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Annual Research Review: Enduring neurobiological effects of childhood abuse and neglect

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Background: Childhood maltreatment is the most important preventable cause of psychopathology accounting for about 45% of the population attributable risk for childhood onset psychiatric disorders. A key breakthrough has been the discovery that maltreatment alters trajectories of brain development. **Methods:** This review aims to synthesize neuroimaging findings in children who experienced caregiver neglect as well as from studies in children, adolescents and adults who experienced physical, sexual and emotional abuse. In doing so, we provide preliminary answers to questions regarding the importance of type and timing of exposure, gender differences, reversibility and the relationship between brain changes and psychopathology. We also discuss whether these changes represent adaptive modifications or stress-induced damage. **Results:** Parental verbal abuse, witnessing domestic violence and sexual abuse appear to specifically target brain regions (auditory, visual and somatosensory cortex) and pathways that process and convey the aversive experience. Maltreatment is associated with reliable morphological alterations in anterior cingulate, dorsal lateral prefrontal and orbitofrontal cortex, corpus callosum and adult hippocampus, and with enhanced amygdala response to emotional faces and diminished striatal response to anticipated rewards. Evidence is emerging that these regions and interconnecting pathways have sensitive exposure periods when they are most vulnerable. **Conclusions:** Early deprivation and later abuse may have opposite effects on amygdala volume. Structural and functional abnormalities initially attributed to psychiatric illness may be a more direct consequence of abuse. Childhood maltreatment exerts a prepotent influence on brain development and has been an unrecognized confound in almost all psychiatric neuroimaging studies. These brain changes may be best understood as adaptive responses to facilitate survival and reproduction in the face of adversity. Their relationship to psychopathology is complex as they are discernible in both susceptible and resilient individuals with maltreatment histories. Mechanisms fostering resilience will need to be a primary focus of future studies. **Keywords:** Child abuse; neglect; neuroimaging; resilience; stress.

Introduction

The deleterious effects of childhood maltreatment and early deprivation are widely reported and acknowledged. Both retrospective and prospective studies document associations between exposure to early maltreatment and poorer psychological and physical functioning in adulthood. Survivors of childhood maltreatment show higher prevalence of depression, anxiety, substance abuse, eating disorders, suicidal symptomatology, psychosis and personality disorder [see (Ball & Links, 2009; Bendall, Jackson, Hulbert, & McGorry, 2008; Norman et al., 2012; Teicher & Samson, 2013) for recent reviews] as well as diminished cognitive functioning (de Bellis, Hooper, Spratt, & Woolley, 2009; Gould et al., 2012) and poorer treatment response (Nanni, Uher, & Danese, 2012; Teicher & Samson, 2013). Green et al. (2010) estimated that maltreatment accounted for 45% of the population attributable risk for childhood onset psychiatric disorders. In addition, survivors of childhood maltreatment show higher adult rates of inflammation (Danese, Pariante, Caspi, Taylor, & Poulton, 2007), metabolic syndrome (Danese et al., 2009), arthritis (Spitzer et al., 2013), ischaemic heart disease (Dong et al., 2004), cancer (Brown et al., 2010) and shortened telomeres (Price, Kao, Burgers, Carpenter, & Tyrka, 2013) associated with reduced life expectancy (Brown et al., 2009). The exact pathways leading to these diverse negative outcomes remain to be revealed.

In this review, we examine the rapidly expanding body of research on the potential neurobiological consequences of childhood abuse and neglect, and summarize the most salient overarching discoveries. For this purpose, we included all studies we could identify that were published in English and presented a statistical analysis on the association between maltreatment (broadly defined) and brain measures of structure, function or connectivity as assessed using magnetic resonance imaging (MRI) or positron emission tomography (PET).

At the present time, a reasonably clear picture is emerging on the relationship between maltreatment and alterations in structure and function of stress-susceptible brain regions. New studies are also revealing substantial alterations in connectivity and network architecture. What is much less clear is the link between these discernible differences and psychopathology, which may require a revision in our understanding of the neurobiological basis of psychiatric disorders and a reconceptualization of resilience. Throughout the review, we will emphasize the importance of type and timing of exposure,

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possible differences between abuse and neglect, and the moderating influence of gender.

Categories of maltreatment

Studies of maltreatment typically examine the deleterious effects of childhood physical, sexual or emotional abuse. Key components of emotional maltreatment include verbal abuse, manipulation (e.g. placing the child in situations intended to elicit shame, guilt or fear in order to serve the emotional needs of the perpetrator or to persuade the child to perform actions against his or her will), denigrating or destroying things of value to the child, or placing the child in situations that are harmful, such as witnessing domestic violence (Teicher & Samson, 2013). Maltreatment also includes parental neglect, which can be physical neglect (failure to provide for the child's basic needs such as food, clothing, physical safety, adequate supervision, medical and dental health) or emotional neglect (failure to provide for the child's basic emotional needs). Emotionally neglectful parents may be emotionally unresponsive to a child's distress, fail to attend to the child's social needs or expect the child to routinely manage situations that are beyond his/her maturity level or are not safe (Teicher & Samson, 2013).

The potential impact of childhood adversity on brain structure and function is a relatively new area of inquiry, and the categories of maltreatment studied have shifted over time. Earlier studies tended to focus specifically on subjects with histories of physical or sexual abuse or who witnessed domestic violence. These trauma-exposed subjects were often preselected for histories of post-traumatic stress disorder (PTSD) (e.g. Bremner et al., 1997; Carrion et al., 2001; De Bellis et al., 1999), borderline personality disorder (e.g. Brambilla et al., 2004; Driessen et al., 2000; Schmahl, Vermetten, Elzinga, & Bremner, 2003) or dissociative identity disorder (e.g. Stein, Koverola, Hanna, Torchia, & McClarty, 1997; Vermetten, Schmahl, Lindner, Loewenstein, & Bremner, 2006), and were likely exposed to multiple types of abuse. This was followed by a large number of studies that used self-report scales, predominantly the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1994). Typically, the CTQ was used as a quantitative measure of severity of exposure (regardless of type) within mixed samples (with and without psychopathology) (Malykhin, Carter, Hegadoren, Seres, & Coupland, 2012), community samples (Teicher, Anderson, & Polcari, 2012) or samples without discernible psychopathology (Dannlowski et al., 2012; Edmiston et al., 2011). Other studies used the CTQ to study the relationship between brain findings and specific categories of abuse; often revealing strong associations with the emotional abuse (Carballedo et al., 2012), emotional neglect (Bogdan, Williamson, & Hariri, 2012; Frodl, Reinhold, Koutsouleris, Donohoe, et al., 2010) or physical neglect (Frodl, Reinhold, Koutsouleris, Reiser, & Meisenzahl, 2010) subscales. A few studies have limited recruitment to subjects exposed to only one type of maltreatment [e.g. parental verbal abuse (Choi, Jeong, Rohan, Polcari, & Teicher, 2009; Tomoda et al., 2011), peer emotional abuse (Teicher, Samson, Sheu, Polcari, & McGreenery, 2010), harsh corporal punishment (Sheu, Polcari, Anderson, & Teicher, 2010; Tomoda, Suzuki, et al., 2009)]. Interestingly, some of the most recent studies have focused predominantly on subjects with emotional maltreatment (Hanson, Hariri, & Williamson, 2015; van der Werff et al., 2013b; van Harmelen, Hauber, et al., 2014; van Harmelen, van Tol, et al., 2014).

Shortly after initial reports of the effects of maltreatment on brain structures were published, studies emerged on the neurobiological consequences of early deprivation, focusing on institutionally reared orphans (e.g. Chugani et al., 2001; Eluvathingal et al., 2006). Mean duration of institutional care varied across studies from 8 (Goff et al., 2013) to 63 months (Tottenham et al., 2010). In many of these studies, the orphans were adopted internationally into relatively affluent families (e.g. Bauer, Hanson, Pierson, Davidson, & Pollak, 2009; Govindan, Behen, Helder, Makki, & Chugani, 2010). These studies provide insight into the consequences of physical and emotional neglect during infancy and early childhood. The Bucharest Early Intervention Project is a remarkable controlled trial in which Romanian orphans were randomly assigned to either a newly established system of high-level foster home care versus continued institutional care (Smyke, Zeanah, Fox, & Nelson, 2009). This study provides compelling data on the impact and reversibility of early neglect on brain development (McLaughlin et al., 2014; Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012).

Key hypotheses regarding maltreatment and brain development

Thoughts about the potential effects of childhood abuse on brain development began with the idea that repeated exposure to stress could kindle the developing limbic system (van der Kolk & Greenberg, 1987). Findings of spike and sharp-wave electroencephalogram (EEG) abnormalities (Ito et al., 1993) and symptoms of 'limbic irritability' (Teicher, Glod, Surrey, & Swett, 1993), similar to the clinical and EEG findings observed in individuals with temporal lobe epilepsy, provided some support, as did early findings of reduced hippocampal volume (Bremner et al., 1997; Stein et al., 1997). Interestingly, 'limbic irritability' has endured, in our studies, as the symptom cluster most strongly associated with exposure to childhood maltreatment (Teicher & Parigger, 2015; Teicher, Samson, Polcari, & McGreenery, 2006; Teicher & Vitaliano, 2011; Teicher et al., 2010).

Based on preclinical studies, we went on to propose a more expansive hypothesis, that abusive experiences would induce a cascade of stress-mediated effects on hormones and neurotransmitters that would affect the development of vulnerable brain regions (Anderson, Teicher, Polcari, & Renshaw, 2002; Teicher, 2000; Teicher, Andersen, Polcari, Anderson, & Navalta, 2002). The first stage of the hypothesized cascade entails stress-induced programming of the glucocorticoid, noradrenergic and vasopressin–oxytocin stress response systems to augment or alter stress responses. These neurohumours, along with stress-induced release of neurotransmitters, would then affect basic processes including neurogenesis, synaptic overproduction and pruning, and myelination during sensitive periods in genetically susceptible individuals. These effects would likely target specific stress-susceptible brain regions including hippocampus, amygdala, neocortex, cerebellum and white matter tracts (Teicher et al., 2002). Brain structures likely to be especially vulnerable to the effects of childhood abuse would have one of more of the following features: (i) a protracted postnatal development; (ii) a high density of glucocorticoid receptors; and (iii) some degree of postnatal neurogenesis (Teicher et al., 2003).

We also introduced an alternative perspective on the nature of these brain changes. The predominant view of researchers in the field is that stress is harmful for the brain and particularly harmful for the developing brain (Lupien, McEwen, Gunnar, & Heim, 2009; National Scientific Council on the Developing Child, 2005). From this viewpoint, stress-induced alterations constitute damage, and psychopathology may then emerge as a result of this damage. However, it does not seem entirely plausible that natural forces have not selected for brains resistant to the effects of early stress, given the degree to which early stress has been an integral part of our ancestry.

Our alternative view is that the brain is modified by early stress in a potentially adaptive way (Teicher, 2000, 2002; Teicher et al., 2003). Briefly, we have proposed that exposure to substantial levels of childhood maltreatment nudges the brain along alternative developmental pathways to facilitate reproduction and survival in what, based on experience, appears to be a malevolent stress-filled world. In this case, psychopathology may emerge due to the mismatch between the world the brain was modified to survive in and the world it finds itself in during subsequent developmental stages.

These two hypotheses are not mutually exclusive. There may be types of exposure that trigger adaptive responses and experiences that are so egregious as to damage the brain in nonadaptive ways. It is also likely that polymorphisms that influence the expression of molecules involved in neurotransmission, stress response or brain development may render some individuals more susceptible to both the positive and negative impact of early experience (e.g. Beaver & Belsky, 2012). We will see however that many of the reported alterations make sense as potentially adaptive responses.

Key questions

In this review, we will touch on eight key questions. First, does childhood abuse affect brain structure and function? Second, does the type of maltreatment matter or are they all stressors? Third, does age at the time of abuse matter? Fourth, what is the temporal association between exposure and brain changes? Fifth, are boys and girls affected in the same way? Sixth, do the observed structural and functional consequences make more sense as adaptive responses or as nonspecific damage? Seventh, are the neurobiological consequences of childhood maltreatment reversible? Finally, what is the relationship between childhood abuse, brain changes and psychiatric illness?

Few of these questions have been explored in a systematic manner. Nevertheless, some preliminary answers can be gleaned from the existing body of literature. There is also a pressing mechanistic question – how does childhood maltreatment 'get under the skin' to produce these neurobiological effects? There are some intriguing insights available from translational studies regarding epigenetic and neuroinflammatory mechanisms but little to say as relevant clinical data are just emerging (e.g. Miller & Cole, 2012; Zhang, Labonte, Wen, Turecki, & Meaney, 2013), although this is an active area of inquiry.

Morphometry – overview

Research on the neurobiological effects of childhood abuse began with studies assessing alterations in electrophysiology (Ito, Teicher, Glod, & Ackerman, 1998; Ito et al., 1993; Schiffer, Teicher, & Papanicolaou, 1995; Teicher et al., 1997), but was quickly eclipsed by MRI studies assessing structural differences, and this constitutes the lion share of research on this topic. Most studies have used a region of interest (ROI) approach and have focused primarily on hippocampus, amygdala and cerebral cortex, as regions known to be stress susceptible. A significant number of studies have also used global approaches, such as voxel-based morphometry and tract-based spatial statistics, to identify alterations without preselection of ROIs.

Hippocampus

The hippocampus is a key limbic structure that is critically involved in the formation and retrieval of memories, including autobiographical memories (Nadel, Campbell, & Ryan, 2007). The hippocampus also contains place cells, which, along with grid cells in the interconnecting entorhinal cortex, provide an

internal positioning system for the spatiotemporal representation of places, routes and associated experiences (Moser, Kropff, & Moser, 2008). Hippocampal abnormalities have been reported in several different psychiatric disorders including post-traumatic stress disorder, major depression, schizophrenia, bipolar disorder and borderline personality disorder (Geuze, Vermetten, & Bremner, 2005).

The hippocampus is also the most obvious target in the brain to reflect the potential effects of childhood maltreatment. Densely populated with glucocorticoid receptors (Morimoto, Morita, Ozawa, Yokoyama, & Kawata, 1996), it is highly susceptible to damage from excessive levels of glucocorticoids (Sapolsky, Krey, & McEwen, 1985) such as cortisol. Further, preclinical studies showed that excessive exposure to glucocorticoids led to reversible atrophy of dendritic processes on pyramidal cells in the Cornu Ammonis (CA, particularly the CA3 subfield) and suppression of neurogenesis within the dentate gyrus (DG) (Sapolsky, 1996).

On balance, there is compelling evidence that adults with histories of maltreatment have smaller hippocampi than nonmaltreated comparison subjects. At the time of writing, we identified 37 papers reporting hippocampal findings in adults with childhood maltreatment, and 30 of these papers reported one or more significant differences between groups with versus without exposure, or an inverse correlation between severity of exposure and volume. Three papers reporting nonsignificant effects reported nearly significant reductions (Cohen et al., 2006) or correlations (Kumari et al., 2013; Woodward, Kuo, Schaer, Kaloupek, & Eliez, 2013) (in the nonviolent sample). Another studied failed to find differences in a geriatric sample (mean age 70.9 ± 3.7) (Ritchie et al., 2012) and may have been confounded by effects of ageing. All three of the remaining studies that did not find significant hippocampal changes examined only female participants and had relatively small sample sizes (Landre et al., 2010; Lenze, Xiong, & Sheline, 2008; Pederson et al., 2004).

These limitations are important as recent research suggests that female hippocampi may be less vulnerable to the effects of stress. For example, Samplin, Ikuta, Malhotra, Szeszko, and Derosse (2013) found in a group of 67 healthy adults without psychopathology that history of emotional abuse was associated with reduced hippocampal volume in males but not females. Frodl, Reinhold, Koutsouleris, Reiser, et al. (2010) reported greater male than female reductions in hippocampal white matter volume with exposure to neglect. Most striking, Everaerd et al. (2012) found in a sample of 357 participants that severe childhood abuse was associated with reduced hippocampal volume but only in males, and specifically in males who carried the short allele of the serotonin transporter promoter polymorphism. Further, a meta-analysis of PTSD studies revealed greater effects of trauma exposure on hippocampal volume in males than females (Karl et al., 2006). Increased resilience in females may be due to a potential neuroprotective effect of oestrogen as observed in translational studies (McEwen, 2010). This is not to say that maltreatment has no effect on hippocampal volume in females. Indeed, 12 of 15 published studies reported reductions in hippocampal volume in samples with all female participants. However, small N studies that only include female participants may well be underpowered given the potentially weaker effects of stress on the female hippocampus.

The relationship between childhood maltreatment and hippocampal volume is less clear when we focus specifically on studies involving children or adolescents, as has been previously reported (e.g. Andersen & Teicher, 2004; Teicher et al., 2003). Overall, we identified 16 relevant papers, in which 9 showed no significant decrease in volume, including two analyses that revealed a significant increase in white (Tupler & De Bellis, 2006) or grey matter volume (Whittle et al., 2013). However, this latter study also showed a significant attenuation in hippocampal development over the next 3.8 years in maltreated subjects, which was indirectly mediated by psychopathology. Paediatric subjects in studies reporting no significant reduction had a mean age of 11.26 ± 2.25 years (n = 596). In contrast, subjects in the studies reporting a significant reduction or growth attenuation had a mean age of 12.65 ± 3.01 years (n = 681), a small but possibly meaningful difference if the positive studies contained a higher percentage of postpubertal participants. This fits with the hypothesis that there may be a silent period between exposure to maltreatment and discernible neurobiological differences, with observable cross-sectional differences becoming fully discernible in the period between puberty and adulthood (Andersen & Teicher, 2004).

