The resilient emotional brain: a 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 how emotional brain structure and functioning may contribute to such 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. CM without psychopathology) vs. vulnerable adults (i.e. CM with psychopathology), or vs. healthy adults without CM. 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 take into account 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) can be defined as; *‘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 comprises of both child abuse and/or neglect (1). CM negatively affects emotional, social and physical wellbeing and mental health (2-6). To reduce the burden of CM related disease, improved understanding of the neurobiological factors that may help individuals retain or regain good mental health in the aftermath of CM (‘resilience’) may prove crucial. Resilience refers to *‘the maintenance or quick recovery of mental health after significant adversity’* (7). As such, resilience refers to the *process* of positive adaptation following adversity and can only be examined in the form of resilient *functioning* at a given time point (7, 8). Understanding the neural correlates of such resilient functioning may reveal novel targets for prevention and interventions aimed to improve resilience in adults with CM.

Here, we provide the first comprehensive narrative review of neuroimaging findings comparing brain structure and function in resilient adults with CM (i.e. CM but no mental illness) vs. vulnerable adults with CM (i.e. CM and mental illness), or vs. healthy adults without CM. We focus on adults, as adaptations to CM in childhood and adolescence may act as resilience mechanisms in high stress family environments, but may constitute vulnerability in adulthood when the environment is no longer stressful (9). We include grey and white matter structure and function at rest and during tasks in the medial prefrontal cortex (mPFC), hippocampus and amygdala (‘limbic regions’) (Figure 1) because of the pivotal role of these regions in emotion processing and regulation, stress response, and self-referential processing (10, 11).

[FIGURE 1 ABOUT HERE]

We investigate white matter tracts, as such tracts connect with or between our ROIs (Figures 2). For instance, the uncinate fasciculus connects the frontal and limbic regions (12) and the cingulum bundle connects frontal, temporal and parietal cortices (Figure 2) (13).

[FIGURE 2 ABOUT HERE]

Finally, we investigate functional connectivity in resting state networks that include the mPFC and limbic regions (Figure 3), such as the salience (SN) and default mode network (DMN), which interact with the central executive network (CEN), during emotion processing and regulation (14). These networks are thought to play an important role in the integration of external and internal information in order to direct attention to salient stimuli (SN) (15, 16), internally directed cognitive activity (e.g. interoceptive awareness, self-focus) (DMN); and the manipulation and maintenance of information in the context of goal directed behaviours (CEN) (17).

By reviewing the role of mPFC and limbic structure, function and connections in resilient adults with CM we provide a first step in understanding the role of these emotional brain regions in resilient functioning after CM.

[FIGURE 3 ABOUT HERE]

2. Methodology

2.1 Search strategy

In April 2019 we searched PubMed using the following keywords for the title and abstract in English-language studies: ((childhood AND abuse OR neglect OR maltreatment OR adversities) AND (function OR structure)) AND Magnetic Resonance Imaging as text keyword. Papers available online ahead of print were also included.

This resulted in 140 studies which were screened for relevance. After duplicate removal, the reference lists of all included studies were screened for additional references. We excluded studies when: i) mean age of sample was <18 years; ii) sample only consisted of patients; iii) study was out-of-scope (e.g. relating to hemi-spatial neglect, substance abuse or intimate partner violence); iv) studies did not report findings in our regions of interest (ROIs), connections and/or networks; v) and we excluded reviews, editorials material, proceeding papers, notes, letters to the editors and meeting abstracts. This resulted in 50 studies including a total of 9047 participants (Figure 4).

[FIGURE 4 ABOUT HERE]

2.3. Strategy

We describe findings in our ROIS from the contrasts of ‘resilient adults’ (i.e. CM without current mental illness) vs. (1) ‘vulnerable adults’: CM with a current mental illness, and vs. (2) ‘healthy controls’: without CM and no current mental illness) in order to explore whether the findings in resilient adults reflect normalization (similarities between resilient adults and healthy controls) or are specific to resilient functioning (differences between resilient adults and healthy controls or vulnerable adults).

