Adverse childhood experiences and brain development: neurobiological mechanisms linking the social environment to psychiatric disorders

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Abstract and Keywords
Adverse childhood experiences are robust determinants of psychiatric disorders with effects that persist across the life course. This chapter argues that childhood social and environmental experience weaves its way into the developing brain and exerts powerful effects on neural structure and function throughout childhood and into adulthood. These experiences ultimately have relevance for understanding population-level patterns of mental illness. Evidence linking adverse childhood experiences to patterns of brain development is reviewed, focusing on the role that disruptions in neurodevelopment play as a mechanism linking childhood social and environmental experience to the onset of mental disorders.
disorders. Specifically addressed are the impact of maltreatment, institutional rearing, and childhood socioeconomic status on brain development.

*Keywords*: childhood adversity, brain development, neurodevelopment, maltreatment, institutionalization, socioeconomic status

23.1 Introduction
Increasing popularity of the life course approach in psychiatric epidemiology has led to renewed interest in the childhood determinants of mental disorders and the mechanisms through which childhood experiences increase risk of psychopathology. The main thesis of this chapter is that social and environmental experience weaves its way into the developing brain and exerts powerful effects on neural structure and function throughout childhood and into adulthood. These experiences ultimately influence the course of human development and have relevance for understanding population-level patterns of mental illness. Here we provide evidence suggesting that the influence of the early social environment on the developing brain may be a primary mechanism linking childhood social experience to later outcomes, including mental illness.

We begin by briefly reviewing recent life course epidemiology studies examining the association between the childhood social environment and psychopathology, with a focus on the lasting impact of adverse childhood experiences such as maltreatment, violence exposure, environmental deprivation, and poverty on mental health. Next, we highlight potential neurobiological mechanisms that might explain the association between these adverse childhood experiences and the later onset of psychopathology. Finally, we review existing literature examining the associations of two specific types of adverse childhood experiences: maltreatment and poverty or socio-economic status (SES), with brain structure and function. In each section, we review neuroimaging studies examining brain structure and function using electroencephalogram (EEG) and both structural and functional magnetic resonance imaging (MRI), focusing on studies that have been conducted in children and adolescents. Although numerous studies have examined brain structure and function in adults who have experienced childhood adversity,\(^1\) the accumulation of life experiences from childhood into adulthood makes it difficult to assume that alterations in brain structure and function observed in adults are the result of early experiences. We conclude by discussing the implications of integrating developmental cognitive neuroscience methods into life course epidemiology and population health approaches to mental disorders.

\(\text{(p.250)}\) 23.2 Childhood adversity and mental disorders
Adverse childhood experiences are robust determinants of psychiatric disorders with effects that persist across the life course. Exposure to maltreatment, environmental deprivation, family violence, and parental instability have lasting detrimental effects on mental health. Retrospective studies consistently identify higher rates of these childhood adversities among individuals with a psychiatric disorder, and prospective data confirm these associations. High rates of mental disorders among individuals with a history of adverse childhood experiences are evident not only in childhood but also in adolescence and adulthood. Importantly, childhood adversities are associated with new disorder onsets in adulthood, even after accounting for the effects of early onset disorders as well as greater chronicity and severity of lifetime mental disorders.

From a population health perspective, childhood adversities are an important set of exposures for several reasons. First, these experiences are common. National surveys estimate that 25–50% of children are exposed to violence or other victimization. Second, the association between adverse childhood experiences and psychopathology is strong. Across numerous studies, individuals with a history of childhood adversities are at least twice as likely to develop a mental disorder as those with no exposure. Finally, childhood adversities account for a substantial proportion of mental disorders in the population. Recent evidence suggests that 30% of lifetime mental disorder onsets in the USA are directly attributable to exposure to childhood adversities, underscoring the significance of these exposures as a population health problem.
23.3 Potential neurobiological mechanisms

There are various neurobiological mechanisms through which exposure to adverse childhood experiences might increase risk for psychopathology. One central pathway involves a network of brain and bodily systems that respond to stress (e.g. changes in the environment that require psychological or physiological adaptation). Many of the adverse childhood experiences reviewed here are considered to be psychologically stressful or traumatic, particularly because they are unpredictable and uncontrollable and have the potential to overwhelm a child’s coping resources.

Physiological responses to stress involve activation of both the sympathetic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis. Activation of the HPA axis initiates a cascade of neuroendocrine responses that culminate in increased levels of circulating cortisol. Two structures in the brain, the hippocampus and the amygdala, are necessary to initiate and modulate the stress response and can be influenced by chronic stress exposure. The hippocampus provides a negative-feedback mechanism, which modulates the HPA axis response. During a typical HPA axis response to stress, glucocorticoids are released and bind to hippocampal glucocorticoid receptors, activating a negative-feedback loop and decreasing the HPA axis response. Chronic stress disrupts hippocampal function, which may in turn disrupt this negative feedback, resulting in extended HPA axis activation following stressful events and increasing the possibility of damage as a result of excessive glucocorticoid exposure. Damage to the hippocampus via exposure to stress disrupts both modulation of the HPA axis response and memory formation and is mediated through glucocorticoid exposure.

