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The effects of childhood maltreatment on brain structure, function and connectivity

Martin H. Teicher[1,2], Jacqueline A. Samson[1,2], Carl M. Anderson[1,2] and Kyoko Ohashi[1,2]

Abstract | Maltreatment-related childhood adversity is the leading preventable risk factor for mental illness and substance abuse. Although the association between maltreatment and psychopathology is compelling, there is a pressing need to understand how maltreatment increases the risk of psychiatric disorders. Emerging evidence suggests that maltreatment alters trajectories of brain development to affect sensory systems, network architecture and circuits involved in threat detection, emotional regulation and reward anticipation. This Review explores whether these alterations reflect toxic effects of early-life stress or potentially adaptive modifications, the relationship between psychopathology and brain changes, and the distinction between resilience, susceptibility and compensation.

Brain development is directed by genes but sculpted by experiences, particularly those occurring during early sensitive or critical periods. Studies suggest that the onset of regional critical periods may be triggered when GABAergic inhibitory influences develop to the point that they come into balance with excitatory influences[1]. This balance allows experience to shape and fine-tune connectivity patterns and network architecture. Contrary to earlier notions, plasticity is not lost but seems to be dampened by molecular 'brakes' that draw critical periods to a close, although these brakes can be lifted through pharmacological manipulations or epigenetic modifications[1]. Together, these developmental processes provide a highly adaptive mechanism for the formation of optimally sculpted neural representations to guide future actions based on early experience, while allowing possible revisions[1].

There are few early experiences as consequential as abuse and neglect. Studies on the effects of childhood maltreatment typically include physically, sexually and emotionally abusive acts and episodes of both physical and emotional neglect. Emotional maltreatment includes intentionally eliciting feelings of guilt, shame or fear to serve the emotional needs of the perpetrator; persuading children to perform inappropriate acts; denigrating or destroying things they value; or placing them in harmful situations, such as witnessing interparental violence[2]. Physical neglect is defined as failure to provide basic needs such as food, clean clothing, shelter, supervision, and dental and paediatric care[2]. Emotional neglect is the failure to provide for fundamental emotional needs, by being emotionally unresponsive to children's distress, failing to attend to their social needs or expecting children to manage situations that are beyond their maturity level or unsafe[2]. Some studies also include exposure to various forms of household dysfunction, such as living with substance-abusing parents.

According to the Adverse Childhood Experiences (ACEs) study, a collaboration between Kaiser Permanente and US Centers for Disease Control and Prevention, exposure to one or more maltreatment-related ACEs accounts for 54% of the population attributable risk (PAR) for depression[3], 67% of the PAR for suicide attempts[3] and 64% of the PAR for addiction to illicit drugs[4]. Exposure to five or more ACEs was associated with a 2-, 3-, 10- or 17-fold increase in risk for receiving a prescription of an anxiolytic, antidepressant, antipsychotic or mood-stabilizing medication, respectively[5]. Individuals exposed to six or more ACEs were found to have a 20-year reduction in lifespan[6], which may be due to accelerated telomere shortening[7]. Understanding how maltreatment increases risk of various psychiatric and medical disorders is of crucial importance to prevent, pre-empt or treat the consequences of abuse and neglect.

We hypothesized several years ago that maltreatment acts as a stressor to produce a cascade of physiological and neurohumoral reactions that alter brain-development trajectories, setting the stage for the emergence of psychiatric symptoms in genetically susceptible individuals[8–10]. Since then, there have been more than 180 original reports showing an association between childhood maltreatment and alterations in brain structure, function,

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connectivity or network architecture. Alterations in specific regions (for example, the adult hippocampus or the anterior cingulate cortex (ACC)) and pathways (such as the corpus callosum) have been consistently associated with childhood maltreatment across laboratories and populations. Hence, the first part of the hypothesis — connecting maltreatment to brain changes — is strongly supported. However, the second part of the hypothesis — linking brain changes to psychiatric disorders — seems to be more complicated than we initially suspected and may challenge current concepts regarding the neurobiology of mental illness.

There are several key aims to this Review. We explore the hypothesis that maltreatment-associated brain abnormalities are experience-dependent, adaptive modifications. We then provide evidence that maltreated and non-maltreated individuals with the same primary psychiatric diagnosis are clinically and neurobiologically distinct. Notably, we highlight the surprising discovery that brain abnormalities in maltreated subjects are not directly tied to psychopathology and can be found in clinically resilient as well as susceptible individuals, indicating that some individuals may be more susceptible to the neurobiological consequences of maltreatment than to the psychiatric consequences. We explore the possibility that psychiatrically resilient individuals who were maltreated as children may have subsyndromal psychiatric symptoms and additional brain differences that enable them to effectively compensate, and we make the case that maltreatment has been an unrecognized confound in psychiatric neuroimaging studies that calls into question the interpretation of prior results.

This Review differs from recent articles on the effects of childhood maltreatment on the brain[2,11–13], as we have endeavoured to organize the relevant research to provide evidence for the hypothesis that maltreatment leads to experience-dependent brain modifications and alterations in circuits and networks. Further, we extend the ecophenotype hypothesis — that maltreated and non-maltreated individuals with the same diagnosis are fundamentally different — to additional disorders, highlight a number of brain and network abnormalities that occur in maltreated individuals with and without psychopathology, and delineate an array of additional brain differences between maltreated individuals with and without psychopathology that may enable some individuals to more effectively compensate for the abnormalities induced by maltreatment.

To accomplish these aims, we first present findings revealing that exposure to single types of abuse is associated with alterations in the specific sensory systems that convey the aversive experience, as initial evidence of adaptation. Second, we discuss two task-based functional MRI abnormalities that may represent adaptations, and show that most recognized maltreatment-induced morphological changes occur in components of these neurocircuits. Third, we review recent findings on alterations in brain network architecture and in specific functional connectivity networks. Last, we review neuroimaging studies of maltreated and unexposed individuals with the same diagnoses, as well as of maltreated subjects without psychopathology, that show vast differences between maltreated and non-maltreated subjects with the same diagnoses and great similarities between maltreated individuals with and without psychopathology.

Studying the effects of maltreatment on the brain is a complex undertaking, and published reports have numerous limitations. Many studies report results from small samples that increase the risk of spurious results. Most studies are cross-sectional and so can be interpreted in many ways, including reflecting the possibility that there are pre-existing abnormalities that run in families and increase the risk of being abused. Similarly, most studies rely on retrospective self-report of maltreatment (although this limitation is not as severe as some might expect[14]) (Supplementary information S1 (box)). Also, there are often socioeconomic and IQ differences between maltreated individuals and controls[15]. Translational studies in rodents and non-human primates can control for these factors and establish a direct causal relationship between early experience and brain changes[16] (BOX 1).

Damage or adaptation?

A key question concerns the fundamental nature of maltreatment-associated brain differences. The prevailing view is that stress is bad for the brain and especially bad for the developing brain[17,18]. From this diathesis–stress perspective, the brain is damaged by excessive exposure to stress, and psychopathology is a direct consequence. However, it seems unlikely that evolutionary forces have not selected for brains that are resistant to the damaging effects of early-life stress (ELS), given how frequently this must have occurred throughout mammalian development.

An alternative perspective is that the brain[19,20] and the way it processes information[21,22] may be selectively modified by ELS in a meaningful manner[23,24]. Specifically, we propose that childhood abuse alters the development of particular brain regions, in an experience-dependent plastic manner, to facilitate survival and reproduction in what seems, so far, to be a threatening and malevolent world. From this perspective, what we construe as psychopathology reflects evolutionarily selected alterations in cognition, affect and behaviour that in the past have facilitated reproductive success in certain environments.

The diathesis–stress and plastic-adaptation hypotheses are not mutually exclusive. Some experiences might be so severe as to damage the brain. However, virtually all of the reported biological and behavioural alterations can be construed as adaptations. As an extreme example, maltreatment can accelerate ageing and shorten lifespan. Although this seems pathological, it may provide a selective advantage if it leads to precocious puberty and early childbirth during perilous eras when others die young before passing along their genes[24].

Sensory systems and specific types of abuse

An intriguing example of potentially adaptive modifications can be seen in studies that assess alterations in sensory cortices and fibre tracts that are associated with exposure to specific types of abuse. This effect on primary

Resilient
Able to withstand stress and trauma so as to maintain or rapidly regain physical and mental well-being.