Two retrospective studies provide data on potential sensitive exposure periods. In a study of women with histories of childhood sexual abuse, Andersen et al. (2008) reported that bilateral hippocampal volume appeared to be most significantly affected by exposure at 3–5 years of age and to a lesser degree at 11–13 years of age. Similarly, in a cross-sectional analysis of a mixed-gender longitudinal sample with disturbed attachment and exposure to emotional abuse and neglect but not sexual abuse, Pechtel, Lyons-Ruth, Anderson, and Teicher (2014) found that right hippocampal volume appeared to be most sensitive to maltreatment at 7 and 14 years of age. These observations are supported by preclinical studies showing that early separation stress has much greater effects on synaptic density in hippocampus than prefrontal cortex, whereas adolescent stress exerts greater effects on prefrontal cortex than hippocampus (Andersen & Teicher, 2004, 2008). Two studies reported that maltreatment was

specifically associated with reduction in volume of hippocampal subfields containing CA3 and dentate gyrus (Pagliaccio et al., 2014; Teicher et al., 2012), revealing that the same portions of the hippocampus known to be susceptible to stress in laboratory animals are also the most susceptible in humans. This is important information as it supports the hypothesis that maltreatment affects dendritic arborization of pyramidal cells in CA3 and neurogenesis in the dentate gyrus.

One recent study by Luby et al. (2013) is worth noting. They assessed hippocampal volume in 3- to 6-year-old preschool children (n = 145, oversampled for risk for major depression), who were followed longitudinally for 3–6 years and scanned at 6–12 years of age (mean 9.7 ± 0.8 years). They found that left hippocampus volume was substantially influenced by affluence versus poverty (income-needs ratio) and that supportive-hostile parenting and stressful life events mediated this relationship. Right hippocampal volume was not significantly associated with income/needs ratio, but was correlated with supportive-hostile parenting. One reason why they may have observed effects on hippocampal volume in young children, while other studies have not, is that they appeared to have assessed exposure to adversity during peak hippocampal sensitive periods (Andersen et al., 2008; Pechtel et al., 2014). Second, they also used a direct observational measure of supportive-hostile parenting during this time. Third, they used regression rather than between group comparisons, which better accounts for graded differences in exposure. Hence, this study appeared to be optimally designed for detecting an early effect.

Interestingly, some studies showed only significant left-sided findings, others only right sided and others both. Adult studies with significant left only findings predominantly recruited samples in which most or all subjects had no psychopathology (3/7) or PTSD (2/7). Adult studies with significant right only findings predominantly recruited samples with borderline personality disorder (BPD) (3/6) or no psychopathology (2/6). Studies with both right and left significant findings predominantly recruited subjects with BPD (4/10) or major depression (3/10). None of the studies with left only significance were based on samples with BPD versus 7/16 with right or right and left significance (Fisher exact, p = 0.057). Further, all studies that we identified that were based on BPD samples and provided separate right/left results had right-sided findings. This suggests a potential role of right hippocampal abnormalities in BPD. It may be the case that maltreatment-related alterations in right hippocampal development serve as a risk factor for BPD. However, there are other possibilities. Reduced right hippocampal volume may have been a pre-existing risk factor for both maltreatment and development of BPD. Alternatively, BPD may arise from other neurobiological factors, but right hippocampal abnormalities may then emerge as a result of BPD symptomatology or behaviours (e.g. intense unstable relationships, suicide attempts, substance use). Nevertheless, this is an intriguing observation worth pursuing through longitudinal studies.

These studies also make a critically important point regarding potential neurobiological differences between maltreated and nonmaltreated individuals with the same primary DSM or ICD diagnosis (Teicher & Samson, 2013). For example, reduced hippocampal volume is probably the most frequently reported neuroimaging finding in studies comparing patients with major depression (MDD) to healthy controls (Cole, Costafreda, McGuffin, & Fu, 2011). However, Vythilingam et al. (2002) and Opel et al. (2014) reported that reduced hippocampal volume was restricted to the MDD subgroup with histories of maltreatment. In addition, any association between depression and hippocampal volume was lost once maltreatment was taken into account (Opel et al., 2014; Teicher et al., 2012). Further, reduced hippocampal volume has also been reported in studies of adults that include resilient subjects exposed to childhood maltreatment who have not developed psychopathology (Baker et al., 2013; Carballedo et al., 2012; Dannlowski et al., 2012; Everaerd et al., 2012; Gatt et al., 2009; Samplin et al., 2013; Teicher et al., 2012).

Overall, maltreatment appears to exert a predominant influence on hippocampal development regardless of presence or absence of psychiatric disorders. Hence, maltreatment has likely been an insidious confound in nearly all psychiatric neuroimaging studies. Eight different psychiatric disorders have been associated with reduced hippocampal volume (Geuze et al., 2005), and maltreatment is a major risk factor for all of these disorders. This suggests that the disordered group likely contained significantly more individuals with histories of maltreatment than the control group, seriously confounding the influence of psychopathology with the effects of maltreatment. Further, healthy control groups also contain a variable proportion of maltreated individuals, which can substantially contaminate the results if undetected (Shenk, Noll, Peugh, Griffin, & Bensman, 2015). If reduced hippocampal volume is primarily a consequence of childhood maltreatment, it would explain why this finding has been seen across a vast array of psychiatric disorders. Moreover, between-study differences in prevalence rates of maltreatment in clinical versus control groups would also explain why findings relating hippocampal volume to psychopathology have been inconsistent. The bottom line is that studies assessing the pathophysiology of psychiatric disorders need to take into account the confounding influence of childhood maltreatment, and claims about the role of hippocampal abnormalities in psychiatric disorders need to be reevaluated.

Amygdala

The amygdala is another key limbic structure that is critically involved in encoding of implicit emotional memories (LeDoux, 1993) and in detecting and responding to salient stimuli such as facial expressions and potential threats (Derntl et al., 2009). Structural or functional abnormalities in the amygdala have been observed in a wide array of psychiatric disorders including post-traumatic stress disorder, social phobias and specific phobias (Shin & Liberzon, 2010); unipolar and bipolar depression (Grotegerd et al., 2014); drug addiction (Koob & Volkow, 2010); autism (Kleinhans et al., 2010); borderline personality disorder (Goodman et al., 2014) and schizophrenia (Suslow et al., 2013).

Like the hippocampus, the amygdala has a high density of glucocorticoid receptors on stress-susceptible pyramidal cells (Sarrieau et al., 1986) and a postnatal developmental trajectory characterized by rapid initial growth followed by more sustained growth to peak volumes between 9 and 11 years with gradual pruning thereafter (Uematsu et al., 2012). Consequently, the amygdala should also be highly susceptible to exposure to early stress, and this vulnerability is borne out in translational studies (Caldji, Francis, Sharma, Plotsky, & Meaney, 2000; Eiland, Ramroop, Hill, Manley, & McEwen, 2012; Malter Cohen et al., 2013). Interestingly, both psychological stressors and stress hormone stimulate dendritic arborization and new spine formation on pyramidal cells in the amygdala, leading to an increase in volume (Mitra, Jadhav, McEwen, Vyas, & Chattarji, 2005; Vyas, Jadhav, & Chattarji, 2006), which is opposite to the effects of stress on the hippocampus. Further, stress-induced amygdala hypertrophy, unlike hippocampal hypotrophy, endures long after cessation of the stressor (Vyas, Pillai, & Chattarji, 2004).

Maltreatment-related alterations in amygdala volume should then be readily discernible based on these translational findings. However, that is not the case. Overall, we identified 27 studies reporting amygdala volume findings in subjects with maltreatment histories, or who were reared for periods of time in an institution, or by chronically depressed mothers. Eight of these studies reported a significant reduction, 13 reported no significant difference, and 4 reported a significant increase. Two studies delineated a more complex relationship, which will be discussed below. However, the results are not that inconsistent on deeper inspection. All but one of the nonsignificant studies that provided data on amygdala volumes (e.g. 9/10) observed a nonsignificant decrease, averaging 5.9% right and 5.0% left. Studies reporting a significant decrease (and providing volume data) reported a mean right/left per cent reduction of 18.8% and 21.6%. Hence, the vast majority of maltreatment studies reported either a nonsignificant or significant decrease (17/21).

Studies reporting a significant increase were distinctly different from those observing some degree of decrease. Two studies reported results from institutionally reared children (Mehta et al., 2009; Tottenham et al., 2010), one study reported results from children with chronically depressed mothers (Lupien et al., 2011), and another reported results from a longitudinal sample in which 83% of the adult maltreated subjects had disturbed attachment bonds as infants (Pechtel et al., 2014). Hence, increased amygdala volumes were observed primarily in subjects with early exposure to emotional and/or physical neglect.

In contrast, studies reporting significant reductions in amygdala volume predominantly evaluated adults or an older adolescent sample (6/8 studies) with exposure to multiple forms of maltreatment across development. Five of the eight studies also focused on subjects with current psychopathology [i.e. BDP (Driessen et al., 2000; Schmahl et al., 2003), dissociative identity disorder (Vermetten et al., 2006), major depression (Malykhin et al., 2012) or substance use disorders (Van Dam, Rando, Potenza, Tuit, & Sinha, 2014)]. Hence, studies showing significant reductions in amygdala volume had, on average, much older participants, greater degrees of psychopathology and exposure to multiple types of abuse during childhood.

Recent studies by Kuo, Kaloupek, and Woodward (2012), Whittle et al. (2013) and Pechtel et al. (2014) provide potentially important insights. Kuo et al. (2012) evaluated a group of 87 combat veterans for whom data were available on exposure to DSM-defined Criterion A traumatic events at or before 13 years of age. Childhood trauma was associated with a nonsignificant increase in amygdala volume and a highly significant interactive effect with degree of combat exposure. Subjects with childhood trauma had a progressive decrease in amygdala volume with increasing levels of combat experience. In contrast, amygdala volume showed no relationship to combat exposure in subjects without childhood trauma. Hence, early exposure appeared to sensitize the amygdala resulting in volume reductions with subsequent exposure to stress.

Whittle et al. (2013) have published the only large sample longitudinal neuroimaging study in maltreated subjects. Imaging was obtained on 139 subjects at 12.6 ± 0.5 years of age and repeated 3.8 ± 0.2 years later ($n = 117$). Maltreatment was associated with a nonsignificant increase in left amygdala volume at baseline. More dramatically, CTQ maltreatment scores were associated with a substantial effect on amygdala growth during late adolescence. Mediation modelling showed a robust direct suppressive effect of maltreatment on amygdala development. Hence, this study also provides some evidence that early exposure to maltreatment may increase volume but that later exposure to maltreatment results in a more reliable decrease in volume.

Pechtel et al. (2014) provided data from a small (n = 18) group of adult subjects in which quality of attachment was evaluated as infants using the strange intruder paradigm. They were compared to a group of healthy controls unexposed to any childhood adversity (n = 33). Right and left amygdala volume was increased in the longitudinal sample. Sensitive period analysis using the Maltreatment and Abuse Chronology of Exposure Scale (MACE) (Teicher & Parigger, 2015) showed that the right amygdala was exquisitely sensitive to exposure to maltreatment at 10–11 years of age and that only a modest degree of exposure was required to produce maximal hypertrophy. Indeed, even a few of the healthy controls, who fell below threshold for moderate exposure to any type of maltreatment, had sufficient exposure during the sensitive period to trigger hypertrophy. They also presented data from this sample (unpublished observation) that left amygdala volume was directly correlated (r = 0.68) with degree of attachment disturbance at 18 months of age. The key findings from this study are that amygdala hypertrophy may be observable in adulthood in a sample with relatively low levels of exposure to adversity after childhood and that left and right amygdala may have very different sensitive exposure periods.

Overall, these studies are compatible with the hypothesis that early exposure to maltreatment or neglect may result in an initial increase in amygdala volume, particularly noticeable during childhood. However, early exposure may also sensitize the amygdala to further stress and result in a substantial reduction in amygdala volume that would be most noticeable in late adolescence or adulthood. Additionally, the relationship between exposure and amygdala volume may be affected independently by presence or absence of psychopathology (Kuo et al., 2012; Whittle et al., 2013). The complex interplay between early exposure, later exposure and presence/absence of psychopathology on amygdala volume may provide a good explanation for between-study variability.

Cerebral cortex – overview

The cerebral cortex, like the hippocampus and amygdala, possesses a population of stress-susceptible pyramidal cells with a high density of glucocorticoid receptors that peak during late adolescence–early adulthood (Sinclair, Webster, Wong, & Weickert, 2011). There is also a population of glucocorticoid receptors on glial cells that are most densely distributed during the neonatal period and gradually decline. This suggests that the cerebral cortex may have two periods of heightened stress sensitivity; one during the period from infancy to early childhood, and the other during the period from late adolescence to early adulthood (Sarrieau et al., 1986). Sensitivity during adolescence to early adulthood also fits with the protracted developmental course of prefrontal cortical regions. Sensory and motor cortical regions, in contrast, develop earlier (Lenroot et al., 2009) and likely have earlier sensitive exposure periods. For this reason, and to foster greater clarity, we will divide our understanding of the potential effects of childhood maltreatment on cortical development into three sections. The first will focus on overall measures of cortical development that are not region specific. The second section will focus on development of higher-order association or polysensory cortex, and the third on primary and secondary sensory cortex.

Maltreatment and overall cortical development

A striking observation that emerged from the Bucharest Early Intervention Project was an overall 6.5% and 6.4% reduction in cortical grey and white matter volume, respectively, in orphans subject to early deprivation and who continued in institutional care (Sheridan et al., 2012). Identically reared orphans who were randomly assigned to high-quality foster care (between 7 and 33 months of age), showed a remarkably similar 6.4% reduction in grey matter volume. However, white matter volume appeared to recover in the adopted group so that the difference between adopted and never institutionalized controls was no longer statistically significant. Likewise, the difference between adopted orphans and those experiencing continued institutional care was nonsignificant, suggesting an intermediate effect. These studies were not adjusted for differences in intracranial volume.

Similar differences can be found in unadjusted cortical grey and white matter volume measures from samples of children selected for exposure to physical abuse, sexual abuse or witnessing domestic violence (e.g. Carrion et al., 2001; De Bellis et al., 1999; De Bellis et al., 2002). For example, De Bellis et al. (2002) provided unadjusted data indicating a 4.8% and 5.9% reduction in grey and white matter volume in a childhood trauma-exposed subjects from a sociodemographically matched sample, which is important factor as poverty is also associated with attenuated cortical grey and white matter development (Luby et al., 2013).

It is worth noting however that maltreatment-related differences in cortical grey and white matter volume disappear if the data are corrected for differences in intracranial volume (De Bellis et al., 1999; De Bellis et al., 2002). This indicates that cortical loss was proportional to the overall reduction in brain size. However, the reduction was not evenly distributed throughout the cortex and appeared to be primarily prefrontal as indicated by a substantial increase in prefrontal cortex cerebrospinal fluid (De Bellis et al., 1999; De Bellis et al., 2002). Consequently, several studies have focused on specific

cortical regions, assessing differences in volume, thickness, surface area and gyrification.

Maltreatment and association cortex

We have identified 41 published studies that provide morphometric data on association or polysensory cortical regions in individuals with histories of childhood maltreatment, neglect or early deprivation. Attenuated development of the anterior cingulate cortex (ACC) was the most consistent findings. These include reports of reduced ACC volume (e.g. Baker et al., 2013; Cohen et al., 2006; Thomaes et al., 2010), diminished thickness (Gupta et al., 2015; Heim, Mayberg, Mletzko, Nemeroff, & Pruessner, 2013) and decreased N-acetylaspartate to creatine ratio, indicative of neuronal loss or neuronal dysfunction (De Bellis, Keshavan, Spencer, & Hall, 2000). Most studies reported both right- and left-sided reductions, although a few found only right-sided differences (Kitayama, Quinn, & Bremner, 2006; Tomoda, Suzuki, et al., 2009), and significant thinning was observed only on the left side (Gupta et al., 2015; Heim et al., 2013).

Two other portions of prefrontal cortex were reported to have reduced volume, or blood flow in multiple studies. Attenuated dorsolateral prefrontal cortex measures have been reported in subjects with borderline personality disorder (Brambilla et al., 2004), with exposure to harsh corporal punishment or physical abuse (Hanson et al., 2010; Sheu et al., 2010; Tomoda, Suzuki, et al., 2009), and in maltreated subjects with no psychopathology (Carballedo et al., 2012; Edmiston et al., 2011). Similarly, reduced grey matter volume, blood flow or thickness has been reported in orbitofrontal cortex of Romanian orphans (Chugani et al., 2001; McLaughlin et al., 2014), subjects with physical, sexual or Department of Social Services documented abuse (De Brito et al., 2013; Hanson et al., 2010; Thomaes et al., 2010) and maltreated subjects without psychopathology (Gerritsen et al., 2012). Total prefrontal grey matter volume appeared to be most sensitive to maltreatment between 14 and 16 years of age (Andersen et al., 2008).

These three portions of prefrontal cortex are believed to play an important role in decision-making and emotional regulation. Moreover, neuroplastic changes in function and connectivity of these structures appear to be a critical factor in the preoccupation/anticipation and disrupted inhibitory control components of addiction (Koob & Volkow, 2010). Maltreatment-related alterations in these structures are but one of the ways that maltreatment affects the brain to enhance risk for addiction.

Sheffield, Williams, Woodward, and Heckers (2013) published an important study in which they used voxel-based morphometry to identify differences in grey matter density in psychotic disorder patients with and without maltreatment and healthy controls. They found that overall grey matter differences correlated with degree of exposure to sexual abuse and were limited to psychotic disorder patients with sexual abuse. Further, they found that psychotically disordered patients with sexual abuse histories differed significantly from healthy controls in medial and inferior frontal, inferior and superior temporal, and precentral gyri as well as inferior parietal lobe. However, psychotically disordered patients without sexual abuse histories only differed significantly from controls in cerebellar grey matter volume. Psychotic disorder patients with versus without sexual abuse histories differed significantly in grey matter volume in bilateral anterior cingulate cortex and left inferior frontal gyrus.

Similarly, Kumari et al. (2014) reported that group differences in anterior cingulate volume between patients with schizophrenia, antisocial personality disorder and healthy controls disappeared once history of psychosocial deprivation was taken into account. Hence, childhood abuse appears to exert a prepotent influence on cortical development even in subjects with the most severe psychiatric disorders, and efforts to identify the neurobiological correlates of psychopathology, as noted above, must disambiguate the confounding effects of abuse or neglect (Sheffield et al., 2013). This concern is underscored by the observation that prefrontal cortical deficits can be reliably observed in adults with childhood maltreatment histories but who show no history of psychopathology (Carballedo et al., 2012; Edmiston et al., 2011; Gerritsen et al., 2012).

