The link between child abuse and psychopathology: A review of neurobiological and genetic research

Eamon McCrory[1,2,3] • Stephane A De Brito[1,2] • Essi Viding[1]

[1]University College London (UCL), London WC1H 0AP, UK
[2]The Anna Freud Centre, London, UK
[3]NSPCC, London, UK
Correspondence to: Eamon McCrory. Email: e.mccrory@ucl.ac.uk

This is the second in a series of three articles on a new clinical concept called violence adapting syndrome

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Summary

Childhood abuse is associated with later psychopathology, including conduct disorder, antisocial personality disorder, anxiety and depression as well as a heightened risk of health and social problems. However, the neurobiological mechanisms by which childhood adversity increases vulnerability to psychopathology remain poorly understood. There is likely to be a complex interaction between environmental experiences (such as abuse) and individual differences in risk versus protective genes, which influences the neurobiological circuitry underpinning psychological and emotional development. Neuroendocrine studies indicate an association between early adversity and atypical development of the hypothalamic-pituitary-adrenal (HPA) axis stress response, which may predispose to psychiatric vulnerability in adulthood. Brain imaging research in children and adults is providing evidence of several structural and functional brain differences associated with early adversity. Structural differences have been reported in the corpus callosum, cerebellum and prefrontal cortex. Functional differences have been reported in regions implicated in emotional and behavioural regulation, including the amygdala and anterior cingulate cortex. These differences at the neurobiological level may represent adaptations to early experiences of heightened stress that lead to an increased risk of psychopathology. We also consider the clinical implications of future neurobiological and genetic research.

The impact of abuse on brain development

A growing body of research has investigated how stress, and specifically different forms of childhood abuse, is associated with neuroendocrine function as well as structural and functional differences at the level of the brain.[1] This research is in part motivated by the need to delineate biological mechanisms that may account for the heightened risk of psychological, social and health problems known to be associated with early adversity, including long-term consequences for adult economic wellbeing.[2,3] This paper selectively reviews recent human research related to early stress, maltreatment and their relationship to psychopathology; a number of earlier seminal studies are also included where these help set the research context. We primarily focus on studies of children who have experienced abuse but we also consider several studies of adults with documented histories of early adversity. We

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begin by briefly considering the evidence for an association between maltreatment or abuse and atypical development of the hypothalamic-pituitary-adrenal (HPA) axis stress response. We then provide a concise overview of neuroimaging studies that have sought to identify differences in regional brain structure and function associated with childhood abuse. We conclude by considering the possible clinical implications of this research.

Methods

This review was based on a selection of peer-reviewed articles in English obtained from PubMed that were published from 1995 to the present day; articles related to the study of maltreatment and adversity with a focus on HPA functioning, functional and structural imaging, and behavioural genetic paradigms.

Child abuse and the HPA system

The HPA axis represents one of the body's core stress response systems. Exposure to stress triggers release of corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) from the paraventricular nucleus of the hypothalamus, which in turn stimulate secretion of adrenocorticotrophic hormone (ACTH) that acts on the adrenal cortex to synthesize cortisol. Feedback loops at several levels ensure that the system is returned to homeostasis since chronically elevated cortisol levels can have deleterious effects on health.[4]

Despite several decades of research, findings from studies investigating HPA axis activity in children and adolescents with a history of maltreatment are mixed.[5] Several studies have reported elevated basal cortisol levels (e.g. Cicchetti and Rogosch[6]) while others have reported no differences.[7] One explanation for these apparently contradictory findings is that elevation is associated with the presence of a concurrent affective disorder;[5] equally, it is possible that different maltreatment experiences that vary in onset and duration lead to differential patterns of adaptation. For example, ongoing exposure to early adversity may be associated with stress habituation over time leading to reduced cortisol levels as observed in some maltreated children with antisocial behaviour.[8] Together these findings suggest that childhood abuse is associated with atypical HPA axis functioning in a substantial minority of abused children and that this may, in turn, be associated with difficulties in emotional and behavioural regulation.

Studies of adults with childhood histories of maltreatment or adversity also report atypical patterns of responsivity in the HPA axis, which may be associated with an increased vulnerability for psychopathology. There is some evidence that HPA hypoactivity tends to characterize adults presenting with post-traumatic stress disorder (PTSD)[9] while hyperactivity of the HPA system tends to characterize adults presenting with depression.[10] Again, these divergent patterns of activity may reflect adaptations of the HPA axis that occur in response to different forms of childhood adversity that vary in onset and chronicity.

Overall, there is a strong case that early stress may lead to an ongoing dysregulation of the HPA axis, which in turn predisposes to psychiatric vulnerability in later life. While there is consensus around this general principle, the putative mechanisms of how the HPA axis might mediate the link between stress and psychopathology and the precise nature of any interaction remain less clear. More studies, especially longitudinal ones, are needed to shed light on these issues.

