



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

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Abstract

Background and Scope—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. 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.

Findings—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. 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.

Conclusion—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

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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 (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 and colleagues (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), ischemic 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, 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., 1999b)), 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 (Dannowski, 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, in press; 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) – 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 (B. 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, et al., 2010; Teicher & Vitaliano, 2011).

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 neurohumors, 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 non-adaptive 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 non-specific 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., (G. E. Miller & Cole, 2012; Zhang, Labonte, Wen, Turecki, & Meaney, 2013)), though 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 were 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 non-maltreated 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 non-significant effects reported nearly significant reductions (Cohen, et al., 2006), or correlations (Kumari, et al., 2013; Woodward, Kuo, Schaer, Kaloupek, & Eliez, 2013) (in the non-violent 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 aging. 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 (Samplin, Ikuta, Malhotra, Szeszko, & 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 et al (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 (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 estrogen 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 gray 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. Pediatric 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 post-pubertal 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 et al., (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 (Luby, et al., 2013) is worth noting. They assessed hippocampal volume in 3–6-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 preexisting 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 behaviors (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 non-maltreated 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 (J. E. 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 9–11 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 non-significant studies that provided data on amygdala volumes (e.g.,

9/10) observed a non-significant decrease, averaging 5.9% right and 5.0% left. Studies reporting a significant decrease (and providing volume data) reported a mean right/left percent reduction of 18.8% and 21.6%. Hence, the vast majority of maltreatment studies reported either a non-significant 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 et al (2012), Whittle et al (2013) and Pechtel and colleagues (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 non-significant 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 non-significant 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 modeling 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 gray 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 – 33 months of age), showed a remarkably similar 6.4% reduction in gray 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 non-significant, suggesting an intermediate effect. These studies were not adjusted for differences in intracranial volume.

Similar differences can be found in unadjusted cortical gray 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., 1999b; De Bellis, et al., 2002). For example, De Bellis et al (2002) provided unadjusted data indicating a 4.8% and 5.9% reduction in gray 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 gray and white matter development (Luby, et al., 2013).

It is worth noting however that maltreatment-related differences in cortical gray and white matter volume disappear if the data are corrected for differences in intracranial volume (De Bellis, et al., 1999b; 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., 1999b; 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, though 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 gray 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 gray matter volume appeared to be most sensitive to maltreatment between 14–16 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 appears 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 is but one of the ways that maltreatment affects the brain to enhance risk for addiction.

Sheffield et al (2013) published an important study in which they used voxel-based morphometry to identify differences in gray matter density in psychotic disorder patients with and without maltreatment and healthy controls. They found that overall gray 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 gray matter volume. Psychotic disorder patients with versus without sexual abuse histories differed significantly in gray 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, Fiber 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 fiber 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 fiber bundles are evaluated without preselecting a pathway of interest. Three fiber 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 fiber 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).

Fibers 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 gray matter density without preselection of regions of interest. A significant cluster of increased gray 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 gray 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 fiber 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 7–13 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 et al., (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 gray 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 11–13 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 gray matter volume in portions of visual cortex and in the pathway interconnecting visual and limbic systems.

VBM and surface-based analyses was 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 non-abusive 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). Gray matter volume was markedly reduced in bilateral primary visual (V1) and visual association cortices of abused subjects. Extent of gray matter reduction was directly related to duration of sexual abuse before age 12 (Tomoda, Navalta, et al., 2009). Gray matter volume of left and right V1 correlated with measure of visual memory. Cortical surface-based analysis indicated that gray 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 gray 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 fiber 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 non-specific 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 and colleagues (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 behavioral 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 Fiber Tracts

One of the earliest and most consistent finding in maltreated children (e.g., (De Bellis, et al., 1999b; 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 preexisting protective factor.

Several studies suggest that exposure to maltreatment is associated with a 2-fold greater reduction in corpus callosum area in boys than girls (De Bellis & Keshavan, 2003; De Bellis, et al., 1999b; De Bellis, et al., 2002; Teicher, et al., 2004; Teicher, et al., 1997). 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 9–10 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 (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 non-significantly 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 non-maltreated 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 – 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 cortices 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 inter-hemispheric 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 (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 fiber 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 fiber 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 three 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 (M. C. 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 fiber 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 (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). Non-significant increases in caudate volume with maltreatment have been reported in three studies (Bremner, et al., 1997; De Bellis, et al., 1999a; De Bellis, et al., 2002), significant decreases in two (Baker, et al., 2013; Cohen, et al., 2006), non-significant 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), non-significant increases in another (De Bellis, et al., 1999a), non-significant mixed hemispheric effects in one (De Bellis, et al., 2002) and a non-significant decrease in a fifth study (McLaughlin, et al., 2014). An overall inverse correlation between CTQ scores and striatal gray matter volume (not distinguishing caudate from putamen) was reported by Edmiston (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 non-human primates has been reported to substantially exceed receptor density in the hippocampus (Sanchez, Young, Plotsky, & Insel, 2000). Second, postnatal neurogenesis occurs in cerebellum, though 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 post-childhood trauma and varying degrees of early life trauma, violent and non-violent adults with schizophrenia, antisocial personality disorder and healthy controls.

Our interest in the cerebellar vermis stems from the work of 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 (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 reexamined 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 center and two smaller images to the right and left below, and select the right or left image that matches the center. Button presses are intended to have participants focus on the task, but not to consciously identify the facial expression. Most studies specifically analyze 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 (E. M. 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 care-giver deprivation (Goff, et al., 2013; Maheu, et al., 2010; Tottenham, et al., 2011), as well as in children exposed to either family violence (McCrary, 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; J. LeDoux, 1996; J. E. 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 fiber 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 fiber 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 non-conscious 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 favoring 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 3–5 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., in press); maltreated children at high risk for depression (Hanson, et al., in press); 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 pedunculo-pontine 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 fiber 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 gray 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-centered mental imagery (Cavanna & Trimble, 2006). The anterior insula plays a critical role in interoception, providing the substrate for all subjective feelings from the body (A. D. 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 (A. D. 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-centered 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-centered 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 non-maltreated 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 non-maltreated 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 non-maltreated 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 (Dannowski, 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 non-maltreated 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., (Dannowski, 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 non-significant 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 toward avoidance.

Adaptive in this sense means that the alterations are experience-dependent responses to the environment and not simply non-specific 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 (B. A. 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 behaviors 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 gray 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 mindfulness (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 and 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 convey 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.