3. Results

3.1. Overview of studies

From the 50 studies, 33 (66%) were based on mixed samples (i.e. samples including participants with and without mental health disorders, or did not specify the mental health of the sample), and 17 (34 %) examined healthy adults only (See Table S1-3 for details). Studies including clinical samples comprised of current patients with major depression (n=9, 27.3%), post-traumatic stress disorder (PTSD) (n=4, 12.1%) or

psychiatric inpatients or outpatients with any diagnosed mental health disorder (n=20, 60.6%). All results were cross-sectional, although 4 studies embedded cross-sectional imaging within a prospective design (18-21). Finally, 2 studies examined males (22, 23), 2 studied females (24, 25) and the remainder included both.

The vast majority of studies assessed CM retrospectively (N=46, 92%) in an interview (N=15; 32.6%; 21, 24, 26-34), a clinician administered scale (N=2; 0.04%; 35-37), or a self-report questionnaire (N=31; 67.4%; 71% used the Childhood Trauma Questionnaire (CTQ; 38)). Four studies used prospective measures to assess CM (8%). 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 ages 8, 21, 33, 47, 61, and 73 months.

3.2. Brain structure in resilient adults

3.2.1. Grey matter

Twenty-one studies were included in this section (supplementary Table S1). All studies examined grey matter using voxel based morphometry (VBM) (n=12) which provides an automated quantitative voxel based distribution of grey and white matter in individuals or groups of subjects (39). Others manually traced ROIs or used volume quantification using FreeSurfer (n=9).

Medial prefrontal cortex (mPFC)

Four studies examined mPFC grey matter volume in resilient vs. vulnerable adults, and did not find significant differences (Table 1; 32, 40-42). Eight studies compared resilient adults vs. healthy controls, and whilst 3 studies reported similar mPFC (Table

1; 40, 43, 44), the majority of these studies reported smaller mPFC volume in resilient adults (22, 26, 32, 37, 41). Importantly, the study with the largest sample (i.e. 22; N=494) reported reductions in the mPFC grey matter volume of resilient adults with a history of CM. In this study, CM was measured prospectively in sequential interviews with the mother over multiple specific time points. Therefore, taking into account the quality of the CM assessment and power of this study, together with the findings in Table 1 the current literature suggests that resilient adults have smaller mPFC grey matter volume when compared to healthy controls, and non-significantly different/similar mPFC volume when compared to vulnerable adults. These results must be considered preliminary as they are based on post-hoc comparisons, often conducted within small (sub-) samples and therefore these studies may not have had sufficient power to detect effects that truly exist, perhaps leading to false negative findings. It is crucial that future studies combine efforts and pool data in order to provide statistically powerful studies to examine the neural underpinnings of resilience after CM (i.e., see 45 for an example).

[INSERT TABLE 1 ABOUT HERE]

Smaller mPFC in resilient vs. healthy adults, and similar mPFC in resilient vs. vulnerable adults is suggestive of the idea that CM, and not resilient functioning, is associated with mPFC structure. This may be due to the detrimental effects of stress on the mPFC as seen in animal models (e.g. 46-48). Furthermore, CM forms a prelude to further negative life events (49), and such recent stressful life events in adulthood also negatively impact on mPFC volume (26). Importantly, the subjective experience of chronic stress has been found to interact with adverse life events causing even larger reductions of the mPFC (26). However, our results suggest that such mPFC grey matter

reductions are found in both vulnerable and resilient adults with CM, and as such may not be related with mental health functioning after CM.

Hippocampus

Seven studies investigated the hippocampus in resilient vs. vulnerable adults (Table 2) and found larger volume (24, 27, 42), or no significant differences (40, 41, 50, 51).