Structural differences

Subcortical structures: hippocampus and amygdala

Animal research has shown that the hippocampus plays a central role in learning and various aspects of memory and that these functions are impaired when animals are exposed to chronic stress. Studies of adults with PTSD who have histories of childhood maltreatment consistently report that these individuals have smaller hippocampal volumes. It is surprising then that structural magnetic resonance imaging (sMRI) studies of children and adolescents with abuse-related PTSD consistently fail to detect decreased hippocampal volume.[11] One possibility is that the impact of stress is delayed and becomes manifest only later in development.

The amygdala, another key subcortical structure, plays a central role in evaluating potentially threatening information, fear conditioning, emotional processing and memory. Given that experiences of abuse typically occur in family environments characterized by unpredictability and threat it might be expected that children growing up in such contexts would show increased amygdala volume, comparable to that found in stress-exposed animals who show increased dendritic arborisation.[12] Until very recently there was a consensus that maltreatment was not associated with differences in amygdala volume.[13] However, in contrast to the existing studies, two recent sMRI investigations that focused on children and adolescents who had experienced prolonged institutional rearing in orphanages in their first two years of life have reported an increase in amygdala volume in maltreated children[14] suggesting that such effects may only be manifest in children who have experienced severe early sensory deprivation. It is noteworthy that the effects of such extreme early adversity on the brain were observed even many years after the adversity had ceased, which is in line with evidence from animal research.[14]

Cortical structures: prefrontal cortex and cerebellum

The prefrontal cortex (PFC) plays a major role in the control of many aspects of behaviour, regulating cognitive and emotional processes through extensive interconnections with other cortical and subcortical regions.

There are mixed findings from studies comparing PFC volume of children with maltreatment-related PTSD and non-maltreated children. Some studies have reported smaller prefrontal volume associated with the experience of maltreatment,[15] and less prefrontal white matter, while other studies have reported larger grey matter volume of the middle-inferior and ventral regions of the PFC in maltreated groups. There are several possible reasons for these inconsistent findings and it is likely that methodological differences across studies, including the use of different imaging techniques and age groups of children, might at least partly account for these reported differences.[1] It is also possible that there are regionally specific windows of vulnerability in brain development. For example, in a unique cross-sectional study, Andersen *et al.*[16] found that grey matter volume of the frontal cortex was maximally affected by abuse at ages 14–16 years, while the hippocampus and corpus callosum were maximally affected at ages 3–5 years and 9–10 years, respectively, indicating that the frontal cortex in this sample was particularly susceptible to structural change following abuse during the adolescent period. Unfortunately, most brain imaging studies have not systematically considered the age at which different kinds of abuse have occurred. From a clinical perspective it would be helpful for further research to systematically investigate the relative susceptibility of different brain regions at different ages to different forms of early adversity.

The cerebellum plays a crucial role in emotion processing and fear conditioning via its connection with limbic structures and the HPA axis.[17] Decreased volume of the cerebellum in children and adolescents with a history of maltreatment has been a consistent finding in the literature.[1]

Corpus callosum and other white matter tracts

The corpus callosum (CC) is the largest white matter structure in the brain and controls inter-hemispheric communication of a host of processes, including, but not limited to, arousal, emotion, and higher cognitive abilities. With the exception of one study, decreases in CC volume have consistently been reported in maltreated children and adolescents compared to non-maltreated peers.[1] Recent studies that have employed diffusion tensor imaging (DTI) have found decreased fractional anisotropy values (indicative of decreased white matter fibre tracts coherence or lower density of white matter fibre tracts) in maltreated children in frontal and temporal white matter regions, including the uncinate fasciculus which connects the orbitofrontal cortex to the anterior temporal lobe, including the amygdala.[18] The reduction in fractional anisotropy observed was associated with longer periods within an orphanage and may underlie some of the socio-emotional and cognitive impairments exhibited by maltreated children.[18]

Functional differences

In contrast to the number of studies examining structural brain differences, only a few have so far investigated possible functional correlates associated with abuse and maltreatment using brain imaging techniques such as functional MRI (fMRI) or electrophysiological techniques.

fMRI studies

To date, five fMRI studies have compared maltreated or previously institutionalised children to typically developing peers. Building on the experimental evidence that maltreated children show hypervigilance to threatening facial cues two fMRI studies have examined the neural correlates of face processing in a related population. These studies have reported that previously institutionalised children are characterized by increased amygdala response to threatening cues in comparison to non-maltreated children.[19] This adds to evidence from sMRI studies suggesting amygdala abnormality in children exposed to early adversity. Two other studies assessed response inhibition and observed increased activation in the anterior cingulate cortex (ACC) in maltreated youths as compared to controls. These results suggest impaired cognitive control in maltreated youths, which, in turn, could confer risk for psychopathology,[20] especially in the context of heightened subcortical responses such as that observed during affective processing. The fifth study used a verbal declarative memory task and compared youths with posttraumatic stress symptoms (PTSS) secondary to maltreatment with healthy controls.[21] During the retrieval component of the task, the youths with PTSS exhibited reduced right hippocampal activity, which was associated with greater severity of avoidance and numbing symptoms.

