The resilient emotional brain: a scoping review of mPFC and limbic structure and function in resilient adults with a history of childhood maltreatment

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Abstract

Childhood Maltreatment (CM) is one of the strongest predictors of adult mental illness, though not all adults with CM develop psychopathology. Here, we describe the structure and function of emotional brain regions that may contribute to resilient functioning after CM. We review studies that report medial prefrontal cortex (mPFC), amygdala and hippocampus ('limbic regions') structure, function, and/or connections, in resilient (i.e., adults reporting CM without psychopathology) vs. vulnerable (i.e., adults reporting CM with psychopathology), or healthy adults (adults without CM with no psychopathology). We find that resilient adults have larger hippocampal grey and white matter volume, and increased connectivity between the central executive network and limbic regions. In addition, resilient adults have improved ability to regulate emotions through mPFC-limbic downregulation, lower hippocampal activation to emotional faces, and increased amygdala habituation to stress. We highlight the need for longitudinal designs that examine resilient functioning across domains and consider gender, type, timing, nature of CM assessments and further stressors, in order to further improve our understanding of the role of the emotional brain in resilient functioning after CM.

Keywords: Childhood maltreatment; abuse; neglect; neurobiology; resilience; psychopathology; brain structure; brain function

1. Introduction

Childhood maltreatment (CM) comprises; *‘any act, or series of acts by a parent or caregiver that results in harm, potential for harm or threat of harm to a child’* and includes abuse and neglect (1). CM negatively affects emotional, social and physical wellbeing and mental health (2-6). Therefore, improved understanding of neurobiological factors that may help individuals retain or regain good mental health in the aftermath of CM (‘resilience’) is crucial. Resilience is a multi-faceted time-dependent construct where one’s functioning on a range of psychological domains is considered resilient if it is better than others with similar CM experiences (7, 8). Understanding the neural correlates of such resilient functioning after CM may reveal novel targets for prevention and intervention. Here, we provide the first comprehensive narrative review of neuroimaging findings of resilient functioning in adults with CM. We focus on adults, as the neurobiological mechanisms that confer resilience in response to high stress childhood environments may confer vulnerability in adulthood when the environment is no longer stressful (9). We include grey matter volume in the medial prefrontal cortex (mPFC), hippocampus and amygdala (‘limbic regions’) because of their role in stress reactivity and emotion processing (10, 11) (Figure 1).

[FIGURE 1 ABOUT HERE]

We also investigate white matter tracts, as these connect our regions of interest (ROIs) (Figure 2); the uncinate fasciculus connects the PFC with limbic regions (12), and the cingulum bundle connects frontal, temporal and parietal cortices (13) (Figure 2).

[FIGURE 2 ABOUT HERE]

We further investigate brain functioning during the performance of tasks and at rest to study functional connectivity in resting state networks that include the mPFC and

limbic regions (Figure 3); the salience (SN), default mode (DMN), and central executive networks (CEN). These networks integrate external and internal information in order to direct attention to salient stimuli (SN) (14-16), direct internal cognitive activity (e.g., interoceptive awareness, self-focus) (DMN); and manipulate and maintain information in the context of goal directed behaviours (CEN) (17). Due to the large degree of heterogeneity in study methodology and reporting, a scoping review of these studies, instead of a standardized quality assessment (i.e., meta-analysis), was most appropriate.

[FIGURE 3 ABOUT HERE]

2. Methodology

2.1 Search strategy

In April 2019, we searched PubMed using these keywords for title and abstract:

((childhood AND abuse OR neglect OR maltreatment OR adversities) AND (function OR structure)), and Magnetic Resonance Imaging as a keyword in the text. We included English-language studies only and papers available online ahead of print. This search retrieved 140 studies, and reference lists of these studies were screened for additional studies. Exclusion criteria were: i) papers on children/adolescents (mean age < 18); ii) studies out-of-scope (e.g., hemi-spatial neglect, substance abuse, intimate partner violence); iii) no reported findings in our ROIs, connections and/or networks; and iv) reviews, editorial material, proceeding papers, notes, letters to the editors and meeting abstracts. Full texts and references were screened independently by LML, KS, AS, AA, KI and ALvH. In case of uncertainty, consensus was sought through discussion.

Ultimately, we included 48 studies including 8544 participants (Figure 4), and reported the results of these studies in accordance with the (PRISMA-ScR) checklist for scoping reviews (see Supplemental Material).

[FIGURE 4 ABOUT HERE]

2.3. Strategy of comparisons between groups

We describe results found for the comparison of resilient adults (adult with CM without a current mental health disorder with (1) adults reporting CM with current psychopathology ('vulnerable adults') or (2) adults without psychopathology who report no CM ('healthy adults'). These contrasts provide information whether findings in resilient vs. vulnerable adults represent mechanisms specific to resilient functioning after CM (more/less than vulnerable and healthy adults), or reflect mechanisms that provide good mental health functioning with or without CM (similar to healthy adults). For completeness, we report findings for the comparison vulnerable adults vs. patients who do not report CM ('patients') in the supplemental material.

3. Results

3.1. Study selection and overview of studies

Thirty-one (64.6%) studies included participants with *and* without mental health disorders, or did not specify the mental health of the samples, the remaining 17 examined only healthy adults (35.4 %) (Table S1-3). Studies on patients comprised of current major depression (n=9, 29%), post-traumatic stress (PTSD) (n=3, 9.7%) or *any* mental health disorder (n=19, 61.3%). All neuroimaging was conducted cross-sectionally, although 5 studies embedded this within a prospective design (18-22). Four studies examined only males (22, 23) or females (24, 25), all other studies examined both genders.

The majority of studies assessed CM retrospectively ((n=44, 91.6%); retrospective interview (N=10; 22.8%; 21, 24, 26-33), clinician administered scale (34-36), self-report questionnaire (N=31 70.4%; (71% used the Childhood Trauma

Questionnaire (CTQ; 37))). Four studies assessed CM prospectively (8.4%). Demers et al. (2017) (18) and Jedd et al. (2015) (20) assessed CM through documented Department of Human Services (DHS) records and the Maternal Maltreatment Classification Interview at age 17. Holz et al. (2017) (19) used a parental interview at ages; 3 months, 2, 4, 8 and 11 years, and Jensen et al. (2015) (22) utilized an adversity checklist at age 8, 21, 33, 47, 61, and 73 months.

3.2. Brain structure in resilient adults

3.2.1. Grey matter structure

Eighteen studies examined grey matter volume (GMV), using voxel-based morphometry (VBM) (n=10), which provides an automated quantitative voxel-based distribution of grey and white matter (38), or using volumetric methods (e.g., manually traced ROI analysis or volume quantification using FreeSurfer) (n=8) (Supplementary Table S1).

Medial prefrontal cortex (mPFC)

Four studies examined mPFC GMV differences between resilient and vulnerable adults (Table 1), and did not find significant differences in mPFC GMV of resilient vs. vulnerable adults (31, 39-41). Eight studies compared mPFC GMV in resilient adults vs. healthy adults (Table 1), and reported similar mPFC (39, 42, 43) or smaller mPFC GMV (22, 26, 31, 36, 40).

[INSERT TABLE 1 ABOUT HERE]

Importantly, the largest study (22; n=494) reported reductions in mPFC GMV in resilient adults. In this study CM was measured prospectively in interviews with the mother at multiple time points. Taking into account the quality of the CM assessment

and power of this study, we argue that the current literature suggests that resilient adults may have smaller mPFC GMV when compared to healthy adults, and similar (n.s.) mPFC GMV vs. vulnerable adults. These results are preliminary as based on post-hoc comparisons in small (sub-) samples, which may have had insufficient power to detect effects that truly exist, perhaps leading to false negative findings. Future studies should combine efforts and pool data to provide powerful samples to examine the neural underpinnings of resilience after CM (i.e., see 44).