Gerritsen et al. (2015) found larger hippocampal volume in resilient adults (i.e. vulnerable vs resilient; Hedge's $g = -.47$, 95% CI $-.78$ to $-.16$) in two large independent samples (study 1 $n = 262$; study 2 $n = 636$; (27)), and used interviews to assess CM which is less sensitive to false positive inflation compared to self-report (52). As these samples were part of larger cohort studies, Gerritsen et al. (2015) were also able to control for important confounding factors (including age, gender, education level, intracranial volume, smoking status, alcohol intake, diastolic blood pressure, diabetes and antidepressant use, and cognitive abilities). In sum, the available evidence suggests that resilient adults have larger hippocampal grey matter volume than vulnerable adults with CM.

Twelve studies investigated hippocampal volume in resilient vs. healthy adults (Table 2). Two studies reported reduced hippocampal volume (41, 53), and ten reported no significant differences (26, 32, 33, 37, 40, 43-45, 50, 54). Crucially, Frodl et al. (2017) conducted a mega-analysis on data from different cohorts ($N = 2078$) and reported no significant hippocampal volume differences in resilient vs. healthy adults (45). In line, a recent meta-analysis showed that hippocampal volume is not associated with CM in healthy adults when gender was taken account of (55).

[INSERT TABLE 2 ABOUT HERE]

Taken together, current findings suggest that resilient adults may have larger hippocampal grey matter volume than vulnerable adults with CM, and similar hippocampal volume compared to healthy controls. In line with the role of the hippocampus in mental health functioning, smaller hippocampal volume has indeed been found to predict the onset of young adult depression in healthy adolescents (56) and was related to PTSD diagnoses (57). In sum, larger hippocampal volume may aid resilient functioning after CM.

Amygdala

Four studies investigated amygdala grey matter volume in resilient vs. vulnerable adults and found no significant differences (Table 3; 31, 40-42). Fourteen studies examined amygdala volume in resilient vs. healthy adults (Table 3), and reported smaller (41) larger (19, 36), or no significant differences (26, 29, 31, 32, 37, 40, 42-45, 54). This pattern of findings suggests that the amygdala may not be involved in resilient functioning after CM and is not influenced by CM. Indeed, recent meta-analyses revealed no amygdala alterations in healthy adults with CM (57, 58), nor in PTSD patients vs. healthy controls (56). In sum, amygdala volume does not aid resilient functioning after CM.

[INSERT TABLE 3 ABOUT HERE]

3.2.2. White matter structure

Ten studies examined white matter volume (n=5) or white matter tract integrity (n=5) in resilient adults (see supplementary Table S2). The five studies on white matter volume found larger hippocampal white matter volume in resilient vs. vulnerable adults

(50, 51), and no significant white matter volume differences or interactions in any of our ROIs when compared to healthy controls (32, 40, 59).

Five studies used diffusion tensor imaging (DTI) to investigate the integrity of white matter tracts in resilient adults with CM. As many of these tracts connect with, or between our ROIs, we report all findings related to resilient adults in these studies. All studies reported DTI metrics in the form of fractional anisotropy (FA), whilst two also reported mean diffusivity (MD; 23, 60). FA measures the directionality of diffusion whilst MD quantifies free diffusion of water within a voxel (61, 62). Lower than expected FA (and the typically associated higher MD) in a region of white matter can be interpreted as an index of compromised white matter integrity.

One study examined resilient and vulnerable adults and showed increased posterior cingulum FA in resilient adults (25; Table S2). This white matter fibre connects the entorhinal and cingulate cortices and has been implicated in self-referential thinking. Reduced structural connectivity along this pathway has been reported in studies of patients with depression, schizophrenia and PTSD (63, 64) and therefore may underlie vulnerability in these patients. The other four studies compared resilient vs. healthy adults (Table S2). Three studies reported reduced FA in numerous tracts associated with performance on attention and affective control tasks; the cingulum bundle by the posterior tail of the left hippocampus, arcuate fasciculus, and fornix (65), the corpus callosum and corona radiata (60), and the anterior thalamic radiation around the middle frontal gyrus, right inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and the precuneus (23). This study found no differences in FA between resilient and healthy controls but reported an interaction between FA and reaction time to positive stimuli on an affective go/no-go task suggesting that CM may be associated

with a distinct brain-behaviour relationship that could be related to other determinants of FA than those present in healthy adults (66).