The amygdala plays an important role in recognizing and learning about emotion, particularly in fear acquisition and interpretation of emotional information such as facial expressions. Humans and non-human primates with bilateral amygdala lesions exhibit indiscriminate friendliness and overly trusting behaviour, and have compromised identification of emotional facial expressions. The amygdala also plays a role in fear conditioning by preparing the body for negative stimuli even prior to conscious awareness. Heightened amygdala activity and larger amygdala volume have
been documented among both children and adults with anxiety disorders.\textsuperscript{21, 22}

A second pathway through which childhood adversity may influence brain development and psychopathology is through deprivation, or absence of experience. Children who are neglected or raised in institutional settings—and potentially even children raised in extreme poverty—confront social and environmental circumstances that deviate from the expectable environments necessary for normal brain development. During sensitive periods of brain development, expected environmental inputs are necessary to guide neural differentiation and pruning. The environmental inputs necessary for proper development of the visual system and for language acquisition, for example, are well characterized.\textsuperscript{23} When the expected environmental conditions necessary for proper neurodevelopment are either absent or inadequate, brain development is likely to be affected in important ways.

The primary neural substrate of executive functioning is the prefrontal cortex (PFC), a large expanse of association cortex that plays a central role in complex cognitive functions including inhibition, planning, and decision-making. When children experience damage to the PFC, they have immediate deficits in executive function and fail to develop typically as adults.\textsuperscript{24} The PFC has a long developmental trajectory;\textsuperscript{25} gross changes in volume and connectivity begin at birth and continue through early adulthood. This protracted development is reflected in children’s increasing competence in behavioural tests of executive functions\textsuperscript{26} and changes in PFC functioning across childhood.\textsuperscript{27}–\textsuperscript{30} Given the long developmental trajectory of the PFC and its central role in complex cognitive function, inadequate exposure to cognitive inputs in childhood may disrupt its development in ways that influence risk for psychopathology, particularly externalizing disorders.

\subsection*{23.4 Neuroimaging studies of childhood adversity}

\subsubsection*{23.4.1 Child maltreatment}

Child maltreatment involves acts of commission or omission that have the potential to harm a child or result in actual harm to a child, regardless of whether harm was intended, and typically includes four broad categories: physical abuse, sexual abuse, emotional abuse, and neglect.\textsuperscript{31} Child maltreatment is perpetrated by parents or other caregivers in the vast majority
of cases.\textsuperscript{9} The following sections review neuroimaging studies that examine potential neurodevelopmental mechanisms through which child maltreatment increases risk for psychopathology.

\textbf{23.4.1.1 Brain structure}

Global differences in brain structure have been consistently reported in studies comparing children with and without exposure to maltreatment. Specifically, maltreated children have been found to have smaller total brain volume than non-maltreated children.\textsuperscript{32}–\textsuperscript{35} Although most studies reporting reduced total brain volume in maltreated youths are based on samples of children with maltreatment-related PTSD, at least one study reported a similar finding in a sample of maltreated children with a low prevalence of mental disorders.\textsuperscript{10} Larger ventricles have also been observed among maltreated children relative to controls.\textsuperscript{36}

The structure of the hippocampus and amygdala has frequently been examined in studies of child maltreatment given their central role in the regulation of stress response systems. However, studies of children have not found an association between maltreatment exposure and hippocampal volume.\textsuperscript{37, 38} Differences in the volume of the amygdala as a function of maltreatment history \textbf{(p.252)} have also not been observed. Despite considerable interest in the effects of stress and trauma on limbic areas, the global structure of the hippocampus and amygdala appear to be preserved in children exposed to maltreatment.

Structural differences in the PFC among maltreated children have been reported, although the results have been inconsistent across studies. In one study, children exposed to physical abuse had smaller total brain volumes than children with no maltreatment exposure and smaller volume of the right orbitofrontal cortex, right ventral–medial PFC, and bilateral dorsolateral PFC.\textsuperscript{10} A study of maltreated children with PTSD also reported globally smaller volume of the PFC in this group relative to controls, although this difference disappeared after adjusting for total brain volume.\textsuperscript{36} Two studies found an opposite pattern of findings, however, with children with maltreatment-related PTSD exhibiting larger gray matter volume in the PFC relative to non-maltreated children.\textsuperscript{39}
Maltreatment is also associated with structural changes in the cerebellum. Smaller volume of the vermis has been observed in physically abused children and children with maltreatment-related PTSD relative to controls. Reduced overall volume of the cerebellum among children with maltreatment-related PTSD relative to controls has also been documented.