Sensory cortex, fibre pathways and exposure to specific types of maltreatment

An intriguing story has emerged from a handful of studies assessing the effects of exposure to a specific type of abuse in relatively homogeneous collections of subjects. The first set of studies focused on young adults whose history of maltreatments was limited to severe exposure to parental verbal abuse. Diffusion tensor imaging (DTI) and tract-based spatial statistics (TBSS) were used to identify fibre tracts that differed significantly in measures of fractional anisotropy (as an indicator of overall integrity) in verbally abused subjects versus healthy controls. TBSS is an unbiased global analytical technique in which all major fibre bundles are evaluated without preselecting a pathway of interest. Three fibre tracts were identified that differed significantly between exposed subjects and unexposed controls (Choi et al., 2009). The most significant difference was found in the left arcuate fasciculus. This is a fibre tract that links the superior temporal gyrus with frontal cortex, interconnects Broca's and Wernicke's areas, and is critically involved in human language (Rilling et al., 2008). Diminished fractional anisotropy measures in this pathway were associated with lower verbal

comprehension and verbal IQ scores (Choi et al., 2009).

Fractional anisotropy was also reduced in the left cingulum bundle and left fornix (Choi et al., 2009). The cingulum bundle supports prefrontal (cingulate), parietal and temporal lobe interactions. Reduced integrity was observed specifically in the parahippocampal subdivision and correlated with depressive and dissociative symptoms (Choi et al., 2009). Reduced FA in this tract has also been observed in adolescence at risk for psychopathology with exposure to physical abuse, sexual abuse or witnessing domestic violence (Huang, Gundapuneedi, & Rao, 2012). Although this pathway has been implicated in major depression, a recent paper reported that FA in the rostral, dorsal and parahippocampal cingulum was strongly influenced by childhood adversity, but was not influenced by presence or absence of major depression (Ugwu, Amico, Carballedo, Fagan, & Frodl, 2014).

Fibres forming the fornix begin in the right and left hippocampi as the fimbria, converge in the midline, course anteriorly and diverge near the anterior commissure. The precommissural portion innervates septal nuclei and nucleus accumbens, while the postcommissural branch innervates mammillary bodies and the anterior nucleus of the thalamus, which projects to cingulate cortex. Reduced integrity in the fornix in these subjects was associated with symptoms of anxiety and somatization (Choi et al., 2009).

MRI scans from an overlapping group of subjects exposed repeatedly to parental verbal abuse but to no other forms of maltreatment were evaluated using voxel-based morphometry (VBM) (Tomoda et al., 2011). This is another unbiased whole-brain techniques that identifies significant clusters of altered grey matter density without preselection of regions of interest. A significant cluster of increased grey matter density was found in the left superior temporal gyrus corresponding to primary auditory cortex (Tomoda et al., 2011). Hence, these two global analytical techniques found that the most reliable correlates of exposure to severe parental verbal abuse were grey matter volume alterations in the left auditory cortex and diminished integrity of the left arcuate fasciculus language pathway.

TBSS and VBM were then used to assess the potential effects of visually witnessing multiple episodes of domestic violence during childhood. TBSS identified one pathway – the left inferior longitudinal fasciculus – that differed significantly in fractional anisotropy between subjects witnessing domestic violence and unexposed controls (Choi, Jeong, Polcari, Rohan, & Teicher, 2012). This fibre tract connects visual (occipital) and temporal cortex and is the key component of the visual-limbic pathway that subserves emotional, learning and memory functions that are modality specific to vision. More detailed analyses indicated that radial but not axial diffusivity was affected suggesting alterations in myelination. Sensitive period analysis using artificial intelligence found that this pathway was most vulnerable to witnessing domestic violence between 7 and 13 years of age (Choi et al., 2012), which corresponds to peak period of rapid myelination. FA values correlated inversely with ratings of depression, anxiety, somatization, 'limbic irritability' and neuropsychological measures of processing speed (Choi et al., 2012).

Tomoda, Polcari, Anderson, and Teicher (2012) evaluated volumetric scans from an overlapping group of subjects who visually witnessed multiple episodes of domestic violence using VBM and surface-based analyses (FreeSurfer) to delineate alterations in volume and thickness. The most robust difference in grey matter density was found in the right lingual gyrus (BA18). Thickness in this region was also reduced, as was thickness in left and right secondary visual cortex (V2) and left occipital pole. The lingual gyrus is an early processing component of the visual system involved in visual memory for shapes, faces and letters, and appears to be involved in nonconscious processing (e.g. processing outside of conscious awareness) (Slotnick & Schacter, 2006). These regions were maximally sensitive to exposure to witnessing domestic violence between 11 and 13 years of age (Tomoda et al., 2012). Regional reductions in GMV and thickness were observed in both psychiatrically susceptible and resilient subjects who witnessed domestic violence. In short, visually witnessing domestic violence was specifically associated with alterations in grey matter volume in portions of visual cortex and in the pathway interconnecting visual and limbic systems.

VBM and surface-based analyses were also used to identify the potential consequences of exposure to multiple episodes of forced sexual abuse in young women without preselection of regions. Subjects in this sample were raised by nonabusive parents but experienced extra-familial sexual abuse or were abuse sexually by relatives who were not part of the household (Tomoda, Navalta, Polcari, Sadato, & Teicher, 2009). Grey matter volume was markedly reduced in bilateral primary visual (V1) and visual association cortices of abused subjects. Extent of grey matter reduction was directly related to duration of sexual abuse before age 12 (Tomoda, Navalta, et al., 2009). Grey matter volume of left and right V1 correlated with measure of visual memory. Cortical surface-based analysis indicated that grey matter volume of abused subjects was reduced in the right lingual gyrus (as seen in subjects witnessing domestic violence) and in the left fusiform and left middle occipital gyri (Tomoda, Navalta, et al., 2009). These are regions involved in facial recognition and processing (Puce, Allison, Gore, & McCarthy, 1995).

In an independent study, Heim et al. (2013) measured cortical thickness in a group of women with or

without prepubertal exposure to abuse or neglect. Exposure to childhood sexual abuse was specifically associated with thinning of the portion of somatosensory cortex representing the clitoris and surrounding genital area (Heim et al., 2013). In contrast, thinning in precuneus bilaterally and the left anterior and posterior cingulate cortex were observed in women reporting emotional abuse (Heim et al., 2013). These regions are part of the default mode network and involved in self-awareness and self-referential thinking. Remarkably, exposure to childhood sexual abuse appeared to target grey matter volume in portions of visual cortex related to facial recognition and processing and thickness of somatosensory cortex specifically involved in processing and experiencing tactile sensations from the genitals.

It is compelling that unbiased analytical techniques found alterations in sensory systems and pathways in maltreated individuals that were specifically tied to one or two sensory modalities. Based on these studies, we hypothesized that brain regions and fibre tracts that process and convey the adverse sensory input of the abuse may be specifically modified by this experience, particularly in subjects exposed to a single type of maltreatment. We have hypothesized that exposure to multiple types of maltreatment may more commonly produce alterations in corticolimbic regions involved in emotional processing and stress response (Choi et al., 2012; Tomoda et al., 2012). These studies provide strong support for the overarching hypothesis that brain changes in maltreated individuals represent modifications or adaptations rather than nonspecific damage. Further, the close correspondence between type of maltreatment and associated sensory system abnormalities provides independent neuroimaging support for the veracity of retrospective self-report regarding type of abuse experienced. Heim et al. (2013) proposed that neuroplastic cortical adaptations may protectively shield a child from the sensory processing of the specific abusive experience. However, thinning of the somatosensory cortex may lead to the development of behavioural problems, such as sexual dysfunction, later in life. Similarly, alterations in visual-limbic and linguistic pathways and associated cortical regions may lead to impairments in verbal comprehension, visual recall and emotional responses to witnessed events.

Corpus callosum and additional fibre tracts

One of the earliest and most consistent finding in maltreated children (e.g. De Bellis et al., 1999; De Bellis et al., 2002; Teicher et al., 2004) and adults (e.g. Andersen et al., 2008; Teicher et al., 2010) is reduced area or integrity of the corpus callosum. Significant reductions in area or fractional anisotropy were reported in 16 of 21 identified studies, with the remaining studies typically reported reductions that fell short of statistical significance.

One interesting variation was a report by Galinowski et al. (2015) who assessed the relationship between exposure to negative life events and fractional anisotropy in a large sample of adolescents. They reported an increase in FA in corpus callosum segments II and III in resilient subjects (i.e. individuals with low risk of mental disorder despite high exposure to lifetime stress). However, they also observed a linear trend for corpus callosal FA to be greater in resilient subjects than controls, and greater in controls than susceptible subjects. Hence, it is possible that the nature of the response of the corpus callosum to early stress may play a significant role in determining psychiatric resilience. However, as this was a cross-sectional study other alternatives need to be considered, such as the possibility that increased fractional anisotropy in the corpus callosum could have been a pre-existing protective factor.

Several studies suggest that exposure to maltreatment is associated with a twofold greater reduction in corpus callosum area in boys than girls (De Bellis & Keshavan, 2003; De Bellis et al., 1999; De Bellis et al., 2002; Teicher et al., 1997; Teicher et al., 2004). We also reported that corpus callosal area appeared to be most susceptible to neglect in males and to sexual abuse in females (Teicher et al., 2004). This may be a result of males having an earlier sensitive period, as neglect tends to be most harmful during infancy and early childhood. In contrast, likelihood of exposure to sexual abuse in females increases with age (Teicher & Parigger, 2015), and we reported that the midportion of the female corpus callosum was particularly susceptible to sexual abuse between 9 and 10 years of age (Andersen et al., 2008). Preclinical studies have identified prominent sex differences in corpus callosum response to early experience (Juraska & Kopcik, 1988).

A particularly important study by Sheridan et al. (2012) provided data on the potential reversibility of the effects of early neglect on the corpus callosum. Using data from the Bucharest Early Intervention Project, they found significant reductions in corpus callosal area in orphans who remained in institutional care. Corpus callosum area, however, was nonsignificantly reduced relative to controls in orphans randomly assigned at about 15 months of age to high-level foster care, suggesting either that the effects of very early neglect were substantially reversed, or that the corpus callosum was significantly affected by experiences taking place in the institutionalized group in the period between random assignment and scanning.

The most frequently reported reductions in corpus callosum area were in segments IV and V (anterior and posterior midbody) followed by segments VI and VII (isthmus and splenium). Maltreatment-related

alterations in anterior portions (I–III, rostrum, genu and rostral body) have been reported in only a few studies, most notably in maltreated subjects with bipolar I disorder versus nonmaltreated bipolar I and healthy controls (Bucker et al., 2014) and in subjects with no psychopathology (Paul et al., 2008). The greater vulnerability of central and posterior segments is consistent with the observation that these portions of the corpus callosum manifest the greatest degree of growth between 5 and 18 years of age (Luders, Thompson, & Toga, 2010).

The corpus callosum is the largest white matter tract and plays a critically important role in interhemispheric communication, particularly between contralateral cortical regions. Motor, somatosensory and parietal association cortices are interconnected through segments IV and V. Superior and inferior temporal cortices, posterior parietal cortex and occipital corticies are interconnected through segments VI and VII. Interestingly, IQ measures correlate most strongly with thickness in these corpus callosum segments, and is consistent with the finding that interhemispheric communication between these more posterior cortical regions plays an important role in problem-solving (Luders et al., 2007).

Reduced corpus callosal thickness has been reported in children with ADHD (Luders et al., 2009) and in children and adults with bipolar disorder (Arnone, McIntosh, Chandra, & Ebmeier, 2008; Baloch, Brambilla, & Soares, 2009). However, a study by Bucker et al. (2014) suggests that reduced corpus callosum thickness may be limited, at least initially, to bipolar patients with histories of childhood maltreatment. This possibility is supported by the observation of an inverse relationship between number of adverse childhood experiences and axial diffusivity in several fibre tracts in hospitalized bipolar patients, including the corpus callosum (Benedetti et al., 2014). These studies buttress our concern that previously reported neuroimaging findings of differences between psychiatric groups and healthy controls need to be reevaluated to take into account the prepotent influence of maltreatment.

We likely know more about the impact of abuse and neglect on the corpus callosum than other fibre tracts, as it is massive, readily discernible on MRI and easy to measure. The development of diffusion tensor imaging and tract-based spatial statistical techniques have made it possible to evaluate maltreatment-related differences in less prominent pathways, including the arcuate fasciculus, cingulum bundle, fornix and inferior longitudinal fasciculus discussed in the previous section. Vulnerability of two additional pathways has come to light.

Eluvathingal et al. (2006) and Govindan et al. (2010) reported that there were significant reductions in FA in the uncinate fasciculus of orphans exposed to about 3 years of early deprivation, and FA in this pathway correlated inversely with duration of time in the orphanage (Govindan et al., 2010). The uncinate fasciculus interconnects limbic regions (i.e. amygdala and hippocampus) with orbitofrontal cortex, and abnormalities in the integrity of this pathway have been associated with a number of different psychiatric disorders including social anxiety disorder (Phan et al., 2009), schizophrenia (Kawashima et al., 2009), bipolar disorder (McIntosh et al., 2008), schizotypal personality disorder (Gurrera et al., 2007), major depression (de Kwaasteniet et al., 2013) and psychopathy (Craig et al., 2009). We do not know the extent to which these clinical relationships are confounded by exposure to neglect or early life stress. We do know that within a hospitalized sample of bipolar I patients that adverse childhood experiences were inversely associated with uncinate fasciculus integrity, suggesting that maltreatment may account for a substantial portion of the variance (Benedetti et al., 2014).

Reduced integrity of the superior longitudinal fasciculus has also been reported in orphans with early deprivation (Govindan et al., 2010), in adolescents exposed to physical abuse, sexual abuse or witnessing domestic violence (Huang et al., 2012), and in hospitalized bipolar adults with childhood adversity (Benedetti et al., 2014). This is a very long fibre pathway that primarily interconnects parietal and frontal cortical regions. This pathway conveys information regarding the spatial location of body parts, awareness of visual space and somatosensory information, such as language articulation, to portions of prefrontal cortex involved in motor planning, working memory and speech. The previously mentioned arcuate fasciculus, which interconnects Wernicke's and Broca's areas, is also considered to be part of this pathway. Reduced FA in the superior longitudinal fasciculus has been observed in children and adults with ADHD (Hamilton et al., 2008; Wolfers et al., 2015), bipolar disorder (Benedetti et al., 2011; Frazier et al., 2007), major depression (Lai & Wu, 2014) and schizophrenia (Clark et al., 2012; Melicher et al., 2015).

Sun et al. (2015) recently reported that first episode individuals with schizophrenia can be clustered into two groups: one with pervasive white matter deficits and another with deficits limited specifically to the superior longitudinal fasciculus. It would be interesting to know whether there is a relationship between these patient clusters and history of exposure to maltreatment.

Striatum

Relatively few studies have reported associations between maltreatment and morphology of striatal regions, and the results have been inconsistent. Interest in this region will likely increase given the recent finding that neuroblasts generated throughout adult life in the lateral ventricle wall migrate

specifically to the striatum and integrate as interneurons (Ernst et al., 2014). Nonsignificant increases in caudate volume with maltreatment have been reported in three studies (Bremner et al., 1997; De Bellis et al., 1999; De Bellis et al., 2002), significant decreases in two (Baker et al., 2013; Cohen et al., 2006), nonsignificant decreases in three (Brambilla et al., 2004; Kumari et al., 2013; McLaughlin et al., 2014) and no difference and no apparent sensitive period in another (Pechtel et al., 2014). Similarly, significantly increased putamen volumes have been reported in two studies (Brambilla et al., 2004; Kumari et al., 2013), nonsignificant increases in another (De Bellis et al., 1999), nonsignificant mixed hemispheric effects in one (De Bellis et al., 2002) and a nonsignificant decrease in a fifth study (McLaughlin et al., 2014). An overall inverse correlation between CTQ scores and striatal grey matter volume (not distinguishing caudate from putamen) was reported by Edmiston et al. (2011).

There are a number of possible explanations for the inconsistent findings. First, these regions may not be sensitive to the effects of early life stress in humans. Second, exposure to certain types of maltreatment at specific ages may result in an increase in volume, and at other times a decrease (e.g. Walsh et al., 2014; Whittle et al., 2013). Third, the effects may be complicated or obscured by psychopathology. Fourth, there could be unrecognized gender differences (Edmiston et al., 2011). Fifth, early life stress may have a more discernible influence on function or connectivity than structure.

In this regard, we observed a prominent increase in T2-relaxation time (an indirect and inverse measure of resting cerebral blood volume) in right caudate, putamen, nucleus accumbens and substantia nigra in young adults exposed to high levels of harsh corporal punishment (Sheu et al., 2010). Further, as will be presented below, there is consistent evidence that maltreatment is associated with reduced anticipatory reward response in portions of the striatum, suggesting a consistent influence of maltreatment on function but not volume.

Cerebellum

Three pieces of information suggest that the cerebellum should be highly sensitive to the effects of early life stress. First, the cerebellum has the highest density of glucocorticoid receptors during the neonatal period in rats (Pavlik & Buresova, 1984), and the density of glucocorticoid receptors in the cerebellum of nonhuman primates has been reported to substantially exceed receptor density in the hippocampus (Sanchez, Young, Plotsky, & Insel, 2000). Second, postnatal neurogenesis occurs in cerebellum, although during a more circumscribed period than in the hippocampus or striatum (Walton, 2012). Third, exposure to high levels of glucocorticoids during early development exerted a more persistent effect on cerebellar than hippocampal volume in rats (Ferguson & Holson, 1999).