Event-related potential (ERP) studies

Much of the existing ERP research has compared the pattern of brain response of adversely treated children and healthy children when processing facial expressions, an ability that is usually mastered by the preschool years. When compared with non-institutionalized peers, institutionalized children who have experienced severe social deprivation showed a pattern of cortical hypoactivation when viewing emotional facial expressions, and familiar and unfamiliar faces.[22] In contrast, a second set of important studies has provided convincing evidence that school-aged children who had been exposed to physical abuse show increases in brain activity specific to angry faces and require more attentional resources to disengage from such stimuli (see Pollak *et al.*[23]). These ERP findings are consistent with recent fMRI evidence and suggest that some maltreated children are allocating more resources and remain hyper-vigilant to potential social threat in their environment, likely to be at the cost of other developmental processes.

The role of genetic influences

It is a common but often striking clinical experience to find that two children who have experienced very similar patterns of early adversity have very different outcomes. While this may be partly due to specific environmental or psychological factors characterizing one child, but not the other, there is increasing evidence that such differential outcome may in part at least be due to genetic differences.[24]

We now know that many of the psychiatric outcomes that are associated with maltreatment, such as PTSD, depression and antisocial behaviour, are partly heritable. However, it is incorrect to think that there are particular genes for these disorders. Rather, we are learning that there are a wide number of genetic variants that may subtly alter the structure and functioning of neural circuitry and hormonal systems that are crucial in calibrating our individual response to social affective cues, and in regulating our stress response.[24] In recent years, researchers have focused in particular on the way in which such genetic variants and adverse environments may interact. Such gene by environment interaction (GxE) research has demonstrated that for a range of genetic variants (known as polymorphisms) childhood abuse can increase the risk of later psychopathology for some children more than others. For example Caspi and colleagues[25] were the first to report on an interaction of a measured genotype (monoamine oxidase A, MAOA) and environment (abuse) for a psychiatric outcome and

demonstrated that individuals who are carriers for the low-activity allele (MAOA-l) were at an increased risk for antisocial behaviour disorders following maltreatment. Imaging genetic studies have found that the risk genotype, MAOA-l, is related to hyper-responsivity of the brain's threat detection system and reduced activation in emotion regulation circuits. This work suggests a neural mechanism by which MAOA genotype engenders vulnerability to reactive aggression following maltreatment.[26]

In other words, GxE research suggests that a child's genotype may partly determine their level of risk and resilience for adult psychiatric outcomes, including depression and PTSD following childhood maltreatment (e.g. Kaufman *et al*.[27]). It is important to bear in mind, however, that positive environmental influences, such as social support, can promote resiliency, even in those children carrying 'risk' polymorphisms exposed to maltreatment.[27] This finding illustrates the important point that when considering a GxE interaction, positive environmental influences (such as contact with a supportive attachment figure), are as relevant to consider as negative environmental influences such as maltreatment. Future research will investigate the influence of clinical interventions as a positive environmental factor that may serve to moderate environmental and genetic risk.

Clinical implications

Developmental neuroscience research is just one small part of a wider societal endeavour to better understand the complex repercussions of child maltreatment, so that as clinicians working with children we become better at early intervention and prevention.[28] This review has highlighted the accumulating evidence pointing to a variety of neurobiological changes associated with child abuse and early adversity. Such changes can, on the one hand, be viewed as a cascade of deleterious effects that are harmful for the child; however, a more evolutionary and developmentally informed view would suggest that such changes are in fact adaptive responses to an early environment characterized by threat. If a child is to respond optimally to the challenges posed by their surroundings then early stress-induced changes in neurobiological systems can be seen as 'programming' or calibrating those systems to match the demands of a hostile environment. From a clinical perspective, such adaptation may heighten vulnerability to psychopathology, partly due to the changes in how emotional and cognitive systems mediate social interaction.[29] For example, early-established patterns of hypervigilance, while adaptive in an unpredictable home environment, may be maladaptive in other settings increasing vulnerability for behavioural, emotional and social difficulties.

While most of the neurobiological research to date has focused on the pathological impact of maltreatment, there is a welcome and growing interest in exploring the concept of resilience and those factors that may promote or enhance neurobiological mechanisms important for emotional regulation and coping. For example, there is emerging genetic and neurobiological evidence supporting the importance of a reliable adult caregiver, and the role they can play in helping to scaffold the vulnerable child's ability to regulate stress.[27,30] There is also work in progress within our own lab to identify possible neural correlates of resilience in children referred to social services for suspected maltreatment or neglect. In our view it is as important to understand the neurobiological functioning of those children who show few ill-effects, despite experiences of adversity, as it is to study those who present with difficulties.

Over the next decade we are likely to see an increasingly rich research agenda addressing why early adversity acts as a generic risk factor for such an array of poor outcomes. While the evidence reviewed here remains preliminary, it points to an interplay between genetic risk and environmental adversity that becomes manifest at the neural level. Specifically, child abuse may lead to atypical development in basic neurocognitive mechanisms for emotional and behavioural regulation in genetically at-risk children. Over time, such 'adaptations' bear a cost in compromising a child's neurocognitive potential to negotiate the everyday social and academic demands of childhood.

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