Smaller mPFC in resilient vs. healthy adults, but similar mPFC in resilient vs. vulnerable, may be suggestive of the idea that CM, and not resilience, is associated with the size of the mPFC. This may be due to the effects of stress on the development of the mPFC as seen in animal models (e.g., 45-47). It may also be that recent stressful life events in both patients, vulnerable and resilient adults contribute to smaller mPFC volume as the subjective experience of chronic stress interacts with adverse life events in predicting greater mPFC reductions (26). CM has a strong link to further negative life events (48), and it is unknown whether such life stressors may indeed provide an explanation for the findings of reduced mPFC after CM in healthy and vulnerable adults. However, our results suggest that mPFC GMV may not be related with resilient functioning after CM.

Hippocampus

Six studies specifically compared resilient to vulnerable adults (Table 2) and reported that resilient adults have larger (24, 27, 41) or similar (no significant differences; n.s.) hippocampal GMV (39, 40, 49). Importantly, Gerritsen et al. (2015) (27) found larger hippocampal GMV in two independent samples (study 1 n=262; study 2 n=636) of resilient vs. vulnerable adults using an interview to assess CM. Interviews are less sensitive to false positive inflation compared to self-report (50). Gerritsen et al. (2015)

(27) were further able to control for many important confounding factors such as age, gender, education level, intracranial volume, smoking status, alcohol intake, diastolic blood pressure, diabetes, and antidepressant use. They also controlled for individual differences in cognitive abilities in their older sample. They found, in both samples that in those with CM, adult patients had a significantly smaller hippocampus with large effect sizes (Hedge's $g = -.47$, 95% CI $-.78$ to $-.16$). Overall, taking into account the differences in sample size, study quality and ability to account for confounds, the available evidence supports the notion that resilient (vs vulnerable) adults have larger hippocampal GMV.

Ten studies examined hippocampal volume in resilient adults vs. healthy adults (Table 2), and reported reduced (40, 51) or similar (n.s.) hippocampal volume (26, 31, 36, 39, 42-44, 52). Especially important is Frodl et al. (44), who combined data from different cohorts ($n=2078$) in a mega-analysis of the effects of CM in depressed and healthy adults and reported similar (n.s.) hippocampal volume in resilient vs. healthy adults.

[INSERT TABLE 2 ABOUT HERE]

Smaller hippocampal GMV may be a vulnerability factor; as it predicted the onset of young adult depression (53), is reported in adults with first onset psychosis (54) MDD (51), and PTSD (55) although, there may be important underlying gender or genotype (56, 57, although see also 58) influences (59, 60). Together, the combined findings suggest that resilient vs. vulnerable adults may have larger hippocampal GMV, and similar hippocampal GMV compared to healthy adults, and thus larger hippocampal volume may aid resilient functioning after CM.

Amygdala

Four studies investigated amygdala GMV in resilient vs. vulnerable adults and found no differences (Table 3; 30, 39-41). Thirteen studies examined amygdala GMV in resilient vs. healthy adults (Table 3) and reported smaller (40), larger (19, 35), or similar/n.s. GMV (26, 30, 31, 36, 39, 41-44, 52).

[INSERT TABLE 3 ABOUT HERE]

This pattern of findings suggests that the amygdala may not be involved in resilient functioning after CM. There are reports that CM is associated with similar (ns.) (32), or smaller amygdala volume in patient samples (54, 59). However, recent meta-analyses did not find amygdala alterations in healthy adults with CM (60, 61), nor in PTSD patients when compared to healthy adults (56). It may be that recent stress, and not CM, induces relatively rapid changes in amygdala volume that normalize when the stressor dissipates (30). Regardless, amygdala volume does not seem to facilitate resilient functioning after CM.

3.2.2. White matter structure

Nine studies examined white matter volume (WMV; n=4) or tract integrity (n=5) in resilient and vulnerable adults and/or healthy adults (Supplementary Table S2).

Four studies yielded similar results to GMV findings (Table S2); one reported that resilient (vs vulnerable) adults show larger hippocampal WMV (49; although this may interact with genotype and/or gender (61)). Meanwhile, studies comparing resilient to healthy adults found no WMV differences or interactions in our ROIs (31, 39, 62).

Five studies used diffusion tensor imaging (DTI) to investigate the integrity of white matter fibres, we report all findings related to resilient adults as many tracts

connect with, or between our ROIs. All studies reported the DTI metric fractional anisotropy (FA) which measures the directionality of diffusion (63, 64), whilst two also reported mean diffusivity (MD; 23, 65) which quantifies free diffusion of water within a voxel. Lower than expected FA (and typically associated higher MD) can index compromised white matter integrity.

One study investigated white matter integrity between 26 resilient and 25 vulnerable adults (Table S2) and showed increased posterior cingulum FA in resilient adults (25), this white matter fibre connects the entorhinal and cingulate cortices, and is implicated in visual memory and self-referential thought. Reduced structural connectivity along this pathway may underlie vulnerability in patients with depression, schizophrenia and PTSD (66, 67). Four studies investigated white matter tracts in resilient vs. healthy adults (Table S2). Three of these studies showed reduced FA in tracts associated with attention and affective control; the cingulum bundle by the posterior tail of the left hippocampus, arcuate fasciculus, and fornix (68), the corpus callosum and corona radiata (65), and the anterior thalamic radiation around the middle frontal gyrus, right inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and the precuneus (23). The last study found no differences in FA in resilient vs. healthy adults but reported an interaction between FA and reaction time to positive stimuli on an affective go/no-go task. Thus, CM may be associated with a distinct brain-behaviour relationship that is related to other determinants of FA than those present in healthy adults (69).

In sum, resilient adults preliminary show larger hippocampal WMV compared to vulnerable adults, and similar (n.s.) hippocampi vs. healthy adults. This in line with the GMV findings and suggest that larger hippocampal volume may aid resilient functioning after CM. Studies investigating white matter tracts tentatively suggest that

resilient adults have increased FA compared to vulnerable adults and decreased FA compared to healthy adults in (parts of) the cingulum tract. Thus, CM may affect the integrity of a tract implicated in self-referential processing. Negative self-referential processing mediates the link between CM and depressive and anxiety symptoms (31). Therefore, white matter integrity of pathways involved in self-referential processing may aid resilient functioning after CM.

3.3 Brain functioning in resilient adults

Twenty-six studies (N=1608) examined brain functioning in resilient adults (Supplementary Table S3).

3.3.1 Brain functioning during tasks

Examining blood oxygen level-dependent (BOLD) fluctuations during task performance allows the exploration of brain responsivity to external stimulation. The studies included used a highly heterogeneous set of tasks which we grouped into: stress reactivity (n=7), face processing (n=11) and emotion processing (n=3).

Stress reactivity

Three studies examined stress reactivity in resilient vs. vulnerable adults (Table S3). Two studies showed similar (n.s.) dorsal mPFC reactivity to social exclusion using the Cyberball task (70), and similar (n.s.) amygdala and mPFC responsivity to emotional conflict using a task where participants were instructed to identify the underlying facial emotion (fearful or happy) while ignoring an overlying emotional distractor (emotion word - “fear” or “happy”) (71). The third study showed that, across repeated stress exposure in response to a mental arithmetic task, resilient vs. vulnerable adults showed increased amygdala habituation and normalized mPFC activity (72).

Four studies compared resilient vs. healthy adults (Table S3). Three found limbic deactivation during the induction of psychological stress using a mental arithmetic challenge under time pressure (73); lower amygdala and subgenual ACC responsivity during fMRI adapted versions of the multi-source interference task (MSIT) and Stroop tasks (74); or increased hippocampal activity using a script-driven individualized imagery method for brief provocation of emotions, acute stress, and anxiety (30). Finally, resilient vs. healthy adults showed increased activation of the hippocampus towards a crying infant during the administration of cortisol (75).

