linear age effects. Since the body coil was changed during the study at the Marburg scanner, a dummy-coded variable was used as an additional covariate of no interest to control for potential changes due to being scanned with a different body coil at baseline than follow-up. This was the case for 128 subjects.

Second, we examined whether cross-sectional associations between SLEs and GMV are present. The presence of a cross-sectional association in a cluster in which no longitudinal association between SLEs and GMV changes was found would indicate that GMV in this brain area is not affected by SLEs, but that GMV in this cluster predicts the LEQ total events score. To investigate whether GMV at baseline is associated with the LEQ total events score, a linear regression model was run with the baseline images and the LEQ total events score as predictor. Age at baseline, TIV at baseline, gender, and two dummy coded variables to account for scanner differences between the three settings (Marburg old body coil, Marburg new body coil and Münster) were used as covariates of no interest.

Similarly, a cross-sectional regression analysis was performed to find associations between follow-up GMV and the LEQ total events score. Since all subjects at follow-up were scanned with the same body coil in Marburg, we controlled for age at follow-up, TIV at

follow-up, gender, and one dummy coded variable to account for scanner differences.

For our region of interest-based approach, we applied a predefined mask consisting of a total of 19,217 voxels. Based on the literature where well-powered cross-sectional studies found correlations between recent SLEs in adulthood and GMV in the mPFC, mOFC, and insula were found (Ansell et al., 2012; Ringwald et al., 2021), this mask included the following areas bilaterally as defined in the Neuromorphometrics Atlas (Neuromorphometrics, Inc., Somerville, MA, USA): anterior and posterior insula, gyrus rectus, medial frontal cortex, medial orbital gyrus, and superior frontal gyrus medial segment. This was done to examine whether cross-sectional associations found in the literature arise because SLEs reduce GMV in these areas or due to other reasons. Additionally, we ran exploratory whole-brain analyses.

We applied threshold-free cluster enhancement (TFCE) using SPM's TFCE toolbox (Version r214, Gaser, University of Jena, Jena, Germany) to identify significant clusters. We ran 10,000 permutations using the Smith permutation method to deal with nuisance variables and default settings. Results were considered significant at an FWE adjusted $\alpha < 0.05$ and an extent threshold of $k = 10$ voxels.

For clusters with a significant association between SLEs in adulthood and longitudinal GMV changes (follow-up GMV – baseline GMV), we extracted the raw GMV cluster values for each subject using the eigenvariate function implemented in SPM. To examine whether ACEs and SLEs interact on GMV changes, we then examined whether the linear LEQ total events score × ACE score interaction term on the GMV cluster values changes was significant. We controlled for the simple effect of the LEQ total events score, the simple effect of the ACE score, age at follow-up, gender and the scanner variable. Since three subjects did not answer the ACE questionnaire, this analysis was performed in 208 subjects. We decided to use this approach to examine whether SLEs have a bigger impact on GMV when subjects are vulnerable (i.e., had ACEs) because the effect size of interactions is typically small (Wahlsten, 1991) and we do not expect large effect sizes on brain structure in healthy subjects.

Pearson's correlation coefficients r between predictor variables in all tested regression models were between -0.64 and 0.23, indicating no multicollinearity (Tables S2–S5).