In sum, studies investigating white matter volume in resilient vs. vulnerable adults show larger hippocampal white matter volume, but no significant differences when comparing resilient with healthy adults. These findings are in line with grey matter findings and suggestive of the idea that larger hippocampal volume may aid resilient functioning after CM. Studies investigating white matter tracts suggest preliminary evidence that resilient adults have increased FA compared to vulnerable adults and decreased FA when compared to healthy adults in (parts of) the cingulum tract. Although preliminary, these results suggest that CM may affect the integrity of a tract that, amongst other functions, underlies self-referential processing. CM is related with more negative self-referential processing in both resilient and vulnerable adults (32). Such negative self-referential processing mediated the link between CM and depressive and anxiety symptoms in these adults (32). As such, the integrity of the pathways involved in self-referential processing may be important in mental health functioning after CM. However, as only one small study examined resilient vs. vulnerable adults, future studies are required before conclusions are drawn with respect to the implications of these findings regarding resilient functioning after CM.

3.3 Brain functioning in resilient adults

In the following paragraphs we provide an overview of the 25 studies that examined brain functioning in resilient adults in a total of N=1969 participants (see Supplementary Table S3).

3.3.1 Brain functioning during tasks

The study of blood oxygen level-dependent (BOLD) fluctuations while performing a task allows the exploration of brain activity in the presence of specific external stimulation. In the literature included in this review, a highly heterogeneous set of tasks have been investigated which can be roughly grouped into three major categories: stress reactivity (N=7), face processing (N=10) and emotion regulation (N=3).

Stress reactivity

Seven studies that examined stress reactivity in resilient adults in our ROIs. Three studies examined resilient vs. vulnerable adults (Table S3) and found non-significant dorsal mPFC reactivity to social exclusion (67), and non-significant amygdala and mPFC responsivity to interpersonal conflict (68). Across repeated stress exposure, resilient vs. vulnerable adults were found to show increased amygdala habituation and sustained (normalized) mPFC activity (69). Although preliminary, these results suggest that although resilient vs vulnerable adults may not have differential stress responses but may be characterized by effective modulation (increased amygdala habituation and normalized mPFC responses) in response to stress.

Four studies compared resilient adults to healthy controls (Table S3) and showed that resilient functioning may be characterized by limbic deactivation (70), lower amygdala and subgenual ACC responsivity (71) and increased hippocampal activity (30). In a slightly different line of enquiry, a study of resilient vs. healthy adults showed differential activation of the hippocampus towards a crying infant during experimental administration of cortisol (72).

Together, the above studies suggest that resilient functioning after CM may be facilitated by improved habituation to stress over time (vs. vulnerable adults), and increased limbic de-activation to acute stress (vs. healthy controls).

Face-processing

Ten studies examined face processing in resilient adults. Two studies investigated resilient vs. vulnerable adults (Table S3) and showed lower hippocampal responses to fearful and neutral faces (73, 74). Four studies compared resilient vs. healthy controls (Table S3), and showed non-significant hippocampal responses to fearful, angry and happy faces (74-76), or increased hippocampal activity to neutral faces (73). Overall, resilient vs. vulnerable adults may be characterized by lower hippocampal activation in response to emotional faces. However, it is unclear whether this represents normalization (similar to healthy controls), or whether this is specific to resilient individuals (better than healthy controls).

