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Interaction of developmental factors and ordinary stressful life events on brain structure in adults

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ABSTRACT

An interplay of early environmental and genetic risk factors with recent stressful life events (SLEs) in adulthood increases the risk for adverse mental health outcomes. The interaction of early risk and current SLEs on brain structure has hardly been investigated.

Whole brain voxel-based morphometry analysis was performed in N = 786 (64.6% female, mean age = 33.39) healthy subjects to identify correlations of brain clusters with commonplace recent SLEs. Genetic and early environmental risk factors, operationalized as those for severe psychopathology (i.e., polygenic scores for neuroticism, childhood maltreatment, urban upbringing and paternal age) were assessed as modulators of the impact of SLEs on the brain.

SLEs were negatively correlated with grey matter volume in the left medial orbitofrontal cortex (mOFC, *FWE p* = 0.003). This association was present for both, positive and negative, life events. Cognitive-emotional variables, i.e., neuroticism, perceived stress, trait anxiety, intelligence, and current depressive symptoms did not account for the SLE-mOFC association. Further, genetic and environmental risk factors were not correlated with grey matter volume in the left mOFC cluster and did not affect the association between SLEs and left mOFC grey matter volume.

The orbitofrontal cortex has been implicated in stress-related psychopathology, particularly major depression in previous studies. We find that SLEs are associated with this area. Important early life risk factors do not interact with current SLEs on brain morphology in healthy subjects.

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1. Introduction

Stressful life events (SLEs) are associated with increased risk of adverse (mental) health outcomes (Cohen et al., 2019). Research on the neural underpinnings of life events has mostly focused on maltreatment in childhood or traumatic events in adulthood, e.g., natural disasters or combat exposure (e.g., (Sekiguchi et al., 2013)). Although less severe SLEs occur frequently in everyday life, fewer studies have tested the association between common recent SLEs and local grey matter volume in middle aged healthy adults (Ansell et al., 2012; Kuhn et al., 2016; Papagni et al., 2011). They have found negative associations between the number of recent SLEs and grey matter volume in stress- and emotion-related regions such as the medial prefrontal cortex (mPFC), insula, anterior cingulate and hippocampus. No positive associations have been found by these studies. However, given the particular research foci of these studies many questions remain unanswered. First, the majority of previous studies restricted their ROI analysis to few brain areas related to stress reaction. Second, they were mostly conducted in small samples. Lastly, and most importantly, previous studies looked mainly at severely threatening SLEs, such as illness and injuries. But positive events can also lead to adverse psychological outcomes. For example, positive events (e.g. falling in love or going on vacation) predict the onset of manic/hypomanic episodes in bipolar disorder (Proudfoot et al., 2012).

According to the adaption definition (Cohen et al., 2019), an SLE is every event that impacts on our life substantially and requires adaption. It implies that SLEs having a bigger impact on our life are more stressful, and that even positive events can be stressful when they add to the overall burden of change. The subjective impact of SLEs on one's life has, to our knowledge, never been used to examine morphological associations with recent SLEs.

The diathesis-stress model suggests interactions of early life risk factors and recent SLEs (Ingram and Luxton, 2005). It states that recent stress is more likely to lead to adverse mental health outcomes when an individual is vulnerable, based on genetic makeup and/or the early environment. One study has tested interactions of stressful events in adulthood and childhood maltreatment as early risk factor on MRI-measured brain morphology and found no interactions (Kuhn et al., 2016). So far, effects of other early environmental or genetic risk factors on brain structure have usually been tested in simple associations (e.g., (Krug et al., 2020)), but not in interaction with recent SLEs. These risk factors were differently associated with brain morphology. Therefore, it is unlikely that the mechanism by which different risk factors for severe psychopathology convey the risk –via brain morphology- is the same for all risk factors. Hence, known risk factors other than childhood abuse might interact with recent SLEs on GMV.

In addition to childhood maltreatment, urban upbringing is one of the strongest early environmental risk factors for adverse mental health outcomes (Uher and Zwicker, 2017). Some genetic risk is expressed by polygenic scores (PGS) for neuroticism due to its genetic association with various adverse psychological outcomes (Luciano et al., 2018). Paternal age is an important risk factor for mental disorders and interesting since it is an environmental factor that seems to increase its risk trough genetic pathways (Miller et al., 2011).

In summary, exclusively the effect of childhood maltreatment as an early environmental risk factor in conjunction with adult, severe SLEs on brain morphology has been investigated, but no clear interaction was found. There are no studies yet testing effects of other environmental or genetic risks in conjunction with SLEs on brain morphology.

This study aimed at associations between recent SLEs defined by the adaption definition (Cohen et al., 2019) and GMV in healthy subjects. For this purpose, we considered the subjective impact of both, negative and positive, recent SLEs. We also aimed to examine if recent SLEs interacted with certain early risk factors for severe psychopathology (childhood maltreatment, paternal age, urban upbringing, and PGS for neuroticism) on GMV using the areas associated with recent SLEs as regions of interest. Therefore, we investigated for the first time the association between the cumulative impact of ordinary recent SLEs on life and grey matter volume (GMV) in a large sample of healthy subjects. This has the advantage, that potentially confounding influences on brain structure, such as mental disorder per se or medication is eliminated. In addition, in follow-up analyses we examined if significant results arise due to the cumulative impact of recent SLEs on life or rather due to potentially confounding or interacting variables related to the cumulative impact of SLEs by: 1) controlling for several SLE-related cognitive-emotional variables, i.e., neuroticism, perceived stress, trait anxiety, intelligence (IQ), and current depressive symptoms, 2) examining if positive and negative events both contribute to the association or if significant results are clearly driven by only one kind of events, and 3) investigating if the association between GMV in significant clusters and the cumulative subjective impact of recent SLEs yields a higher correlation coefficient than an association between GMV and the number of SLEs. Furthermore, we examined if early risks factors operationalized as those for severe psychopathology (i.e., childhood maltreatment, paternal age, urban upbringing, and PGS for neuroticism) interact with SLEs on GMV. We expected that SLEs defined by the adaption definition are negatively associated with GMV in the medial prefrontal cortex (mPFC), insula, anterior cingulate and hippocampus. In addition, we expected that early risk factors moderate this association as predicted by the diathesis stress model leading to stronger or weaker associations depending on the vulnerability of an individual.

2. Methods and materials

2.1. Sample

In this study, data of 786 healthy subjects (278 male, 508 female) drawn from the FOR2107 cohort (Kircher et al., 2019) were examined. FOR2107 is a bi-center study with scanning sites in Marburg and Münster, Germany. All study protocols were approved by the Ethics committee of the Medical Faculties, University of Marburg and University of Münster, respectively, in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before study participation and they subsequently received financial compensation. Subjects were 18 – 65 years old (mean, standard deviation (SD); 33.39, 12.58), had Western-European ancestry, and underwent a Structured Clinical Interview for DSM-IV Axis I Disorders (Wittchen et al., 1997) to ensure no history of or current psychiatric illness. Further exclusion criteria were neurological abnormalities, history of severe medical disorders, IQ < 80 (Multiple Choice Word Test-B; (Lehrl, 2005)), current or previous substance abuse or dependence, and general MRI contraindications.