Ecophenotype
Observable outward characteristics or traits that result from adaptation to environmental agents and that may closely mimic more-intrinsic, genetically determined phenotypes.

Box 1 | **Translational studies and causality**

Proving that maltreatment alters trajectories of brain development is difficult, as individuals cannot be randomly assigned to experience abuse or neglect[10]. However, strong support for a causal relationship emerges in translational studies assessing effects of early-life stress (ELS) or various forms of abuse or neglect in rodents and non-human primates[16]. Studies in this area have used manipulations to increase stress, such as handling or extended periods of maternal separation in rodents[151], rearing monkeys in peer groups without their mothers[152] or disrupting maternal behaviour by varying the availability and effort required to obtain food[153]. Other studies have examined naturally occurring differences in the degree to which rat mothers lick and groom their pups[154] and the natural tendency of a small percentage of non-human primate mothers to physically abuse their offspring[155].

Rodent studies have been particularly useful in identifying molecular changes[74,156] and epigenetic mechanisms[157] associated with ELS. These studies have also shown, at a more anatomical level, that the corpus callosum is strongly affected, in a sex-specific manner, by early experience[158] and that the dentate gyrus and CA3 (REF. 159) are the most vulnerable portions of the hippocampus. Rodent studies have also provided evidence for a delayed effect of ELS on synaptic density in the hippocampus, such that ELS before weaning did not result in a significant decrease in hippocampal synaptic density until early adulthood[160]. Furthermore, rodent studies have delineated the exposure-sensitive periods during which the hippocampus[161] and portions of the neocortex were most susceptible[161,162] and showed that the male hippocampus was more stress sensitive than the female hippocampus[163].

There are strong parallels between experimental findings in rodents and observations in maltreated individuals. For example, ELS-induced epigenetic modifications of the neuron-specific glucocorticoid receptor gene in the rodent hippocampus have been observed in autopsied hippocampi of maltreated individuals who committed suicide but not in non-maltreated individuals who died by suicide or other causes[157]. Furthermore, the hippocampal subfields that are most susceptible to ELS in laboratory animals are the subfields that differ most markedly between individuals with and without histories of maltreatment[52,146]. Similarly, many human studies indicate that maltreatment-associated reductions in hippocampal volume do not consistently emerge until well after puberty[2] and that there seem to be sensitive periods when hippocampus, neocortex and other structures may be most susceptible to childhood abuse[50,67,75]. Likewise, there are parallel sex-related differences in associations between maltreatment, corpus callosum area[15,94,95] and hippocampal vulnerability[128,142]. Rodent studies also strongly support the hypothesis that ELS produces potentially adaptive brain modifications. For example, hippocampi of adult rats that experienced low levels of licking and grooming in infancy had shorter dendritic branch length, lower spine density and impaired long-term potentiation (LTP) under basal conditions[164]. However, when corticosterone levels were elevated, LTP in these animals exceeded that of controls, and their memory was enhanced relative to controls when tested in a stressful contextual fear-conditioning paradigm.

Non-human primate studies also provide evidence for a causal effect of neglect and ELS on corpus callosum area[153,165], with the most consistent alterations reported in segments III, IV and VII[153]. Similarly, non-human primate studies indicate that ELS reduces hippocampal volume[153], whereas maternal physical abuse increases amygdala volume[166].

There are important parallels between results of non-human primate studies and clinical observations, such as the finding that childhood maltreatment is associated with alterations in the area or integrity of that corpus callosum that typically involve the same segments[15,50,94–96,143,167,168], the reliable finding of reduced hippocampal volume in adults with maltreatment histories[37,51,52], and findings of increased amygdala volumes in institutionally reared orphans[64,65], children of chronically depressed mothers[66] and in high-neglect-risk individuals with disrupted attachment[67,169]. Additional support for a causal relationship is provided by the few available longitudinal neuroimaging studies[68,83,170].

sensory systems is consistent with the findings of translational studies showing that these systems, the brain's first filters of information from the outside world, manifest some of the most dramatic experience-dependent plastic responses[1].

In a voxel-based morphometry (VBM) analysis of MRI scans of young adults who did or did not experience repeated episodes of parental verbal abuse (but no other types of abuse) during childhood[25], the most prominent revealed difference in grey-matter density was in the primary auditory cortex within the left superior temporal gyrus[25] (FIG. 1a; Supplementary information S2–S4 (tables)). The integrity of fibre tracts in an overlapping group of subjects who experienced parental verbal abuse was evaluated using tract-based spatial statistics (TBSS) to analyse diffusion tensor images. The most significant difference was found in an important language-processing pathway, the left arcuate fasciculus[26] (FIG. 1b), which interconnects Broca's area and the surrounding frontal cortex with Wernicke's area and the superior temporal gyrus. Diminished arcuate fasciculus integrity (assessed using measures of fractional anisotropy (FA)) was associated with lower verbal IQ and comprehension[26]. Hence, both of these studies revealed that exposure to parental verbal abuse targets the auditory cortex and the arcuate fasciculus language pathway.

VBM and TBSS were also used to assess the neurobiological consequences of seeing (not just hearing) multiple episodes of interparental violence during childhood, in separate groups of individuals. After controlling for exposure to verbal abuse, VBM and surface-based analyses revealed that visually witnessing domestic violence was associated with attenuated grey-matter density in the right lingual gyrus (Brodmann area 18)[27] (FIG. 1c) and with reduced thickness of other portions of the visual cortex, including the left occipital pole and bilateral secondary visual cortex. Observing domestic violence between 11 and 13 years of age had the most considerable effect on thickness and volume[27].

Further, whole-brain analyses using diffusion tensor imaging and TBSS in an overlapping group of individuals found that the integrity of the left inferior longitudinal fasciculus[28] was specifically attenuated by having visually witnessed interparental violence (FIG. 1d). This

Voxel-based morphometry (VBM). An unbiased technique to identify brain anatomical differences in regional density of grey or white matter between groups.

Tract-based spatial statistics (TBSS). An unbiased global analysis for assessing group differences in fractional anisotropy and other diffusion measures in white-matter pathways.

Fractional anisotropy (FA). The degree to which the diffusion of molecules is directionally dependent. Its measures reflect the integrity (involving fibre density, axon diameter and myelination) of white matter.