The studies examining amygdala reactivity to facial emotion processing in resilient adults 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 (76), or lower amygdala activation to fearful and neutral faces (74). Ten studies compared resilient to healthy adults and showed non-significant amygdala activity to fearful, angry, and happy faces (74, 75), increased amygdala activity to angry, sad, happy and/or neutral faces (54, 76-78) or decreased amygdala responses to fearful and angry facial expressions (19, 79). Finally, CM (vs. no CM) related increased amygdala (together with decreased superior mPFC) responsivity to negative facial expressions was found to mediate the link between CM and anxiety symptoms in a mixed sample of adult patients and controls (80). It may be that recent stress, and not CM, is associated with such increased amygdala reactivity to emotional faces (75). However, as of yet, the literature is too mixed to draw conclusions on amygdala responsivity to emotional faces in resilient adults. Thus, although there is some support for the notion that lower hippocampal activation to emotional faces may be an aspect of

resilient functioning after CM, the role of amygdala responsivity to emotional faces in resilient functioning after CM needs further examination.

Emotion processing

Three studies examined emotion processing in resilient vs. healthy controls (Table S3). Two of them examined brain activation and connectivity in an emotion matching fMRI task and reported no significant activations in our ROIs. These studies showed that increased fronto-limbic functional connectivity during emotion processing was related to lower emotion-matching accuracy in resilient vs. healthy adults (18, 20). 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 controls revealed reduced recruitment of the mPFC and middle temporal gyrus, and increased down-regulation of the amygdala in response to negative emotional material in the group of resilient adults which was associated with better ability to regulate emotions in response to negative stimuli (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 ability to regulate emotional responses in resilient adults.

3.3.2 Brain functioning at rest

In the last few years, our understanding of brain functioning has benefited from studies on the functional connectivity during spontaneous low frequency BOLD fluctuations observed in the absence of any specific external stimulation. Resting state functional connectivity (RSFC) examines the relationships between anatomically remote brain regions or, the level of functional connectivity between regions also described as ‘networks’ (81). The networks most extensively investigated in the studies included

were those involved in regulating emotions; the SN, CEN and DMN (82, 83). Whereas limbic and SN response to stress appears to represent bottom-up reactivity, the CEN, which consist of prefrontal regions such as the dorsolateral prefrontal cortex (DLPFC), is believed to exert top-down regulation of limbic systems (84, 85).

Five studies examined RSFC in resilient adults. Four studies (Table S3) investigated resilient vs. vulnerable adults and reported enhanced connectivity between the SN (i.e., dorsal ACC) and limbic areas (e.g. thalamus, lingual gyrus) (28, 34, 86). This is of interest as the dorsal ACC plays an important role in cognitive control processes such as attention control (87), conflict monitoring (88, 89) and error detection (90, 91). One study showed that adults with high (vs. low) psychological growth following adverse experiences (measured as self-reported degree of positive change following those experiences) had stronger activation in prospective or working memory areas within the CEN (i.e., positive association between psychological growth and the functional connectivity between the superior parietal lobule and supramarginal gyrus) (35). Interestingly, the supramarginal gyrus is involved in reasoning about the mental states of others (i.e. ‘mentalizing’, 92), which plays a significant role in social interactions. Thus, increased connectivity and flexibility between the SN and subcortical regions and within the CEN and the supramarginal gyrus may be important in facilitating resilient functioning after CM.

One study investigated resting state DMN connectivity in resilient vs. healthy controls and reported decreased DMN connectivity, and trend-level increases in connectivity between the mPFC and the amygdala (93). Decreased connectivity in the DMN has been reported in multiple psychiatric disorders whose aetiologies include links to stress during early brain development, including PTSD (94), major depressive

disorder (95, 96), and schizophrenia (97, 98) and may be associated with the disturbances in self-referential processing often observed in these populations.

In sum, resilient adults may have stronger connectivity between the SN and limbic regions and within the CEN and the supramarginal gyrus when compared with vulnerable adults, and decreased DMN connectivity when compared with healthy controls. These findings suggest that resilient adults may have stronger functional connectivity between areas associated with cognitive control and social interactions and decreased connectivity in areas associated with self-referential processing.