2.2. Recent stressful life events

Recent SLEs were assessed with the German version of the Life Events Questionnaire (LEQ, (Norbeck, 1984)). The LEQ is an 82-item questionnaire in which subjects mark life events that have occurred in the recent past (last six months), indicate whether the event was considered positive or negative, and rate the event's impact on their life on a 4-point scale, ranging from "no effect" to "great effect" (scored 0 to 3). Exemplary items include changing to a new type of work, getting married, death of a family member or close friend, major change in finances, and involvement in an accident. Three scores were obtained from the LEQ: 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 cognitive-emotional variables

We assessed five cognitive-emotional variables which may account for associations between LEQ scores and GMV in the brain. These cognitive-emotional variables were current subclinical depressive symptoms (Beck Depression Inventory-II sum score, BDI, (Beck et al., 1996)) and trait anxiety (trait subscale of the State-Trait Anxiety Inventory, STAI-T, (Spielberger et al., 1970)) as typical psychiatric variables associated with SLEs (Norbeck, 1984). Neuroticism (neuroticism subscale of the NEO Five-Factor Inventory questionnaire, NEO-FFI, (Costa and McCrae, 1992)) and verbal intelligence (IQ, Multiple Choice Word Test-B, MWT-B, (Lehrl, 2005)) are traits that influence the subjective appraisal of SLEs (Mikolajczak and Luminet, 2008; Schneider et al., 2012). Lastly, we assessed perceived stress (14-items Perceived Stress Scale questionnaire, PSS, (Cohen et al., 1983)) as it represents a stress domain which is different from the impact of SLEs on one's life (Monroe, 2008).

2.4. Assessment of risk variables

Genetic and early environmental factors increasing the risk of adverse mental health outcomes later in life were assessed with four risk variables: a PGS for neuroticism, paternal age at birth, urban upbringing, and childhood maltreatment.

Genetic risk was estimated calculating a PGS for neuroticism, based on the genome-wide association study (GWAS) by Luciano et al. (Luciano et al., 2018), calculated on imputed probabilities using the PGS-CS method (Ge et al., 2019) with a pre-selected $\varphi = 0.01$ (as recommended for highly polygenic traits). PGS summarize the effects of genetic variants associated with a trait or disorder (Andlauer and Nöthen, 2020). PGS-CS utilizes a Bayesian regression framework to correct the GWAS effect sizes, used as weights for the individual variants, for linkage disequilibrium, i.e., correlations between the variants.

Genotyping was performed using Illumina Infinium PsychArray-24 BeadChips on DNA extracted from blood samples. Quality control (QC) and imputation were conducted, as described previously (Andlauer et al., 2019), in PLINK (Chang et al., 2015) v1.90b6.10 and R v3.4.3. In brief, individuals were removed from the risk variable analysis if they met any of the following criteria: genotyping rate < 98% (1 subject), gender mismatches or other X-chromosome-related issues (0 subjects), genetic duplicates (2 subjects), cryptic relatedness with pi-hat ≥ 12.5 (20 subjects), genetic outlier with a distance from the mean of >4 SD in any of the first eight ancestry components (1 subject), or a deviation of the autosomal or X-chromosomal heterozygosity from the mean >4 SD (0 subjects). Ancestry components were calculated in PLINK using multidimensional scaling (MDS). The first three components were used in the analyses to adjust for population stratification. Variant-level QC included removal of variants with call rates < 98%, minor allele frequencies (MAF) < 1%, or a Hardy-Weinberg equilibrium test p-value < 1×10^{-6}, as well as non-autosomal variants, A/T and G/C polymorphisms, and variants not in the reference panel. The genotype data were imputed to the 1000 Genomes phase 3 reference panel using SHAPEIT v2 (r837) and IMPUTE2 v2.3.2 (Delaneau et al., 2013; Howie et al., 2012, 2009). After imputation, variants with an INFO metric < 0.8 or a MAF of < 1% were removed.

Childhood maltreatment was assessed with the German version of the brief Childhood Trauma Questionnaire (CTQ, (Wingenfeld et al., 2010)). The 28 items of the retrospective self-report questionnaire cover items on emotional neglect, physical neglect, emotional abuse, physical abuse, and sexual abuse. In the analyses, the overall CTQ sum score was used.

Urban upbringing was assessed by means of the Lederbogen urbanicity score (Lederbogen et al., 2011). It assigns a specific value to each subject depending on how many years he or she lived in cities with more than 100,000 inhabitants, in towns with more than 10,000 inhabitants, and in rural areas with <10,000 inhabitants until the age of 15.

Paternal age at birth was assessed by asking participants to indicate their father's year of birth.

2.5. MRI acquisition and pre-processing

T1-weighted structural images were acquired using a 3 T MRI scanner (Marburg: Tim Trio, 12-channel head matrix Rx-coil, Siemens, Erlangen, Germany; Münster: Prisma, 20-channel head matrix Rx-coil, Siemens, Erlangen, Germany). A 3D MP-RAGE sequence was used with a slice thickness of 1.0 mm, a voxel size of 1.0 × 1.0 × 1.0 mm, a field of view of 256 mm, and the following parameters at the two sites: Marburg: repetition time (TR) = 1.9 s, echo time (TE) = 2.26 ms, inversion time (TI) = 900 ms, flip angle = 9°; Münster: TR = 2.13 s, TE = 2.28 ms, TI = 900 ms, flip angle = 8°. Based on extensive quality assurance protocols, imaging data from both centers were pooled (Vogelbacher et al., 2018). Since the gradient coil was exchanged after 307 of 459 scans at the Marburg scanner, a dummy-coded variable for gradient coil and a dummy-coded variable for site were used as covariates of no interest in the statistical analyses to account for scanner differences.

Scans were pre-processed using the pipeline of the CAT12 toolbox (build 1184, Gaser, Structural Brain Mapping group, Jena University Hospital, Jena, Germany) implemented in SPM12 (Statistical Parametric Mapping, Institute of Neurology, London, UK), running under MATLAB (version R2017a, The MathWorks, USA) with default parameter settings. Images were segmented into grey matter, white matter, and cerebrospinal fluid. Segmentation in CAT12 includes the standard SPM segmentation (Ashburner and Friston, 2005) which is followed by an adaptive maximum a posteriori segmentation step (Rajapakse et al., 1997). This segmentation step is then refined by applying a partial volume estimation (Tohka et al., 2004). The tissue segments were then spatially normalized to the template provided by CAT12 using the DARTEL algorithm (Ashburner, 2007). All images passed visually quality control by a senior, MRI experienced clinician (inspection for artifacts and image quality). Modulated grey matter images were smoothed with a Gaussian kernel of 8 mm full width at half maximum (FWHM).

2.6. Statistical analyses

Whole brain VBM regression analysis was applied using the CAT12 toolbox with an absolute grey matter threshold of 0.1 and otherwise default parameter settings to find associations between LEQ total events score and GMV. Age, sex, total intracranial volume (TIV), site, and gradient coil were entered as covariates of no interest. Results were considered significant at $p < 0.05$ *FWE* (family-wise error) correction at voxel-level for multiple comparisons (Kurth et al., 2015).