Although preliminary, these results suggest that resilient adults have similar stress responses (vs vulnerable and healthy adults), but possibly more effective stress modulation (increased amygdala habituation and normalized mPFC responses), possibly leading to pervasive blunted responses to cognitively challenging tasks (vs. healthy adults).

Face-processing

Eleven studies examined face processing. Two studies investigated resilient vs. vulnerable adults (Table S3) and showed lower hippocampal activation to fearful and neutral faces (76, 77). Four studies compared resilient vs. healthy adults (Table S3), and showed similar (n.s.) hippocampal activity to fearful, angry and happy faces (32, 77, 78), or increased hippocampal activity to neutral faces (76). Overall, resilient vs. vulnerable adults may show lower hippocampal activation to emotional faces. However, it is unclear whether this represents normalization (similar to healthy adults), or whether this is specific to resilient individuals (better than healthy adults).

The studies examining amygdala reactivity to facial emotion processing paint a mixed picture. Two studies examined resilient vs. vulnerable adults (Table S3), and

show similar amygdala activation to angry, sad, happy, and fearful faces (32) or lower amygdala activation to fearful and neutral faces (77).

Ten studies examined resilient vs. healthy adults and showed similar (n.s.) amygdala activity to fearful, angry, and happy faces (77, 78), increased amygdala activity to angry, sad, happy and/or neutral faces (32, 52, 79, 80) or decreased amygdala responses to fearful and angry facial expressions (19, 81). Increased amygdala reactivity may form a risk factor, as CM (vs. no CM) related (together with decreased superior mPFC) responsivity to negative facial expressions mediated the link between CM and anxiety symptoms in patients and healthy adults (82) and CM related amygdala reactivity has been reported in patients with MDD (83). Alternatively, recent stress, and not CM, may underlie increased amygdala reactivity to emotional faces (78). Thus, lower hippocampal, but not amygdala, activation to emotional faces may aid resilient functioning after CM.

Emotion processing

Three studies examined emotion processing in resilient vs. healthy adults (Table S3). Two utilized an emotion matching task and reported similar (n.s.) activations in our ROIs (18, 20). These studies found increased fronto-limbic functional connectivity during emotion processing related to lower emotion-matching accuracy in resilient vs. healthy adults. Therefore, enhanced fronto-limbic connectivity during emotion processing may represent a vulnerability, possibly due to CM. The only study that examined emotion regulation in resilient vs. healthy adults revealed reduced mPFC and middle temporal gyrus recruitment, and increased amygdala down-regulation and improved emotion regulation to negative emotional material (21). Thus, although increased mPFC-limbic activations may not result in improved emotion processing,

lower activations in these regions may reflect improved modulatory responses that result in improved emotion regulation capacity in resilient adults.

3.3.2 Brain functioning at rest

Resting state functional connectivity (RSFC) allows the exploration of activity in the absence of external stimulation between anatomically remote brain regions or, in other words, the level of functional connectivity between regions also described as ‘networks’ (84). Five studies (Table S3) examined RSFC in resilient adults in networks involved in regulating emotions; the limbic, salience (SN), central executive (CEN) and Default mode (DMN) networks (85, 86). Whereas the limbic and SN responses represent bottom-up salience reactivity, the CEN, consisting of prefrontal regions such as the dorsolateral prefrontal cortex (DLPFC) exerts top-down regulation of limbic systems (87, 88).

Four studies (Table S3) investigated resilient vs. vulnerable adults. Three studies reported enhanced connectivity between the SN (i.e., dorsal ACC) and limbic areas (e.g., thalamus, lingual gyrus) in resilient adults (28, 33, 89). The dorsal ACC aids cognitive control processes such as attention control (90), conflict monitoring (91, 92) and error detection (93, 94). The fourth study showed a positive association between psychological growth (i.e. self-reported degree of positive change following adverse experiences) and RSFC between a prospective or working memory area within the CEN; the superior parietal lobule and supramarginal gyrus (34). The supramarginal gyrus is involved in reasoning about the mental states of others, which is critical in social interactions (95). Therefore, increased connectivity and flexibility between the SN and subcortical regions and within the CEN and the supramarginal gyrus may aid resilient functioning after CM.

One study investigated resting state DMN connectivity in resilient vs. healthy adults and showed decreased DMN connectivity, and trend-level increases in connectivity between the mPFC and the amygdala (96). Decreased connectivity in the DMN is reported in stress related psychiatric disorders including PTSD (97), major depressive disorder (98, 99), and schizophrenia (100, 101), and may underlie disturbances in self-referential processing observed in these populations. Overall, resilient adults may benefit from stronger connectivity with cognitive control and social interactions areas and decreased connectivity to self-referential processing areas.

4. Discussion

We reviewed the literature to examine the neural mechanisms that aid resilient functioning after CM. Resilient (vs vulnerable) adults show increased hippocampal GMV and WMV, increased FA in the posterior cingulum and RSFC between the SN and limbic regions. In addition, there is preliminary support that resilient vs. healthy adults show improved ability to regulate emotions, dampen threat processing and habituate stress responses, potentially through stronger CEN-limbic connectivity, lower hippocampal activation to emotional faces and increased amygdala habituation to stress.

We reviewed the literature as comprehensively as possible, however, this is not a systematic review and we did not include grey literature. The 48 studies included showed substantial heterogeneity in methods used (e.g., differences in scanner spatial resolution, manual vs. automated segmentation, ROIs vs. whole-brain). Combined with the degree of flexibility that exists in pre-processing and analysis of neuroimaging data and the pressure to publish novel findings, this may account for the heterogeneity in reported findings. A quantitative integration of available evidence would be in order to account for potential publication bias. However, due to the large number of studies

reporting null findings without statistics (e.g., ‘*no main effect of CM*’, ‘*no CM x diagnosis interactions were found*’), and differential methodological approaches used, we did not consider it feasible to conduct a meta-analysis of the studies described. To aid future meta-analyses we urge researchers to report all statistics, including null findings, according to best practice approaches (e.g., 102).

This review is preliminary for the following reasons. We identified resilient adults as those with a history of CM that were free from (current or lifetime) psychopathology (see supplemental Tables S1-S3). However, CM negatively impacts functioning across a range of domains, including personality, academic and social functioning, and the absence of a mental health disorder does not indicate resilient functioning on all those domains. Therefore, future studies examining resilient functioning after CM should capture functioning across social, emotional and cognitive domains (8, 103).

The majority of studies included assessed CM using retrospective self-report questionnaires (70.4% of all studies), and patients may over report CM (104). Still, it is a contested issue whether this invalidates retrospective approaches (105) as reduced reporting in healthy populations may equally bias retrospective reports (106). Moreover, retrospective and prospective reporting capture largely non-overlapping groups of individuals (107, 108). Regardless, the neuroimaging literature to-date covers mostly the group characterized by retrospectively reported CM. Few studies reviewed here were able to address reporting biases by employing prospective longitudinal designs (109). Such prospective studies are especially important here, as resilience is dynamic and may change over time (7, 110). In addition, our focus on adults precluded the investigation of resilience across development. Future longitudinal designs may provide insights into whether the neurobiological characteristics that facilitate resilient

functioning after CM are similar or distinct across time, represent adaptations to stressful environments, or reflect pre-existing resilience factors in resilient individuals.

CM is highly correlated with further stress, and such recent stress may serve as an alternative explanation for observed brain findings (e.g., 30, 35) and only some studies were able to control for recent stress (e.g., 22). Finally, most studies examined multiple types of CM together, using self-report in adulthood. Therefore, we were unable to investigate whether the neurobiological mechanisms of resilient functioning after CM depend on the type and timing of CM, whilst this may differentially affect neurobiology (111-113). Future studies should examine the neurobiological factors and mechanisms that facilitate resilient functioning in conjunction with the type and timing of CM.