4. Discussion

We aimed to provide a first step in understanding the neural correlates of resilient functioning after CM. We found that, compared to vulnerable adults, resilient adults show increased hippocampal volume, increased FA in the posterior cingulum and RSFC between the SN and limbic regions. In addition, resilient adults showed improved ability to regulate emotions, dampen threat processing and habituate stress responses when compared to healthy controls. This may potentially happen through stronger CEN-limbic connectivity, lower hippocampal activation to emotional facial expressions and increased amygdala habituation to stress.

There are a number of reasons why this review should be viewed as a preliminary. First, there was a large degree of heterogeneity in neuroimaging designs, procedures and analytic approaches (e.g. sample size, populations, imaging paradigms used, differences in scanner spatial resolution, manual vs. automated segmentation, use of a priori ROIs vs. whole-brain analyses). Furthermore, a large number of studies reported null findings without statistics on our contrast of interest (e.g. '*no main effect of CM*', '*no CM x diagnosis interactions were found*'). Therefore, we did not consider it

feasible to conduct a quality assessment or meta-analysis on the studies described here. To aid future reviews and meta-analyses, the report of statistics for null findings is especially important, and in line with current best practice approaches (e.g. 99).

Second, we identified resilient adults as those with a history of CM that were free from mental health disorders (see supplemental Tables S1, S2 and 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 necessarily indicate resilient functioning on all those domains. Therefore, future studies examining resilient functioning after CM should examine whether results hold when resilient functioning is assessed across social, emotional and cognitive domains (100, 101).

Third, the majority of studies included assessed CM using retrospective self-report questionnaires (67.4%). However, it could be argued that retrospective assessments are biased by the fact that patients may report more CM due to their low mood (102). Still, it is a contested issue whether this invalidates the retrospective approach (103). Reduced reporting in healthy populations may equally bias retrospective reports (104). Moreover, recent evidence suggests that retrospective and prospective reporting capture largely non-overlapping groups of individuals (105, 106). Thus, 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 (107). Such prospective studies are especially important in investigating resilience after CM, as resilience is dynamic and may change over time (7, 108). Longitudinal designs can therefore provide insights into whether the neurobiological characteristics that facilitate resilient functioning after CM are similar or distinct across time periods, represent adaptations to stressful

environments, or reflect pre-existing resilience factors in resilient individuals.

Therefore, future studies should utilize longitudinal designs to further our understanding of the neurobiological mechanisms that facilitate resilient functioning after CM.

Fourth, CM is highly correlated with further stress, and such recent stress may serve as an alternative explanation for observed functional and structural brain alterations (e.g. 31, 36). However, only a small number of studies included here investigated whether recent stress was a confounding factor (e.g. 22). Furthermore, since most studies reported here examined multiple types of CM together using self-report in adulthood, we were unable to discuss whether the neurobiological factors and mechanisms of resilience after CM depend on the type and/or timing of CM during development. The type and/or timing of CM may have differential effects on neurobiology (109-111). For example, timing of CM and related inflammation biomarkers are more predictive of future development of depressive illness (112-113), compared to accumulation of CM experiences. Future studies should examine the neurobiological factors and mechanisms that facilitate resilient functioning in conjunction with the type and timing of CM.

Another consideration for future research is that rather than examining structural regions in isolation, examining their connections (or covariance) may provide a more complete picture. The brain is a complex network of interconnected regions, where important regions, or ‘hubs’, are highly connected to other hubs, as well as with adjacent regions (114). The characteristics of these brain networks can be examined using network analysis. To our knowledge, only two studies have examined CM related structural brain networks (115, 116). These studies have found that CM is related with the alteration of global and regional network architecture. The last of these studies found that resilient and vulnerable individuals have comparable abnormalities in global

network architecture but differ from each other in degree of centrality (i.e., resilient individuals have lower degree of centrality in a small subset of nodes including the amygdala). Hyper-reactivity to threatening stimuli is one of the most consistent functional abnormalities found in maltreated individuals (e.g. 77, 78). Thus, reduced degree of centrality could be a compensatory adaptation that enabled some individuals to regain mental well-being following exposure to maltreatment (115).