For significant results in whole brain analysis, raw cluster values were extracted using the eigenvariate function in SPM and the following analyses were all performed with these extracted cluster values in MATLAB R2017a. The cluster values were first used to check if only stressful events perceived as positive or negative may account for this effect and to compare the association of the impact ratings and GMV and the association of the number of events a person reported and GMV. Therefore, we calculated the Pearson correlation coefficient between these cluster values and the LEQ total events score, the LEQ positive events score, the LEQ negative events score, the number of all experienced events, the number of the positive events, and the number of the negative events, respectively, using age, sex, TIV, site, and gradient coil as covariates of no interest. Correlations of the positive and negative events score were considered significant at $p < 0.05$.

Secondly, to examine whether cognitive-emotional variables may account for significant associations, the correlation between cluster values and total events score was calculated correcting for the previous covariates (age, sex, TIV, site, and gradient coil) plus the cognitive-emotional variables which were correlated with the LEQ total events

score.

In a last step, it was examined whether genetic or early environmental risk factors for adverse mental health outcomes modulate impact of SLEs on brain morphology. The correlations between mean cluster values and risk variables as well as the risk variables × LEQ interaction effects (in multiple linear regression models) were examined using MATLAB R2017a. Since the risk factors were not available for all subjects, this was done in a "risk subsample" excluding 124 subjects with incomplete risk variables or subjects who met our exclusion criteria for the genetic analysis (see 2.4). To calculate the correlations between the total events score and each of the risk factors (i.e., PGS neuroticism, CTQ sum score, urbanicity score, and paternal age), four correlation analyses were performed using age, sex, TIV, site, and gradient coil as covariates. In the correlation analyses between the total events score and PGS neuroticism the first three MDS components were also included as covariates of no interest. Furthermore, four interaction analyses between total events score and PGS neuroticism, CTQ sum score, urbanicity score, and paternal age were performed, one for each risk factor respectively, correcting for the same covariates of no interest as in the correlation analyses plus the main effect of the LEQ total events score and the main effect of the respective risk variable in the interaction analyses. Since four risk factors were examined, correlations and interaction effects were considered significant at $p < 0.0125$ (Bonferroni correction).

As an additional step, four exploratory whole brain analyses were performed using an absolute grey matter threshold of 0.1 to detect significant interactions between LEQ total events score and the risk factors PGS neuroticism, CTQ sum score, urbanicity score, paternal age on a whole brain level. The same covariates of no interest were used as in the previous ROI interaction analyses. Results were considered significant at $p < 0.05$ FWE peak level-correction for multiple comparisons.

3. Results

3.1. Associations between stressful life events and GMV

In the whole brain VBM analysis, the LEQ total events score was associated with GMV in a cluster in the left medial orbitofrontal cortex (mOFC, $k = 83$ voxels, $F(779) = 28.94$, $FWE\ p = 0.003$, x/y/z = −9/34/−22, Fig. 1. For an effect size map see Supplementary Fig. 1). An additional quadratic age term as covariate of no interest in a further whole brain analyses led only to small changes in mOFC cluster size and no additional significant clusters were detected, therefore we used the results with linear age covariate for further analyses. The Pearson correlation coefficient for the association between the GMV in the mOFC (extracted cluster values) and the total events score was $r = -0.18$ ($p = 2 \times 10^{-7}$). The cluster values were also negatively correlated with the negative events score ($r = -0.14$, $p = 1 \times 10^{-4}$) and the positive events score ($r = -0.15$, $p = 2 \times 10^{-5}$), supporting the notion that the total event score association with GMV is caused by positive and negative events. Furthermore, the number of all experienced events ($r = -0.10$, $p = 7 \times 10^{-3}$) and the number of negative events ($r = -0.10$, $p = 7 \times 10^{-3}$) were correlated with the GMV, however, with a smaller r than the impact scores. The number of positive events was not correlated with the GMV ($r = -0.06$, $p = 0.095$). LEQ scores and number of experienced events were significantly correlated with each other (Supplementary Table 1). Age did not interact with the LEQ total events score on cluster values. Hence, no evidence for an age-depended effect of SLEs on mOFC GMV was found.

The Pearson correlation coefficient r between all the cognitive-emotional variables and the total events score was between −0.12 and 0.75 indicating no significant multicollinearity problem (Supplementary Table 2). All cognitive-emotional variables (for descriptives see Table 1) had a modest but significant correlation with the LEQ total events score and: IQ ($r = -0.12$, $p = 6 \times 10^{-4}$), perceived stress ($r = 0.23$, $p = 10^{-10}$), neuroticism ($r = 0.20$, $p = 2 \times 10^{-8}$), depressive symptoms ($r = 0.21$, $p = 2 \times 10^{-9}$), and trait anxiety ($r = 0.20$, $p = 2 \times 10^{-8}$). To examine whether these variables may account for the association between LEQ