Few studies, however, have examined the associations between maltreatment and cerebellar measures. Overall, 8 of 10 identified studies reported significantly lower volume measures in one or more portions of the cerebellum and another study reported an increase in resting T2-relaxation time, corresponding to a decrease in cerebral blood volume, in the cerebellar vermis of women with histories of childhood sexual abuse (Anderson, Teicher, et al., 2002). Altogether, five studies reported significant alterations in the vermis (Anderson, Teicher, et al., 2002; Baldacara et al., 2011; Carrion et al., 2009; Hanson et al., 2010; Walsh et al., 2014), which is the midsagittal portion interconnecting the two hemispheres. Six studies have identified significantly lower volumes in the hemispheres or the entire structure (Bauer et al., 2009; De Bellis & Kuchibhatla, 2006; Edmiston et al., 2011; Hanson et al., 2010; Kumari et al., 2013; Walsh et al., 2014). These studies are heterogeneous with samples that include children exposed to physical abuse, sexual abuse or witnessing domestic violence with PTSD symptoms or diagnosis, adoptees from Rumania, Russia, China and other Eastern countries, children without psychopathology, older adolescents studied longitudinally, adults with histories of childhood sexual abuse, PTSD resilient and susceptible adults with postchildhood trauma and varying degrees of early life trauma, violent and nonviolent adults with schizophrenia, antisocial personality disorder and healthy controls.

Our interest in the cerebellar vermis stems from the work of Harlow, Dodsworth, and Harlow (1965) on the deleterious effects of maternal separation and early isolation. Mason and Berkson (1975) showed that the availability of a swinging wire primate surrogate greatly diminished the degree of psychopathology (aggression, self-stimulation) seen in adults as a result of early maternal deprivation. Prescott (1980) suggested that both proprioceptive and vestibular stimulation was protective, and this information is integrated and processed within the flocculus and ventral paraflocculus or the cerebellum proper and lobules IX and X of the cerebellar vermis (Meng, Laurens, Blazquez, & Angelaki, 2015).

Heath (1972) found that primates reared in isolation had epileptiform EEG patterns in their fastigial nuclei, which project from the vermis to the limbic system and modulate seizure susceptibility (Cooper & Upton, 1978, 1985; Heath, 1977). Interestingly, we found a strong inverse relationship between resting cerebral blood volume in the vermis and symptoms of limbic irritability (Anderson, Teicher, et al., 2002). Based on its connections, the vermis has been described as the 'limbic cerebellum' (Snow, Stoesz, & Anderson, 2015). Abnormal vermal volume measures have been reported in autism (Courchesne, Yeung-Courchesne, Press, Hesselink,

& Jernigan, 1988), as well as in schizophrenia, bipolar disorder, major depression and attention deficit hyperactivity disorder (Baldacara, Borgio, Lacerda, & Jackowski, 2008). Indeed, volumetric deficits in lobules VIII–X are amongst the strongest morphometric findings in ADHD (Berquin et al., 1998; Bledsoe, Semrud-Clikeman, & Pliszka, 2009; Castellanos et al., 2001). Further, blood flow and metabolic activity in the vermis is strongly affected by the stimulant drug methylphenidate (Anderson, Polcari, Lowen, Renshaw, & Teicher, 2002; Volkow et al., 2003), and chronic treatment appears to reverse vermal abnormalities in children with ADHD (Bledsoe et al., 2009). The relationship between psychopathology and cerebellar abnormalities, however, needs to be re-examined to take into account the potential confounding effects of childhood maltreatment.

Functional imaging studies

In recent years, there has been a marked increase in studies using specific tasks to assess differences between maltreated individuals and unexposed controls in functional brain response. Two tasks have received the most attention. In the emotional faces paradigm, subjects view images of faces with different emotional expressions. Typically, subjects see neutral, angry, sad, fearful and sometimes happy faces. In some versions of this task, they press a button to indicate the subject's gender. In another version, they see a relatively large image of a face in the upper centre and two smaller images to the right and left below, and select the right or left image that matches the centre. Button presses are intended to have participants focus on the task, but not to consciously identify the facial expression. Most studies specifically analyse the blood oxygen level dependent (BOLD) response of the amygdala to negative versus neutral images to provide information on the functional properties of a brain circuit involved in threat detection, evaluation and response (Ohman, 2005; Suslow et al., 2006).

Another substantial number of studies use the monetary incentive delay task (Knutson, Adams, Fong, & Hommer, 2001). Briefly, in this task subjects are given a cue regarding the monetary value of a trial and then following a delay perform a task to try to either receive the payment or avoid the anticipated loss, and then receive the results. This is a clever task that can provide information on reward prediction, anticipation, outcome processing and consumption. There are three key features of this task. First, the ventral striatum (which contains the nucleus accumbens and more ventral aspects of the caudate and putamen) is activated proportionally to the magnitude of the anticipated gain but not loss (Knutson, Adams, et al., 2001). Second, received reward activates portions of the ventromedial frontal cortex (Knutson, Fong, Adams, Varner, & Hommer, 2001). Third, response in the dorsal striatum (dorsal caudate and putamen) is related to the valence (positive/negative) and the subject's level of motivation (Miller, Shankar, Knutson, & McClure, 2014). Overall, these two tasks provide important information of the positive and negative valence system and play a critical role in approach and avoidance decisions.

Threat detection and response

Overall, we identified nine functional imaging studies assessing response to emotional faces in this paradigm, and all are consistent in reporting that maltreatment is associated with enhanced amygdala reactivity to emotional faces. Increased amygdala activation has been observed in orphans who experienced caregiver deprivation (Goff et al., 2013; Maheu et al., 2010; Tottenham et al., 2011), as well as in children exposed to either family violence (McCrory et al., 2011), stressful life events (Suzuki et al., 2014) or physical or sexual abuse with symptoms of post-traumatic stress (Garrett et al., 2012). It has also been reported in maltreated adults with depression (Grant, Cannistraci, Hollon, Gore, & Shelton, 2011), as well as in adults selected from the general population (Bogdan et al., 2012) and resilient maltreated adults with no history of psychopathology (Dannlowski et al., 2012).

Interestingly, brain regions and pathways involved in regulating response to threatening stimuli (Herman & Mueller, 2006; LeDoux, 1996; LeDoux, 2002; Maren, Phan, & Liberzon, 2013) overlap extensively with regions found to differ structurally in maltreated individuals (Teicher & Samson, 2013). These include thalamus, visual cortex, anterior cingulate cortex, ventromedial prefrontal cortex, amygdala and hippocampus. Further, diminished integrity has also been observed in the fibre tracts that interconnect these regions in subjects with histories of maltreatment. Affected pathways in this circuit include the inferior longitudinal fasciculus, superior longitudinal fasciculus/arcuate fasciculus, uncinate fasciculus, cingulum bundle and fornix. Hence, most of the previously discussed regions and fibre tracts turn out to be key components of this threat detection and response circuit. Overall, these findings fit with the hypothesis that maltreatment-related alterations can be best understood as adaptive modifications, which in this case lead to enhanced threat detection and more rapid recognition of fearful stimuli (Masten et al., 2008). Interestingly, this circuit has a rapidly responsive nonconscious subcortical path and a slower conscious cortical path to the amygdala. Maltreatment-related alterations in sensory cortex, as noted above, may diminish the influence of the conscious component favouring a rapid but less nuanced response via the subcortical pathway.

Evidence is also emerging regarding sensitive exposure periods for a number of regions and pathways within this circuit. This includes the hippocampus (Andersen et al., 2008; Pechtel et al., 2014), amygdala (Pechtel et al., 2014), prefrontal regions (Andersen et al., 2008; Baker et al., 2013), visual cortex (Tomoda et al., 2012) and inferior longitudinal fasciculus (Choi et al., 2012). Peak periods of sensitivity vary from 3 to 5 years of age in hippocampus to 14–16 years of age in prefrontal cortex (Andersen et al., 2008), with the other components falling in between. Taken together, the circuit as a whole appears to be vulnerable throughout childhood, even though the individual parts appear to have more circumscribed periods of risk. This also fits with the hypothesis that enhanced threat detection is a highly conserved adaptive response to maltreatment that can occur regardless of age at the time of exposure. If this finding holds it may have important clinical implication, as degree of reversibility may depend on regions affected (e.g. amygdala versus hippocampus), and optimal treatment strategies may vary based on whether affected components are cortical or subcortical.

Reward anticipation

Another consistent functional imaging finding reported in six studies is diminished BOLD response in the striatal regions of maltreated individuals to anticipated reward in the monetary incentive delay task. This finding has been observed in both children and adults and includes orphans experiencing early deprivation (Mehta et al., 2010); children with reactive attachment disorder (Takiguchi et al., 2015); maltreated children at high risk for depression (Hanson et al., 2015); a birth cohort studied as adults who experienced early family adversity (Boecker et al., 2014); and adults reporting exposure to physical, sexual or emotional abuse (Dillon et al., 2009).

The principal regions regulating this response are key components of the reward system and consist of the mesolimbic and striatal target territories of the midbrain dopamine neurons (Haber & Knutson, 2010). These include the anterior cingulate cortex, orbital prefrontal cortex, ventral striatum and ventral pallidum. Other structures regulating this circuit include dorsal prefrontal cortex, amygdala, hippocampus, thalamus, lateral habenular nucleus, and pedunculopontine and raphe nuclei in the brainstem (Haber & Knutson, 2010). As noted above, maltreatment-related morphological differences have been observed in many of these regions. In particular, findings of reduced volume, thickness or blood flow have been reported in anterior cingulate cortex (Baker et al., 2013; Cohen et al., 2006; Heim et al., 2013; Thomaes et al., 2010), orbitofrontal cortex (Chugani et al., 2001; Gerritsen et al., 2012; Hanson et al., 2010; Thomaes et al., 2010), dorsolateral prefrontal cortex (Brambilla et al., 2004; Carballedo et al., 2012; Edmiston et al., 2011; Hanson et al., 2010; Sheu et al., 2010; Tomoda, Suzuki, et al., 2009) and hippocampus (e.g. Dannlowski et al., 2012; Everaerd et al., 2012; Opel et al., 2014; Pagliaccio et al., 2014; Teicher et al., 2012).

Interestingly, while all of the monetary incentive delay task studies showed reduced striatal response to anticipated reward anticipation, morphological studies focusing on the striatum have been inconsistent. There are two likely possibilities. First, the consistent observation of diminished striatal activation to reward anticipation in maltreated individuals may stem from molecular changes within the striatum that are not accompanied by reliable morphological differences (e.g. Brake, Zhang, Diorio, Meaney, & Gratton, 2004). Second, reduced striatal response may arise as a secondary consequence of alterations in other portions of the circuit. These same considerations also apply to the observation of enhanced amygdala response to threatening stimuli in maltreated individuals, which is a more consistent finding than maltreatment-related alterations in amygdala volume.

Reduced BOLD response to anticipated reward magnitude in the ventral striatum can also be construed as a potentially adaptive response. Indeed, it goes hand-in-hand with increased amygdala response to threat, as both may serve to tip the balance in an approach–avoidance conflict situation to avoidance. This shift in balance may be judicious and increase likelihood of survival and reproductive success (i.e. the passing of genes onto subsequent generations) in an environment fraught with danger. The downside is that they may also lead to symptoms of depression/anhedonia (Pizzagalli et al., 2009; Wacker, Dillon, & Pizzagalli, 2009) or anxiety (Etkin et al., 2004; Redlich, Grotegerd et al., 2014) and enhance risk for addiction (Balodis & Potenza, 2015).

Maltreatment and network architecture

Neuroimaging studies of maltreated individuals have predominantly focused on region of interest in an effort to assess differences in morphology or connectivity. While these studies have played a critical role in shaping our understanding of the impact of maltreatment on the developing brain, there is increasing recognition that the brain is organized into complex networks and that alterations in network architecture may provide a means to better understand the causes and consequences of psychopathology.

Brain network architecture is studied using techniques from social network analysis and graph theory (He & Evans, 2010), which have been applied to four types of networks. The lion share of interest has been devoted to functional connectivity networks discernible in resting-state fMRI followed by

structural connectivity networks based on diffusion tensor imaging of fibre tracts (He & Evans, 2010) and electrophysiological networks derived from electroencephalography or magnetoencephalography (van Straaten & Stam, 2013).

Interestingly, structural connectivity networks can also be delineated by studying between subject intraregional correlations in measures of cortical thickness or grey matter volume, as regions that correlate in size with each other across a large number of subjects tend to be interconnected through white matter tracts or functionally coupled (He & Evans, 2010). We employed this approach to study cortical network architecture in 256 subjects with and without histories of maltreatment (Teicher, Anderson, Ohashi, & Polcari, 2014). We evaluated a 112 node network consisting of all cortical regions and used graph theory to determine the central importance of each node in the maltreated and unexposed networks. Overall, 9 nodes differed significantly between maltreated and control subjects in two or more measures of central importance. The most significant differences between these networks were marked reductions in the centrality of the left anterior cingulate and left temporal pole, and increased centrality of right precuneus and right anterior insula in the maltreated networks (Teicher et al., 2014).

Regions with greater centrality in the healthy control network are involved in emotional regulation, attention or social cognition. The anterior cingulate plays an important role in the regulation of emotions (Stevens, Hurley, & Taber, 2011) and monitoring of motivation, cognitive and motor responses in situations of potential conflict (Haber & Knutson, 2010). The temporal pole is involved in social cognition, especially theory of mind, in which an individual accurately attributes thought, intentions or beliefs to others (Ross & Olson, 2010). The occipital pole is the first cortical region where visual information is processed, conveyed to visual association cortex and through reciprocal connections contributes to conscious awareness (Silvanto, Lavie, & Walsh, 2005). The rostral anterior portion of the middle frontal gyrus is activated by social cognition tasks, which involve self-knowledge, person perception and mentalizing (Amodio & Frith, 2006).

Regions with greater centrality in the maltreated network, in contrast, appear to be involved primarily in aspects of self-awareness. The precuneus is a major component of the posterior default mode network and is involved in self-referential thinking and self-centred mental imagery (Cavanna & Trimble, 2006). The anterior insula plays a critical role in interoception, providing the substrate for all subjective feelings from the body (Craig, 2009). The anterior insula is often activated in conjunction with the anterior cingulate and together act as limbic sensory and motor cortices that, respectively, engender the feelings (insula) and the motivations (cingulate) that constitute emotions (Craig, 2009). Craig (2009) has hypothesized that the anterior insula plays a critical role in self-awareness.

Taken together, the cortical network organization of maltreated individuals may result in a diminished capacity to regulate impulses and emotions, accurately attribute thoughts and intentions to others, and to be mindful of oneself in a social context. Conversely, this network structure may lead to a heightened experience of internal emotions and cravings along with a greater tendency to think about oneself and to engage in self-centred mental imagery. This fits with the knowledge that psychotherapies have been designed over the years to enhance emotional regulation, to correct misconceptions about self and others, to diminish focus on internal feelings and to reduce harmful self-centred thinking.

A number of other studies have emerged in recent years focusing on resting-state networks in maltreated individuals (e.g. Cisler et al., 2013; Elton et al., 2014). The most comprehensive examined a high-density resting-state network in depressed patients with and without histories of neglect and healthy controls (Wang et al., 2014). There were some overlapping network differences that distinguished both groups of depressed subjects from controls. However, the major finding was that depressed patients with histories of early neglect had much more prominent alterations in prefrontal-limbic-thalamic-cerebellar functional connectivity than depressed patients without histories of neglect (Wang et al., 2014). Marked network differences between maltreatment and nonmaltreated individuals with the same primary diagnosis raise important questions about the relationship between neurobiology and psychopathology.

Ecophenotypes

We have recently summarized data that suggests that maltreated and nonmaltreated individuals with the same primary psychiatric diagnosis are clinically, neurobiologically and genetically distinct. Further, we proposed that the maltreated subgroup be considered a unique ecophenotype and so designated diagnostically (Teicher & Samson, 2013). This claim is most clearly supported by neuroimaging studies that reveal the prepotent role of childhood maltreatment. As indicated above, reduced hippocampal volume has been considered an important component in the pathophysiology of major depression (Cole et al., 2011). However, this finding appears to be restricted to the maltreated ecophenotype (Chaney et al., 2014; Opel et al., 2014; Vythilingam et al., 2002). Further, it is more directly a consequence of maltreatment than a link to depression as it is reliably observed in adults with histories of maltreatment but no history of depression or psychopathology (Baker et al., 2013; Carballedo

et al., 2012; Dannlowski et al., 2012; Samplin et al., 2013). Hence, within the maltreated ecophenotype with major depression, and other disorders associated with reduced hippocampal volume (Geuze et al., 2005), a critical question becomes the factors determining susceptibility versus resilience (defined here as presence or absence of overt psychopathology in maltreated individuals) as both outcomes are associated in adults with reduced hippocampal volume. One possibility is that reduced hippocampal volume may have no particular role and emerge an incidental finding. Another possibility is that reduced hippocampal volume may be of major importance, but masked in resilient individuals by compensatory changes in other regions (e.g. Galinowski et al., 2015; van der Werff et al., 2013a) or through alterations in molecular expression. These compensatory adaptations could then serve as novel therapeutic targets that may be exploited to counterbalance maltreatment-related hippocampal abnormalities. This line of research, however, would have no relevance to depressed individuals unexposed to maltreatment, underscoring the importance of distinguishing these subtypes.

Reduced hippocampal volume is not the only neurobiological finding that distinguishes maltreated and nonmaltreated subgroups within a diagnostic category. Hyperreactive amygdala response to emotional stimuli has been considered an important contributor to the pathophysiology of mood and anxiety disorders (Mayberg, 1997; Sheline et al., 2001; Stein, Simmons, Feinstein, & Paulus, 2007; Thomas et al., 2001). However, this finding may be limited to the maltreated subgroup (Grant et al., 2011) and is also discernible in maltreated subjects without psychopathology (Dannlowski et al., 2012; McCrory et al., 2011). If these observations are replicated, it would imply that enhance amygdala reactivity to emotional stimuli would be relevant to susceptible and resilient individuals with histories of maltreatment, but not relevant to unexposed subjects with anxiety or depression.