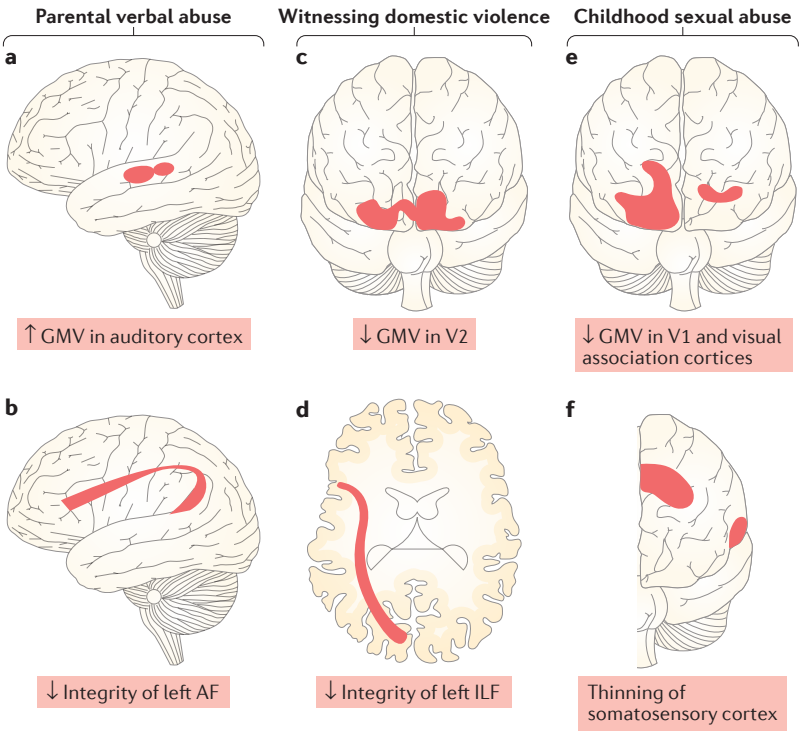

Figure 1 | **Abuse type-specific effects on the developing brain.** Images depicting the potential effects of exposure to specific types of childhood maltreatment on grey-matter volume (GMV) or thickness and fibre-tract integrity. Exposure to parental verbal abuse was associated with increased GMV in the auditory cortex portion of the left superior temporal gyrus[25] (part **a**) and decreased integrity of the left arcuate fasciculus (AF) interconnecting Wernicke's area and Broca's area[26] (part **b**). Visually witnessing multiple episodes of domestic violence was associated with reduced GMV in right lingual gyrus, left occipital pole and bilateral secondary visual cortex (V2)[27] (part **c**) and decreased integrity of the left inferior longitudinal fasciculus (ILF), which serves as a visual–limbic pathway[28] (part **d**). Adults reporting exposure to multiple episodes of childhood forced-contact sexual abuse were found to have reduced GMV in right and left primary visual cortex (V1) and visual association cortices, as well as reduced thickness in right lingual, left fusiform and left middle occipital gyri[29] (part **e**) and portions of the somatosensory cortex representing the clitoris and surrounding genital area[30] (part **f**). Part **a** is adapted with permission from REF. 25, Elsevier. Part **b** is adapted with permission from REF. 26, Elsevier. Part **c** is adapted from REF. 27. Part **d** is adapted with permission from REF. 28, Elsevier. Part **e** is adapted with permission from REF. 29, Elsevier. Part **f** is adapted from an image courtesy of C. Heim, Charité Universitätsmedizin Berlin, Germany, and J. Pruessner, McGill University, Canada.

tract is a major constituent of the visual–limbic pathway interconnecting the occipital and temporal cortices, and supports vision-specific emotional, memory and learning processes. Sensitive-period analysis found that observing interparental violence between 7 and 13 years of age, a peak period of active myelination, had the greatest effect on this pathway[28]. Microstructure analysis provided additional support for effects on myelin (rather than fibre number or diameter), as radial, but not axial, diffusivity seemed to be altered by this experience[28]. In short, repeatedly observing acts of domestic violence was associated with attenuated volume and thickness in portions of visual cortex and diminished myelination of a key fibre tract interconnecting visual and limbic systems.

VBM was also used to assess the neurobiological consequences of repeated episodes of sexual abuse enforced by non-parental adults[29]. Sexual abuse was associated with a substantial bilateral reduction in grey-matter volume (GMV) in the primary visual cortex and visual association cortices (FIG. 1e). This reduction in volume correlated directly with duration of exposure before the age of 12 years[29] and was also associated with a graded deficit in measures of visual memory. Surface-based analysis identified specific regions of GMV loss in the right lingual gyrus (as in individuals observing interparental violence) and in the left fusiform and middle occipital gyri[29] — regions involved in facial recognition and processing.

A separate study[30] measured cortical thickness in a group of adult women that included individuals with or without reported childhood abuse before puberty onset. Childhood sexual abuse was found to be associated with thinning of portions of somatosensory cortex, specifically the region representing the clitoris and extended genital area[30] (FIG. 1f). By contrast, exposure to emotional abuse was associated with thinning in left anterior and posterior cingulate cortex and bilateral precuneus[30] — regions involved in self-awareness and self-evaluation. In summary, exposure to childhood sexual abuse was associated with GMV reduction in parts of visual cortex involved in facial recognition and with thinning of portions of somatosensory cortex involved in processing tactile sensations from the genitals.

Overall, these differences can be explained as specific modifications to sensory systems and pathways that convey the aversive experience to consciousness, as a means of attenuating the effects of repeated exposures and thus reducing distress. Further, these modifications may shift how an individual responds to traumatic reminders, by altering conscious perception but leaving intact the subcortical pathways that provide a non-conscious route to circuits that can generate a rapid behavioural or emotional response to threats, as described below. These findings, however, are based on a series of isolated reports and require replication.

Threat detection and response

Maltreatment-related alterations make compelling sense as adaptive modifications when isolated region-of-interest findings are seen to be interconnected and part of specific circuits (Supplementary information S5 (table)). Abusive experiences can be construed as threats to survival, body integrity or sense of self[13]. The most reliable functional imaging finding in individuals with maltreatment histories is an increased amygdala response to emotional faces, particularly those seen as threatening or more broadly as salient. This phenomenon has been observed in maltreated individuals during childhood[31–33] and adulthood[34–36] and even in childhood-maltreated adults without psychopathology[32–35,37].

FIGURE 2 illustrates a 'threat-detection and response circuit' (based primarily on the work of LeDoux[38,39], with updates[2,40–43]) involved in regulating amygdala responses to auditory and visual stimuli. This circuit is also a component of the negative valence system. The diagram indicates regions and pathways in the circuit that reportedly differ morphologically between individuals with and without histories of maltreatment. Affected regions

Sensitive-period analysis
A statistical procedure used to identify time periods when exposure to a particular experience most strongly influences a future outcome.

Negative valence system
A functional construct domain involved in responses to acute threat, potential harm, sustained threat, frustrative non-reward and loss.

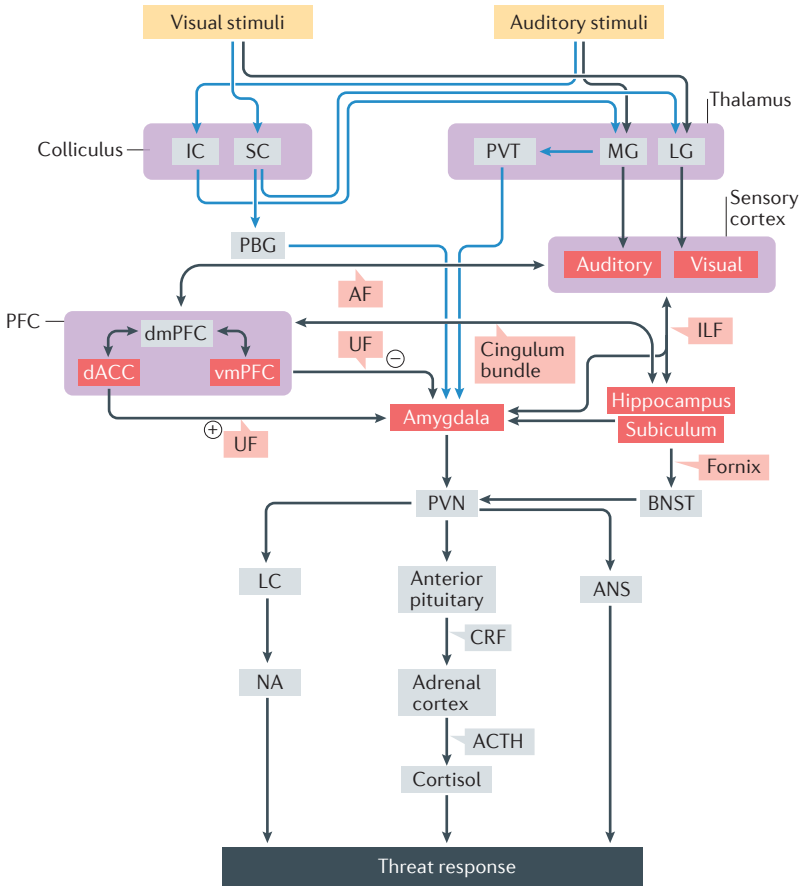

Figure 2 | **Circuitry underlying threat detection and response.** Simplified component diagram delineating brain regions found to be involved in detecting and responding to threatening sights and sounds. The figure is based primarily on work of LeDoux[38,39], with updates from translational studies[2,40–43]. Regions and pathways labelled in red have been reported to be altered in volume or integrity by childhood maltreatment. Visual information from the eyes is relayed to the superior colliculus (SC) and lateral geniculate nucleus (LG). From the SC, information can go to the LG or to the parabigeminal nucleus (PBG) and then to the amygdala. From the LG, information is projected to the visual cortex. Auditory information from the ears is relayed to the inferior colliculus (IC) or the medial geniculate nucleus (MG), with output from the IC projecting to the MG. From the MG, information can go to the auditory cortex or to the paraventricular thalamus (PVT) and then to the amygdala. Blue arrows delineate pathways through which information coding threatening sights or sounds can rapidly reach the amygdala without conscious awareness. Sensory cortical regions project to the amygdala, prefrontal cortex (PFC) and hippocampus. The PFC modulates the amygdala response, with the dorsal anterior cingulate cortex (dACC) amplifying this response (in the image, indicated by '+') and the ventromedial PFC (vmPFC) attenuating it (in the image, indicated by '–'). The dorsomedial PFC (dmPFC) helps to regulate the degree of dACC and vmPFC involvement. The hippocampus provides contextual information to the amygdala. The amygdala, in turn, projects to the paraventricular nucleus of the hypothalamus (PVN), which helps to regulate autonomic responses as well as pituitary adrenal and locus coeruleus (LC) responses. The PVN is also regulated by information from the hippocampus, via the subiculum and the bed nucleus of the stria terminalis (BNST). ACTH, adrenocorticotropic hormone; AF, arcuate fasciculus; ANS, autonomic nervous system; CRF, corticotropin-releasing factor; ILF, inferior longitudinal fasciculus; NA, noradrenaline; UF, uncinate fasciculus.