Future studies may benefit from using graph theory approaches to examine the brain as a complex network of interconnected regions, where important regions, or ‘hubs’, are highly connected to other hubs, as well as with adjacent regions (114). To date, two studies reported CM related alteration to global and regional network architecture examined CM related structural brain networks (115, 116). In addition, resilient *and* vulnerable adults had comparable abnormalities in global network architecture but differed from each other in degree centrality (i.e., resilient individuals had lower degree centrality in a small subset of nodes, including the amygdala) (115). Amygdala hyperactivity to threat is one of the most consistent findings in maltreated adults (e.g., 79, 80). Therefore, reduced amygdala degree centrality could be a compensatory adaptation that aids resilient functioning after CM.

Numerous studies have reported gender differences in structural (e.g., 60, 61, 117-119) and functional alterations after CM (e.g., 120). Therefore, future studies

should investigate whether the neurobiological basis of resilient functioning after CM is similar or distinct in males vs. females.

The directionality of the associations between CM and mental health disorders are unknown. Due to the very limited number of studies specifically examining CM effects within patient populations (see Tables S1-3), we were unable to investigate whether reported findings represent scarring due to mental health disorders, and not CM. However, one would not expect to find (similar) CM effects within patient, or healthy populations. CM has been associated with worse cognitive function and smaller amygdala volume in first-episode psychosis (57), and increased right amygdala response to sad faces in patients with depression (82). Likewise, we showed that CM is associated with functional and structural changes, including increased amygdala responsivity, in the brain in healthy adults without any history of psychiatric disorders (see also; 79, 121). Regardless, future studies should investigate whether CM effects represent mental health scarring, or vice versa.

We present a synthesis of available evidence on the role of the emotional brain in resilient adult functioning after CM. We suggest that resilient vs. vulnerable functioning after CM may be facilitated by larger hippocampal GMV and WMV, increased FA in the posterior cingulum, and positive RSFC connectivity between the CEN and limbic regions. In addition, resilient vs. healthy adults may have improved ability to adequately regulate emotions, dampen threat processing and habituate to chronic stress, facilitated by mPFC-limbic downregulation, lower hippocampal activation to emotional facial expressions, and increased amygdala habituation to stress. We highlight the need for further longitudinal studies that examine resilient functioning across a range of domains, and take into account gender, type, timing, nature of CM assessments, further stress experiences, and that examine brain networks. We hope to

fuel further research that will promote our understanding of the role of the emotional brain in facilitating resilient functioning in adults who have experienced CM.

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Declaration of interest

The authors have no declaration of any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, this work.

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Figure captions

Figure 1. Regions of interest included in the review. The figure presents the medial prefrontal cortex (mPFC) (light pink), hippocampus (light blue) and amygdala (fuchsia). The regions of interest were bilaterally defined using the AAL toolbox implemented in the Wake Forest University (WFU)-Pickatlas (122) and visualised in BrainNet Viewer (<http://www.nitrc.org/projects/bnv/>) (123). The mPFC included the dorsomedial and ventromedial prefrontal cortex, and the anterior cingulate cortex (ACC). L=Left; R=Right.

Figure 2. White matter tracts regions of interest included in the review. The figure presents the uncinate fasciculus white matter tract (yellow) which connects the frontal and limbic regions and the cingulum white matter tract (green), which connects frontal, temporal and parietal cortices. The white matter tracts were visualised using a browser-based tool for visualization and analysis of diffusion MRI data (<http://YeatmanLab.github.io/AFQBrowser-demo>) (124). L=Left; R=Right.

Figure 3. Networks included in the review. The figure presents the salience (pink), central executive (blue) and default mode networks (orange). The networks were created using the coordinates included in Power et al. (2011) (125) and visualised in BrainNet Viewer (<http://www.nitrc.org/projects/bnv/>) (123). L=Left; R=Right.

Figure 4. Flowchart of literature search. The systematic search was performed in April 2019 on Medline (PubMed). Exclusion criteria were: i) papers that included children or adolescents (mean age of the sample <18 years); ii) studies of clinical samples only, iii) studies out-of-scope (e.g., relating to hemi-spatial neglect, substance abuse or intimate partner violence); iv) studies that did not report findings in our ROIs and/or networks; v) reviews, editorial material, proceeding papers, notes, letters to the editors and meeting abstracts. Please note that some studies in the final set examined more than one brain area included in the final analysis.

Table 1. mPFC volume in resilient adults

Resilient vs. vulnerable adults					
No significant differences or no CM * diagnosis interaction	Chaney et al. (2014) (39) n=30, M, W+R, S, MF	Opel et al. (2016) (40) n=40, M, W+R, S, MF	van Harmelen et al. (2010) (31) n=84, M, W+R, I, MF	Saleh et al. (2017) (41) n=42, M, R, S, M/F	
Resilient vs. healthy adults					
No significant differences	Chaney et al. (2014) (39) n=46, M, W+R, S, M/F	Tomoda et al. (2011) (42) n=40, H, W, S, M/F	Yang et al. (2017) (43) n=84, M, W, S, M/F		
Smaller mPFC volume in resilient adults	Ansell et al. (2012) (26) n=103, H, W, I, M/F	Jensen et al. (2015) (22) n=494, M, R, I*, Ma	Opel et al. (2016) (40) n=36/40, M, W+R, S, M/F	Tomoda et al. (2009) (36) n=45, H, W, I+S, M/F	van Harmelen et al. (2010) (31) n=53, M, W+R, I, M/F

H=Healthy Sample; I=Interview to assess childhood maltreatment; M=Mixed sample; Ma=Male; M/F=Male and female; n=Total number of participants in the contrast of interest (not the entire sample of the study); R=ROI analysis; S=Self-report to assess childhood maltreatment; W=Whole-brain analysis; *Prospective assessment of childhood maltreatment, all others used retrospective assessments of childhood maltreatment.

Table 2. Hippocampal GM volume in resilient adults

Resilient vs. vulnerable adults								
No significant differences or no CM * diagnosis interaction	Chaney et al. (2014) (39) n=30, M, W+R, S, M/F	Frodl et al. (2010a) (49) n=44, M, W+R, S, M/F	Opel et al. (2016) (40) n=40, M, W+R, S, M/F					
Larger hippocampal volume in resilient adults	Bremner et al. (2003) (24) n=22, M, W+R, I, F	Gerritsen et al. (2015) (27); Sample 1 n=262, M, R, I, M/F	Gerritsen et al. (2015) (27); Sample 2 n=636, M, R, I, M/F	Saleh et al. (2017) (41) n=42, M, R, S, M/F				
Resilient vs. healthy adults								
No significant differences or no CM * diagnosis interaction	Ansell et al. (2012) (26) n=103, H, W, I, M/F	Chaney et al. (2014) (39) n=46, M, W+R, S, M/F	Dannlowski et al. (2016) (52) n=309, M, R, S, M/F	Frodl et al. (2017) (44) n=2078, M, R, S, M/F	Tomoda et al. (2009) (36) n=45, H, W, S, M/F	Tomoda et al. (2011) (42) n=40, H, W, S, M/F	van Harmelen et al. (2010) (31) n=53, M, W+R, I, M/F	Yang et al. (2017) (43) n=84, M, W, S, M/F
Smaller hippocampal volume in resilient adults	Opel et al. (2014) (51) n=85, M, W+R, S, M/F	Opel et al. (2016) (40) n=36/40, M, W+R, S, M/F						

H=Healthy Sample; F=Female; I=Interview to assess childhood maltreatment; M=Mixed sample; M/F=Male and female; n=Total number of participants in the contrast of interest (not the entire sample of the study); R=ROI analysis; S=Self-report to assess childhood maltreatment; W=Whole brain analysis; All studies used retrospective assessments of childhood maltreatment.