A third major maltreatment-related finding is reduced volume of the anterior cingulate cortex. This region has been proposed to play an important role in major depression (Redlich, Almeida, et al., 2014), anxiety disorders (Shang et al., 2014), psychotic disorders (Witthaus et al., 2009) and substance abuse (Koob & Volkow, 2010). Recent studies have shown that reduced anterior cingulate volume may be restricted to maltreated but not nonmaltreated individuals with depression (Malykhin et al., 2012) and psychotic disorders (Sheffield et al., 2013). Further, this finding is also reliably observed in maltreated subjects with no history of psychopathology (Baker et al., 2013; Carballedo et al., 2012; Cohen et al., 2006; Gerritsen et al., 2012; Tomoda, Suzuki, et al., 2009). Hence, further research may indicate that volumetric abnormalities in the anterior cingulate are relevant to susceptible and resilient subjects with histories of maltreatment but not to psychiatrically ill subjects without maltreatment.

This concern may also apply to other regions and pathways that have been reported to differ significantly between maltreated individuals without psychopathology and healthy unexposed controls. The list includes dorsolateral prefrontal cortex (Carballedo et al., 2012; Edmiston et al., 2011; Gatt et al., 2009; Tomoda, Suzuki, et al., 2009), occipital cortex (Edmiston et al., 2011; Tomoda, Navalta, et al., 2009) and findings of decreased FA in portions of the corpus callosum (Paul et al., 2008; Seckfort et al., 2008; Teicher et al., 2010). In short, we believe that there is a compelling reason to subtype individuals by histories of maltreatment or early life stress and that this may turn out to be one of the most important distinctions to be made by researchers and clinicians.

Conclusions

We set out in this review with a series of questions in mind and have provided some answers. First, childhood abuse has been repeatedly found to be associated with alterations in brain structure and function. This is very likely a causal relationship as some identical regional findings can be seen in animals randomly assigned to experience early life stress (Teicher, Tomoda, & Andersen, 2006), and many studies have reported a clear dose–response relationship between severity of exposure and magnitude of the neurobiological findings (e.g. Dannlowski et al., 2012; Edmiston et al., 2011; Teicher et al., 2012; Treadway et al., 2009). Further, results for many regions are consistent across laboratories and populations, and the temporal relationship is supported by the available longitudinal studies (Boecker et al., 2014; Carrion, Weems, & Reiss, 2007; De Bellis, Hall, Boring, Frustaci, & Moritz, 2001; Walsh et al., 2014; Whittle et al., 2013). Hence, the primary maltreatment-related neuroimaging findings appear, by-in-large, to satisfy Hill's most important criteria for a causal association (Hill, 1965).

Second, type of maltreatment appears to matter. This is best illustrated in the studies showing that exposure to specific types of abuse appear to selectively target sensory systems and pathways that convey and process the aversive experience. On the other hand, there are many similar findings between studies assessing the impact of exposure to early neglect versus those assessing the consequence of exposure to more active forms of abuse. A few differences, however, have been observed. Increased amygdala volume has been reported specifically in individuals exposed to caregiver neglect, raised with chronically depressed mothers, or who experienced disrupted attachments. In contrast, studies assessing effects of abuse have reported either significant or nonsignificant reductions in amygdala volume.

Similarly, reduced hippocampal volume has been reported with good consistency in adults with histories of maltreatment, but has rarely been reported in subjects with early deprivation or neglect [negative: (Hanson et al., 2015; Lupien et al., 2011; Sheridan et al., 2012; Tottenham et al., 2010); positive: (Mehta et al., 2009)]. However, this observation is confounded, as the average age of subjects in the negative neglect studies was only about 10 years of age but 16 years of age in the positive study. Deficits in hippocampal volume are more reliably discerned in maltreated adolescents and adults than in prepubertal subjects. We also reported that corpus callosal area appeared to be most susceptible to neglect in males and to sexual abuse in females.

These findings show that type of maltreatment matters and they raise concerns about the alternative approach of counting up adverse childhood experiences to provide a simple composite score. If different types of maltreatment are associated with specific neurobiological alterations and therefore pose risk for differing forms of psychopathology, then this information may prove critical in designing or selecting optimal treatments. Further, findings of a progressive increase in risk, symptom severity or brain change in association with composite exposure scores has led to the premature conclusion that the key factor determining outcome of early adversity is 'cumulative burden' (Khan et al., 2015). An alternative explanation is that exposure to more types of adversity increases the risk of experiencing a critical type of abuse at a critical age. We have recently reported that type and timing of exposure provides a much better explanation regarding risk for depression in maltreated individuals than cumulative burden (Khan et al., 2015).

This leads to the third point, which is that age of exposure matters. There is emerging evidence for sensitive exposure periods for hippocampus, amygdala, prefrontal cortex, occipital cortex and inferior longitudinal fasciculus. Fourth, the temporal association between exposure and brain changes is unclear. Almost all of the key neuroimaging findings have been observed in both children and adults, suggesting that effects likely emerge with a few years. The notable exception pertains to reports of reduced hippocampal volume, which have been observed much more reliably in maltreated adults than children. This is consistent with the presence of a silent period between exposure and affect. Longitudinal studies, however, suggest that differences in trajectories of hippocampal development can be seen within a few years in maltreated children (De Bellis et al., 2001; Luby et al., 2013; Whittle et al., 2013). A reasonable explanation is that relatively small effects of maltreatment on hippocampus development occur shortly after exposure and that these can be detected using within subject longitudinal designs. However, robust differences that can be reliably observed in cross-sectional studies may take many years to emerge, or may be unmasked by developmental alterations taking place following puberty (Andersen & Teicher, 2004).

Fifth, gender differences have been reported in several studies. Maltreatment is associated with a greater reduction in corpus callosum area in boys than girls. Hippocampal volume also appears to be more strongly affected by exposure to stress in males than females. On the other hand, differences in resting-state functional connectivity between anterior cingulate and hippocampus or amygdala may be more reliably observed in females (Herringa et al., 2013). Also, males and females have been reported to show different regional patterns of response in an emotional oddball task that used fearful faces or scrambled face distractors (Crozier, Wang, Huettel, & De Bellis, 2014) and in a stop signal attention task (Elton et al., 2014).

Sixth, many of the maltreatment-related findings appear to make sense as neuroplastic adaptive responses. These include alterations in auditory cortex and arcuate fasciculus in children experiencing verbal abuse, visual cortex and visual-limbic pathway in subjects visually witnessing domestic violence, and thinning of genital representation area in somatosensory cortex of sexually abused females. Also, enhanced amygdala response to emotional faces, and diminished striatal response to anticipated reward also makes sense as adaptations that would tip the balance in approach avoidance situations towards avoidance.

Adaptive in this sense means that the alterations are experience-dependent responses to the environment and not simply nonspecific stress-induced impairments. We need to reiterate the hypothesis that these alterations are adaptations to an anticipated stress-filled malevolent world. In a just society, they will appear maladaptive and in need of treatment, just as adaptations that soldiers make during prolonged periods of combat may be maladaptive back home (van der Kolk, 2014). Childhood adversity is associated with markedly increased risk of teenage pregnancy (Hillis et al., 2004), which is linked to greatly increased risk for subsequent pregnancies. It is also strongly associated in males with risk of impregnating a teen (Anda et al., 2002) and in both men and women with having a large number of sexual partners (Dube, Felitti, Dong, Giles, & Anda, 2003). From a psychosocial and medical perspective, these are troubling behaviours but can also be viewed as an adaptive strategy for passing on your genes in an uncertain world.

Seventh, we know little regarding the reversibility of the potential neurobiological consequences of childhood maltreatment. The Bucharest Early Intervention Study suggests that white matter abnormalities may be more reversible than grey matter abnormalities. We are currently conducting a trial of mindfulness meditation in maltreated young adults with Diane Yan and Sara Lazar. Preliminary findings have been presented showing that mindful-

ness (versus waiting list control) is associated in improvement in a hippocampal-dependent cognitive performance measure, and with an increase in hippocampal subfield volumes. This will be a fruitful area for further research.

Finally, the relationship between childhood abuse, brain changes and psychiatric illness is perplexing. There is good evidence to suggest that some of the key neuroimaging findings that have been tied to psychopathology, such as reduced hippocampal and anterior cingulate volumes, attenuated corpus callosal area, and enhanced amygdala response to fearful faces may be restricted within each diagnostic group to the maltreated ecophenotype. However, the observation that these neuroimaging findings can also be observed in apparently resilient individuals with histories of maltreatment but without psychopathology raises concerns about the relationship between these findings and psychiatric disorders. Our best guess is that these morphological and functional findings play an important role in psychiatric symptomatology but that they may be balanced by compensatory changes in resilient subjects. This will also be an important focus of future studies. Another key point is that the high incidence of comorbid conditions and the apparent problems the field has encountered with categorical approaches to diagnosis may be due, at least in part, to maltreatment-related alterations in brain structure and function that appear to result in the same constellation of neurobiological alterations across a wide array of diagnoses. What is clear is that studies on the neurobiological basis of psychopathology must take maltreatment history into account. Abuse and neglect have confounded neuroimaging studies on psychopathology for the last 30 years and may be responsible for many erroneous assumptions and conclusions.

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Key points

- Childhood maltreatment is associated with consistent alterations in corpus callosum, anterior cingulate, dorsolateral prefrontal, orbitofrontal cortex and adult hippocampus.
- Maltreatment is consistently associated with enhanced amygdala response to threatening stimuli and diminished striatal response to anticipated reward.
- Brain regions and pathways reported to differ in maltreated individuals are predominantly part of circuits regulating threat detection and reward anticipation.
- Exposure to single types of abuse is associated with specific alterations in regions and pathways that covey the aversive experience.
- Maltreatment-associated brain changes make sense as adaptive responses to early adversity that can alter stress response and shift approach–avoidance decisions.
- Relationships between brain changes and psychopathology are complex as these changes have been reported in maltreated subjects without psychopathology.

References

Amodio, D.M., & Frith, C.D. (2006). Meeting of minds: The medial frontal cortex and social cognition. *Nature Reviews Neuroscience*, *7*, 268–277.

Anda, R.F., Chapman, D.P., Felitti, V.J., Edwards, V., Williamson, D.F., Croft, J.B., & Giles, W.H. (2002). Adverse childhood experiences and risk of paternity in teen pregnancy. *Obstetrics and Gynecology*, *100*, 37–45.

Andersen, S.L., & Teicher, M.H. (2004). Delayed effects of early stress on hippocampal development. *Neuropsychopharmacology*, *29*, 1988–1993.

Andersen, S.L., & Teicher, M.H. (2008). Stress, sensitive periods and maturational events in adolescent depression. *Trends in Neurosciences*, *31*, 183–191.

Andersen, S.L., Tomoda, A., Vincow, E.S., Valente, E., Polcari, A., & Teicher, M.H. (2008). Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. *Journal of Neuropsychiatry and Clinical Neurosciences*, *20*, 292–301.

Anderson, C.M., Polcari, A., Lowen, S.B., Renshaw, P.F., & Teicher, M.H. (2002). Effects of methylphenidate on functional magnetic resonance relaxometry of the cerebellar vermis in

boys with ADHD. *American Journal of Psychiatry*, *159*, 1322–1328.

Anderson, C.M., Teicher, M.H., Polcari, A., & Renshaw, P.F. (2002). Abnormal T2 relaxation time in the cerebellar vermis of adults sexually abused in childhood: Potential role of the vermis in stress-enhanced risk for drug abuse. *Psychoneuroendocrinology*, *27*, 231–244.

Arnone, D., McIntosh, A.M., Chandra, P., & Ebmeier, K.P. (2008). Meta-analysis of magnetic resonance imaging studies of the corpus callosum in bipolar disorder. *Acta Psychiatrica Scand.*, *118*, 357–362.

Baker, L.M., Williams, L.M., Korgaonkar, M.S., Cohen, R.A., Heaps, J.M., & Paul, R.H. (2013). Impact of early vs. late childhood early life stress on brain morphometrics. *Brain Imaging and Behavior*, *7*, 196–203.

Baldacara, L., Borgio, J.G., Lacerda, A.L., & Jackowski, A.P. (2008). Cerebellum and psychiatric disorders. *Revista Brasileira de Psiquiatria*, *30*, 281–289.

Baldacara, L., Jackowski, A.P., Schoedl, A., Pupo, M., Andreoli, S.B., Mello, M.F., … & Bressan, R.A. (2011). Reduced cerebellar left hemisphere and vermal volume in adults with PTSD from a community sample. *Journal of Psychiatric Research*, *45*, 1627–1633.

Ball, J.S., & Links, P.S. (2009). Borderline personality disorder and childhood trauma: Evidence for a causal relationship. *Current Psychiatry Reports*, *11*, 63–68.

Baloch, H.A., Brambilla, P., & Soares, J.C. (2009). Corpus callosum abnormalities in pediatric bipolar disorder. *Expert Review of Neurotherapeutics*, *9*, 949–955.

Balodis, I.M., & Potenza, M.N. (2015). Anticipatory reward processing in addicted populations: A focus on the monetary incentive delay task. *Biological Psychiatry*, *77*, 434–444.

Bauer, P.M., Hanson, J.L., Pierson, R.K., Davidson, R.J., & Pollak, S.D. (2009). Cerebellar volume and cognitive functioning in children who experienced early deprivation. *Biological Psychiatry*, *66*, 1100–1106.

Beaver, K.M., & Belsky, J. (2012). Gene-environment interaction and the intergenerational transmission of parenting: Testing the differential-susceptibility hypothesis. *Psychiatric Quarterly*, *83*, 29–40.

de Bellis, M.D., Hooper, S.R., Spratt, E.G., & Woolley, D.P. (2009). Neuropsychological findings in childhood neglect and their relationships to pediatric PTSD. *Journal of the International Neuropsychological Society*, *15*, 868–878.

Bendall, S., Jackson, H.J., Hulbert, C.A., & McGorry, P.D. (2008). Childhood trauma and psychotic disorders: A systematic, critical review of the evidence. *Schizophrenia Bulletin*, *34*, 568–579.

Benedetti, F., Bollettini, I., Radaelli, D., Poletti, S., Locatelli, C., Falini, A., … & Colombo, C. (2014). Adverse childhood experiences influence white matter microstructure in patients with bipolar disorder. *Psychological Medicine*, *44*, 3069–3082.

Benedetti, F., Yeh, P.H., Bellani, M., Radaelli, D., Nicoletti, M.A., Poletti, S., … & Brambilla, P. (2011). Disruption of white matter integrity in bipolar depression as a possible structural marker of illness. *Biological Psychiatry*, *69*, 309–317.

Bernstein, D.P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., … & Ruggiero, J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. *American Journal of Psychiatry*, *151*, 1132–1136.

Berquin, P.C., Giedd, J.N., Jacobsen, L.K., Hamburger, S.D., Krain, A.L., Rapoport, J.L., & Castellanos, F.X. (1998). Cerebellum in attention-deficit hyperactivity disorder – A morphometric MRI study. *Neurology*, *50*, 1087–1093.

Bledsoe, J., Semrud-Clikeman, M., & Pliszka, S.R. (2009). A magnetic resonance imaging study of the cerebellar vermis in chronically treated and treatment-naive children with attention-deficit/hyperactivity disorder combined type. *Biological Psychiatry*, *65*, 620–624.

Boecker, R., Holz, N.E., Buchmann, A.F., Blomeyer, D., Plichta, M.M., Wolf, I., … & Laucht, M. (2014). Impact of early life adversity on reward processing in young adults: EEG-fMRI results from a prospective study over 25 years. *PLoS ONE*, *9*, e104185.

Bogdan, R., Williamson, D.E., & Hariri, A.R. (2012). Mineralocorticoid receptor Iso/Val (rs5522) genotype moderates the association between previous childhood emotional neglect and amygdala reactivity. *American Journal of Psychiatry*, *169*, 515–522.

Brake, W.G., Zhang, T.Y., Diorio, J., Meaney, M.J., & Gratton, A. (2004). Influence of early postnatal rearing conditions on mesocorticolimbic dopamine and behavioural responses to psychostimulants and stressors in adult rats. *European Journal of Neuroscience*, *19*, 1863–1874.

Brambilla, P., Soloff, P.H., Sala, M., Nicoletti, M.A., Keshavan, M.S., & Soares, J.C. (2004). Anatomical MRI study of borderline personality disorder patients. *Psychiatry Research*, *131*, 125–133.

Bremner, J.D., Randall, P., Vermetten, E., Staib, L., Bronen, R.A., Mazure, C., … & Charney, D.S. (1997). Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse–a preliminary report. *Biological Psychiatry*, *41*, 23–32.

Brown, D.W., Anda, R.F., Felitti, V.J., Edwards, V.J., Malarcher, A.M., Croft, J.B., & Giles, W.H. (2010). Adverse childhood experiences are associated with the risk of lung cancer: A prospective cohort study. *BMC Public Health*, *10*, 20.

Brown, D.W., Anda, R.F., Tiemeier, H., Felitti, V.J., Edwards, V.J., Croft, J.B., & Giles, W.H. (2009). Adverse childhood experiences and the risk of premature mortality. *American Journal of Preventive Medicine*, *37*, 389–396.

Bucker, J., Muralidharan, K., Torres, I.J., Su, W., Kozicky, J., Silveira, L.E., … & Yatham, L.N. (2014). Childhood maltreatment and corpus callosum volume in recently diagnosed patients with bipolar I disorder: Data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM). *Journal of Psychiatric Research*, *48*, 65–72.

Caldji, C., Francis, D., Sharma, S., Plotsky, P.M., & Meaney, M.J. (2000). The effects of early rearing environment on the development of GABAA and central benzodiazepine receptor levels and novelty-induced fearfulness in the rat. *Neuropsychopharmacology*, *22*, 219–229.

Carballedo, A., Lisiecka, D., Fagan, A., Saleh, K., Ferguson, Y., Connolly, G., … & Frodl, T. (2012). Early life adversity is associated with brain changes in subjects at family risk for depression. *The World Journal of Biological Psychiatry*, *13*, 569–578.

Carrion, V.G., Weems, C.F., Eliez, S., Patwardhan, A., Brown, W., Ray, R.D., & Reiss, A.L. (2001). Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. *Biological Psychiatry*, *50*, 943–951.