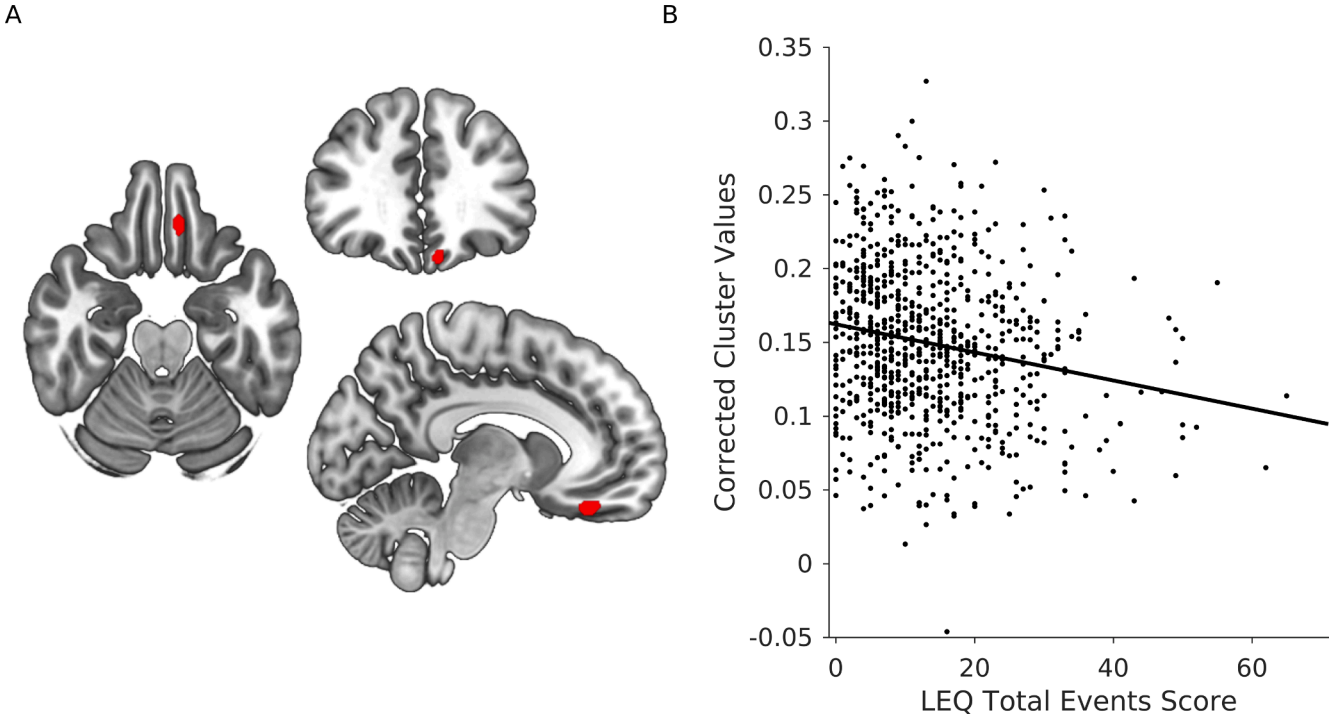

Fig. 1. A) Cluster of significant association between cumulative impact of recent stressful events and grey matter volume (x/y/z = −9/34/−22). **B)** Extracted cluster values and Regression line corrected for age, sex, TIV, site, and gradient coil.

Table 1
Sample descriptives (N = 786, 64.6% female).

	Mean	SD
Age	33.39	12.57
LEQ Total Events Score	13.55	10.17
LEQ number of events	7.15	6.30
LEQ Negative Events Score	4.37	5.41
LEQ number of positive events	4.73	4.90
LEQ Positive Events Score	9.19	7.54
LEQ number of negative events	2.42	3.25
IQ (MWT-B)	115.10	13.45
STAI-T Sum Score	33.34	8.31
PSS Sum Score	16.04	7.22
BDI Sum Score	3.92	4.21
NEO-FFI Neuroticism	15.20	7.44

SD, standard deviation; LEQ, Life Events Questionnaire; MWT-B, Multiple Choice Word Test-B; STAI-T, trait subscale of the State-Trait Anxiety Inventory; PSS, 14-items Perceived Stress Scale questionnaire; BDI, Beck Depression Inventory-II; NEO-FFI Neuroticism, neuroticism subscale of the NEO Five-Factor Inventory questionnaire.

and GMV, we calculated the correlation between the LEQ total events score and the cluster values while correcting for age, sex, TIV, site, and gradient coil plus the cognitive-emotional variables. When adding these cognitive-emotional variables as covariates of no interest to the regression model, the association between LEQ and GMV remained significant ($r = -0.18$, $p = 2 \times 10^{-7}$).

3.2. Associations between risk variables and GMV

Genetic and early environmental factors might modulate the impact of recent stress. Therefore, we examined the interaction of early life risk factors and LEQ total events score on GMV in the found cluster. Risk variables were available for n = 662 participants: urbanicity score (mean, SD; 26.59, 12.58), CTQ sum score (31.96, 7.94), and paternal age (31.73, 5.84).

No significant linear interaction with the LEQ total events score on the cluster values was found for neuroticism PGS ($t(650) = 0.540$, $p = 0.590$), paternal age ($t(653) = 0.508$, $p = 0.612$), CTQ sum score ($t(653) = 0.001$, $p = 0.999$), or the urbanicity score ($t(653) = -0.174$, $p = 0.862$). Only the LEQ total events score, but none of the risk variables, were correlated with the extracted cluster values in this subsample: LEQ Total Events Score ($r = -0.17$, $p = 1 \times 10^{-5}$), urbanicity score ($r = -0.02$, $p = 0.549$), CTQ sum score ($r = -0.07$, $p = 0.081$), paternal age ($r = 0.01$, $p = 0.708$), neuroticism PGS ($r = 0.02$, $p = 0.688$).

The four exploratory whole brain analyses revealed no significant interactions between the LEQ total events score and neuroticism PGS, paternal age, CTQ sum score, or the urbanicity score on GMV on a whole brain level. In summary, no interaction between early life risk and current stressful life events on GMV was found.

4. Discussion

In this study, we examined the influence of early life risk for adverse psychological outcomes and adulthood stress variables on regional GMV. A higher cumulative impact of recent commonplace SLEs was associated with smaller GMV in the left mOFC. This association was present separately for both, positive and negative, life events, and remained significant after correction for cognitive-emotional variables, i.e., neuroticism, perceived stress, trait anxiety, IQ, and current depressive symptoms. Genetic and early environmental risk variables (i.e., neuroticism PGS, paternal age at birth, urban upbringing, childhood maltreatment) were not correlated with GMV in the left mOFC cluster and did not affect the association between SLEs and left mOFC volume.

The mOFC is part of the limbic system and heavily connected with other brain regions related to stress reactions, such as the amygdala and hippocampus (Fettes et al., 2017). The medial division of the OFC is reciprocally connected with the basolateral amygdala, the anterior cingulate cortex, the posterior parahippocampal cortex, and the hippocampus and is part of a cortico-striatal-thalamic loop which is anatomically distinct from the lateral OFC loop (Fettes et al., 2017). The OFC has been implicated in emotional processing and the generation of affective states as well as reward learning and reinforcement-based decision-making (Fettes et al., 2017). Morphological alterations and altered responses of the OFC have been observed across a wide range of stress-related mental disorders including anxiety disorders (Brühl et al., 2014; Menzies et al., 2008), substance use disorder (Fettes et al., 2017), schizophrenia (Nakamura et al., 2020), and, most importantly, major depressive disorder (Arnone et al., 2012; Suh et al., 2019).

Animal models showed that main targets of stress-induced structural remodeling are hippocampus, amygdala, and prefrontal cortex including the OFC. These structural alterations happened sometimes within short time intervals and affected behavioral and physiological responses (McEwen, 2007). Importantly, in a longitudinal human study, reduced GMV induced by stress after an earthquake in the left OFC but not in other regions was associated with stronger subclinical post-traumatic stress disorder symptoms in healthy adults (Sekiguchi et al., 2013). Stress-induced alterations of responses in the OFC in fMRI or PET activation studies in healthy humans have also been well documented. Activity in stress related regions like the medial OFC decreased for example during acute stress and this decrease was more pronounced only in the medial OFC in subjects who experienced more stressful events (Seo et al., 2014) and acute stress in healthy subjects altered responses of the OFC and striatum during reward-processing (Porcelli et al., 2012). This literature suggest that the direction of the association is rather SLEs affect mOFC than the other way round.

Not only the impact ratings but also the number of experienced events were correlated with GMV. Another study on SLEs also found a negative association between the number of stressful events in the last year and GMV in the right insula and the bilateral mPFC including the mOFC (Ansell et al., 2012), which corroborates our findings. We show that also SLEs perceived as positive are associated with this cluster. However, we found this association only for the positive event score and not for the number of positive events which might indicate that positive events are only associated with GMV if they add to the overall burden of change. Since the other study focused only on negative (Acosta et al., 2021) and threatening recent stressful events, their associations with GMV in some brain regions that do not overlap with our results, might be exclusive for more threatening events.