Table 3. Amygdala GM volume in resilient adults

Resilient vs. vulnerable adults										
No significant differences or no CM * diagnosis interaction	Chaney et al. (2014) (39) n=30, M, W+R, S, M/F	Opel et al. (2016) (40) n=40, M, W+R, S, M/F	Saleh et al. (2017) (41) n=42, M, R, S, M/F	Sublette et al. (2016) (30) n=121, M, R, I+S, M/F						
Resilient vs. healthy adults										
No significant differences or no CM * diagnosis interaction	Ansell et al. (2012) (26) n=103, H, W, I+S, M/F	Chaney et al. (2014) (39) n=46, M, W+R, S, M/F	Dannlowski et al. (2016) (52) n=309, H, W, S, M/F	Frodl et al. (2017) (44) n=2078, M, R, S, M/F	Saleh et al. (2017) (41) n=53, M, R, S, M/F	Sublette et al. (2016) (30) n=60, M, R, I+S, M/F	Tomoda et al. (2009) (36) n=45, H, W, S, M/F	Tomoda et al. (2011) (42) n=40, H, W, S, M/F	van Harmelen et al. (2010) (31) n=53, M, W+R, I, M/F	Yang et al. (2017) (43) n=84, M, W, S, M/F
Larger amygdala volume in resilient adults	Holz et al. (2017) (19) n=181, H, W+R, I*, M/F	Pechtel et al. (2014) (35) n=51, H, R, S, M/F								
Smaller amygdala volume in resilient adults	Opel et al. (2016) (40) n=36/40, M, W+R, S, M/F									

H=Healthy Sample; I=Interview to assess childhood maltreatment; M=Mixed sample; M/F=Male and female; n=Total number of participants in the contrast of interest (not the entire sample of the study); R=ROI analysis; S=Self-report to assess childhood maltreatment; W=Whole brain analysis; *Prospective assessment of childhood maltreatment, all others used retrospective assessments of childhood maltreatment.

Supplementary material

Table S1. Summary of studies investigating grey matter structure in resilient adults

Authors	Study design	Sample	Specification of “healthy”	n	Age	Imaging analysis	ROIs	Measure of CM
Ansell et al. (2012) (26)	Cross-sectional	Healthy sample	Healthy individuals had no substance dependence (apart from nicotine) and were not prescribed medication	103	27.71(8)	Whole-brain VBM analysis performed with SPM8	No a priori defined ROIs	Stressful life events were evaluated retrospectively using the CAI
Bremner et al. (2003) (24)	Cross-sectional	Mixed sample	Healthy individuals had no PTSD	Resilient 12; vulnerable 10; HC 11	Resilient 32(8); vulnerable 35(6); HC 38(7)	Whole-brain and ROI analysis. ROI were manually traced. Analysis were performed using Analyze	Hippocampus	History of childhood abuse was assessed retrospectively with the Early Trauma Inventory
Chaney et al. (2014) (39)	Cross-sectional	Mixed sample	Healthy individuals never experienced any psychiatric disorder (axis I or axis II)	MDD 37; HC 46	MDD 40.2(10); HC 36.6(11.8)	Whole-brain and ROI VBM analysis were performed using SPM8	Hippocampus, ACC, DLPFC, DMPFC, OFC	Maltreatment experienced as a child or teenager was assessed retrospectively using the self-report CTQ
Dannowski et al. (2016) (52)	Cross-sectional	Healthy sample	Healthy individuals were free of life-time Axis-I psychiatric disorders	AA/AG 170; GG 139	AA/AG 34.6(11.2); GG 33.9(11.2)	Whole-brain VBM analysis. Preprocessing and analysis were performed using SPM8	No a priori defined ROIs	Maltreatment during childhood was assessed retrospectively using the self-report CTQ
Frodl et al. (2010a) (49)	Cross-sectional	Mixed sample	Neither the healthy group nor their first-degree relatives had history of neurological or mental illness	MDD 43; HC 44	MDD: 44.2(12.2); HC 41.1(12.5)	Whole-brain VBM and ROI analysis. ROI were manually traced. VBM analysis were performed using SPM5	Hippocampus	Childhood stress was assessed retrospectively using the self-report CTQ
Frodl et al. (2017) (44)	Cross-sectional	Mixed sample	Healthy individuals were free of MDD in all sub-samples (free of axis-I psychiatric disorders and free of medication in the majority of sub-samples)	MDD 958; HC 2078	MDD 42.4(14.3); HC 46.3(15.2)	ROI analysis. Preprocessing and analyses performed with FreeSurfer	7 subcortical ROIs	Childhood adversity was assessed retrospectively using the self-report CTQ
Gerritsen et al. (2015) (27)	Cross-sectional	Mixed sample	Healthy individuals had no history of psychiatric diagnosis	NESDA 262; SMART 636	NESDA 37.8(10.2); SMART 61.5(9.5)	ROI analysis. Preprocessing and analysis performed with FreeSurfer	Hippocampus	Childhood maltreatment was assessed retrospectively using the Nemesis Trauma Interview
Holz et al. (2017) (19)	Cross-sectional from longitudinal	Healthy sample	Healthy individuals were free of Axis-I psychiatric disorders	181	25	Whole-brain and ROIs VBM analysis. Images were preprocessed and analysed with SPM8	Caudate, putamen and amygdala	Childhood family adversity was assessed using a prospective parental interview
Jensen et al. (2015) (22)	Cross-sectional from longitudinal	Mixed sample	Participants came from a longitudinal cohort and had various levels of psychopathology	507	19.6(1.8)	Calculation of grey matter volume, cortical thickness, and surface area using FreeSurfer. Complete dataset for MRI analysis n=494	30 different ROIs identified using GingerALE	Childhood adversity was assessed prospectively by their mothers using a family adversity checklist
Opel et al. (2014) (51)	Cross-sectional	Mixed sample	Healthy individuals scored <10 on Beck's Depression Inventory and were free from any history of psychiatric disorders or any psychotropic medication	MDD 85; HC 85	MDD 37.6(12); HC 37.2(11.8)	Surface and ROI VBM analysis. Images were analysed using FSL-FIRST and SPM8	Hippocampus	Childhood maltreatment was evaluated retrospectively using the self-report CTQ
Opel et al. (2016) (40)	Cross-sectional	Mixed sample	Healthy individuals had no history of MDD	MDD 20; FH+ 16; HC-CM+ 20; HC 20	MDD 37.9(10.9); FH+ 34.1(14); HC-CM+ 38.7(11.6); HC 36.3(12.1)	Combined VBM/pattern recognition approach using a machine-learning algorithm implemented in the Machine toolbox and SPM8	No a priori defined ROIs	Childhood maltreatment was evaluated retrospectively using the self-report CTQ
Pechtel et al. (2014) (35)	Cross-sectional	Mixed sample	Healthy individuals had no history of psychopathology or neurological disorders or substance abuse in the last 6 months	ELS 18; HC 33	ELS 29.3(0.5); HC 23.4(1.5)	ROI analysis performed with FreeSurfer	Amygdala, caudate and thalamus	Childhood maltreatment was assessed retrospectively using the self-report MACE
Saleh et al. (2017) (41)	Cross-sectional	Mixed sample	Healthy individuals had no current or past Axis-I or II psychiatric disorder apart from MDD, or acute suicidality or family history of bipolar disorders	MDD 64; HC 65	MDD 35.1(8.9); HC 29.7(9.2)	Regional volumes and cortical thickness were calculated using FreeSurfer. Whole-brain and ROIs analysis. Complete dataset for MRI analysis n=104	OFC, hippocampus, amygdala, caudate, ACC	Exposure to childhood stressors was assessed retrospectively using the self-report ELSQ