include the ACC[44–47] and ventromedial prefrontal cortex (ventromedial PFC; also known as orbitofrontal cortex (OFC))[48,49], the hippocampus[50–52] and subiculum[52], the thalamus[53,54] and sensory cortices[27,29,30,46,49]. Further, fibre tracts interconnecting these regions, including the inferior longitudinal fasciculus[28], all portions of the superior longitudinal fasciculus (including the arcuate fasciculus)[26,55,56], the uncinate fasciculus[56,57], cingulum bundle[26,55–57] and fornix[26,57], show evidence of diminished integrity. Consistent with this, maltreated individuals show altered measures of resting-state functional connectivity; for example, there is an inverse correlation between maltreatment severity and resting-state functional connectivity between the amygdala and cortical regions including the ACC[58–61] (FIG. 3; see Supplementary information S2–S10 (tables) for details of specific studies on morphometry, fibre tracts and connectivity).

An interesting feature of this circuit, as reported by LeDoux[38,39] and expanded on in recent studies, is that amygdala activity can be modulated through both a conscious portion of the circuit (including primary and secondary sensory cortices) and an entirely subcortical, non-conscious portion[62]. Supporting the existence of such subcortical circuits, optogenetic and tracing studies in rodents have revealed auditory and visual pathways to the ventrolateral amygdala from the medial geniculate nucleus and posterior paraventricular thalamic nuclei[42] and from the superior colliculus via the parabigeminal nuclei[43]. So far, maltreatment seems to be most strongly associated with reduction in the GMV and integrity of regions and pathways that are primarily involved in the conscious perception of threat and contextual memories. Thus, the heightened amygdala response in maltreated individuals may be due to a more-dominant involvement of the subcortical, versus conscious, component. Consistent with this, differences in amygdala activation between maltreated and non-maltreated children to angry, fearful or sad faces occur during early phases of the response, when the more-rapidly engaged, non-conscious component is likely to predominate[33,63].

Curiously, although the amygdala displays an increased blood-oxygen-level-dependent (BOLD) response to emotional faces in almost all the studies of maltreated individuals of which we are aware, the potential effect of maltreatment on amygdala volume is inconsistent[11]. Most studies report a non-significant decrease[11], but volumes larger than controls have also been reported — primarily in individuals experiencing care-giver neglect[64–67] — and amygdala volumes significantly smaller than controls have been reported in childhood-maltreated adults who show severe psychopathology[11] (Supplementary information S8 (table)). Inconsistencies probably occur because ELS seems to produce a small enlargement of the amygdala but also sensitizes it to subsequent stressors, resulting in a graded reduction in volume[11,68–70]. Based on differences in exposure-sensitivity periods, we hypothesize that the left amygdala may be particularly vulnerable to early abandonment or disrupted attachment[11,71] (possibly leading to an approach response[72]), whereas the right amygdala may be more vulnerable to physical, sexual or emotional abuse[11,67] (and may lead to a withdrawal response[72]).

Interestingly, preclinical studies have shown that environmental experiences (for example, being in an enriched environment) that lead to behavioural changes

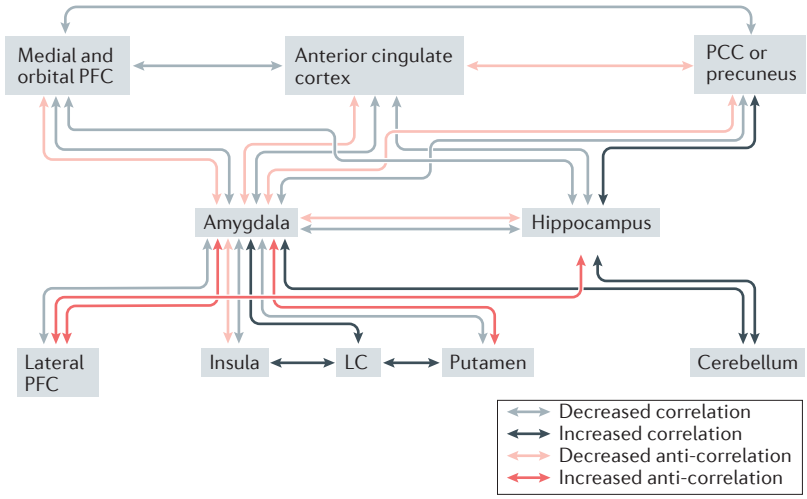

Figure 3 | **Maltreatment-associated changes in functional connectivity.** Summary of alterations in resting-state functional connectivity reported in individuals with histories of childhood maltreatment[58,60,91,121,171]. Alterations are expressed in relationship to the degree and direction of connectivity in unexposed controls. Decreased correlation indicates that there were positive correlations in blood-oxygen-level-dependent (BOLD) signal fluctuations between regions in controls and that the degree of correlation was reduced to a less positive or negative degree in maltreated individuals. Decreased anti-correlation indicates that there was an inverse correlation in BOLD signal between regions in controls and that this was reduced to a less negative or positive degree in maltreated subjects. Increased correlation and increased anti-correlation indicate that the correlation between regions was in the same direction in maltreated subjects as in controls but was present to a greater — more positive or more negative — degree, respectively. Multiple arrows between regions indicate discrepant findings, which probably stem from methodological differences between studies in the way that global signals related to blood flow or movements were handled. Reports of both decreased correlation and decreased anti-correlation suggest that the regions are less coupled in maltreated individuals. Decreased correlation and increased anti-correlation suggest that the coupling is shifting from a positive relationship to a negative (reciprocal) relationship in maltreated subjects. These studies provide evidence for reduced coupling of the amygdala with medial–orbital prefrontal cortex (PFC), anterior cingulate cortex, posterior cingulate cortex (PCC) or precuneus, hippocampus and insula, as well as a shift in the direction of coupling of the amygdala with lateral PFC and putamen, plus increased connectivity of the amygdala with locus coeruleus (LC) and cerebellum. These studies also indicate that maltreatment is associated with reduced coupling of the hippocampus with the medial–orbital PFC and anterior cingulate cortex, but increased positive or negative coupling of the hippocampus with the PCC or precuneus, cerebellum and lateral PFC. Overall, these findings are indicative of reduced top-down regulation of the amygdala by prefrontal regions, reduced contextual input to the amygdala from hippocampus, and increased connectivity of the amygdala with LC and cerebellum that may result in a more rapid noradrenergic and postural response following amygdala activation.

(for example, improved reaching behaviour) may be associated with either an increase or decrease in synaptic spine density in sensory and motor cortices, depending on the age at which the experience occurred[73]. Similarly, increases or decreases in amygdala volume may be strongly dependent on the ages of exposure to maltreatment[68,69] but result in comparable consequences.