Carrion, V.G., Weems, C.F., & Reiss, A.L. (2007). Stress predicts brain changes in children: A pilot longitudinal study on youth stress, posttraumatic stress disorder, and the hippocampus. *Pediatrics*, *119*, 509–516.

Carrion, V.G., Weems, C.F., Watson, C., Eliez, S., Menon, V., & Reiss, A.L. (2009). Converging evidence for abnormalities of the prefrontal cortex and evaluation of midsagittal structures in pediatric posttraumatic stress disorder: An MRI study. *Psychiatry Research*, *172*, 226–234.

Castellanos, F.X., Giedd, J.N., Berquin, P.C., Walter, J.M., Sharp, W., Tran, T., … & Rapoport, J.L. (2001). Quantitative brain magnetic resonance imaging in girls with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, *58*, 289–295.

Cavanna, A.E., & Trimble, M.R. (2006). The precuneus: A review of its functional anatomy and behavioural correlates. *Brain*, *129*(Pt 3), 564–583.

Chaney, A., Carballedo, A., Amico, F., Fagan, A., Skokauskas, N., Meaney, J., & Frodl, T. (2014). Effect of childhood maltreatment on brain structure in adult patients with major depressive disorder and healthy participants. *Journal of Psychiatry and Neuroscience*, *39*, 50–59.

Choi, J., Jeong, B., Polcari, A., Rohan, M.L., & Teicher, M.H. (2012). Reduced fractional anisotropy in the visual limbic pathway of young adults witnessing domestic violence in childhood. *NeuroImage*, *59*, 1071–1079.

Choi, J., Jeong, B., Rohan, M.L., Polcari, A.M., & Teicher, M.H. (2009). Preliminary evidence for white matter tract abnormalities in young adults exposed to parental verbal abuse. *Biological Psychiatry*, *65*, 227–234.

Chugani, H.T., Behen, M.E., Muzik, O., Juhasz, C., Nagy, F., & Chugani, D.C. (2001). Local brain functional activity following early deprivation: A study of postinstitutionalized Romanian orphans. *NeuroImage*, *14*, 1290–1301.

Cisler, J.M., James, G.A., Tripathi, S., Mletzko, T., Heim, C., Hu, X.P., … & Kilts, C.D. (2013). Differential functional connectivity within an emotion regulation neural network among individuals resilient and susceptible to the depressogenic effects of early life stress. *Psychological Medicine*, *43*, 507–518.

Clark, K., Narr, K.L., O'Neill, J., Levitt, J., Siddarth, P., Phillips, O., … & Caplan, R. (2012). White matter integrity, language, and childhood onset schizophrenia. *Schizophrenia Research*, *138*, 150–156.

Cohen, R.A., Grieve, S., Hoth, K.F., Paul, R.H., Sweet, L., Tate, D., … & Williams, L.M. (2006). Early life stress and morphometry of the adult anterior cingulate cortex and caudate nuclei. *Biological Psychiatry*, *59*, 975–982.

Cole, J., Costafreda, S.G., McGuffin, P., & Fu, C.H. (2011). Hippocampal atrophy in first episode depression: A meta-analysis of magnetic resonance imaging studies. *Journal of Affective Disorders*, *134*, 483–487.

Cooper, I.S., & Upton, A.R. (1978). Effects of cerebellar stimulation on epilepsy, the EEG and cerebral palsy in man. *Electroencephalography & Clinical Neurophysiology*, (Suppl. 34), 349–354.

Cooper, I.S., & Upton, A.R. (1985). Therapeutic implications of modulation of metabolism and functional activity of cerebral cortex by chronic stimulation of cerebellum and thalamus. *Biological Psychiatry*, *20*, 811–813.

Courchesne, E., Yeung-Courchesne, R., Press, G.A., Hesselink, J.R., & Jernigan, T.L. (1988). Hypoplasia of cerebellar vermal lobules VI and VII in autism. *New England Journal of Medicine*, *318*, 1349–1354.

Craig, A.D. (2009). How do you feel–now? The anterior insula and human awareness. *Nature Reviews Neuroscience*, *10*, 59–70.

Craig, M.C., Catani, M., Deeley, Q., Latham, R., Daly, E., Kanaan, R., … & Murphy, D.G. (2009). Altered connections on the road to psychopathy. *Molecular Psychiatry*, *14*, 946–953, 907.

Crozier, J.C., Wang, L., Huettel, S.A., & De Bellis, M.D. (2014). Neural correlates of cognitive and affective processing in maltreated youth with posttraumatic stress symptoms: Does gender matter? *Development and Psychopathology*, *26*, 491–513.

Danese, A., Moffitt, T.E., Harrington, H., Milne, B.J., Polanczyk, G., Pariante, C.M., … & Caspi, A. (2009). Adverse childhood experiences and adult risk factors for age-related disease: Depression, inflammation, and clustering of metabolic risk markers. *Archives of Pediatrics and Adolescent Medicine*, *163*, 1135–1143.

Danese, A., Pariante, C.M., Caspi, A., Taylor, A., & Poulton, R. (2007). Childhood maltreatment predicts adult inflammation in a life-course study. *Proceedings of the National Academy of Sciences of the United States of America*, *104*, 1319–1324.

Dannlowski, U., Stuhrmann, A., Beutelmann, V., Zwanzger, P., Lenzen, T., Grotegerd, D., … & Kugel, H. (2012). Limbic scars: Long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biological Psychiatry*, *71*, 286–293.

De Bellis, M.D., Hall, J., Boring, A.M., Frustaci, K., & Moritz, G. (2001). A pilot longitudinal study of hippocampal volumes in pediatric maltreatment-related posttraumatic stress disorder. *Biological Psychiatry*, *50*, 305–309.

De Bellis, M.D., & Keshavan, M.S. (2003). Sex differences in brain maturation in maltreatment-related pediatric posttraumatic stress disorder. *Neuroscience and Biobehavioral Reviews*, *27*, 103–117.

De Bellis, M.D., Keshavan, M.S., Clark, D.B., Casey, B.J., Giedd, J.N., Boring, A.M., … & Ryan, N.D. (1999). Developmental traumatology. Part II: Brain development. *Biological Psychiatry*, *45*, 1271–1284.

De Bellis, M.D., Keshavan, M.S., Shifflett, H., Iyengar, S., Beers, S.R., Hall, J., … & Ryan, N.D. (2002). Brain structures in pediatric maltreatment-related posttraumatic stress disorder: A sociodemographically matched study. *Biological Psychiatry*, *52*, 1066–1078.

De Bellis, M.D., Keshavan, M.S., Spencer, S., & Hall, J. (2000). N-Acetylaspartate concentration in the anterior cingulate of maltreated children and adolescents with PTSD. *American Journal of Psychiatry*, *157*, 1175–1177.

De Bellis, M.D., & Kuchibhatla, M. (2006). Cerebellar volumes in pediatric maltreatment-related posttraumatic stress disorder. *Biological Psychiatry*, *60*, 697–703.

De Brito, S.A., Viding, E., Sebastian, C.L., Kelly, P.A., Mechelli, A., Maris, H., & McCrory, E.J. (2013). Reduced orbitofrontal and temporal grey matter in a community sample of maltreated children. *Journal of Child Psychology and Psychiatry*, *54*, 105–112.

Derntl, B., Habel, U., Windischberger, C., Robinson, S., Kryspin-Exner, I., Gur, R.C., & Mosur, E. (2009). General and specific responsiveness of the amygdala during explicit emotion recognition in females and males. *BMC Neuroscience*, *10*, 91.

Dillon, D.G., Holmes, A.J., Birk, J.L., Brooks, N., Lyons-Ruth, K., & Pizzagalli, D.A. (2009). Childhood adversity is associated with left basal ganglia dysfunction during reward anticipation in adulthood. *Biological Psychiatry*, *66*, 206–213.

Dong, M., Giles, W.H., Felitti, V.J., Dube, S.R., Williams, J.E., Chapman, D.P., & Anda, R.F. (2004). Insights into causal pathways for ischemic heart disease: Adverse childhood experiences study. *Circulation*, *110*, 1761–1766.

Driessen, M., Herrmann, J., Stahl, K., Zwaan, M., Meier, S., Hill, A., … & Petersen, D. (2000). Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. *Archives of General Psychiatry*, *57*, 1115–1122.

Dube, S.R., Felitti, V.J., Dong, M., Giles, W.H., & Anda, R.F. (2003). The impact of adverse childhood experiences on health problems: Evidence from four birth cohorts dating back to 1900. *Preventive Medicine*, *37*, 268–277.

Edmiston, E.E., Wang, F., Mazure, C.M., Guiney, J., Sinha, R., Mayes, L.C., & Blumberg, H.P. (2011). Corticostriatal-limbic gray matter morphology in adolescents with self-reported exposure to childhood maltreatment. *Archives of Pediatrics and Adolescent Medicine*, *165*, 1069–1077.

Eiland, L., Ramroop, J., Hill, M.N., Manley, J., & McEwen, B.S. (2012). Chronic juvenile stress produces corticolimbic dendritic architectural remodeling and modulates emotional behavior in male and female rats. *Psychoneuroendocrinology*, *37*, 39–47.

Elton, A., Tripathi, S.P., Mletzko, T., Young, J., Cisler, J.M., James, G.A., & Kilts, C.D. (2014). Childhood maltreatment is associated with a sex-dependent functional reorganization of a brain inhibitory control network. *Human Brain Mapping*, *35*, 1654–1667.

Eluvathingal, T.J., Chugani, H.T., Behen, M.E., Juhasz, C., Muzik, O., Maqbool, M., … & Makki, M. (2006). Abnormal brain connectivity in children after early severe socioemotional deprivation: A diffusion tensor imaging study. *Pediatrics*, *117*, 2093–2100.

Ernst, A., Alkass, K., Bernard, S., Salehpour, M., Perl, S., Tisdale, J., … & Frisen, J. (2014). Neurogenesis in the striatum of the adult human brain. *Cell*, *156*, 1072–1083.

Etkin, A., Klemenhagen, K.C., Dudman, J.T., Rogan, M.T., Hen, R., Kandel, E.R., & Hirsch, J. (2004). Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. *Neuron*, *44*, 1043–1055.

Everaerd, D., Gerritsen, L., Rijpkema, M., Frodl, T., van Oostrom, I., Franke, B., … & Tendolkar, I. (2012). Sex modulates the interactive effect of the serotonin transporter gene polymorphism and childhood adversity on hippocampal volume. *Neuropsychopharmacology*, *37*, 1848–1855.

Ferguson, S.A., & Holson, R.R. (1999). Neonatal dexamethasone on day 7 causes mild hyperactivity and cerebellar stunting. *Neurotoxicology and Teratology*, *21*, 71–76.

Frazier, J.A., Breeze, J.L., Papadimitriou, G., Kennedy, D.N., Hodge, S.M., Moore, C.M., … & Makris, N. (2007). White matter abnormalities in children with and at risk for bipolar disorder. *Bipolar Disorders*, *9*, 799–809.

Frodl, T., Reinhold, E., Koutsouleris, N., Donohoe, G., Bondy, B., Reiser, M., & Meisenzahl, E.M. (2010). Childhood stress, serotonin transporter gene and brain structures in major depression. *Neuropsychopharmacology*, *35*, 1383–1390.

Frodl, T., Reinhold, E., Koutsouleris, N., Reiser, M., & Meisenzahl, E.M. (2010). Interaction of childhood stress with hippocampus and prefrontal cortex volume reduction in major depression. *Journal of Psychiatric Research*, *44*, 799–807.

Galinowski, A., Miranda, R., Lemaitre, H., Paillere Martinot, M.L., Artiges, E., Vulser, H., … & IMAGEN Consortium. (2015). Resilience and corpus callosum microstructure in adolescence. *Psychological Medicine*, *45*, 2285–2294.

Garrett, A.S., Carrion, V., Kletter, H., Karchemskiy, A., Weems, C.F., & Reiss, A. (2012). Brain activation to facial expressions in youth with PTSD symptoms. *Depression and Anxiety*, *29*, 449–459.

Gatt, J.M., Nemeroff, C.B., Dobson-Stone, C., Paul, R.H., Bryant, R.A., Schofield, P.R., … & Williams, L.M. (2009). Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. *Molecular Psychiatry*, *14*, 681–695.

Gerritsen, L., Tendolkar, I., Franke, B., Vasquez, A.A., Kooijman, S., Buitelaar, J., … & Rijpkema, P. (2012). BDNF Val66Met genotype modulates the effect of childhood adversity on subgenual anterior cingulate cortex volume in healthy subjects. *Molecular Psychiatry*, *17*, 597–603.

Geuze, E., Vermetten, E., & Bremner, J.D. (2005). MR-based in vivo hippocampal volumetrics: 2. Findings in neuropsychiatric disorders. *Molecular Psychiatry*, *10*, 160–184.

Goff, B., Gee, D.G., Telzer, E.H., Humphreys, K.L., Gabard-Durnam, L., Flannery, J., & Tottenham, N. (2013). Reduced nucleus accumbens reactivity and adolescent depression following early-life stress. *Neuroscience*, *249*, 129–138.

Goodman, M., Carpenter, D., Tang, C.Y., Goldstein, K.E., Avedon, J., Fernandez, N., … & Hazlet, E.A. (2014). Dialectical behavior therapy alters emotion regulation and amygdala activity in patients with borderline personality disorder. *Journal of Psychiatric Research*, *57*, 108–116.

Gould, F., Clarke, J., Heim, C., Harvey, P.D., Majer, M., & Nemeroff, C.B. (2012). The effects of child abuse and neglect on cognitive functioning in adulthood. *Journal of Psychiatric Research*, *46*, 500–506.

Govindan, R.M., Behen, M.E., Helder, E., Makki, M.I., & Chugani, H.T. (2010). Altered water diffusivity in cortical association tracts in children with early deprivation identified with Tract-Based Spatial Statistics (TBSS). *Cerebral Cortex*, *20*, 561–569.

Grant, M.M., Cannistraci, C., Hollon, S.D., Gore, J., & Shelton, R. (2011). Childhood trauma history differentiates amygdala response to sad faces within MDD. *Journal of Psychiatric Research*, *45*, 886–895.

Green, J.G., McLaughlin, K.A., Berglund, P.A., Gruber, M.J., Sampson, N.A., Zaslavsky, A.M., … & Kessler, R.G. (2010). Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: Associations with first onset of DSM-IV disorders. *Archives of General Psychiatry*, *67*, 113–123.

Grotegerd, D., Stuhrmann, A., Kugel, H., Schmidt, S., Redlich, R., Zwanzger, P., … & Dannlowski, U. (2014). Amygdala excitability to subliminally presented emotional faces distinguishes unipolar and bipolar depression: An fMRI and pattern classification study. *Human Brain Mapping*, *35*, 2995–3007.

Gupta, A., Labus, J., Kilpatrick, L.A., Bonyadi, M., Ashe-McNalley, C., Heendeniya, N., … & Mayer, E.A. (2015). Interactions of early adversity with stress-related gene polymorphisms impact regional brain structure in females. *Brain Structure and Function*. [Epub ahead of print]

Gurrera, R.J., Nakamura, M., Kubicki, M., Dickey, C.C., Niznikiewicz, M.A., Voglmaier, M.M., … & Seidman, L.J. (2007). The uncinate fasciculus and extraversion in schizotypal personality disorder: A diffusion tensor imaging study. *Schizophrenia Research*, *90*, 360–362.

Haber, S.N., & Knutson, B. (2010). The reward circuit: Linking primate anatomy and human imaging. *Neuropsychopharmacology*, *35*, 4–26.

Hamilton, L.S., Levitt, J.G., O'Neill, J., Alger, J.R., Luders, E., Phillips, O.R., … & Narr, K.L. (2008). Reduced white matter integrity in attention-deficit hyperactivity disorder. *NeuroReport*, *19*, 1705–1708.

Hanson, J.L., Chung, M.K., Avants, B.B., Shirtcliff, E.A., Gee, J.C., Davidson, R.J., & Pollak, S.D. (2010). Early stress is associated with alterations in the orbitofrontal cortex: A tensor-based morphometry investigation of brain structure and behavioral risk. *Journal of Neuroscience*, *30*, 7466–7472.

Hanson, J.L., Hariri, A.R., & Williamson, D.E. (2015). Blunted ventral striatum development in adolescence reflects emotional neglect and predicts depressive symptoms. *Biological Psychiatry*, *78*, 598–605.

Hanson, J.L., Nacewicz, B.M., Sutterer, M.J., Cayo, A.A., Schaefer, S.M., Rudolph, K.D., … & Davidson, R.J. (2015). Behavioral problems after early life stress: Contributions of the hippocampus and amygdala. *Biological Psychiatry*, *77*, 314–323.