Sublette et al. (2016) (30)	Cross-sectional	Mixed sample	Healthy individuals had no Axis I diagnosis, or first-degree relatives with a mood disorder or schizophrenia	MDD 61; HC 60	MDD 37.8(11.8); HC 34.9(13.8)	The amygdala was manually traced with an electronic mouse	Amygdala	Stressful life events were assessed retrospectively with the St. Paul-Ramsey Interview
Tomoda et al. (2009) (36)	Cross-sectional	Mixed sample	Healthy individuals had no current or past Axis-I disorder	HCP 23; HC 22	HCP 21.7(2.2); HC 21.7(1.8)	Whole-brain VBM analysis performed using SPM5	No a priori defined ROIs	History of corporal punishment was assessed retrospectively using the self-report LEQ
Tomoda et al. (2011) (42)	Cross-sectional	Mixed sample	Healthy individuals had no current or past Axis-I disorder	PVA 21; HC 19	PVA 21.2(2.4); HC 21.1(1.9)	Whole-brain VBM analysis performed using SPM5	No a priori defined ROIs	Parental verbal aggression was assessed retrospectively using the self-report PVAS
van Harmelen et al. (2010) (31)	Cross-sectional	Mixed sample	Healthy individuals had no current psychopathology (depression, anxiety)	CEM 84; HC 97	CEM 38.7(1.1); HC 36.6(1.1)	Whole brain and ROI VBM analysis using SPM5	mPFC, amygdala, hippocampus	Childhood maltreatment was assessed retrospectively using the Nemesis Trauma Interview
Yang et al. (2017) (43)	Cross-sectional	Mixed sample	Healthy individuals had no MDD	MDD 84; HC 84	MDD 30.9(7.74); HC 30.4(6.7)	Cortical reconstruction and volumetric segmentation were performed using FreeSurfer	Hippocampus, amygdala and ACC	Childhood maltreatment was evaluated retrospectively using the self-report CTQ

Mixed sample=A sample including participants with and without mental health disorders or unspecified. AA/AG=A-allele carriers; ACC=Anterior cingulate cortex; CAI=Cumulative adversity interview; CECA.Q=Childhood experiences of care and abuse questionnaire; CEM=Childhood emotional maltreatment; CM+=History of childhood maltreatment; CM-=No history of childhood maltreatment; CTQ=Childhood trauma questionnaire; DLPFC=Dorsolateral prefrontal cortex; DMPFC=Dorsomedial prefrontal cortex; ELS=Early life stress; ELSQ=Early Life Stress Questionnaire; FH+=healthy first-degree relatives of MDD patients; GG=GG homozygotes; HC=Healthy adults; HC-CM+=Healthy subjects exposed to former childhood maltreatment; HCP=Exposed to harsh corporal punishment; LEQ=Life experiences questionnaire; MACE=Maltreatment and Abuse Chronology of Exposure scale; MDD=Major depressive disorder; mPFC=Medial prefrontal cortex; PVAS=Parental verbal Aggression Scale; OFC=Orbitofrontal cortex; PTSD=Post-traumatic stress disorder; ROI=Regions of interest; TEC=Traumatic Experiences Checklist; VAL/MET=VAL/MET carriers; VAL/VAL=VAL/VAL carriers; VBM=Voxel-based morphometry.

Table S2. Summary of studies investigating white matter structure and integrity in resilient adults

Authors	Study design	Sample	Specification of “healthy”	n	Age	Imaging analysis	ROIs	Measure of CM
Choi et al. (2009) (68)	Cross-sectional	Mixed sample	No history of DSM-IV Axis-I psychiatric disorders on structured diagnostic interview	Resilient 16; HC 16	Resilient 21.9(2.4); HC 21.0(1.6)	The Tract-Based Spatial Statistics (TBSS) tool in FSL was used to calculate tract-based differences in FA	No a priori defined ROIs	Exposure to PVA was assessed retrospectively using the VAS
Chaney et al. (2014) (39)	Cross-sectional	Mixed sample	Healthy individuals never experienced any psychiatric disorder (axis I or axis II)	MDD 37; HC 46	MDD 40.2(10); HC 36.6(11.8)	Whole-brain and ROI VBM analysis were performed using SPM8	Hippocampus, ACC, DLPFC, DMPFC, OFC	Maltreatment experienced as a child or teenager was assessed retrospectively using the self-report CTQ
Cohen et al. (2006) (62)	Cross-sectional	Healthy sample	No major affective or anxiety disorders, schizophrenia, substance abuse, neurological disease, or major medical conditions that could affect cognition (e.g., stroke, heart disease, cancer) currently or in the past	250	39.9(17.2)	Whole-brain VBM analyses. Data were preprocessed and analysed with SPM2	No a priori defined ROIs	Early life stress events were assessed retrospectively using the self-report ELSQ
Corbo et al. (2016) (69)	Cross-sectional	Mixed sample	No history of neurological illness (other than TBI), seizures, current diagnosis of schizophrenia spectrum or other psychotic disorders (not related to PTSD), current active suicidal and/or homicidal ideation, intent or plan requiring crisis intervention or cognitive disorder due to general medical condition other than TBI	ELT+ 80; ELT- 160	ELT+ 33.73(8.2); ELT- 30.85(8.4)	The Tract-Based Spatial Statistics (TBSS) tool in FSL was used to calculate tract-based differences in FA	No a priori defined ROIs	Early life trauma was assessed retrospectively using the TLEQ
Fani et al. (2012) (25)	Cross-sectional	Mixed sample	Healthy individuals had no PTSD	Resilient 26; PTSD 25	Resilient 38 (12.8); PTSD 34 (12.5)	The Tract-Based Spatial Statistics (TBSS) tool in FSL was used to calculate tract-based differences in FA	No a priori defined ROIs	Childhood maltreatment was assessed retrospectively using the self-report CTQ
Frodal et al. (2010a) (49)	Cross-sectional	Mixed sample	Neither the healthy group nor their first-degree relatives had history of neurological or mental illness	MDD 43; HC 44	MDD: 44.2(12.2); HC 41.1(12.5)	Whole-brain and ROI VBM analysis. ROI were manually traced. VBM analysis were performed using SPM5	Hippocampus	Childhood stress was assessed retrospectively using the self-report CTQ
Teicher et al. (2010) (65)	Cross-sectional	Healthy sample	No history of Axis I psychiatric disorders	63	21.9(1.9)	The Tract-Based Spatial Statistics (TBSS) tool in FSL was used to calculate tract-based differences in FA and diffusivity (MD, RD, RA).	No a priori defined ROIs	Exposure to PVA was assessed retrospectively using the VAS
Tendolkar et al. (2018) (23)	Cross-sectional	Healthy sample	No history of somatic disease potentially affecting the brain, current or past psychiatric or neurological disorder, medication or illicit drug use during the preceding 6 months, history of substance abuse or current or past alcohol dependence	120	21.9(2.9)	The Tract-Based Spatial Statistics (TBSS) tool in FSL was used to calculate tract-based differences in FA and diffusivity (MD).	No a priori defined ROIs	Childhood maltreatment was assessed retrospectively using the self-report CTQ
van Harmelen et al. (2010) (31)	Cross-sectional	Mixed sample	Healthy individuals had no current psychopathology (depression, anxiety)	CEM 84; HC 97	CEM 38.7(1.1); HC 36.6(1.1)	Whole brain and ROI VBM analysis using SPM5	mPFC, amygdala, hippocampus	Childhood maltreatment was assessed retrospectively using the Nemesis Trauma Interview

Mixed sample=A sample including participants with and without mental health disorders or not specified. ACC=Anterior cingulate cortex; CEM=Childhood emotional maltreatment; CTQ=Childhood trauma questionnaire; DLPFC=Dorsolateral prefrontal cortex; DMPFC=Dorsomedial prefrontal cortex; ELSQ=Early Life Stress Questionnaire; ELT+=Early life trauma; ELT-=No early life trauma; FA=Fractional anisotropy; HC=Healthy adults; MACE=Maltreatment and abuse chronology of exposure scale; MD=Mean diffusivity; MDD=Major depressive disorder; mPFC=Medial prefrontal cortex; OFC=Orbitofrontal cortex; PTSD=Post-traumatic stress disorder; RA=Relative anisotropy; RD=Radial diffusivity; ROI=Regions of interest; TLEQ=Traumatic life events questionnaire; VAS=Verbal abuse scale; VBM=Voxel-based morphometry.