It has previously been shown that cognitive-emotional variables, such as perceived stress, trait anxiety, neuroticism, IQ, and current depressive symptoms, are related to the subjective processing of stressful events (Mikolajczak and Luminet, 2008; Monroe, 2008; Norbeck, 1984; Schneider et al., 2012). Further, they have been related to brain morphology (Besteher et al., 2019; Li et al., 2014; Tadayon et al., 2020; Wright et al., 2006). In line with this literature, we found these traits and current, subclinical depressive symptoms to be associated with the cumulative severity of SLE. Therefore, we controlled for these variables and showed that the association between SLEs and mOFC GMV is not caused by these SLE-related factors. In particular, we were interested in "perceived stress" estimated with the PSS. Perceived stress assesses our current emotional reaction to SLEs (i.e., how stressed we feel due to events). On the other hand, the LEQ measures to what extent stressful events change our life and how much we have to restructure and adapt our life due to events. Hence, we showed by controlling for perceived stress that the subjective influence an event had on our life, independent of how stressful or uncontrollable it feels, was associated with brain morphology. This is also in line with our result that not only negative but also positive events were associated with smaller GMV. Likewise, previous work found associations between GMV and recent SLEs but not with the felt chronic stress (Ansell et al., 2012).

The diathesis-stress model postulates interactions of early risk factors with recent stressful events as risk factors for the majority of adverse

mental health outcomes. Therefore, we expected a similar interaction of SLES and early stress on GMV. In our study, only recent stress but not its interaction with genetic or early environmental risk factors (i.e., neuroticism PGS, paternal age at birth, urban upbringing, and childhood maltreatment) were associated with mOFC GMV changes. In addition, our whole brain analyses revealed no clusters with significant interactions. Hence, we found no evidence on a morphological level (GMV) that risk factors moderate the influence recent SLEs have on the brain.

Severe psychopathology is a complex, multi-causal phenomenon (Uher and Zwicker, 2017). An explanation why we did not find interactions between risk factors and recent SLEs might be that our subjects were healthy. Recent SLEs might only interact with neurodevelopmental risk factors when the diathesis (i.e., other pre-existing risk) is strong enough to trigger severe psychopathology (i.e., other factors might moderate interactions between recent SLEs and single risk factors). Healthy subjects might similarly show resilience preventing interactions between recent SLEs from interacting with risk factors.

Since we only analyzed healthy subjects, it is also not clear if the association signifies vulnerability to develop adverse mental health outcomes or a sign of resilience. The brain of healthy subjects could for example undergo remodeling to cope with SLEs and thereby stay healthy. Future studies should analyze patients with mental disorders.

Some further limitations should be mentioned. In this study a weak association ($r = -0.18$ for extracted cluster values) between SLEs and GMV in the mOFC was found. However, with our study design we could not disentangle whether SLEs decrease GMV or a smaller left mOFC causes a higher subjective impression of how much an SLE impacted one's own life. Alternatively, a smaller mOFC could also lead to the experience of more SLEs by influencing behavior. A longitudinal study design could shed light on this issue. Furthermore, there are early life environmental (e.g., low birth weight (Köhler et al., 2018)) and genetic risk factors that might interact with current stress which we did not test. However, we think that with our study, including a well characterized large sample and multiple risk factors, we have pushed forward the discussion of testing interactions of risk factors for adverse psychological outcomes on a brain morphological level.

5. Conclusions

This study provides new insights into neurobiological correlates of ordinary recent life events in adulthood. A higher cumulative impact of ordinary stressful events on life was associated with smaller GMV in the left mOFC of healthy subjects, independent of neurodevelopmental risk factors and current stress related variables.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

Acosta, H., Jansen, A., Kircher, T., 2021. Larger bilateral amygdalar volumes are associated with affective loss experiences. J. Neurosci. Res. 1–17 https://doi.org/10.1002/jnr.24835.

Andlauer, T.F.M., Guzman-Parra, J., Streit, F., Strohmaier, J., González, M.J., Gil Flores, S., Cabaleiro Fabeiro, F.J., del Río Noriega, F., Perez, F.P., Haro González, J., Orozco Diaz, G., de Diego-Otero, Y., Moreno-Küstner, B., Auburger, G., Degenhardt, F., Heilmann-Heimbach, S., Herms, S., Hoffmann, P., Frank, J., Foo, J.C., Treutlein, J., Witt, S.H., Cichon, S., Kogevinas, M., Stahl, E.A., Breen, G., Forstner, A.J., McQuillin, A., Ripke, S., Trubetskoy, V., Mattheisen, M., Wang, Y., Coleman, J.R.I., Gaspar, H. A., de Leeuw, C.A., Steinberg, S., Pavlides, J.M.W., Trzaskowski, M., Pers, T.H., Holmans, P.A., Abbott, L., Agerbo, E., Akil, H., Albani, D., Alliey-Rodriguez, N., Als,