There are several important points to draw from these findings. First, most differences between maltreated and non-maltreated individuals are expressed in this threat-detection and response circuit. Consequently, these effects of maltreatment may have an adaptive effect on threat detection. Second, the enhanced amygdala response to emotional faces is a more consistent finding in maltreated individuals than are the alterations in amygdala volume. This relative inconsistency of the reported effects of maltreatment on amygdala volume may be related to differences in age at maltreatment exposure[73], to molecular alterations within the amygdala that do not manifest as volumetric differences (for example, see REF. 74) or to alterations in other components of the circuit that result in an increased response in the amygdala without directly affecting the amygdala morphology. Third, the handful of studies delineating exposure-sensitive periods for the amygdala[67], hippocampus[50,67], visual cortex[27], PFC regions[50,75] and inferior longitudinal fasciculus[28] suggest that key circuit elements have relatively brief and unique periods of maximal susceptibility to maltreatment (FIG. 4). For example, preliminary data suggest that the hippocampus may be most susceptible to effects of maltreatment between 3 and 5 years of age and again during the peripubertal period (between 11 and 13 years of age)[50], and this is supported by new findings on the association between early adoption and hippocampal volume[76,77]. Consequently, the circuit itself may be susceptible throughout childhood, even though each individual component may have more-circumscribed periods of risk. Overall, these findings are consistent with the hypothesis that enhanced threat detection and response, leading to more-rapid recognition of fearful stimuli[78], is an adaptive reaction to maltreatment that might occur throughout childhood via alterations in different portions of this circuit. Although these changes may help individuals to avoid threats, they also sensitize individuals to subsequent stressors and increase the risk of anxiety or depression[79,80]. These regions are also involved in extinguishing learned fear responses, and alterations in these structures may play an important part in the development of post-traumatic stress disorder (PTSD)[81].

Reward anticipation

Another consistent functional imaging finding in maltreated individuals is a diminished BOLD response of striatal regions to anticipated or received reward in the monetary incentive delay task. This finding has been observed in: children with reactive attachment disorder[82]; maltreated children at high risk of depression[83]; orphans experiencing early deprivation[84]; a birth cohort of adults who had experienced early family adversity[85]; young adults studied longitudinally since kindergarten[86]; and adults reporting childhood exposure to emotional, physical or sexual abuse[87]. The ventral striatal response to reward receipt seems to be particularly susceptible to maltreatment from birth[81] to about 9 years of age[82,86].

Briefly, the key components of the reward circuit are the mesolimbic and striatal regions that are targeted by midbrain dopamine neurons[88]. These include the ventral striatum, ventral pallidum, ACC and orbital PFC (FIG. 5). Other structures that regulate the reward circuit include the amygdala, hippocampus and subiculum, lateral habenular nucleus, thalamus and dorsal PFC, and the pedunculopontine and raphe nuclei in the brainstem[88].

Monetary incentive delay task
A task in which individuals respond to target stimuli that are presented after incentive cues to win or avoid losing indicated rewards.

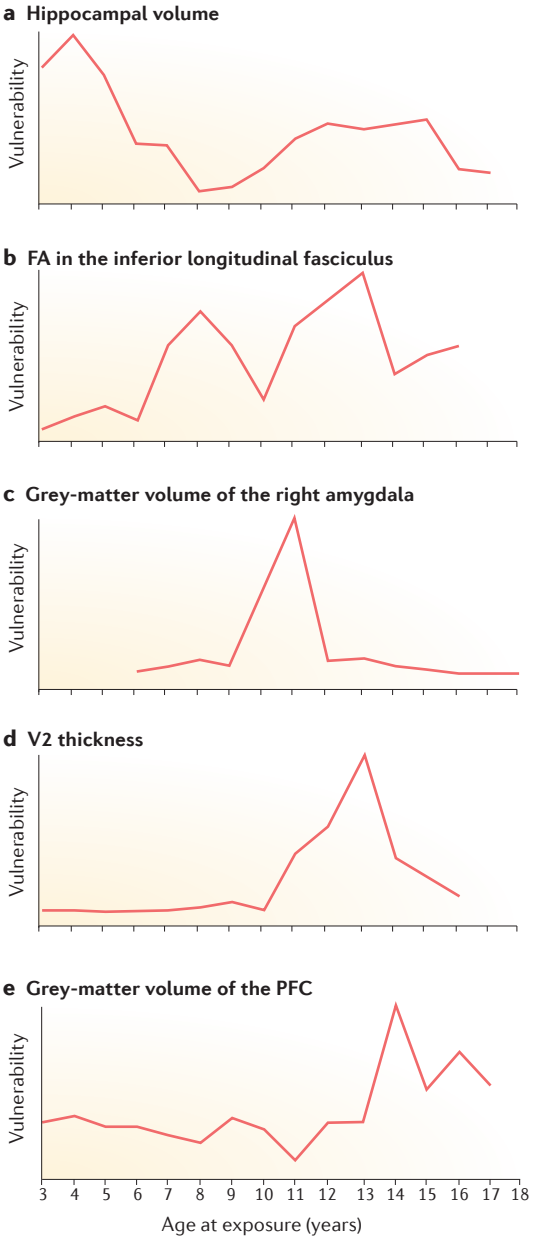

Figure 4 | **Maltreatment-sensitivity periods for different brain areas.** Developmental differences in sensitivity to effects of specific forms of childhood maltreatment on grey-matter measures or fibre-tract integrity (fractional anisotropy (FA)) show that different regions and pathways are maximally susceptible to maltreatment at different ages. **a** | Ages of exposure to sexual abuse in females are inversely correlated to reductions in hippocampal volume[50]. **b** | Predictive importance of visually witnessing domestic violence at specific ages and FA in the inferior longitudinal fasciculus, as assessed using predictive analytics and machine learning[28]. **c** | Predictive importance of maltreatment (composite score) at specific ages on reduction of the grey-matter volume of the right amygdala[67]. **d** | Predictive importance of visually witnessing domestic violence at specific ages on thinning of the secondary visual cortex (V2)[27]. **e** | Ages at exposure to sexual abuse in females show inverse correlation with grey-matter volume of the prefrontal cortex (PFC)[50].

Approach–avoidance situation
A situation in which the same goal has elements that both attract and repel. Behavioural responses depend on the disparity between the drive to approach versus the drive to avoid.

The ACC is the cortical region most frequently identified as abnormal in maltreated individuals, with reports of reduced volume[45,75,89], connectivity[90,91], thickness[30] and *N*-acetylaspartate/creatine ratio (indicative of neuronal loss or neuronal dysfunction)[44] in these individuals[90,91] (Supplementary information S6 (table)). Findings of structural and functional deficits in the OFC have also been frequently reported, and include reduced resting blood flow in orphans with early deprivation[48], and reduced volume in children with physical abuse[53], adults without psychopathology who were exposed to threatening life events during childhood[92] and adults who were exposed to childhood physical or sexual abuse and have chronic symptoms of post-traumatic stress[89] (Supplementary information S6 (table)).

Morphological abnormalities in the striatum have been reported in a few studies of childhood-maltreatment effects[11] (Supplementary information S9 (table)). Notably, however, most of the positive findings pertain to the caudate and putamen and do not distinguish between ventral and dorsal portions, an important distinction for reward processing[88]. Further, some studies have found no morphological differences in the striatum after childhood maltreatment[11]. Thus, as with the amygdala, diminished striatal activation in response to reward anticipation in maltreated individuals is a more consistent observation than alterations in striatal volume. The diminished ventral striatal response to reward anticipation may be an important risk factor for[83], or component of[87], depression and may increase risk of drug addiction[93].

We do not know to what extent the augmented amygdala response to emotional faces and the diminished ventral striatal response to reward anticipation in maltreated individuals cross-correlate. However, it is likely that an increased awareness of potentially threatening stimuli and a diminished anticipation of reward would tip the balance in an approach–avoidance situation towards avoidance. Thus, these findings also make sense as potentially protective adaptations to dangerous environments.

Corpus callosum and integration

A prominent and reliable finding in maltreated children[15,94,95] and adults who were maltreated as children[50,96] is the reduced area or integrity of the corpus callosum (Supplementary information S4 (table)). Reductions in corpus callosum area were most frequently observed in segments IV and V (also known as the anterior midbody and the posterior midbody, respectively) and, next most frequently, in segments VI and VII (also known as the isthmus and the splenium, respectively). Reductions in the area of anterior portions of the corpus callosum (segments I–III) were observed in individuals exposed to childhood maltreatment in only a few studies[97,98]. Segments IV–VII display the greatest degree of growth between 5 and 18 years of age[99], possibly rendering them particularly susceptible to maltreatment during this period[99].