To summarize, we have presented a synthesis of available evidence of mPFC and limbic brain structure and function in resilient adults with a history of CM. We suggest that resilient (vs vulnerable) adults show larger hippocampal volume, increased FA in the posterior cingulum and positive RSFC connectivity between the CEN and limbic regions. In addition, resilient adults are characterized by an improved ability to adequately regulate emotions, dampen threat processing and habituate to chronic stress when compared to healthy adults, possibly through 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 type, timing, nature of CM assessments, further stress experiences, and that examine brain anatomy as a network of interconnected regions. We hope that such further research 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 (117) and visualised in BrainNet Viewer (<http://www.nitrc.org/projects/bnv/>) (118). 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>) (119). 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) (120) and visualised in BrainNet Viewer (<http://www.nitrc.org/projects/bnv/>) (122). 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.

Table 1. mPFC volume in resilient adults

Resilient vs. vulnerable adults					
No significant differences or no CM * diagnosis interaction	Chaney et al. (2014) (40) n=30, M, W+R, S, MF	Opel et al. (2015) (41) n=40, M, W+R, S, MF	van Harmelen et al. (2010) (32) n=84, M, W+R, I, MF	Saleh et al. (2017) (42) n=42, M, R, S, M/F	
Resilient vs. healthy controls					
No significant differences	Chaney et al. (2014) (40) n=46, M, W+R, S, M/F	Tomoda et al. (2011) (43) n=40, H, W, S, M/F	Yang et al. (2017) (44) n=84, M, W, S, M/F		
Reduced 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. (2015) (41) n=36/40, M, W+R, S, M/F	Tomoda et al. (2009) (37) n=45, H, W, I+S, M/F	van Harmelen et al. (2010) (32) 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) (40) n=30, M, W+R, S, M/F	Frodl et al. (2010a) 50 n=87, M, W+R, S, M/F	Frodl et al. (2010b) (51) n=44, M, W+R, S, M/F	Opel et al. (2015) (41) 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) (42) n=42, M, R, S, M/F						
Resilient adults vs. healthy controls										
No significant differences or no CM * diagnosis interaction	Ansell et al. (2012) (26) n=103, H, W, I, M/F	Chaney et al. (2014) (40) n=46, M, W+R, S, M/F	Dannlowski et al. (2016) (54) n=309, M, R, S, M/F	Frodl et al. (2010a) (50) n=27, M, W+R, S, M/F	Frodl et al. (2017) (45) n=2078, M, R, S, M/F	Tomoda et al. (2009) (37) n=45, H, W, S, M/F	Tomoda et al. (2011) (43) n=40, H, W, S, M/F	van Harmelen et al. (2010) (32) n=53, M, W+R, I, M/F	van Velzen et al. (2016) (33) n=289, M, R, I, M/F	Yang et al. (2017) (44) n=84, M, W, S, M/F
Reduced hippocampal volume in resilient adults	Opel et al. (2014) (53) n=85, M, W+R, S, M/F	Opel et al. (2015) (41) 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; 11 studies examined childhood maltreatment retrospectively.