3 | RESULTS

### 3.1 | Associations between SLEs and GMV changes

We examined associations between the LEQ total events score and corresponding GMV changes during a 2-year period. As the main result, there was a negative association between the LEQ total events score and GMV changes across the 2-year follow-up period in the left mPFC ($k = 29$ voxels, TFCE $= 317.6$, FWE $p = 0.043$, x/y/z $= -6/36/45$) in the ROI analysis. Subjects with a higher 2-year LEQ total events score showed a stronger GMV reduction (Figure 1). The studentized residuals of the model calculated with the extracted mPFC GMV cluster value change (2-year follow-up – baseline) were normally distributed (Shapiro–Wilk $p = 0.412$), indicating reliable results. The Pearson correlation coefficient for the association between the GMV extracted mPFC GMV cluster value change and the LEQ total events score was $r = -0.258$. The cluster value change was also negatively correlated with the negative events score ($r = -0.255$), the positive events score ($r = -0.167$), the total number of events ($r = -0.254$), the number of negative events ($r = -0.241$), and the number of positive events ($r = -0.170$), controlling for the previously used covariates. To examine whether the correlation coefficient of the negative events score is significantly different from the positive events score, we converted them into z-scores using Fisher's r-to-z transformation and computed the asymptotic covariance of the estimates (Steiger, 1980). An asymptotic z-test showed that the correlation coefficient between the negative events score and the mPFC GMV cluster value change was significantly higher than the correlation coefficient of the positive events score (z-score $= 2.601$, $p = .009$). This indicates that SLEs perceived as negative have a bigger influence on mPFC GMV than SLEs perceived as positive. LEQ scores
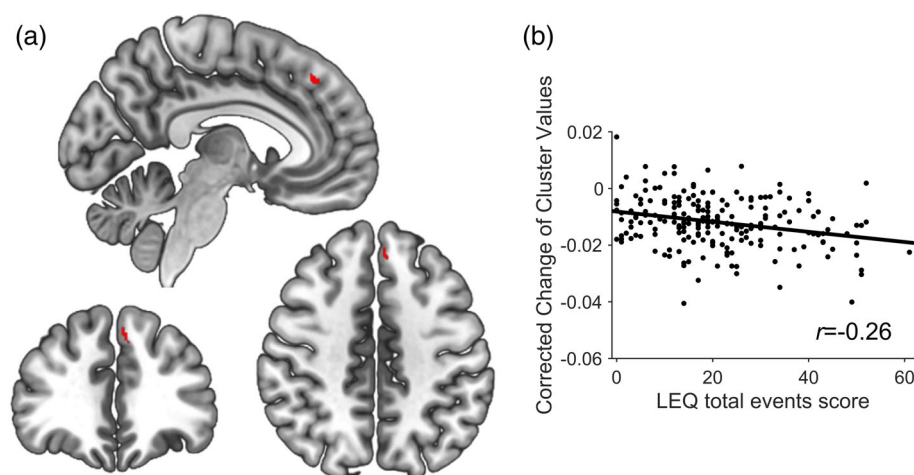
FIGURE 1 (a) Significant association between cumulative impact of stressful life events (LEQ total events score) and change of grey matter volume during the 2-year follow-up period in $N = 212$ healthy subjects in the left medial prefrontal cortex ($k = 29$, x/y/z $= -6/36/45$). (b) Change of left medial prefrontal cortex grey matter volume cluster values (2-year follow-up – Baseline) and regression line for the life events questionnaire (LEQ) total events score

and number of experienced events were highly correlated with each other (Table S6). Furthermore, the mPFC cluster value change was not correlated with the change in subclinical anxiety symptoms, measure with the state subscale sum score of the State–Trait Anxiety Inventory (Spielberger et al., 1970, $t[204] = -0.171$, $p = .864$) and depressive symptoms, measure with the Beck Depression Inventory-II sum score (Beck et al., 1996, $t[201] = 0.888$, $p = .376$) controlling for age at follow-up, gender, and body coil change, suggesting that these variables do not account for the found association. The whole-brain analysis with the total events score revealed no significant clusters. An interactive visualization of the TFCE images, the parametric t-maps, and the nonparametric t-maps of all whole-brain analyses can be found as open source at https://neurovault.org/collections/ZVQPDXFK/.