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B., Frisén, L., Gade, K., Gage, D., Garnham, J., Giambartolomei, C., Pedersen, M.G., Goldstein, J., Gordon, S.D., Gordon-Smith, K., Green, E.K., Green, M.J., Greenwood, T.A., Grove, J., Guan, W., Parra, J.G., Hamshere, M.L., Hautzinger, M., Heilbronner, U., Herms, S., Hipolito, M., Hoffmann, P., Holland, D., Huckins, L., Jamain, S., Johnson, J.S., Juréus, A., Kandaswamy, R., Karlsson, R., Kennedy, J.L., Kittel-Schneider, S., Knowles, J.A., Kogevinas, M., Koller, A.C., Kupka, R., Lavebratt, C., Lawrence, J., Lawson, W.B., Leber, M., Lee, P.H., Levy, S.E., Li, J.Z., Liu, C., Lucae, S., Maaser, A., MacIntyre, D.J., Mahon, P.B., Maier, W., Martinsson, L., McCarroll, S., McGuffin, P., McInnis, M.G., McKay, J.D., Medeiros, H., Medland, S.E., Meng, F., Milani, L., Montgomery, G.W., Morris, D.W., Mühleisen, T.W., Mullins, N., Nguyen, H., Nievergelt, C.M., Adolfsson, A.N., Nwulia, E.A., O'Donovan, C., Loohuis, L.M.O., Ori, A.P.S., Oruc, L., Ösby, U., Perlis, R.H., Perry, A., Pfennig, A., Potash, J.B., Purcell, S.M., Regeer, E.J., Reif, A., Reinbold, C.S., Rice, J.P., Richards, A.L., Rivas, F., Rivera, M., Roussos, P., Ruderfer, D.M., Ryu, E., Sánchez-Mora, C., Schatzberg, A. F., Scheftner, W.A., Schork, N.J., Weickert, C.S., Shehktman, T., Shilling, P.D., Sigurdsson, E., Slaney, C., Smeland, O.B., Sobell, J.L., Hansen, C.S., Spijker, A.T., Clair, D.S., Steffens, M., Strauss, J.S., Streit, F., Strohmaier, J., Szelinger, S., Thompson, R.C., EThorgeirsson, T., Treutlein, J., Vedde, H., Wang, W., Watson, S.J., Weickert, T.W., Witt, S.H., Xi, S., Xu, W., Young, A.H., Zandi, P., Zhang, P., Zollner, S., Adolfsson, R., Agartz, I., Alda, M., Backlund, L., Baune, B.T., Bellivier, F., Berrettini, W.H., Biernacka, J.M., Blackwood, D.H.R., Boehnke, M., Børglum, A.D., Corvin, A., Craddock, Nicholas, Daly, M.J., Dannlowski, U., Esko, T., Etain, B., Frye, M., Fullerton, J.M., Gershon, E.S., Gill, M., Goes, F., Grigoroiu-Serbanescu, M., Hauser, J., Hougaard, D.M., Hultman, C.M., Jones, I., Jones, L.A., Kahn, R.S., Kirov, G., Landén, M., Leboyer, M., Lewis, C.M., Li, Q.S., Lissowska, J., Martin, N.G., Mayoral, Fermin, McElroy, S.L., McIntosh, A.M., McMahon, F.J., Melle, I., Metspalu, A., Mitchell, P.B., Morken, G., Mors, O., Mortensen, P.B., Müller-Myhsok, B., Myers, R.M., Neale, B.M., Nimgaonkar, V., Nordentoft, M., Nöthen, M.M., O'Donovan, M.C., Oedegaard, K.J., Owen, M.J., Paciga, S.A., Pato, C., Pato, M.T., Posthuma, D., Ramos-Quiroga, J.A., Ribasés, M., Rietschel, M., Rouleau, G.A., Schalling, M., Schofield, P.R., Schulze, T.G., Serretti, A., Smoller, J.W., Stefansson, H., Stefansson, K., Stordal, E., Sullivan, P.F., Turecki, G., Vaaler, A.E., Vieta, E., Vincent, J.B., Werge, T., Nurnberger, J.I., Wray, N.R., Florio, A. Di, Edenberg, H.J., Cichon, S., Ophoff, R.A., Scott, L.J., Andreassen, O.A., Kelsoe, J., Sklar, P., Wray, N.R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E.M., Abdellaoui, A., Adams, M.J., Agerbo, E., Air, T.M., Andlauer, T.F.M., Bacanu, S.A., Bækvad-Hansen, M., Beekman, A.T.F., Bigdeli, T.B., Binder, E.B., Bryois, J., Buttenschøn, H.N., Bybjerg-Grauholm, J., Cai, N., Castelao, E., Christensen, J.H., Clarke, T.K., Coleman, J.R.I., Colodro-Conde, L., Couvy-Duchesne, B., Craddock, Nick, Crawford, G.E., Davies, G., Deary, I.J., Degenhardt, F., Derks, E.M., Direk, N., Dolan, C. V., Dunn, E.C., Eley, T.C., Escott-Price, V., Kiadeh, F.F.H., Finucane, H.K., Foo, J.C., Forstner, A.J., Frank, J., Gaspar, H.A., Gill, M., Goes, F.S., Gordon, S.D., Grove, J., Hall, L.S., Hansen, C.S., Hansen, T. F., Herms, S., Hickie, I.B., Hoffmann, P., Homuth, G., Horn, C., Hottenga, J.J., Hougaard, D.M., Howard, D.M., Ising, M., Jansen, R., Jones, I., Jones, L.A., Jorgenson, E., Knowles, J.A., Kohane, I.S., Kraft, J., Kretzschmar, W.W., Kutalik, Z., Li, Y., Lind, P.A., MacIntyre, D.J., MacKinnon, D.F., Maier, R.M., Maier, W., Marchini, J., Mbarek, H., McGrath, P., McGuffin, P., Medland, S.E., Mehta, D., Middeldorp, C.M., Mihailov, E., Milaneschi, Y., Milani, L., Mondimore, F.M., Montgomery, G.W., Mostafavi, S., Mullins, N., Nauck, M., Ng, B., Nivard, M.G., Nyholt, D.R., O'Reilly, P.F., Oskarsson, H., Owen, M.J., Painter, J.N., Pedersen, C.B., Pedersen, M.G., Peterson, R.E., Pettersson, E., Peyrot, W.J., Pistis, G., Posthuma, D., Quiroz, J.A., Qvist, P., Rice, J.P., Riley, B.P., Rivera, M., Mirza, S.S., Schoevers, R., Schulte, E.C., Shen, L., Shi, J., Shyn, S.I., Sigurdsson, E., Sinnamon, G.C.B., Smit, J. H., Smith, D.J., Stefansson, H., Steinberg, S., Streit, F., Strohmaier, J., Tansey, K.E., Teismann, H., Teumer, A., Thompson, W., Thomson, P.A., Thorgeirsson, T.E., Traylor, M., Treutlein, J., Trubetskoy, V., Uitterlinden, A.G., Umbricht, D., Van der Auwera, S., van Hemert, A.M., Viktorin, A., Visscher, P.M., Wang, Y., Webb, B.T., Weinsheimer, S.M., Wellmann, J., Willemsen, G., Witt, S.H., Wu, Y., Xi, H.S., Yang, J., Zhang, F., Arolt, V., Baune, B.T., Berger, K., Boomsma, D.I., Cichon, S., Dannlowski, U., de Geus, E.J.C., DePaulo, J.R., Domenici, E., Domschke, K., Esko, T., Grabe, H.J., Hamilton, S.P., Hayward, C., Heath, A.C., Kendler, K.S., Kloiber, S., Lewis, G., Li, Q.S., Lucae, S., Madden, P.A.F., Magnusson, P.K., Martin, N.G., McIntosh, A.M., Metspalu, A., Mors, O., Mortensen, P.B., Müller-Myhsok, B., Nordentoft, M., Nöthen, M.M., O'Donovan, M.C., Paciga, S.A., Pedersen, N.L., Penninx, B.W.J.H., Perlis, R.H., Porteous, D.J., Potash, J.B., Preisig, M., Rietschel, M., Schaefer, C., Schulze, T.G., Smoller, J.W., Stefansson, K., Tiemeier, H., Uher, R., Völzke, H., Weissman, M.M., Werge, T., Lewis, C.M., Levinson, D.F., Breen, G., Børglum, A.D., Sullivan, P.F., Rivas, F., Mayoral, Fermín, Müller-Myhsok, B., Forstner, A.J., Nöthen, M.M., Rietschel, M., 2019. Bipolar multiplex families have an increased burden of common risk variants for psychiatric disorders. Mol. Psychiatry 468975. https://doi.org/10.1038/s41380-019-0558-2.

Andlauer, T.F.M., Nöthen, M.M., 2020. Polygenic scores for psychiatric disease: from research tool to clinical application. Medizinische Genet. 32, 39–45. https://doi.org/10.1515/medgen-2020-2006.

Ansell, E.B., Rando, K., Tuit, K., Guarnaccia, J., Sinha, R., 2012. Cumulative adversity and smaller gray matter volume in medial prefrontal, anterior cingulate, and insula regions. Biol. Psychiatry 72, 57–64. https://doi.org/10.1016/j.biopsych.2011.11.022.