Callosal morphology is thought to reflect the capacity for interhemispheric communication, especially between contralateral cortical regions (for example, the left and right somatosensory cortex). Segment IV and

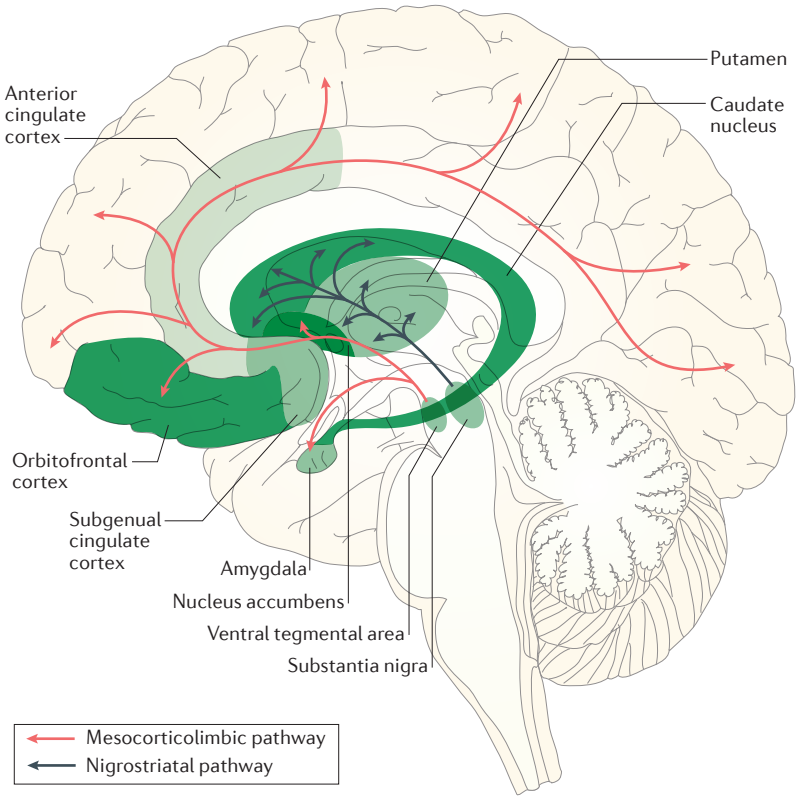

Figure 5 | **The dopaminergic reward system.** Anatomical location of key structures that make up the reward system and mesocorticolimbic (red) and nigrostriatal (black) ascending dopaminergic pathways. Dopamine-neuron cell bodies for these ascending pathways are located primarily in the ventral tegmental area and substantia nigra. Dopaminergic neurons in the substantia nigra project to dorsal portions of the striatum (caudate and putamen), whereas dopaminergic neurons in the ventral tegmental area project to ventral portions of the striatum (particularly the nucleus accumbens and more ventral aspects of the caudate and putamen), as well as limbic regions (that is, the amygdala) and cortical regions (particularly the orbitofrontal cortex and anterior cingulate cortex). Childhood maltreatment has been reported to be associated with alterations in blood flow to the caudate, putamen, portions of prefrontal cortex, substantia nigra and nucleus accumbens[48,172], as well as reductions in size of the striatum[37,49,75], alterations in developmental trajectory of the nucleus accumbens[173], and reduced volume, thickness or connectivity of the anterior cingulate cortex[30,45,75,89–91] and orbitofrontal cortex[53,89,92]. Maltreatment is also consistently associated with an attenuated striatal response to anticipation or receipt of reward in functional MRI tasks[82–87]. Green-shaded regions represent cell body regions or primary target regions of the ascending dopamine system.

segment V interconnect the motor, somatosensory and parietal association cortices of the two hemispheres, whereas segments VI and VII interconnect contralateral portions of the temporal, posterior parietal and occipital cortices. Interestingly, the thickness of these four segments of the corpus callosum correlates most strongly with IQ measures, consistent with the idea that interhemispheric communication between these cortical regions plays an important part in problem solving[100].

There seem to be marked sex differences in the vulnerability of the corpus callosum to maltreatment, as several studies reported a twofold greater reduction in corpus callosum area in maltreated males than in maltreated females[15,94,95,101,102] (but see REF. 98). We also observed that, in males, corpus callosum area was most affected by exposure to neglect, whereas, in females, it was most affected by exposure to sexual abuse[95]. These observations are consistent with animal model studies reporting substantial sex differences in the corpus callosum response to early experience[103].

In an interesting twist following these findings, another study[104] assessed the relationship between negative life events and FA in a large sample of adolescents. Resilient individuals had increased FA in corpus callosum segments II and III compared with non-exposed controls, whereas FA was greater in controls than in susceptible individuals. These findings suggest that the integrity of the corpus callosum may be diminished primarily in susceptible individuals, and that development of enhanced connectivity following exposure could confer resilience. However, this was a cross-sectional study, so it is also possible that increased FA in segments II and III was a pre-existing protective factor.

Another important study[105] of children in the Bucharest Early Intervention Project addressed whether the effects of early neglect on the corpus callosum were reversible. In this remarkable randomized, controlled trial, Romanian orphans were randomly assigned to high-level foster care or to continued care in the orphanage (usual care). The study was ethical, as foster care did not exist before the study and was created for this purpose, and the number of orphans that could be assigned was limited by the small number of families identified as suitable for foster-family training. As previously observed, orphans who received usual care had significantly smaller corpus callosum areas than did age-matched, non-orphaned controls when they were imaged at age 8–11 years. However, orphans assigned at about 15 months of age to high-level foster care had non-significantly smaller corpus callosum areas compared with controls when scanned between 8 and 11 years of age. This finding suggests that the effects of very early neglect on the corpus callosum were substantially reversed by early intervention, whereas other differences, such as reductions in cortical GMV, were not. However, an alternative interpretation is that random assignment at about 15 months of age did not reverse the effect but spared the children from experiencing stress or neglect at older ages, which may have had a more direct effect on corpus callosum development, as we have previously reported that the corpus callosum was most sensitive to adversity at 9–10 years of age, at least in females[50].

Little is known about the potential functional consequences of maltreatment-related thinning of the corpus callosum. One possible outcome of callosal thinning is diminished hemispheric integration. In an early study, we used probe auditory evoked potentials to measure right and left hemispheric processing of background tones in healthy adult individuals with or without childhood exposure to emotional abuse — first during recall of a neutral memory, and then during recall of an upsetting early memory[9]. The emotionally maltreated group displayed marked shifts in cortical activity during the two memory tasks. When these individuals were thinking about a neutral memory, their left auditory cortex was more actively engaged in the recall task and

Bucharest Early Intervention Project
A randomized, longitudinal, controlled trial of high-level foster care as an intervention for children placed in one of six institutions in Bucharest, Romania, at birth.

was thus less available to process the auditory probes than the right cortex. The opposite was observed when these individuals recalled the unpleasant memory: their right auditory cortex was more engaged in the recall task and less responsive to the probes than the left cortex. Healthy, emotionally non-maltreated controls, by contrast, seemed to use left and right auditory cortices to equivalent degrees during recall of neutral or negative memories. This suggests that hemispheric activity is more lateralized, or less integrated, in childhood-abused people. These findings are consonant with observations from a positron-emission tomography study[106] that revealed that individuals with PTSD (including those with childhood trauma) showed specific activation of their limbic system in the right, but not left, hemisphere and suppression of left-sided language centres when their traumatic memories were reactivated.

The differential hemispheric response that is seen in maltreated individuals can also be interpreted as a potential adaptation. We have speculated that these maltreatment-related alterations may provide a basis for a psychological defence mechanism that is often seen in patients with borderline personality disorder (BPD) and referred to as 'black and white' thinking, or 'splitting' (REF. 10). This is an unconscious process in which an individual fails to integrate both positive and negative qualities of the self or others into a cohesive whole and splits the mental representation of the entity into two opposing realities (for example, 'good mother' and 'bad mother'). It manifests in over-idealizing a person at one point in time and devaluing that person at another point in time, with repeated shifts between these two irreconcilable views. This process typically results in great distress and unstable, tumultuous relationships. However, if powerful individuals in a person's life are at times nurturing and at other times abusive, then splitting may provide a safer approach–avoidance strategy than one derived from a nuanced, 'shade of grey' perspective. Alterations in hemispheric balance go hand in hand with shifts in approach–avoidance decisions[72], anger and aggression[107]. In particular, hypotheses about hemispheric specialization have advanced from an emotional valence hypothesis (for example, the left hemisphere is specialized for processing and expression of positive emotions, and the right hemisphere for negative emotions) to a motivational hypothesis (that is, the left hemisphere is specialized for approach responses, and the right hemisphere for avoidance responses) based primarily on electroencephalogram-asymmetry studies of response prediction[72].