Next, we examined whether the association between SLEs and GMV changes depends on the number of experienced ACEs. Most subjects did not experience any ACEs ($n = 119$). Fifty-four subjects experience one ACE, twenty-three subjects experience two ACEs, seven subjects experienced three ACEs, four subjects experience four ACEs and one subject experienced seven ACEs. There was a significant LEQ total events score × ACE score interaction on the extracted mPFC GMV cluster value changes (LEQ × ACE effect: $\beta = -9.665 \times 10^{-5}$, $t[201] = -2.197$, $p = .029$, $sr^2 = 0.0205$; overall model: $R^2 = 0.149$; Figure 2). This interaction remained significant after excluding the subject who experienced seven ACEs ($p = .030$). The studentized residuals of the model were normally distributed (Shapiro–Wilk $p = .502$), indicating reliable results. The ACE would only moderate the effect SLEs had on extracted mPFC GMV cluster value changes, but there was no main effect of the ACE score on GMV changes controlling for age at follow-up, gender, and body coil change.
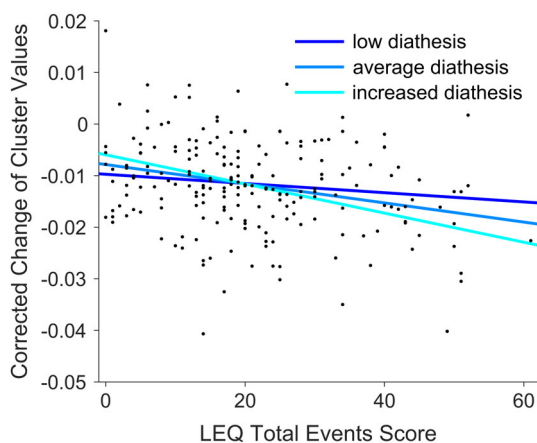
FIGURE 2 Change of the grey matter volume cluster values (2-year follow-up – Baseline) in the left medial prefrontal cortex ($k = 29$, x/y/z = $-6/36/45$) and regression lines for the life events questionnaire (LEQ) total events score as a function of adverse childhood experiences (ACE). For illustrative purposes, the regression lines represent subjects with a low (i.e., subjects experienced zero ACEs), average (i.e., subjects experienced one ACEs), or increased diathesis (i.e., subjects experienced two ACEs)

3.2 | Associations between baseline GMV and LEQ total events score

A brain region with only cross-sectional but not longitudinal associations between GMV and SLEs would indicate that GMV in this brain area is not affected by SLEs, but that GMV in this cluster predicts SLEs. Therefore, we also examined cross-sectional associations.

In our first cross-sectional model, we investigated associations between GMV at baseline and LEQ total events score during 2-year follow-up. However, ROI-based analysis and the exploratory whole-brain analysis revealed no significant clusters.

3.3 | Associations between follow-up GMV and LEQ total events score

In the second cross-sectional model, we examined associations between GMV at follow-up and LEQ total events score during 2-year follow-up. Here, ROI-based analysis and the exploratory whole-brain analysis revealed no significant clusters as well.

4 | DISCUSSION

In this study, we examined whether stressful life events (SLEs) within a 2-year period impact on GMV in healthy adult subjects. We found a negative association between SLEs and GMV changes within 2 years in the left mPFC. Furthermore, the GMV reduction was stronger when subjects had adverse childhood experiences (ACEs). We conclude that SLEs cause brain changes in the mPFC similar to findings in experimental animal models. ACEs increase vulnerability leading to a stronger impact of SLEs on the adult brain structure. These cerebral structural alterations might be a pathophysiological basis for an increased risk for the onset and/or chronicity of stress-related mental and somatic disorders.

Multiple animal studies have shown that experimentally induced chronic stress (e.g., immobilization) leads to dendritic spine loss and debranching of dendrites in the mPFC (Arnsten, 2009; McEwen & Morrison, 2013), although a subpopulation of interneurons also shows hypertrophy in the mPFC of stressed mice (Gilabert-Juan et al., 2013). Such alterations of dendrites lead to MRI-measurable GMV reductions (Kassem et al., 2013). Therefore, the longitudinal GMV reduction in this study might point that dendrites in the mPFC are being altered by stress in adult humans. Importantly, stress-induced structural alterations in the mPFC in animal models have also been associated with reduced mPFC function (Liston et al., 2006). Therefore, these changes are most likely not adaptations of the brain to deal with stress without affecting health (i.e., a sign of resilience to stress) but rather lead to adverse health outcomes. One cross-sectional human study also found a reduced GMV in subjects who experienced more threatening SLEs in the last year in a dorsal anterior cingulate cortex cluster close to the cluster found in our study (Kuhn et al., 2016).