Table 3. Amygdala GM volume in resilient adults

Resilient vs. vulnerable adults											
No significant differences or no CM * diagnosis interaction	Chaney et al. (2014) (40) n=30, M, W+R, S, M/F	Opel et al. (2015) (41) n=40, M, W+R, S, M/F	Saleh et al. (2017) (42) n=42, M, R, S, M/F	Sublette et al. (2016) (31) n=121, M, R, I+S, M/F							
Resilient adults vs. healthy controls											
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) (40) n=46, M, W+R, S, M/F	Dannlowski et al. (2016) (54) n=309, H, W, S, M/F	Frodl et al. (2017) (45) n=2078, M, R, S, M/F	Molendijk et al. (2012) (29) n=31, M, W, I, M/F	Saleh et al. (2017) (42) n=53, M, R, S, M/F	Sublette et al. (2016) (31) n=60, M, R, I+S, M/F	Tomoda et al. (2009) (37) n=45, H, W, S, M/F	Tomoda et al. (2011) (43) n=40, H, W, S, M/F	van Harmelen et al. (2010) (32) n=53, M, W+R, I, M/F	Yang et al. (2017) (44) n=84, M, W, S, M/F
Larger amygdala volume in resilient adults vs. healthy controls	Holz et al. (2017) (19) n=181, H, W+R, I*, M/F	Pechtel et al. (2014) (36) n=51, H, R, S, M/F									
Smaller amygdala volume in resilient adults vs. healthy controls	Opel et al. (2015) (41) n=36/40, M, W+R, S, M/F										

H=Healthy Sample; I=Interview to assess childhood maltreatment; 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.

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 and analysis were performed using ANALYZE	Hippocampus	History of childhood abuse was assessed retrospectively with the Early Trauma Inventory
Chaney et al. (2014) (40)	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) (54)	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) (50)	Cross-sectional	Mixed sample	Neither the healthy group nor their first-degree relatives had history of neurological or mental illness	MDD 24; HC 27	MDD 43.8(11.9); HC 41.9(13.2)	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. (2010b) (51)	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) (45)	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
Molendijk et al. (2012) (29)	Cross-sectional	Mixed sample	Healthy individuals had no psychopathology (depression, anxiety)	val/val 103; val/met 54	val/val 37.1(9.6); val/met 37.9(10.4)	Whole-brain and ROIs VBM analysis. Images were preprocessed and analysed with SPM5	Hippocampus	Childhood maltreatment was assessed retrospectively using the Nemesis Trauma Interview
Opel et al. (2014) (53)	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. (2015) (41)	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) (36)	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) (42)	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) (31)	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) (37)	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 Life Experiences Questionnaire
Tomoda et al. (2011) (43)	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) (32)	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
van Velzen et al. (2016) (33)	Cross-sectional	Mixed sample	Healthy individuals had no psychopathology (MDD, subgroup of anxiety disorders)	CM+ 146 CM- 143	CM+ 38.4(9.7); CM- 36.9(10.6)	ROI analysis performed with FreeSurfer	ACC, Amygdala, hippocampus	Childhood maltreatment was assessed retrospectively using the Nemesis Trauma Interview
Yang et al. (2017) (44)	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; 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 controls; 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; 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) (65)	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) (40)	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) (59)	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) (66)	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 Trauma Life Events Questionnaire (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
Frodl et al. (2010a) (50)	Cross-sectional	Mixed sample	Neither the healthy group nor their first-degree relatives had history of neurological or mental illness	MDD 24; HC 27	MDD 43.8(11.9); HC 41.9(13.2)	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. (2010b) (51)	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) (60)	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) (32)	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 controls; 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) (71)	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) (72)	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) (68)	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) (70)	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) (30)	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) (67)	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) (69)	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) (77)	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) (78)	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) (54)	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) (73)	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) (74)	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) (80)	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
Herringa et al. (2013) (75)	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) (79)	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) (76)	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) (35)	Cross-sectional	Healthy sample	Healthy individuals had no current Axis I or II disorders, a history of major medical 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) (93)	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) (86)	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) (34)	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 controls; 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; ICA/IVA=Independent component analysis/Independent vector analysis; ICA=Independent component analysis; mPFC=Medial prefrontal 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 controls; VLPFC=Ventrolateral prefrontal cortex; VMPFC=Ventromedial prefrontal cortex.