One of the most consistently identified structural differences between maltreated and non-maltreated children is the corpus callosum, a white matter structure with dense fibres connecting the left and right hemispheres. Reduced corpus callosum volume—specifically in the anterior and posterior mid-body and splenium—in children who have been maltreated has been reported in several studies. This pattern is consistent with findings from a diffusion tensor imaging study that documented reduced fractional anisotropy—a marker of structural connectivity and myelination in white matter tracts—in the corpus callosum of maltreated compared with non-maltreated children.
**23.4.1.2 Brain function**

Disruptions in neural function related to child maltreatment have been studied using a variety of tasks designed to assess emotional processing and more global aspects of cognitive functioning. We first review studies that have utilized EEG and event-related potentials (ERPs) in response to specific visual stimuli. The EEG records electrical activity at the scalp, and the signal is decomposed into oscillations that occur in different frequency bands. The frequency bands that have been most frequently examined in developmental studies are beta (13–20 Hz), alpha (7–12 Hz), and theta (4–6 Hz). ERPs assess scalp-derived changes in brain electrical activity, measured using EEG, occurring in a time-locked fashion following presentation of a stimulus. ERP analysis typically examines the amplitude and latency of responses to specific stimuli.

EEG methods have been used to examine the influence of child maltreatment on patterns of frontal EEG asymmetry. Frontal regions of the cerebral cortex are differentially lateralized to process positive and negative stimuli and underlie behavioural and expressive responses to emotional information. The left frontal region is activated by positive emotional stimuli and promotes approach behaviour, whereas the right frontal region is activated by negative stimuli and underlies withdrawal or avoidance behaviour.\(^{13, 42}\) Individual differences in relative hemispheric activation of the frontal cortex—as indexed by EEG alpha power—are associated with emotional reactivity, behavioural inhibition, and psychopathology.\(^{15}\) Poor quality maternal caregiving is associated with a pattern of asymmetry characterized by greater activation in the right relative to the left frontal cortex in infants.\(^{43}\) This pattern has also been observed among adolescents exposed to child maltreatment.\(^{44}\)

**(p.253)** EEG methods have also been used to examine whether child maltreatment influences patterns of cortical differentiation. EEG coherence provides a measure of the degree of spatial synchrony between electrical signals measured at different parts of the scalp. Higher coherence indicates greater synchrony in the oscillations across scalp regions and is thought to reflect greater strength or coupling of cortical synaptic connections.\(^{45}\) Reduced coherence reflects a pattern of greater cortical differentiation associated with more complex neuronal networks.\(^{46}\) At least two studies have observed increased left hemisphere EEG coherence in...
maltreated children and adolescents relative to non-maltreated youths. In both studies, this pattern of EEG coherence was interpreted as a sign of reduced left hemisphere cortical differentiation in maltreated children.

Cognitive processing of facial emotion provides important social information that is necessary to facilitate appropriate social interactions and can be disrupted by child maltreatment. Pollak et al. documented differences in ERPs in response to facial displays of emotion among maltreated and non-maltreated youths. Children exposed to physical abuse and/or neglect exhibited larger ERP amplitudes to angry faces compared with happy faces and larger amplitudes to angry faces than controls, whereas non-maltreated children displayed similar ERP amplitude to both types of emotional stimuli. These alterations in neural processing of facial emotion are consistent with behavioural findings, suggesting that physically abused children identify facial displays of anger more quickly and with less sensory information than non-maltreated children.

Although the vast majority of fMRI studies of child maltreatment and neural function have been conducted in adults, several recent studies have examined neural function in maltreated youths using fMRI. The first documented deficits in cognitive control in maltreated children with PTSD. Non-maltreated children had greater activation in the middle frontal gyrus during response inhibition trials, whereas maltreated children exhibited greater activation in the anterior cingulate, a region activated by response conflict, and the medial frontal gyrus. These findings suggest that different areas of the PFC are engaged during tasks involving sustained attention and response inhibition for children with maltreatment-related PTSD than controls. A second study documented lower right hippocampal activation among children with maltreatment-related PTSD than non-maltreated children during retrieval trials on a verbal declarative memory task, suggesting that maltreatment exposure is associated with reduced hippocampal functioning in children.

23.4.2 Socio-economic status
There are strong social gradients in mental disorders according to socio-economic status (SES), such that lower SES is associated with greater psychopathology across the entire income distribution. SES is an aggregate measure intended to capture social standing, which is often estimated with measures of family income, educational attainment, and occupational status. Measures of family SES are strongly linked to child emotional and behavioural problems and risk of mental disorders. These inequalities in mental health are evident early in childhood and persist or worsen across development into adulthood.