ACEs increased the effect of SLEs on GMV changes. ACEs and SLEs in adulthood are both important risk factors for poor general health outcomes (Cohen et al., 2019; Hughes et al., 2017). However, compared with SLEs in adulthood, ACEs are not a proximal predictor for MDD in adulthood but make an individual more vulnerable later in life. The diathesis-stress model (Ingram & Luxton, 2005) predicts that SLEs are more likely to lead to poor health outcomes if subjects are more vulnerable. We found a potential neural basis for this effect. The reduction of GMV in the mPFC caused by SLEs was stronger when subjects experienced more ACEs potentially leading to stronger imbalances in the PFC.

The PFC is involved in working memory, executive function, self-regulatory behavior, and goal-directed behavior (McEwen & Morrison, 2013). Acute stress impairs these functions (Arnsten, 2009), and it is hypothesized that long-lasting structural alterations in the PFC induced by stress may be involved in the development of psychopathological symptoms (Kaul et al., 2021). Medial PFC grey matter alterations have for example been linked to occupational exhaustion syndrome (Savic et al., 2018), major depression (Zheng et al., 2021), bipolar disorder (Ganzola & Duchesne, 2017), schizophrenia (Glahn et al., 2008), and post-traumatic stress disorder (Bromis et al., 2018). Furthermore, the magnitude of mPFC alterations has been associated with progression and severity of these disorders, e.g., number of episodes, disorder duration, and treatment resistance (Belleau et al., 2019; Dusi et al., 2017).

We found no cross-sectional associations between GMV and SLEs in a 2-year period. We examined whether cross-sectional associations are present in a cluster in which no longitudinal association between SLEs and GMV changes were found to investigate whether previously found cross-sectional associations arise due to other reasons than that SLEs reduce GMV. Cross-sectional associations could for example arise because structural features are associated with a different appraisal of SLEs or with traits which lead to the experience of more SLEs or because SLEs reduce GMV. However, due to the absence of cross-sectional associations in our current analysis, we cannot make assumptions whether such causal associations exist.

Two cross-sectional studies have found associations between the number of SLEs in the previous 12 months or the impact of SLEs on life in the previous 6 months with GMV in the mPFC, mOFC, and insula (Ansell et al., 2012; Ringwald et al., 2021). In our study, the number of SLEs was highly correlated with the impact SLEs had on life. However, we did not find such cross-sectional associations. A reason for this might be that SLEs in these former studies were assessed over a shorter time interval. Stress-induced GMV reductions in the mPFC are reversible in the absence of stress (Arnsten & Shanafelt, 2021). In animal models, it has been shown that dendrites recover after a few weeks without the induced stress (Bloss et al., 2011; Radley et al., 2005). In a human study, MRI-measured thinning of PFC associated with chronic occupational stress was normalized after 1–2 years in patients with exhaustion syndrome (Savic et al., 2018). Some SLEs might lead to short lasting, others to longer lasting GMV reductions. Short-lasting reductions might recover in periods without stress. Therefore, they might not be detectable when

investigating SLEs over a longer time period. However, in the longitudinal analysis we found an association in a small mPFC cluster. A reason why we found this cluster in the longitudinal but not in a cross-sectional analysis might be that inter-individual variability does not have such a strong effect on longitudinal analyses, therefore they have more statistical power.

Some limitations of the current study should be noted. First, we defined SLEs according to the adaptation definition (Cohen et al., 2019). Different types of stress seem to be associated with different brain areas (Kaul et al., 2021). Second, we assessed SLEs retrospectively and they might therefore be biased (Coughlin, 1990). Finally, although this is a longitudinal study and we found associations between GMV changes and SLEs in a cluster in the mPFC, we still cannot strictly infer causality (i.e., SLEs reducing GMV). SLEs and GMV might for example both be affected by a third factor which increases the number of SLEs and reduces GMV. However, longitudinal designs have the advantage that inter-individual variability in variables that are mostly stable over time is controlled for. We tested subclinical depressive and anxiety symptoms, which were not correlated with the found cluster, suggesting that the mPFC-SLEs association does not arise due to these factors. Additionally, by analyzing healthy subjects, we made sure that many confounding factors such as treatment or illness per se were absent.

5 | CONCLUSIONS

With our large sample and longitudinal design, we pushed forward evidence for effects of SLEs on the human, adult brain. This gives us novel insight into a potential neural basis of the diathesis-stress model.

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