Harlow, H.F., Dodsworth, R.O., & Harlow, M.K. (1965). Total social isolation in monkeys. *Proceedings of the National Academy of Sciences of the United States of America*, *54*, 90–97.

van Harmelen, A.L., Hauber, K., Gunther Moor, B., Spinhoven, P., Boon, A.E., Crone, E.A., & Elzinga, B.M. (2014). Childhood emotional maltreatment severity is associated with dorsal medial prefrontal cortex responsivity to social exclusion in young adults. *PLoS ONE*, *9*, e85107.

van Harmelen, A.L., van Tol, M.J., Dalgleish, T., van der Wee, N.J., Veltman, D.J., Aleman, A., … & Elzinga, B.M. (2014). Hypoactive medial prefrontal cortex functioning in adults

reporting childhood emotional maltreatment. *Social Cognitive and Affective Neuroscience*, *9*, 2026–2033.
He, Y., & Evans, A. (2010). Graph theoretical modeling of brain connectivity. *Current Opinion in Neurology*, *23*, 341–350.
Heath, R.G. (1972). Electroencephalographic studies in isolation-raised monkeys with behavioral impairment. *Diseases of the Nervous System*, *33*, 157–163.
Heath, R.G. (1977). Modulation of emotion with a brain pacemaker. Treatment for intractable psychiatric illness. *Journal of Nervous and Mental Disease*, *165*, 300–317.
Heim, C.M., Mayberg, H.S., Mletzko, T., Nemeroff, C.B., & Pruessner, J.C. (2013). Decreased cortical representation of genital somatosensory field after childhood sexual abuse. *American Journal of Psychiatry*, *170*, 616–623.
Herman, J.P., & Mueller, N.K. (2006). Role of the ventral subiculum in stress integration. *Behavioural Brain Research*, *174*, 215–224.
Herringa, R.J., Birn, R.M., Ruttle, P.L., Burghy, C.A., Stodola, D.E., Davidson, R.J., & Essex, M.J. (2013). Childhood maltreatment is associated with altered fear circuitry and increased internalizing symptoms by late adolescence. *Proceedings of the National Academy of Sciences of the United States of America*, *110*, 19119–19124.
Hill, A.B. (1965). The environment and disease: Association or causation? *Proceedings of the Royal Society of Medicine*, *58*, 295–300.
Hillis, S.D., Anda, R.F., Dube, S.R., Felitti, V.J., Marchbanks, P.A., & Marks, J.S. (2004). The association between adverse childhood experiences and adolescent pregnancy, long-term psychosocial consequences, and fetal death. *Pediatrics*, *113*, 320–327.
Huang, H., Gundapuneedi, T., & Rao, U. (2012). White matter disruptions in adolescents exposed to childhood maltreatment and vulnerability to psychopathology. *Neuropsychopharmacology*, *37*, 2693–2701.
Ito, Y., Teicher, M.H., Glod, C.A., & Ackerman, E. (1998). Preliminary evidence for aberrant cortical development in abused children: A quantitative EEG study. *Journal of Neuropsychiatry and Clinical Neurosciences*, *10*, 298–307.
Ito, Y., Teicher, M.H., Glod, C.A., Harper, D., Magnus, E., & Gelbard, H.A. (1993). Increased prevalence of electrophysiological abnormalities in children with psychological, physical, and sexual abuse. *Journal of Neuropsychiatry and Clinical Neurosciences*, *5*, 401–408.
Juraska, J.M., & Kopcik, J.R. (1988). Sex and environmental influences on the size and ultrastructure of the rat corpus callosum. *Brain Research*, *450*, 1–8.
Karl, A., Schaefer, M., Malta, L.S., Dorfel, D., Rohleder, N., & Werner, A. (2006). A meta-analysis of structural brain abnormalities in PTSD. *Neuroscience and Biobehavioral Reviews*, *30*, 1004–1031.
Kawashima, T., Nakamura, M., Bouix, S., Kubicki, M., Salisbury, D.F., Westin, C.F., … & Shenton, M.E. (2009). Uncinate fasciculus abnormalities in recent onset schizophrenia and affective psychosis: A diffusion tensor imaging study. *Schizophrenia Research*, *110*, 119–126.
Khan, A., McCormack, H.C., Bolger, E.A., McGreenery, C.E., Vitaliano, G., Polcari, A., & Teicher, M. H. (2015). Childhood maltreatment, depression, and suicidal ideation: Critical importance of parental and peer emotional abuse during developmental sensitive periods in males and females. *Frontiers in Psychiatry*, *6*, 42.
Kitayama, N., Quinn, S., & Bremner, J.D. (2006). Smaller volume of anterior cingulate cortex in abuse-related posttraumatic stress disorder. *Journal of Affective Disorders*, *90*, 171–174.
Kleinhans, N.M., Richards, T., Weaver, K., Johnson, L.C., Greenson, J., Dawson, G., & Aylward, E. (2010). Association between amygdala response to emotional faces and social anxiety in autism spectrum disorders. *Neuropsychologia*, *48*, 3665–3670.
Knutson, B., Adams, C.M., Fong, G.W., & Hommer, D. (2001). Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *Journal of Neuroscience*, *21*, RC159.
Knutson, B., Fong, G.W., Adams, C.M., Varner, J.L., & Hommer, D. (2001). Dissociation of reward anticipation and outcome with event-related fMRI. *NeuroReport*, *12*, 3683–3687.
van der Kolk, B.A. (2014). *The body keeps the score: Brain, mind and body in the healing of trauma*. New York: Viking.
van der Kolk, B., & Greenberg, M.S. (1987). The psychobiology of the trauma response: Hyperarousal, constriction, and addiction to traumatic reexposure. In B. van der Kolk (Ed.), *Psychological trauma* (pp. 63–87). Washington, DC: American Psychiatric Press.
Koob, G.F., & Volkow, N.D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology*, *35*, 217–238.
Kumari, V., Gudjonsson, G.H., Raghuvanshi, S., Barkataki, I., Taylor, P., Sumich, A., … & Das, M. (2013). Reduced thalamic volume in men with antisocial personality disorder or schizophrenia and a history of serious violence and childhood abuse. *European Psychiatry*, *28*, 225–234.
Kumari, V., Uddin, S., Premkumar, P., Young, S., Gudjonsson, G.H., Raghuvanshi, S., … & Das, M. (2014). Lower anterior cingulate volume in seriously violent men with antisocial personality disorder or schizophrenia and a history of childhood abuse. *Australian and New Zealand Journal of Psychiatry*, *48*, 153–161.
Kuo, J.R., Kaloupek, D.G., & Woodward, S.H. (2012). Amygdala volume in combat-exposed veterans with and without posttraumatic stress disorder: A cross-sectional study. *Archives of General Psychiatry*, *69*, 1080–1086.
de Kwaasteniet, B., Ruhe, E., Caan, M., Rive, M., Olabarriaga, S., Groefsema, M., … & Denys, D. (2013). Relation between structural and functional connectivity in major depressive disorder. *Biological Psychiatry*, *74*, 40–47.
Lai, C.H., & Wu, Y.T. (2014). Alterations in white matter micro-integrity of the superior longitudinal fasciculus and anterior thalamic radiation of young adult patients with depression. *Psychological Medicine*, *44*, 2825–2832.
Landre, L., Destrieux, C., Baudry, M., Barantin, L., Cottier, J.P., Martineau, J., … & El Hage, W. (2010). Preserved subcortical volumes and cortical thickness in women with sexual abuse-related PTSD. *Psychiatry Research*, *183*, 181–186.
LeDoux, J.E. (1993). Emotional memory systems in the brain. *Behavioural Brain Research*, *58*, 69–79.
LeDoux, J. (1996). Emotional networks and motor control: A fearful view. *Progress in Brain Research*, *107*, 437–446.
LeDoux, J.E. (2002). *Synaptic self: How our brains become who we are*. Harmondsworth, England: Viking Penguin.
Lenroot, R.K., Schmitt, J.E., Ordaz, S.J., Wallace, G.L., Neale, M.C., Lerch, J.P., … & Giedd, J.N. (2009). Differences in genetic and environmental influences on the human cerebral cortex associated with development during childhood and adolescence. *Human Brain Mapping*, *30*, 163–174.
Lenze, S.N., Xiong, C., & Sheline, Y.I. (2008). Childhood adversity predicts earlier onset of major depression but not reduced hippocampal volume. *Psychiatry Research*, *162*, 39–49.
Luby, J., Belden, A., Botteron, K., Marrus, N., Harms, M.P., Babb, C., … & Barch, D. (2013). The effects of poverty on childhood brain development: The mediating effect of caregiving and stressful life events. *JAMA Pediatrics*, *167*, 1135–1142.
Luders, E., Narr, K.L., Bilder, R.M., Thompson, P.M., Szeszko, P.R., Hamilton, L., & Toga, A.W. (2007). Positive correlations between corpus callosum thickness and intelligence. *NeuroImage*, *37*, 1457–1464.

Luders, E., Narr, K.L., Hamilton, L.S., Phillips, O.R., Thompson, P.M., Valle, J.S., ... & Levitt, J.G. (2009). Decreased callosal thickness in attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *65*, 84–88.

Luders, E., Thompson, P.M., & Toga, A.W. (2010). The development of the corpus callosum in the healthy human brain. *Journal of Neuroscience*, *30*, 10985–10990.

Lupien, S.J., McEwen, B.S., Gunnar, M.R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10*, 434–445.

Lupien, S.J., Parent, S., Evans, A.C., Tremblay, R.E., Zelazo, P.D., Corbo, V., ... & Seguin, J.R. (2011). Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. *Proceedings of the National Academy of Sciences of the United States of America*, *108*, 14324–14329.

Maheu, F.S., Dozier, M., Guyer, A.E., Mandell, D., Peloso, E., Poeth, K., & Ernst, M. (2010). A preliminary study of medial temporal lobe function in youths with a history of caregiver deprivation and emotional neglect. *Cognitive, Affective and Behavioral Neuroscience*, *10*, 34–49.

Malter Cohen, M., Jing, D., Yang, R.R., Tottenham, N., Lee, F.S., & Casey, B.J. (2013). Early-life stress has persistent effects on amygdala function and development in mice and humans. *Proceedings of the National Academy of Sciences of the United States of America*, *110*, 18274–18278.

Malykhin, N.V., Carter, R., Hegadoren, K.M., Seres, P., & Coupland, N.J. (2012). Fronto-limbic volumetric changes in major depressive disorder. *Journal of Affective Disorders*, *136*, 1104–1113.

Maren, S., Phan, K.L., & Liberzon, I. (2013). The contextual brain: Implications for fear conditioning, extinction and psychopathology. *Nature Reviews Neuroscience*, *14*, 417–428.

Mason, W.A., & Berkson, G. (1975). Effects of maternal mobility on the development of rocking and other behaviors in rhesus monkeys: A study with artificial mothers. *Developmental Psychobiology*, *8*, 197–211.

Masten, C.L., Guyer, A.E., Hodgdon, H.B., McClure, E.B., Charney, D.S., Ernst, M., ... & Monk, C.S. (2008). Recognition of facial emotions among maltreated children with high rates of post-traumatic stress disorder. *Child Abuse and Neglect*, *32*, 139–153.

Mayberg, H.S. (1997). Limbic-cortical dysregulation: A proposed model of depression. *Journal of Neuropsychiatry and Clinical Neurosciences*, *9*, 471–481.

McCrory, E.J., De Brito, S.A., Sebastian, C.L., Mechelli, A., Bird, G., Kelly, P.A., & Viding, E. (2011). Heightened neural reactivity to threat in child victims of family violence. *Current Biology*, *21*, R947–R948.

McEwen, B.S. (2010). Stress, sex, and neural adaptation to a changing environment: Mechanisms of neuronal remodeling. *Annals of the New York Academy of Sciences*, *1204*(Suppl 1), E38–E59.

McIntosh, A.M., Munoz Maniega, S., Lymer, G.K., McKirdy, J., Hall, J., Sussmann, J.E., ... & Laurie, S.M. (2008). White matter tractography in bipolar disorder and schizophrenia. *Biological Psychiatry*, *64*, 1088–1092.

McLaughlin, K.A., Sheridan, M.A., Winter, W., Fox, N.A., Zeanah, C.H., & Nelson, C.A. (2014). Widespread reductions in cortical thickness following severe early-life deprivation: A neurodevelopmental pathway to attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *76*, 629–638.

Mehta, M.A., Golembo, N.I., Nosarti, C., Colvert, E., Mota, A., Williams, S.C., ... & Sonuga-Barke, E.J. (2009). Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: The English and Romanian adoptees study pilot. *Journal of Child Psychology and Psychiatry*, *50*, 943–951.

Mehta, M.A., Gore-Langton, E., Golembo, N., Colvert, E., Williams, S.C., & Sonuga-Barke, E. (2010). Hyporesponsive reward anticipation in the basal ganglia following severe institutional deprivation early in life. *Journal of Cognitive Neuroscience*, *22*, 2316–2325.

Melicher, T., Horacek, J., Hlinka, J., Spaniel, F., Tintera, J., Ibrahim, I., ... & Hoschl, C. (2015). White matter changes in first episode psychosis and their relation to the size of sample studied: A DTI study. *Schizophrenia Research*, *162*, 22–28.

Meng, H., Laurens, J., Blazquez, P.M., & Angelaki, D.E. (2015). In vivo properties of cerebellar interneurons in the macaque caudal vestibular vermis. *Journal of Physiology*, *593*, 321–330.

Miller, G.E., & Cole, S.W. (2012). Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. *Biological Psychiatry*, *72*, 34–40.

Miller, E.M., Shankar, M.U., Knutson, B., & McClure, S.M. (2014). Dissociating motivation from reward in human striatal activity. *Journal of Cognitive Neuroscience*, *26*, 1075–1084.

Mitra, R., Jadhav, S., McEwen, B.S., Vyas, A., & Chattarji, S. (2005). Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdala. *Proceedings of the National Academy of Sciences of the United States of America*, *102*, 9371–9376.

Morimoto, M., Morita, N., Ozawa, H., Yokoyama, K., & Kawata, M. (1996). Distribution of glucocorticoid receptor immunoreactivity and mRNA in the rat brain: An immunohistochemical and in situ hybridization study. *Neuroscience Research*, *26*, 235–269.

Moser, E.I., Kropff, E., & Moser, M.B. (2008). Place cells, grid cells, and the brain's spatial representation system. *Annual Review of Neuroscience*, *31*, 69–89.

Nadel, L., Campbell, J., & Ryan, L. (2007). Autobiographical memory retrieval and hippocampal activation as a function of repetition and the passage of time. *Neural Plasticity*, *2007*, 90472.

Nanni, V., Uher, R., & Danese, A. (2012). Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: A meta-analysis. *American Journal of Psychiatry*, *169*, 141–151.

National Scientific Council on the Developing Child. (2005). Excessive Stress Disrupts the Architecture of the Developing Brain, Working Paper #3.

Norman, R.E., Byambaa, M., De, R., Butchart, A., Scott, J., & Vos, T. (2012). The long-term health consequences of child physical abuse, emotional abuse, and neglect: A systematic review and meta-analysis. *PLoS Medicine*, *9*, e1001349.

Ohman, A. (2005). The role of the amygdala in human fear: Automatic detection of threat. *Psychoneuroendocrinology*, *30*, 953–958.

Opel, N., Redlich, R., Zwanzger, P., Grotegerd, D., Arolt, V., Heindel, W., ... & Dannlowski, U. (2014). Hippocampal atrophy in major depression: A function of childhood maltreatment rather than diagnosis? *Neuropsychopharmacology*, *39*, 2723–2731.

Pagliaccio, D., Luby, J.L., Bogdan, R., Agrawal, A., Gaffrey, M.S., Belden, A.C., ... & Barch, D.M. (2014). Stress-system genes and life stress predict cortisol levels and amygdala and hippocampal volumes in children. *Neuropsychopharmacology*, *39*, 1245–1253.

Paul, R., Henry, L., Grieve, S.M., Guilmette, T.J., Niaura, R., Bryant, R., ... & Gordon, E. (2008). The relationship between early life stress and microstructural integrity of the corpus callosum in a non-clinical population. *Neuropsychiatric Disease and Treatment*, *4*, 193–201.

Pavlik, A., & Buresova, M. (1984). The neonatal cerebellum: The highest level of glucocorticoid receptors in the brain. *Brain Research*, *314*, 13–20.

Pechtel, P., Lyons-Ruth, K., Anderson, C.M., & Teicher, M.H. (2014). Sensitive periods of amygdala development: The role

of maltreatment in preadolescence. *NeuroImage*, *97*, 236–244.

Pederson, C.L., Maurer, S.H., Kaminski, P.L., Zander, K.A., Peters, C.M., Stokes-Crowe, L.A., & Osborn, R.E. (2004). Hippocampal volume and memory performance in a community-based sample of women with posttraumatic stress disorder secondary to child abuse. *Journal of Traumatic Stress*, *17*, 37–40.

Phan, K.L., Orlichenko, A., Boyd, E., Angstadt, M., Coccaro, E.F., Liberzon, I., & Arfanakis, K. (2009). Preliminary evidence of white matter abnormality in the uncinate fasciculus in generalized social anxiety disorder. *Biological Psychiatry*, *66*, 691–694.

Pizzagalli, D.A., Holmes, A.J., Dillon, D.G., Goetz, E.L., Birk, J.L., Bogdan, R., … & Fava, M. (2009). Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *American Journal of Psychiatry*, *166*, 702–710.

Prescott, J.W. (1980). Somatosensory affectional deprivation (SAD) theory of drug and alcohol use. *NIDA Research Monograph*, *30*, 286–296.

Price, L.H., Kao, H.T., Burgers, D.E., Carpenter, L.L., & Tyrka, A.R. (2013). Telomeres and early-life stress: An overview. *Biological Psychiatry*, *73*, 15–23.

Puce, A., Allison, T., Gore, J.C., & McCarthy, G. (1995). Face-sensitive regions in human extrastriate cortex studied by functional MRI. *Journal of Neurophysiology*, *74*, 1192–1199.

Redlich, R., Almeida, J.J., Grotegerd, D., Opel, N., Kugel, H., Heindel, W., … & Dannlowski, U. (2014). Brain morphometric biomarkers distinguishing unipolar and bipolar depression. A voxel-based morphometry-pattern classification approach. *JAMA Psychiatry*, *71*, 1222–1230.

Redlich, R., Grotegerd, D., Opel, N., Kaufmann, C., Zwitserlood, P., Kugel, H., & Dannlowski, U. (2014). Are you gonna leave me? Separation anxiety is associated with increased amygdala responsiveness and volume. *Social Cognitive and Affective Neuroscience*, *10*, 278–284.

Rilling, J.K., Glasser, M.F., Preuss, T.M., Ma, X., Zhao, T., Hu, X., & Behrens, T.E. (2008). The evolution of the arcuate fasciculus revealed with comparative DTI. *Nature Neuroscience*, *11*, 426–428.

Ritchie, K., Jaussent, I., Portet, F., Courtet, P., Malafosse, A., Maller, J., … & Ancelin, M.L. (2012). Depression in elderly persons subject to childhood maltreatment is not modulated by corpus callosum and hippocampal loss. *Journal of Affective Disorders*, *141*, 294–299.

Ross, L.A., & Olson, I.R. (2010). Social cognition and the anterior temporal lobes. *NeuroImage*, *49*, 3452–3462.

Samplin, E., Ikuta, T., Malhotra, A.K., Szeszko, P.R., & Derosse, P. (2013). Sex differences in resilience to childhood maltreatment: Effects of trauma history on hippocampal volume, general cognition and subclinical psychosis in healthy adults. *Journal of Psychiatric Research*, *47*, 1174–1179.