Arnone, D., McIntosh, A.M., Ebmeier, K.P., Munafò, M.R., Anderson, I.M., 2012. Magnetic resonance imaging studies in unipolar depression: Systematic review and meta-regression analyses. Eur. Neuropsychopharmacol. 22, 1–16. https://doi.org/10.1016/j.euroneuro.2011.05.003.

Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. Neuroimage 38, 95–113. https://doi.org/10.1016/j.neuroimage.2007.07.007.

Ashburner, J., Friston, K.J., 2005. Unified segmentation. Neuroimage 26, 839–851. https://doi.org/10.1016/j.neuroimage.2005.02.018.

Beck, A., Steer, R., Brown, G., 1996. Beck Depression Inventory, 2nd ed. Manual. The Psychological Corporation, San Antonio.

Besteher, B., Gaser, C., Nenadić, I., 2019. Brain Structure and subclinical symptoms: A dimensional perspective of psychopathology in the depression and anxiety spectrum. Neuropsychobiology 79, 270–283. https://doi.org/10.1159/000501024.

Brühl, A.B., Delsignore, A., Komossa, K., Weidt, S., 2014. Neuroimaging in social anxiety disorder-A meta-analytic review resulting in a new neurofunctional model. Neurosci. Biobehav. Rev. 47, 260–280. https://doi.org/10.1016/j.neubiorev.2014.08.003.

Chang, C.C., Chow, C.C., Tellier, L.C.A.M., Vattikuti, S., Purcell, S.M., Lee, J.J., 2015. Second-generation PLINK: Rising to the challenge of larger and richer datasets. Gigascience 4, 7. https://doi.org/10.1186/s13742-015-0047-8.

Cohen, S., Kamarck, T., Mermelstein, R., 1983. A global measure of perceived stress. J. Health Soc. Behav. 24, 385–396. https://doi.org/10.2307/2136404.

Cohen, S., Murphy, M.L.M., Prather, A.A., 2019. Ten surprising facts about stressful life events and disease risk. Annu. Rev. Psychol. 70, 577–597. https://doi.org/10.1146/annurev-psych-010418-102857.

Costa, P.T., McCrae, R.R., 1992. Revised NEO personality inventory (NEO-PI-R) and NEO five-factor inventory (NEO-FFI). Psychological Assessment Resources, Odessa, FL.

Delaneau, O., Zagury, J.F., Marchini, J., 2013. Improved whole-chromosome phasing for disease and population genetic studies. Nat. Methods 10, 5–6. https://doi.org/10.1038/nmeth.2307.

Fettes, P., Schulze, L., Downar, J., 2017. Cortico-striatal-thalamic loop circuits of the orbitofrontal cortex: Promising therapeutic targets in psychiatric illness. Front. Syst. Neurosci. 11, 25. https://doi.org/10.3389/fnsys.2017.00025.

Ge, T., Chen, C.Y., Ni, Y., Feng, Y.C.A., Smoller, J.W., 2019. Polygenic prediction via Bayesian regression and continuous shrinkage priors. Nat. Commun. 10, 1776. https://doi.org/10.1038/s41467-019-09718-5.

Howie, B., Fuchsberger, C., Stephens, M., Marchini, J., Abecasis, G.R., 2012. Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. Nat. Genet. 44, 955–959. https://doi.org/10.1038/ng.2354.

Howie, B.N., Donnelly, P., Marchini, J., 2009. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS Genet. 5, e1000529 https://doi.org/10.1371/journal.pgen.1000529.

Ingram, R.E., Luxton, D.D., 2005. Vulnerability-stress models. In: Hankin, B.L., Abela, J. R.Z. (Eds.), Development of Psychopathology: A Vulnerability-Stress Perspective. Sage, Thousand Oaks, pp. 32–46 https://doi.org/10.4135/9781452231655.n2.

Kircher, T., Wöhr, M., Nenadic, I., Schwarting, R., Schratt, G., Alferink, J., Culmsee, C., Garn, H., Hahn, T., Müller-Myhsok, B., Dempfle, A., Hahmann, M., Jansen, A., Pfefferle, P., Renz, H., Rietschel, M., Witt, S.H., Nöthen, M., Krug, A., Dannlowski, U., 2019. Neurobiology of the major psychoses: a translational perspective on brain structure and function—the FOR2107 consortium. Eur. Arch. Psychiatry Clin. Neurosci. 269, 949–962. https://doi.org/10.1007/s00406-018-0943-x.

Köhler, C.A., Evangelou, E., Stubbs, B., Solmi, M., Veronese, N., Belbasis, L., Bortolato, B., Melo, M.C.A., Coelho, C.A., Fernandes, B.S., Olfson, M., Ioannidis, J.P. A., Carvalho, A.F., 2018. Mapping risk factors for depression across the lifespan: An umbrella review of evidence from meta-analyses and Mendelian randomization studies. J. Psychiatr. Res. 103, 189–207. https://doi.org/10.1016/j.jpsychires.2018.05.020.

Krug, A., Wöhr, M., Seffer, D., Rippberger, H., Sungur, A.Ö., Dietsche, B., Stein, F., Sivalingam, S., Forstner, A.J., Witt, S.H., Dukal, H., Streit, F., Maaser, A., Heilmann-Heimbach, S., Andlauer, T.F.M., Herms, S., Hoffmann, P., Rietschel, M., Nöthen, M. M., Lackinger, M., Schratt, G., Koch, M., Schwarting, R.K.W., Kircher, T., 2020. Advanced paternal age as a risk factor for neurodevelopmental disorders: a translational study. Mol. Autism 11, 54. https://doi.org/10.1186/s13229-020-00345-2.

Kuhn, M., Scharfenort, R., Schümann, D., Schiele, M.A., Münsterkötter, A.L., Deckert, J., Domschke, K., Haaker, J., Kalisch, R., Pauli, P., Reif, A., Romanos, M., Zwanzger, P., Lonsdorf, T.B., 2016. Mismatch or allostatic load? Timing of life adversity differentially shapes gray matter volume and anxious temperament. Soc. Cogn. Affect. Neurosci. 11, 537–547. https://doi.org/10.1093/scan/nsv137.

Kurth, F., Luders, E., Gaser, C., 2015. Voxel-Based Morphometry. Brain Mapp. An Encycl. Ref. 1, 345–349. https://doi.org/10.1016/B978-0-12-397025-1.00304-3.

Lederbogen, F., Kirsch, P., Haddad, L., Streit, F., Tost, H., Schuch, P., Wüst, S., Pruessner, J.C., Rietschel, M., Deuschle, M., Meyer-Lindenberg, A., 2011. City living and urban upbringing affect neural social stress processing in humans. Nature 474, 498–501. https://doi.org/10.1038/nature10190.

Lehrl, S., 2005. Mehrfachwahl-Wortschatz-Intelligenztest MWT-B. Straube, Erlangen.

Li, H., Li, W., Wei, D., Chen, Q., Jackson, T., Zhang, Q., Qiu, J., 2014. Examining brain structures associated with perceived stress in a large sample of young adults via voxel-based morphometry. Neuroimage 92, 1–7. https://doi.org/10.1016/j.neuroimage.2014.01.044.