Table S3. Summary of studies investigating brain function in resilient adults

Authors	Study design	Sample	Specification of “healthy”	n	Age	fMRI Task	Imaging analysis	ROIs	Measure of CM
Stress Reactivity									
Banihashemi et al. (2015) (74)	Cross-sectional	Healthy sample	Healthy individuals had no current psychiatric diagnoses of substance abuse or mood disorder	155	40.7(6.2)	Multi-Source Interference Task and Stroop task	ROI analysis with SPM. Complete dataset for fMRI analyses n=138	PVN, BNST, amygdala and subgenual ACC	Childhood maltreatment was evaluated retrospectively using the self-report CTQ
Bos et al. (2014) (75)	Cross-sectional	Healthy sample	Healthy individuals had no history of physical or mental health problems or substance misuse	21	22.8(2.7)	Cry Task	Whole-brain and ROI analysis performed with SPM8	Hippocampus, insula, amygdala, and thalamus	Childhood maltreatment was evaluated retrospectively using the self-report CTQ. Only a minority of participants had moderate scores, the rest were low-to-none
Fonzo et al. (2016a) (71)	Cross-sectional	Mixed sample	Healthy individuals had no PTSD, acute stress disorder or met criteria for lifetime mental disorder	PTSD-CM 22; PTSD 20; TEHCs 20	PTSD-CM 39.7(10.8); PTSD 37.1(10.4); TEHCs 32.5(12.4)	Emotional Conflict Task	Whole-brain and ROI analysis performed with FSL.	Amygdala, insula, vmPFC, dorsal ACC, and DLPFC	Childhood maltreatment was evaluated retrospectively using the self-report CTQ
Grimm et al. (2014) (73)	Cross-sectional	Healthy sample	Healthy individuals had no history of neurological or psychiatric disorder	ELS 14; HC 17	ELS 29.5(4.5); HC 29(5.1)	Montreal Imaging Stress Task (MIST)	Whole brain and ROI analyses with SPM8	No a priori defined ROIs	Childhood maltreatment was evaluated retrospectively using the self-report CTQ
Seo et al. (2014) (29)	Cross-sectional	Healthy sample	Healthy individuals were free of medication and history of axis-I psychiatric disorders	highCA 25; midCA 25; lowCA 25	highCA 28.8(8.9); midCA 26.6(7.9); lowCA 27.4(7.6)	Script-driven individualized imagery method to induce emotions, acute stress, and anxiety states	Whole-brain analyses. Data were preprocessed with SPM and analysed using BioImageSuite and AFNI	No a priori defined ROIs	Stressful life events were evaluated retrospectively using the CAI
van Harmelen et al. (2014) (70)	Cross-sectional	Mixed sample	Healthy individuals were free of medication and had no history of psychiatric disorders	CEM 26; HC 20	CEM 18.3(1.2); HC 18.9(1.9)	Cyberball Task (reactivity to social exclusion)	Whole brain and ROI analyses with SPM8	ACC, mPFC and Insula	Childhood maltreatment was evaluated retrospectively using the self-report CTQ - emotional abuse and neglect
Wang et al. (2013) (72)	Cross-sectional	Healthy sample	Healthy individuals had no current or history of neurological and psychiatric disorders, drug abuse, or current medication use	19	27.1(7.2)	Counterbalanced stress (mental arithmetic) and Mindfulness tasks	Whole-brain analyses using FSL	No a priori defined ROIs	Childhood maltreatment was evaluated retrospectively using the self-report CTQ
Face Processing									
Dannlowski et al. (2012) (79)	Cross-sectional	Healthy sample	Healthy individuals were free of life-time Axis-I psychiatric disorders. Trait anxiety and depression were included in analyses as regressors of no interest	145	33.8(10.4)	Face-matching fMRI Task	Whole-brain and ROI of the amygdala with SPM8. Complete dataset for fMRI analysis=114	Amygdala	Childhood maltreatment was evaluated retrospectively using the self-report CTQ
Dannlowski et al. (2013) (80)	Cross-sectional	Healthy sample	Healthy individuals were free of life-time Axis-I psychiatric disorders. Trait anxiety and depression were included in analyses as regressors of no interest	134	34.5(10.6)	Subliminal Affective Priming fMRI task	Whole-brain and ROI with SPM8. Complete dataset for fMRI analysis=134	Amygdala	Childhood maltreatment was evaluated retrospectively using the self-report CTQ
Dannlowski et al. (2016) (52)	Cross-sectional	Healthy sample	Healthy individuals were free of life-time Axis-I psychiatric disorders	AA/AG 170; GG 139	AA/AG 34.6(11.2); GG 33.9(11.2)	Face-matching fMRI task	Data were preprocessed and analysed with SPM. Whole brain and ROI analyses. Complete dataset for fMRI analysis=264	Amygdala	Childhood maltreatment was evaluated retrospectively using the self-report CTQ
Edmiston & Blackford (2013) (76)	Cross-sectional	Mixed sample	Participants had various degrees of mood disorder psychopathology	18	23.4(2.9)	Passive viewing of both novel and recently familiarized faces with neutral expressions task	ROI analyses. Data were preprocessed and analysed with SPM	Amygdala, hippocampus, fusiform gyrus	Childhood maltreatment was evaluated retrospectively using the self-report CTQ
Felmingham et al. (2010) (77)	Cross-sectional	Mixed sample	Healthy individuals had no PTSD	Resilient 21; PTSD 23; HC 42	Resilient 32.4(13.9); PTSD 37.4(10.6); HC 28.7(11.5)	Fear Perception Task	Data were preprocessed and analysed with SPM2. Whole-brain and ROI analyses	Brainstem, hippocampus, insula, amygdala, ACC	Trauma history with the Traumatic Event Questionnaire
Fonzo et al. (2016b) (82)	Cross-sectional	Mixed sample	Participants had various types and levels of anxiety psychopathology but no psychotic disorder, organic mental disorder, mental retardation, bipolar disorder, substance dependence in the year, and substance abuse in the past month	182	30.7(11.3)	A modified version of the Emotion Face Assessment Task	Whole-brain and ROI analyses with FSL	Insula, amygdala, ACC/mPFC	Emotional abuse and neglect were assessed retrospectively using the self-report CTQ