Sanchez, M.M., Young, L.J., Plotsky, P.M., & Insel, T.R. (2000). Distribution of corticosteroid receptors in the rhesus brain: Relative absence of glucocorticoid receptors in the hippocampal formation. *Journal of Neuroscience*, *20*, 4657–4668.

Sapolsky, R.M. (1996). Stress, glucocorticoids, and damage to the nervous system: The current state of confusion. *Stress*, *1*, 1–19.

Sapolsky, R.M., Krey, L.C., & McEwen, B.S. (1985). Prolonged glucocorticoid exposure reduces hippocampal neuron number: Implications for aging. *Journal of Neuroscience*, *5*, 1222–1227.

Sarrieau, A., Dussaillant, M., Agid, F., Philibert, D., Agid, Y., & Rostene, W. (1986). Autoradiographic localization of glucocorticosteroid and progesterone binding sites in the human post-mortem brain. *Journal of Steroid Biochemistry*, *25*, 717–721.

Schiffer, F., Teicher, M.H., & Papanicolaou, A.C. (1995). Evoked potential evidence for right brain activity during the recall of traumatic memories. *Journal of Neuropsychiatry and Clinical Neurosciences*, *7*, 169–175.

Schmahl, C.G., Vermetten, E., Elzinga, B.M., & Bremner, J.D. (2003). Magnetic resonance imaging of hippocampal and amygdala volume in women with childhood abuse and borderline personality disorder. *Psychiatry Research-Neuroimaging*, *122*, 193–198.

Seckfort, D.L., Paul, R., Grieve, S.M., Vandenberg, B., Bryant, R.A., Williams, L.M., … & Gordon, E. (2008). Early life stress on brain structure and function across the lifespan: A preliminary study. *Brain Imaging and Behavior*, *2*, 49–58.

Shang, J., Fu, Y., Ren, Z., Zhang, T., Du, M., Gong, Q., … & Zhang, W. (2014). The common traits of the ACC and PFC in anxiety disorders in the DSM-5: Meta-analysis of voxel-based morphometry studies. *PLoS ONE*, *9*, e93432.

Sheffield, J.M., Williams, L.E., Woodward, N.D., & Heckers, S. (2013). Reduced gray matter volume in psychotic disorder patients with a history of childhood sexual abuse. *Schizophrenia Research*, *143*, 185–191.

Sheline, Y.I., Barch, D.M., Donnelly, J.M., Ollinger, J.M., Snyder, A.Z., & Mintun, M.A. (2001). Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: An fMRI study. *Biological Psychiatry*, *50*, 651–658.

Shenk, C.E., Noll, J.G., Peugh, J.L., Griffin, A.M., & Bensman, H.E. (2015). Contamination in the prospective study of child maltreatment and female adolescent health. *Journal of Pediatric Psychology*, pii:jsv017. [Epub ahead of print]

Sheridan, M.A., Fox, N.A., Zeanah, C.H., McLaughlin, K.A., & Nelson, C.A., 3rd (2012). Variation in neural development as a result of exposure to institutionalization early in childhood. *Proceedings of the National Academy of Sciences of the United States of America*, *109*, 12927–12932.

Sheu, Y.S., Polcari, A., Anderson, C.M., & Teicher, M.H. (2010). Harsh corporal punishment is associated with increased T2 relaxation time in dopamine-rich regions. *NeuroImage*, *53*, 412–419.

Shin, L.M., & Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology*, *35*, 169–191.

Silvanto, J., Lavie, N., & Walsh, V. (2005). Double dissociation of V1 and V5/MT activity in visual awareness. *Cerebral Cortex*, *15*, 1736–1741.

Sinclair, D., Webster, M.J., Wong, J., & Weickert, C.S. (2011). Dynamic molecular and anatomical changes in the glucocorticoid receptor in human cortical development. *Molecular Psychiatry*, *16*, 504–515.

Slotnick, S.D., & Schacter, D.L. (2006). The nature of memory related activity in early visual areas. *Neuropsychologia*, *44*, 2874–2886.

Smyke, A.T., Zeanah, C.H., Jr, Fox, N.A., & Nelson, C.A., 3rd (2009). A new model of foster care for young children: The Bucharest early intervention project. *Child and Adolescent Psychiatric Clinics of North America*, *18*, 721–734.

Snow, W.M., Stoesz, B.M., & Anderson, J.E. (2015). The cerebellum in emotional processing: Evidence from human and non-human animals. *AIMS Neuroscience*, *1*, 96–119.

Spitzer, C., Wegert, S., Wollenhaupt, J., Wingenfeld, K., Barnow, S., & Grabe, H.J. (2013). Gender-specific association between childhood trauma and rheumatoid arthritis: A case-control study. *Journal of Psychosomatic Research*, *74*, 296–300.

Stein, M.B., Koverola, C., Hanna, C., Torchia, M.G., & McClarty, B. (1997). Hippocampal volume in women victimized by childhood sexual abuse. *Psychological Medicine*, *27*, 951–959.

Stein, M.B., Simmons, A.N., Feinstein, J.S., & Paulus, M.P. (2007). Increased amygdala and insula activation during

emotion processing in anxiety-prone subjects. *American Journal of Psychiatry*, *164*, 318–327.
Stevens, F.L., Hurley, R.A., & Taber, K.H. (2011). Anterior cingulate cortex: Unique role in cognition and emotion. *Journal of Neuropsychiatry and Clinical Neurosciences*, *23*, 121–125.
van Straaten, E.C., & Stam, C.J. (2013). Structure out of chaos: Functional brain network analysis with EEG, MEG, and functional MRI. *European Neuropsychopharmacology*, *23*, 7–18.
Sun, H., Lui, S., Yao, L., Deng, W., Xiao, Y., Zhang, W., … & Gong, Q. (2015). Two patterns of white matter abnormalities in medication-naive patients with first-episode schizophrenia revealed by diffusion tensor imaging and cluster analysis. *JAMA Psychiatry*, *72*, 678–686.
Suslow, T., Lindner, C., Dannlowski, U., Walhofer, K., Rodiger, M., Maisch, B., … & Kugel, H. (2013). Automatic amygdala response to facial expression in schizophrenia: Initial hyperresponsivity followed by hyporesponsivity. *BMC Neuroscience*, *14*, 140.
Suslow, T., Ohrmann, P., Bauer, J., Rauch, A.V., Schwindt, W., Arolt, V., … & Kugel, H. (2006). Amygdala activation during masked presentation of emotional faces predicts conscious detection of threat-related faces. *Brain and Cognition*, *61*, 243–248.
Suzuki, H., Luby, J.L., Botteron, K.N., Dietrich, R., McAvoy, M.P., & Barch, D.M. (2014). Early life stress and trauma and enhanced limbic activation to emotionally valenced faces in depressed and healthy children. *Journal of the American Academy of Child and Adolescent Psychiatry*, *53*, 800–813, e810.
Takiguchi, S., Fujisawa, T.X., Mizushima, S., Saito, D.N., Okamoto, Y., & Shimada, K., & Tomoda, A. (2015). Ventral striatum dysfunction in children and adolescents with reactive attachment disorder: A functional MRI study. *BJPsych Open*. (in press)
Teicher, M.H. (2000). Wounds that time won't heal: The neurobiology of child abuse. *Cerebrum*, *4*, 50–67.
Teicher, M.H. (2002). Scars that won't heal: The neurobiology of child abuse. *Scientific American*, *286*, 68–75.
Teicher, M.H., Andersen, S.L., Polcari, A., Anderson, C.M., & Navalta, C.P. (2002). Developmental neurobiology of childhood stress and trauma. *Psychiatric Clinics of North America*, *25*, 397–426, vii-viii.
Teicher, M.H., Andersen, S.L., Polcari, A., Anderson, C.M., Navalta, C.P., & Kim, D.M. (2003). The neurobiological consequences of early stress and childhood maltreatment. *Neuroscience and Biobehavioral Reviews*, *27*, 33–44.
Teicher, M.H., Anderson, C.M., Ohashi, K., & Polcari, A. (2014). Childhood maltreatment: Altered network centrality of cingulate, precuneus, temporal pole and insula. *Biological Psychiatry*, *76*, 297–305.
Teicher, M.H., Anderson, C.M., & Polcari, A. (2012). Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum. *Proceedings of the National Academy of Sciences of the United States of America*, *109*, E563–E572.
Teicher, M.H., Dumont, N.L., Ito, Y., Vaituzis, C., Giedd, J.N., & Andersen, S.L. (2004). Childhood neglect is associated with reduced corpus callosum area. *Biological Psychiatry*, *56*, 80–85.
Teicher, M.H., Glod, C.A., Surrey, J., & Swett, C., Jr (1993). Early childhood abuse and limbic system ratings in adult psychiatric outpatients. *Journal of Neuropsychiatry and Clinical Neurosciences*, *5*, 301–306.
Teicher, M.H., Ito, Y., Glod, C.A., Andersen, S.L., Dumont, N., & Ackerman, E. (1997). Preliminary evidence for abnormal cortical development in physically and sexually abused children using EEG coherence and MRI. *Annals of the New York Academy of Sciences*, *821*, 160–175.
Teicher, M.H., & Parigger, A. (2015). The 'Maltreatment and Abuse Chronology of Exposure' (MACE) scale for the retrospective assessment of abuse and neglect during development. *PLoS ONE*, *10*, e0117423.
Teicher, M.H., & Samson, J.A. (2013). Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. *American Journal of Psychiatry*, *170*, 1114–1133.
Teicher, M.H., Samson, J.A., Polcari, A., & McGreenery, C.E. (2006). Sticks, stones, and hurtful words: Relative effects of various forms of childhood maltreatment. *American Journal of Psychiatry*, *163*, 993–1000.
Teicher, M.H., Samson, J.A., Sheu, Y.S., Polcari, A., & McGreenery, C.E. (2010). Hurtful words: Association of exposure to peer verbal abuse with elevated psychiatric symptom scores and corpus callosum abnormalities. *American Journal of Psychiatry*, *167*, 1464–1471.
Teicher, M.H., Tomoda, A., & Andersen, S.L. (2006). Neurobiological consequences of early stress and childhood maltreatment: Are results from human and animal studies comparable? *Annals of the New York Academy of Sciences*, *1071*, 313–323.
Teicher, M.H., & Vitaliano, G.D. (2011). Witnessing violence toward siblings: An understudied but potent form of early adversity. *PLoS ONE*, *6*, e28852.
Thomaes, K., Dorrepaal, E., Draijer, N., de Ruiter, M.B., van Balkom, A.J., Smit, J.H., & Veltman, D.J. (2010). Reduced anterior cingulate and orbitofrontal volumes in child abuse-related complex PTSD. *Journal of Clinical Psychiatry*, *71*, 1636–1644.
Thomas, K.M., Drevets, W.C., Dahl, R.E., Ryan, N.D., Birmaher, B., Eccard, C.H., … & Casey, B.J. (2001). Amygdala response to fearful faces in anxious and depressed children. *Archives of General Psychiatry*, *58*, 1057–1063.
Tomoda, A., Navalta, C.P., Polcari, A., Sadato, N., & Teicher, M.H. (2009). Childhood sexual abuse is associated with reduced gray matter volume in visual cortex of young women. *Biological Psychiatry*, *66*, 642–648.
Tomoda, A., Polcari, A., Anderson, C.M., & Teicher, M.H. (2012). Reduced visual cortex gray matter volume and thickness in young adults who witnessed domestic violence during childhood. *PLoS ONE*, *7*, e52528.
Tomoda, A., Sheu, Y.S., Rabi, K., Suzuki, H., Navalta, C.P., Polcari, A., & Teicher, M.H. (2011). Exposure to parental verbal abuse is associated with increased gray matter volume in superior temporal gyrus. *NeuroImage*, *54*(Suppl 1), S280–S286.
Tomoda, A., Suzuki, H., Rabi, K., Sheu, Y.S., Polcari, A., & Teicher, M.H. (2009). Reduced prefrontal cortical gray matter volume in young adults exposed to harsh corporal punishment. *NeuroImage*, *47*(Suppl 2), T66–T71.
Tottenham, N., Hare, T.A., Millner, A., Gilhooly, T., Zevin, J.D., & Casey, B.J. (2011). Elevated amygdala response to faces following early deprivation. *Developmental Science*, *14*, 190–204.
Tottenham, N., Hare, T.A., Quinn, B.T., McCarry, T.W., Nurse, M., Gilhooly, T., … & Casey, B.J. (2010). Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. *Developmental Science*, *13*, 46–61.
Treadway, M.T., Grant, M.M., Ding, Z., Hollon, S.D., Gore, J.C., & Shelton, R.C. (2009). Early adverse events, HPA activity and rostral anterior cingulate volume in MDD. *PLoS ONE*, *4*, e4887.
Tupler, L.A., & De Bellis, M.D. (2006). Segmented hippocampal volume in children and adolescents with posttraumatic stress disorder. *Biological Psychiatry*, *59*, 523–529.
Uematsu, A., Matsui, M., Tanaka, C., Takahashi, T., Noguchi, K., Suzuki, M., & Nishijo, H. (2012). Developmental trajectories of amygdala and hippocampus from infancy to early adulthood in healthy individuals. *PLoS ONE*, *7*, e46970.

Ugwu, I.D., Amico, F., Carballedo, A., Fagan, A.J., & Frodl, T. (2014). Childhood adversity, depression, age and gender effects on white matter microstructure: A DTI study. *Brain Structure and Function*, *220*, 1997–2009.

Van Dam, N.T., Rando, K., Potenza, M.N., Tuit, K., & Sinha, R. (2014). Childhood maltreatment, altered limbic neurobiology, and substance use relapse severity via trauma-specific reductions in limbic gray matter volume. *JAMA Psychiatry*, *71*, 917–925.

Vermetten, E., Schmahl, C., Lindner, S., Loewenstein, R.J., & Bremner, J.D. (2006). Hippocampal and amygdalar volumes in dissociative identity disorder. *American Journal of Psychiatry*, *163*, 630–636.

Volkow, N.D., Wang, G.J., Ma, Y., Fowler, J.S., Zhu, W., Maynard, L., … & Swanson, J.M. (2003). Expectation enhances the regional brain metabolic and the reinforcing effects of stimulants in cocaine abusers. *Journal of Neuroscience*, *23*, 11461–11468.

Vyas, A., Jadhav, S., & Chattarji, S. (2006). Prolonged behavioral stress enhances synaptic connectivity in the basolateral amygdala. *Neuroscience*, *143*, 387–393.

Vyas, A., Pillai, A.G., & Chattarji, S. (2004). Recovery after chronic stress fails to reverse amygdaloid neuronal hypertrophy and enhanced anxiety-like behavior. *Neuroscience*, *128*, 667–673.

Vythilingam, M., Heim, C., Newport, J., Miller, A.H., Anderson, E., Bronen, R., … & Bremner, J.D. (2002). Childhood trauma associated with smaller hippocampal volume in women with major depression. *American Journal of Psychiatry*, *159*, 2072–2080.

Wacker, J., Dillon, D.G., & Pizzagalli, D.A. (2009). The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: Integration of resting EEG, fMRI, and volumetric techniques. *NeuroImage*, *46*, 327–337.

Walsh, N.D., Dalgleish, T., Lombardo, M.V., Dunn, V.J., Van Harmelen, A.L., Ban, M., & Goodyer, I.M. (2014). General and specific effects of early-life psychosocial adversities on adolescent grey matter volume. *NeuroImage Clinical*, *4*, 308–318.

Walton, R.M. (2012). Postnatal neurogenesis: Of mice, men, and macaques. *Veterinary Pathology*, *49*, 155–165.

Wang, L., Dai, Z., Peng, H., Tan, L., Ding, Y., He, Z., … & Li, L. (2014). Overlapping and segregated resting-state functional connectivity in patients with major depressive disorder with and without childhood neglect. *Human Brain Mapping*, *35*, 1154–1166.

van der Werff, S.J., Pannekoek, J.N., Veer, I.M., van Tol, M.J., Aleman, A., Veltman, D.J., … & van der Wee, N.J. (2013a). Resilience to childhood maltreatment is associated with increased resting-state functional connectivity of the salience network with the lingual gyrus. *Child Abuse and Neglect*, *37*, 1021–1029.

van der Werff, S.J., Pannekoek, J.N., Veer, I.M., van Tol, M.J., Aleman, A., Veltman, D.J., … & van der Wee, N.J. (2013b). Resting-state functional connectivity in adults with childhood emotional maltreatment. *Psychological Medicine*, *43*, 1825–1836.

Whittle, S., Dennison, M., Vijayakumar, N., Simmons, J.G., Yucel, M., Lubman, D.I., … & Allen, N.B. (2013). Childhood maltreatment and psychopathology affect brain development during adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry*, *52*, 940–952, e941.

Witthaus, H., Kaufmann, C., Bohner, G., Ozgurdal, S., Gudlowski, Y., Gallinat, J., … & Juckel, G. (2009). Gray matter abnormalities in subjects at ultra-high risk for schizophrenia and first-episode schizophrenic patients compared to healthy controls. *Psychiatry Research*, *173*, 163–169.

Wolfers, T., Onnink, A.M., Zwiers, M.P., Arias-Vasquez, A., Hoogman, M., Mostert, J.C., … & Franke, B. (2015). Lower white matter microstructure in the superior longitudinal fasciculus is associated with increased response time variability in adults with attention-deficit/hyperactivity disorder. *Journal of Psychiatry and Neuroscience*, *40*, 140154.

Woodward, S.H., Kuo, J.R., Schaer, M., Kaloupek, D.G., & Eliez, S. (2013). Early adversity and combat exposure interact to influence anterior cingulate cortex volume in combat veterans. *NeuroImage Clinical*, *2*, 670–674.

Zhang, T.Y., Labonte, B., Wen, X.L., Turecki, G., & Meaney, M.J. (2013). Epigenetic mechanisms for the early environmental regulation of hippocampal glucocorticoid receptor gene expression in rodents and humans. *Neuropsychopharmacology*, *38*, 111–123.

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