Maltreatment and network architecture

The brain is organized into networks, and alterations in network architecture may underlie many forms of psychopathology[108]. We assessed network architecture in 142 maltreated and 123 non-maltreated individuals[90] by delineating between subject intraregional correlations in cortical thickness — as regions that correlate in size tend to be interconnected[109] — and evaluated a 112-node network encompassing the entire cortex. Graph theory was used to determine the central importance of each node. In the maltreated-individuals network, centrality was markedly reduced in the left ACC, temporal pole and middle frontal gyrus, and was increased in the right anterior insula and precuneus[90] (FIG. 6).

Regions with greater centrality in the control group compared with the maltreated group seem to have an important role in emotional regulation, attention and social cognition. The ACC is involved in regulating emotions[110] and in monitoring cognitive and motor responses during potential conflict situations[88]. Both the temporal pole and middle frontal gyri are involved in aspects of social cognition such as theory of mind[111], person perception and mentalizing[112]. By contrast, regions with greater centrality in maltreated versus control individuals seem to be primarily linked to self-awareness. The precuneus may be a critical region for self-centred mental imagery and self-referential thinking[113]. Increased precuneus centrality in maltreated individuals may be analogous to the enhanced functional connectivity within the precuneus-based posterior default-mode network (DMN) in patients with depression[114], who often have histories of maltreatment. The anterior insula is a locus for interoception, providing the substrate for internal body sensations such as thirst, hunger, heart rate, respiration and the need to void or eliminate[115]. The anterior insula and ACC function together in a manner analogous to sensory and motor cortices to give rise to the feelings (insula) and motivations (ACC) underlying emotions[115]. The anterior insula may also have a crucial role in self-awareness[115].

Several other maltreatment-related network studies[59,61] have emerged in the past few years (Supplementary information S10 (table)). One study examined a high-density resting-state network in depressed individuals with or without histories of neglect and in healthy controls[61]. There were a few shared network differences that, to some degree, distinguished both of the depressed groups from the controls. However, the most-prominent differences were observed between depressed individuals with and without early neglect; these groups differed markedly in PFC–limbic–thalamic–cerebellar functional connectivity[61]. This raises the crucial question of the associations between maltreatment, neurobiology and psychopathology.

There is also a growing body of research on the potential effects of maltreatment on specific functional networks, particularly the DMN. We identified nine studies investigating the DMN in maltreatment- or ELS-exposed individuals (Supplementary information S10 (table)). Four of the five studies comparing resting-state measures in childhood-maltreated adults and controls reported decreases in one or more measures of DMN connectivity in adults who experienced childhood maltreatment[116–119]. Studies also reported that maltreatment was associated with reduced connectivity between the DMN and the salience network[120] and increased DMN deactivation during working memory tasks[121]. By contrast, a study examining infants reported stronger DMN connectivity in those

Probe auditory evoked potentials
Electroencephalogram responses to irrelevant auditory probes such as clicks. The degree to which these responses are attenuated reflects the level of brain involvement in a competing cognitive task.

Graph theory
The study and use of graphs — collections of vertices (points or nodes) connected by edges (lines) — to represent, for example, brain regions and their interconnectivity.

Centrality
A graph-theory measure that indicates the importance of nodes in a graph or network.

Theory of mind
The ability to attribute mental states such as beliefs, intentions and desires to ourselves and others, and to recognize that the mental state of others is different from our own.

Default-mode network
(DMN). A network of brain regions that are activated when the brain is resting and not engaged in cognitive or goal-directed tasks.

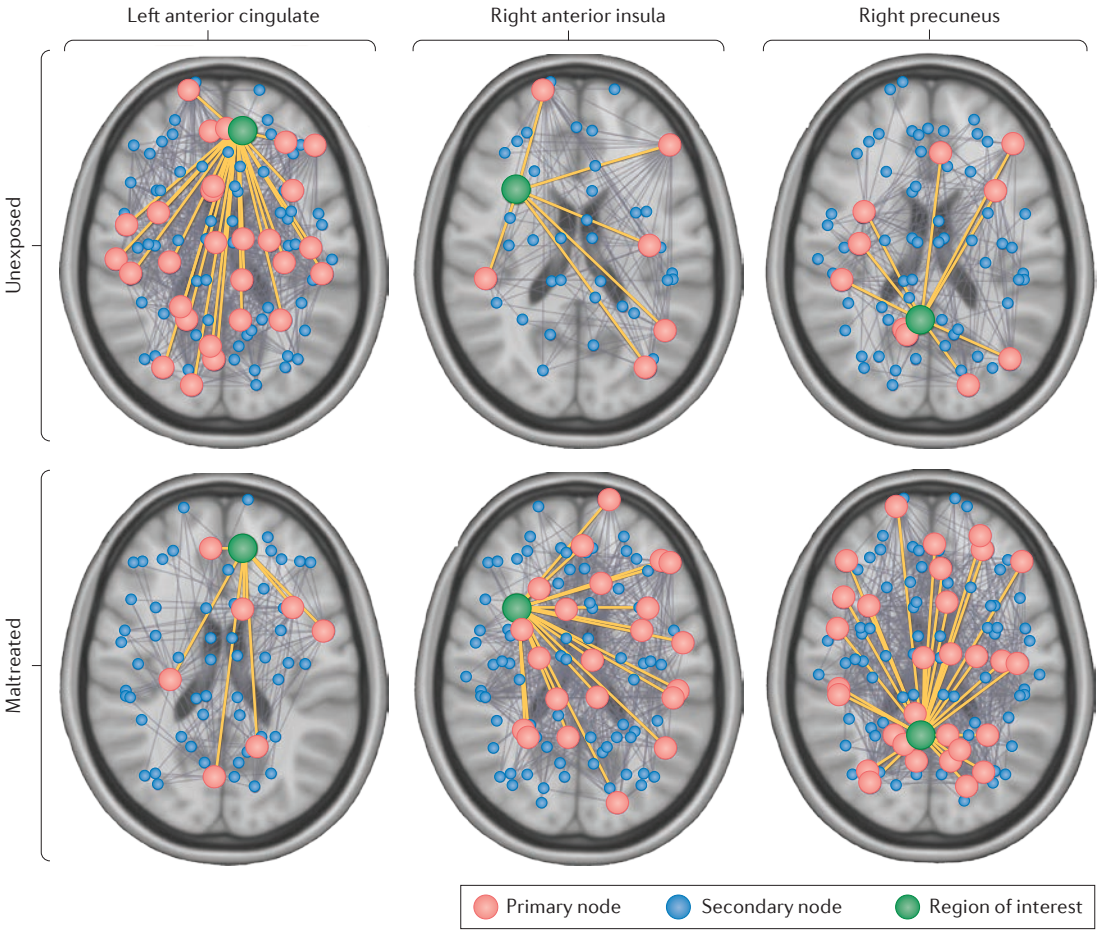

Figure 6 | **Network changes associated with childhood maltreatment.** Maltreatment during childhood has been found to be associated with changes in structural connectivity at the network level. Here, the entire cerebral cortex of young adults with ($n = 142$) or without ($n = 123$) histories of childhood maltreatment was divided into 112 regional nodes. Within each group, between-subject correlations in the cortical thicknesses of each nodal pairing were used to infer connectivity, as brain regions that co-vary reliably in size between subjects are either structurally or functionally interconnected[90]. Network architecture and the centrality of each node were then determined by applying graph theory to the 112 × 112-node maltreated and non-maltreated cross-correlation matrices. Three key differences in structural nodal centrality between maltreated and non-maltreated groups are shown here. Green circles indicate nodal centres (the regions of interest) in each case for the left anterior cingulate cortex (left), the right anterior insula (middle) and the right precuneus (right). Red circles indicate primary nodes, which are regions with direct connections to the nodal centre. Blue circles delineate secondary nodes, which have direct connections with the nodal centre but do not have direct connections with the nodal centre. Childhood maltreatment was associated with a marked decrease in the centrality of the left anterior cingulate, as indicated by a substantial decrease in primary and secondary connections. Conversely, maltreatment was associated with a significant increase in the centrality of the right anterior insula and the right precuneus, as indicated by the greater number of primary and secondary nodal connections in these regions in the maltreated group. Adapted with permission from REF. 90, Elsevier.

individuals experiencing higher levels of interparental conflict[122]. Unfortunately, however, all nine studies were small, with an average of only 15 participants per group.