Luciano, M., Hagenaars, S.P., Davies, G., Hill, W.D., Clarke, T.K., Shirali, M., Harris, S.E., Marioni, R.E., Liewald, D.C., Fawns-Ritchie, C., Adams, M.J., Howard, D.M., Lewis, C.M., Gale, C.R., McIntosh, A.M., Deary, I.J., 2018. Association analysis in over 329,000 individuals identifies 116 independent variants influencing neuroticism. Nat. Genet. 50, 6–11. https://doi.org/10.1038/s41588-017-0013-8.

McEwen, B.S., 2007. Physiology and neurobiology of stress and adaptation: Central role of the brain. Physiol. Rev. 87, 873–904. https://doi.org/10.1152/physrev.00041.2006.

Menzies, L., Chamberlain, S.R., Laird, A.R., Thelen, S.M., Sahakian, B.J., Bullmore, E.T., 2008. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: The orbitofronto-striatal model revisited. Neurosci. Biobehav. Rev. 32, 525–549. https://doi.org/10.1016/j.neubiorev.2007.09.005.

Mikolajczak, M., Luminet, O., 2008. Trait emotional intelligence and the cognitive appraisal of stressful events: An exploratory study. Pers. Individ. Dif. 44, 1445–1453. https://doi.org/10.1016/j.paid.2007.12.012.

Miller, B., Messias, E., Miettunen, J., Alaräisänen, A., Järvelin, M.R., Koponen, H., Räsänen, P., Isohanni, M., Kirkpatrick, B., 2011. Meta-analysis of paternal age and schizophrenia risk in male versus female offspring. Schizophr. Bull. 37, 1039–1047. https://doi.org/10.1093/schbul/sbq011.

Monroe, S.M., 2008. Modern approaches to conceptualizing and measuring human life stress. Annu. Rev. Clin. Psychol. 4, 33–52. https://doi.org/10.1146/annurev.clinpsy.4.022007.141207.

Nakamura, M., Nestor, P.G., Shenton, M.E., 2020. Orbitofrontal sulcogyral pattern as a transdiagnostic trait marker of early neurodevelopment in the social brain. Clin. EEG Neurosci. 51, 275–284. https://doi.org/10.1177/1550059420904180.

Norbeck, J.S., 1984. Modification of Life Event Questionnaires for Use with Female Respondents. Res. Nurs. Health 7, 61–71. https://doi.org/10.1002/nur.4770070110.

Papagni, S.A., Benetti, S., Arulanantham, S., McCrory, E., McGuire, P., Mechelli, A., 2011. Effects of stressful life events on human brain structure: A longitudinal voxel-based morphometry study. Stress 14, 227–232. https://doi.org/10.3109/10253890.2010.522279.

Porcelli, A.J., Lewis, A.H., Delgado, M.R., 2012. Acute stress influences neural circuits of reward processing. Front. Neurosci. 6, 157. https://doi.org/10.3389/fnins.2012.00157.

Proudfoot, J., Whitton, A., Parker, G., Doran, J., Manicavasagar, V., Delmas, K., 2012. Triggers of mania and depression in young adults with bipolar disorder. J. Affect. Disord. 143, 196–202. https://doi.org/10.1016/j.jad.2012.05.052.

Rajapakse, J.C., Giedd, J.N., Rapoport, J.L., 1997. Statistical approach to segmentation of single-channel cerebral mr images. IEEE Trans. Med. Imaging 16, 176–186. https://doi.org/10.1109/42.563663.

Schneider, T.R., Rench, T.A., Lyons, J.B., Riffle, R.R., 2012. The influence of neuroticism, extraversion and openness on stress responses. Stress Heal. 28, 102–110. https://doi.org/10.1002/smi.1409.

Sekiguchi, A., Sugiura, M., Taki, Y., Kotozaki, Y., Nouchi, R., Takeuchi, H., Araki, T., Hanawa, S., Nakagawa, S., Miyauchi, C.M., Sakuma, A., Kawashima, R., 2013. Brain structural changes as vulnerability factors and acquired signs of post-earthquake stress. Mol. Psychiatry 18, 618–623. https://doi.org/10.1038/mp.2012.51.

Seo, D., Tsou, K.A., Ansell, E.B., Potenza, M.N., Sinha, R., 2014. Cumulative Adversity sensitizes neural response to acute stress: Association with health symptoms. Neuropsychopharmacology 39, 670–680. https://doi.org/10.1038/npp.2013.250.

Spielberger, C.D., Gorsuch, R.L., Lushene, R.E., 1970. Manual for the State-Trait Anxiety Inventory (Self-evaluation questionnaire). Consulting Psychologists Press, Palo Alto, CA.

Suh, J.S., Schneider, M.A., Minuzzi, L., MacQueen, G.M., Strother, S.C., Kennedy, S.H., Frey, B.N., 2019. Cortical thickness in major depressive disorder: A systematic review and meta-analysis. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 88, 287–302. https://doi.org/10.1016/j.pnpbp.2018.08.008.

Tadayon, E., Pascual-Leone, A., Santarnecchi, E., 2020. Differential Contribution of Cortical Thickness, Surface Area, and Gyrification to Fluid and Crystallized Intelligence. Cereb. cortex 30, 215–225. https://doi.org/10.1093/cercor/bhz082.

Tohka, J., Zijdenbos, A., Evans, A., 2004. Fast and robust parameter estimation for statistical partial volume models in brain MRI. Neuroimage 23, 84–97. https://doi.org/10.1016/j.neuroimage.2004.05.007.

Uher, R., Zwicker, A., 2017. Etiology in psychiatry: embracing the reality of poly-gene-environmental causation of mental illness. World Psychiatry 16, 121–129. https://doi.org/10.1002/wps.20436.

Vogelbacher, C., Möbius, T.W.D., Sommer, J., Schuster, V., Dannlowski, U., Kircher, T., Dempfle, A., Jansen, A., Bopp, M.H.A., 2018. The Marburg-Münster Affective Disorders Cohort Study (MACS): A quality assurance protocol for MR neuroimaging data. Neuroimage 172, 450–460. https://doi.org/10.1016/j.neuroimage.2018.01.079.

Wingenfeld, K., Spitzer, C., Mensebach, C., Grabe, H., Hill, A., Gast, U., Schlosser, N., Höpp, H., Beblo, T., Driessen, M., 2010. The German version of the childhood trauma questionnaire (CTQ): preliminary psychometric properties. Psychother. Psychosom. Med. Psychol. 60, 442–450. https://doi.org/10.1055/s-0030-1253494.

Wittchen, H.-U., Wunderlich, U., Gruschitz, S., Zaudig, M., 1997. Strukturiertes Klinisches Interview für DSM-IV, Achse I (SKID-I). Hogrefe, Göttingen.

Wright, C.I., Williams, D., Feczko, E., Barrett, L.F., Dickerson, B.C., Schwartz, C.E., Wedig, M.M., 2006. Neuroanatomical correlates of extraversion and neuroticism. Cereb. Cortex 16, 1809–1819. https://doi.org/10.1093/cercor/bhj118.