Grant et al. (2011) (83)	Cross-sectional	Mixed sample	Healthy individuals were free of life-time Axis-I psychiatric disorders with the exception of one subject who was diagnosed with mild agoraphobia without panic disorder	MDD 20; HC 16	MDD 34.5(10.7); HC 31.1(9.2)	A selective attention task	Whole-brain and ROI analyses with Brain Voyager QX.	Amygdala	Childhood maltreatment was evaluated using a modified version of the self-report CTQ
Herringa et al. (2013) (78)	Cross-sectional	Mixed sample	Eighteen subjects met criteria for PTSD. Three subjects met criteria for current major depressive disorder. No history of psychotic or bipolar disorder or recent substance misuse or suicidality	28	26.6(2.6)	Dynamic Faces Task	Whole-brain and ROI analyses with SPM8	VMPFC, hippocampus, amygdala, insula	Childhood maltreatment was evaluated retrospectively using the self-report CTQ
Holz et al. (2017) (19)	Cross-sectional from longitudinal	Healthy sample	Healthy individuals were free of Axis-I psychiatric disorders	181	25	Face-matching task	Whole-brain and ROIs analysis. Images were preprocessed and analysed with SPM8	Caudate, putamen and amygdala	Childhood family adversity 'enriched index was assessed at five time points using a cumulative prospective parental interview
Taylor et al. (2006) (81)	Cross-sectional	Healthy sample	Healthy individuals had no history of serious mental health problems	30	18-36 years	Observation of negative faces while labelling the emotional character of those faces	Whole-brain and ROI analyses. Data were preprocessed and analysed with SPM99	Amygdala, VLPFC	Childhood family environment was assessed retrospectively with the Risky Families Questionnaire
van Harmelen et al. (2013) (32)	Cross-sectional	Mixed sample	Healthy individuals had no current diagnosis of depression and/or anxiety on the DSM-IV	No abuse 75; CEM 60	No abuse 34.9(1.2); CEM 38.2(1.3)	The Faces Task	Whole-brain and ROI analyses. Data were preprocessed and analysed with SPM5	Amygdala, mPFC	Childhood maltreatment was assessed retrospectively using the Nemesis Trauma Interview
Emotion processing									
Demers et al. (2017) (18)	Cross-sectional from longitudinal	Mixed sample	Both groups had similar levels of psychopathology measured by the Adult Self Report measure and BDI-II	CM+ 41; CM- 39	CM+ 30.8(3.3); CM- 29.3(3.5)	Emotionally expressive faces and geometric shapes matching task	Whole-brain analysis. Imaging data were analysed with FSL	No a priori defined ROIs	Childhood maltreatment was documented by DHS records and the Maternal Maltreatment Classification Interview
Jedd et al. (2015) (20)	Cross-sectional from longitudinal	Mixed sample	Both groups had similar levels of psychopathology measured by the Adult Self Report measure and BDI-II	CM+ 33; CM- 38	CM+ 30.6(3.2); CM- 29.5(3.6)	Emotion matching task	Whole-brain analysis. Imaging data were analysed with FSL	No a priori defined ROIs	Childhood maltreatment was documented by DHS records and the Maternal Maltreatment Classification Interview
Schweizer et al. (2016) (21)	Cross-sectional from longitudinal	Healthy sample	Healthy individuals had no current psychopathology on the DSM-IV	CM+ 23; CM- 30	CM+ 20.1(0.6); CM- 20.1(0.7)	Emotional regulation task	ROIs analysis. Imaging data were analysed with SPM5	Inferior middle and medial frontal gyrus, middle temporal gyrus, amygdala	Childhood adversity was assessed retrospectively with the CAMEEI
Resting state fMRI									
Fujisawa et al. (2015) (34)	Cross-sectional	Healthy sample	Healthy individuals had no current Axis I or II disorders, a history of major medial or neurological illnesses, including epilepsy or significant head trauma, or a lifetime history of alcohol or drug dependence	30	21.5(3.4)	Resting state fMRI	Whole-brain analysis. Data were preprocessed with SPM8. ICA was conducted using the Group ICA/IVA of fMRI Toolbox	No a priori defined ROIs	Post-traumatic symptoms experienced after stressful or traumatic life events were assessed retrospectively using the self-report IES-R
Kaiser et al. (2017) (28)	Cross-sectional	Mixed sample	All analyses were performed controlling for psychiatric diagnosis	70	26.4(6.2)	Resting state fMRI	Preprocessing performed with SPM12. Seed-based functional connectivity analyses performed using the CONN toolbox and in-house scripts written in Matlab	Amygdala	Threat-related early life stress was evaluated retrospectively using the TAI
Philip et al. (2013) (96)	Cross-sectional	Healthy sample	Healthy individuals had no current Axis I psychiatric disorder	ELS 13; HC 9	ELS 36(10); HC 34(9)	Resting state fMRI	Preprocessing with AFNI and SPM. Seed-based analysis	PCC, mPFC and amygdala	Early life stress events were assessed retrospectively using the self-report ELSQ
Philip et al. (2016) (89)	Cross-sectional	Mixed sample	Healthy individuals had no current Axis I diagnosis and were free from any psychotropic medication	ELS+/DIS+ 14; ELS+/DIS- 14; ELS-/DIS- 18	ELS+/DIS+ 51(13); ELS+/DIS- 37(10); ELS-/DIS- 32(9)	Resting state fMRI	Whole-brain and seed-based analysis based on the regions identified. Preprocessing and imaging analysis with AFNI	No a priori defined ROIs	Childhood maltreatment was evaluated retrospectively using the self-report CTQ
van der Werff et al. (2013) (33)	Cross-sectional	Mixed sample	Healthy individuals had no lifetime psychopathologies	Resilient 11; Vulnerable 11; HC 11	Resilient 40.4(10.9); Vulnerable 39.7(9.6); HC 40.5(9.5)	Resting state fMRI	Preprocessing and analysis using FSL. Seed-based analysis	Amygdala, dorsal ACC, PCC	Childhood maltreatment was assessed retrospectively using the Nemesis Trauma Interview

Mixed sample=A sample including participants with and without mental health disorders or not specified. AA/AG=A-allele carriers; ACC=Anterior cingulate cortex; AFNI=Analysis of functional neuroimages; BNST=Bed nucleus of the stria terminalis; CA=Cumulative adversity; CAI=Cumulative adversity interview; CAMEEI=Cambridge early experience interview; CEM=Childhood emotional maltreatment; CM+=History of childhood maltreatment; CM-=No history of childhood maltreatment; CONN=Functional connectivity toolbox; CTQ=Childhood trauma questionnaire; DHS=Department of human services; ELS-/DIS-=Medication-free healthy adults; ELS+/DIS+=Patients with trauma-related disorders associated with negative affect states; ELS+/DIS-=Medication-free participants with ELS and without psychiatric disorders; ELS=Early life stress; ELSQ=Early life stress questionnaire; IES-R=Impact of event scale-revised; GG=GG homozygotes; HC=Healthy control adults; ICA/IVA=Independent component analysis/Independent vector analysis; ICA=Independent component analysis; mPFC=Medial prefrontal cortex; PCC=Posterior cingulate cortex; BNST=Bed nucleus of the stria terminalis; PTSD=Post-traumatic

stress disorder; PTSD-CM=Post-traumatic stress disorder with moderate-to-severe history of childhood maltreatment; PVN=Paraventricular nucleus of the hypothalamus; ROI=Regions of interest; TAI=Traumatic antecedents questionnaire; TEHC=Trauma-exposed healthy adults; VLPFC=Ventrolateral prefrontal cortex; VMPFC=Ventromedial prefrontal cortex.

Table S4. Vulnerable vs Patients (PT + CM vs PT no CM) comparisons (or interactions)

Structure	Amygdala	Smaller	Aas et al. (2012) (57) n=45, M, R, S, M/F				
	Hippocampus	Similar (n.s.)	Frodl et al. (2010b) (49), n=44, M, W+R, S, M/F (GMV)	Frodl et al. (2017) (44), n=2078, M, R, S, M/F			
	MPFC	Smaller	Chaney et al. (2014) (39), n=30, M, W+R, S, MF	Opel et al. (2014) (51), n=85, M, W+R, S, M/F	Gerritsen et al. (2015) (27), Sample 1 n=262, M, R, I, M/F	Gerritsen et al. (2015) (27), Sample 2 n=636, M, R, I, M/F	Frodl et al. (2010a) (49), n=44, M, W+R, S, M/F (WMV)
		Similar (n.s.)	van Harmelen et al. (2010) (31), n=84, M, W+R, I, MF				
		Larger	Yang et al. (2017) (43), n=84, M, W, S, M/F				
Functioning	Amygdala	Similar (n.s.)	van Harmelen et al. (2013) (32), n=95, M, W+R, I, M/F	Fonzo et al. (2016a) (71), n=42, M, W+R, S, M/F			
		Decreased	Grant et al. (2011) (83), n=20, S, W+R, M/F				
RSFC	Amygdala	Similar (n.s.)	Kaiser et al., (2017) (28), n=70, M, I, R, F				
		Stronger	Demers et al. (2017) (18), n=80, M, I, W, M/F				

I=Interview to assess childhood maltreatment; M=Mixed sample; M/F=Male and female; n=Total number of participants in the contrast of interest (not the entire sample of the study); PT=Patients; R=ROI analysis; S=Self-report to assess childhood maltreatment; W=Whole brain analysis; All studies used retrospective assessments of childhood maltreatment.