Findings of decreased DMN connectivity may be at odds with our observation of maltreatment-related increased precuneus centrality[90] and increased precuneus volume in a large, independent, longitudinal sample[47]. A key difference was that the individuals in these two studies were selected from the community and were less symptomatic than individuals in the DMN studies (who were mostly adults with a persistent dissociative type of PTSD related to childhood trauma, or childhood-maltreated adults with BPD)[118,119,123]. In this regard, the findings of increased precuneus centrality and volume are similar to DMN findings in patients with major depression[114], which was the most prevalent clinical diagnosis in the sample in our study. Conversely, reduced DMN connectivity and synchronicity were associated with depersonalization or derealization and with PTSD severity[123]. Overall, it is likely that maltreatment is associated with altered development of the DMN, and that the way in which it is altered may have important clinical implications.

Psychopathology and resilience

We have recently argued that maltreated and non-maltreated individuals with the same primary psychiatric diagnosis need to be clearly differentiated, as the maltreated subgroup constitutes a unique ecophenotype with distinct clinical, neurobiological and genetic features[2]. This hypothesis is most clearly supported by studies assessing neuroimaging differences.

Reduced hippocampal volume is probably the most frequently reported imaging finding in studies comparing individuals with depression with healthy controls[124]. However, there is now good evidence that this finding is restricted to the maltreated ecophenotype[51,125,126]. Furthermore, maltreatment is a prepotent determinant, such that any statistically significant association between depression and hippocampal volume is lost once maltreatment is taken into account[51,52,126] or such that the relationship between depression and hippocampal volume is only discernible in the ecophenotype[127]. Hence, the clinical implications of the association between depression and reduced hippocampal volume are unclear, as smaller hippocampal volumes are also prevalent in resilient maltreated subjects without psychopathology[37,75,128].

To complicate matters, reduced hippocampal volume has been observed in several other psychiatric disorders, including PTSD, BPD, schizophrenia, dissociative identity disorder and antisocial personality disorder[129]. As childhood maltreatment is a major risk factor for all of these disorders, it may well have been an unrecognized confound in the original studies. Research is needed to determine whether the hippocampal loss observed in these disorders is limited to the maltreatment-related ecophenotype — although this is likely, given that smaller hippocampi are evident even in maltreated individuals without psychopathology[37,75,128]. Moreover, the possible contributions of reduction in hippocampal volume to risk, symptomatology and treatment response need to be re-evaluated. Further analyses have shown that marked neurobiological differences between healthy controls and individuals with psychiatric disorders are primarily restricted to the maltreated subset. These include differences in: ACC volume[130], network architecture[61] and amygdala responses to sad faces[34] in subjects with major depression; corpus callosum and white-matter microstructure in patients with bipolar disorder[56,97]; ACC, dorsolateral PFC and thalamic volume in subjects with schizophrenia or antisocial personality disorder[54,131]; and frontal, temporal and parietal GMV in subjects with psychotic disorders[132]. In these studies, the ecophenotypic variant of maltreated individuals differs markedly from controls in these brain measures, whereas in non-maltreated individuals with the same psychiatric diagnosis it does not.

Perhaps the most puzzling and intriguing set of findings come from studies of maltreated individuals in which none, or only a subset, has psychopathology. Our initial hypothesis was that maltreatment-related brain changes and psychopathology would go hand in hand, such that maltreatment-related brain differences would be seen primarily in individuals with psychopathology, whereas brains of resilient subjects would resemble brains of unexposed healthy controls. Some studies comparing maltreated individuals with and without PTSD support this hypothesis[81,133–135]. However, we identified many more studies, across various disorders, that suggest that maltreatment-associated abnormalities were, by and large, independent of the presence or absence of psychopathology[27,30,36,50–52,83,91,95,126,136–139] (Supplementary information S11 (table)) and were evident in maltreated children and adults with no previous or current psychopathology[37,45,49,55,75,83,92,96,98,116,128,140–143] (Supplementary information S12 (table)). Thus, there is a subgroup of maltreated individuals with abnormalities in stress-susceptible regions or pathways but without overt psychopathology, suggesting that these individuals are more susceptible to the neurobiological consequences of maltreatment than to the psychiatric consequences.

There are several ways to interpret this observation, including the null hypothesis that maltreatment-associated brain differences have no bearing on psychopathology. A more plausible possibility is that there may be additional differences in the brains of the resilient subjects (either pre-existing or adaptive) that enable these individuals to compensate for abnormalities in stress-susceptible structures. The likelihood that resilient subjects are compensating, rather than unaffected, is consistent with the finding that maltreated individuals without psychopathology differed from healthy controls in the way they regulated their mood from hour-to-hour and day-to-day, even though there were no differences in their average mood scores. Specifically, resilient maltreated individuals showed greater variability in ratings of positive affect and heightened persistence of negative affect[144].

There are a handful of reported differences that potentially distinguish maltreated, resilient individuals from both maltreated, susceptible individuals and unexposed controls. These include: increased fibre density of the anterior corpus callosum[104]; increased connectivity of the ventrolateral PFC[59]; increased connectivity of the dorsal ACC to lingual and fusiform gyri[145]; increased thickness of extrastriate visual cortex[27]; and larger left amygdala[81]. It is unclear whether increases in the ventral striatal response to reward[86] or in right hippocampal volume[81] represent resilience factors or the absence of risk factors. Identifying neurobiological differences between psychiatrically susceptible and resilient individuals is of paramount importance, as such studies may provide crucial therapeutic insights. Although the obvious therapeutic strategy is to endeavour to reverse maltreatment-related abnormalities that are associated with psychopathology, an effective alternative may be to foster or strengthen compensatory brain adaptations.

Conclusion

Imaging studies have provided a remarkable view of the potential effects of childhood abuse on brain structure, function and connectivity. With few exceptions, consistent evidence has emerged for maltreatment-associated structural deficits in the adult hippocampus, corpus callosum, ACC, OFC and dorsolateral PFC. Consistent functional deficits have been observed in

the amygdala when viewing emotional faces and in the striatum when anticipating a reward. Alterations in the sensory systems and pathways that convey the adverse experience have been reported in individuals who experienced specific forms of childhood abuse. These observations are concordant with an experience-dependent adaptation hypothesis that suggests that such alterations promote avoidance and diminish approach responses. The similarity among findings is compelling, as maltreated children in these studies are from remarkably different sample populations; they may have been Romanian orphans, children without psychopathology or members of a birth cohort, or individuals selected because they had reactive attachment disorder, depressed mothers, were at high-risk for depression or had PTSD. Likewise, similar neuroimaging findings have been reported in a diverse array of adults with histories of childhood maltreatment, including subjects selected from the community without regard to psychopathology or specifically selected because they had no psychopathology, or had major depression, chronic PTSD, bipolar disorder, psychotic disorders or personality disorders.

Importantly, previously reported findings of structural and functional differences between psychiatric groups and healthy controls need to be re-evaluated to take into account the possible prepotent confounding influence of maltreatment. In particular, studies comparing susceptible and resilient individuals with comparable exposure histories are needed to understand what role maltreatment-related alterations have in psychiatric symptomatology. We also probably know little about neurobiological abnormalities in non-maltreated individuals with psychiatric disorders, and this knowledge will only be gained by specifically comparing non-maltreated clinical groups with non-maltreated, healthy controls.

Studies in rodents and non-human primates demonstrate the influence that early experience exerts on trajectories of brain development (BOX 1). The human brain seems to be sculpted to at least the same degree by experience, with maltreatment standing out as a particularly potent factor. The vulnerability of brain structures to the effects of early experience may be moderated to a considerable degree by genetics[35,146–148] (Supplementary information S13 (table)). Belsky and Pluess[24] discuss the intriguing hypothesis that certain polymorphisms may together determine how malleable an individual is to both positive and negative experiences (phenotypic plasticity). In genetically susceptible individuals, maltreatment-induced epigenetic modifications that alter trajectories of brain development may, in many cases, represent the beginning of a crucial chain of events leading to psychopathology and risk of substance abuse[149,150]. Novel means of enhancing resilience and pre-empting the adverse consequences of exposure will probably a rise from future studies on the mechanisms linking maltreatment, brain development and psychopathology.

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Competing interests statement
The authors declare no competing interests.

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