Socio-economic status is a broad variable that is measured using numerous indicators and predicts exposure to a broad array of experiences. As such, there are numerous pathways through which childhood SES may influence brain development in ways that increase risk for psychopathology. These include deprivation in material resources needed to sustain health, such as nutrition, clothing, shelter, and health care; differential exposure to childhood traumatic events; parental psychopathology; deficits in the complexity and amount of language exposure within the home, school, and community; and differences in the degree of structure in educational and home settings. We now review studies that examine SES differences in brain structure and function in children.
23.4.3.1 Brain structure
Several reviews have emphasized the importance of the stress response system as a mechanism by which SES influences neural structure and function, suggesting that low SES will be associated with decreased hippocampus volume and increased amygdala volume.\textsuperscript{61, 62} However, the associations between childhood SES and limbic structure volume are complex. In a recent study, a positive association was observed between family income-to-needs ratio and child hippocampal volume, such that greater resources were associated with larger hippocampal volume, but a negative association was found between hippocampal volume and parental education.\textsuperscript{53} Although the divergent associations of hippocampal volume with different measures of SES are perplexing, a similar pattern has been reported in other studies. Family income was positively associated with child hippocampal volume in one of these studies.\textsuperscript{54} In a second study, hippocampal volume was negatively associated with parental nurturance and unrelated to degree of enrichment in the home.\textsuperscript{55} One interpretation of this pattern of results is that measures that directly or indirectly assess parenting behaviour are negatively associated with hippocampal volume, whereas markers of environmental enrichment are positively associated with hippocampal volume. Amygdala volume has been inconsistently associated with SES in children. In the recent study by Noble et al., the associations between amygdala volume and SES were reported to be similar to those found in the hippocampus.\textsuperscript{53} However, these were not replicated in two other studies.\textsuperscript{54, 55}

The consistent finding that children from low SES families perform more poorly on tests of executive functioning than children from middle-class families has led some to argue that childhood SES may influence the development of the PFC.\textsuperscript{56, 63–65} This hypothesis was supported by a recent study in young adults. Subjective social status was positively associated with anterior cingulate cortex volume, a part of the PFC involved in conflict monitoring.\textsuperscript{58} However, a subsequent study did not observe an association between PFC structure and SES in children.\textsuperscript{54}

23.4.3.2 Brain function
Recent fMRI studies have documented associations between childhood SES and function of the limbic system. Children whose parents reported low subjective social status activated the hippocampus less in a long term memory encoding paradigm than children whose parents had high subjective social status. These findings extend previous work demonstrating decrements in performance on long term memory tasks in children from low SES families. Childhood SES has also been related to amygdala function. Low parental SES, as rated by adolescent participants, was associated with greater amygdala activation during a task that involved passive viewing of emotional faces.

Parental SES has been consistently associated with PFC function in neuroimaging studies. Using EEG methods, Otero et al. reported higher levels of low frequency brain electrical activity (theta) in frontal regions among children living in low SES families relative to children living in middle-class families. This pattern is similar to the pattern of brain electrical activity observed in children raised in institutional settings and likely represents a delay in maturation of the PFC. Poor PFC function among children raised in low SES families was also reported in two ERP studies such that low SES was associated with reduced ability to suppress neural responses to distracting stimuli.

Two recent studies examined the association between SES and PFC function using fMRI methods. Children from low-SES families exhibited an inefficient pattern of PFC recruitment involving greater activation of the right PFC while learning a complex stimulus–response association despite worse task performance compared to children from middle-class families. Activation of the lateral PFC during this task was associated with complexity of parental language used in the home environment. In a related study of adults, parental education during childhood was associated with greater activation of both the anterior cingulate and of the lateral PFC during a complex card guessing game, even after controlling for the participant’s own educational attainment. Taken together these results are consistent with the idea that childhood SES may influence the development of the PFC, potentially through both enrichment and stress exposure pathways.
23.5 Summary
We have presented converging evidence that different types of adverse childhood experience influence brain development via three neurodevelopmental pathways. The first of these is a stress-related pathway involving disruptions in emotional processing and limbic structures, including the hippocampus and amygdala. The second pathway implicated in the association between childhood adversity and psychopathology involves the PFC and associated executive functions. Finally, diverse forms of childhood adversity are associated with decrements in white matter volume, corpus callosum volume, and both structural and functional connectivity. To better inform interventions aimed at preventing the onset of mental disorders in children exposed to adverse childhood environments, the specific psychological, neurobiological, and social mechanisms linking these experiences to the onset of mental disorders must be identified. Incorporating methods from developmental cognitive and affective neuroscience into population health approaches provides the opportunity to investigate these central neurobiological mechanisms linking the social environment to the propensity for mental disorders, thereby elucidating potential targets of intervention.

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Adverse childhood experiences and brain development: neurobiological mechanisms linking the social environment to psychiatric disorders

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Adverse childhood experiences and brain development: neurobiological mechanisms linking the social environment to psychiatric disorders

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