CHAPTER SEVEN

Neural Development in Context: Differences in Neural Structure and Function Associated with Adverse Childhood Experiences

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Adversity refers to hardship or negative circumstances that threaten an individual's typical functioning. A wide variety of adverse experiences can occur during childhood, potentially posing challenges to development across multiple domains and producing lasting impacts on mental health and academic achievement. Indeed, evidence from epidemiological studies suggests a dose-response association in which greater exposure to childhood adversity is linked with a higher risk of negative long-term outcomes (Felitti et al., 1998). New research is extending this work by investigating the ways in which early adversity influences children's brain development. In this chapter, we focus on one of the most prevalent types of early adversity, poverty or socioeconomic disadvantage, which is estimated to affect more than 1 in 5 children from birth to 5 years of age in the United States (US Census Bureau, 2015). Low socioeconomic status (SES), which is typically indicated by low parental income, education, or occupational status, is a distal marker indicating a higher risk of more stressful and less cognitively enriching proximal environments (Evans, 2004). We also discuss several examples of more severe types of early adversity, including child maltreatment (i.e., abuse or neglect on the part of a caregiver) and early institutionalization (i.e., orphanage rearing). Children with these backgrounds tend to experience extreme adversity such as trauma or profound cognitive and social-emotional deprivation (Smyke et al., 2007).
Extensive evidence has indicated that exposure to adverse experiences early in life is associated with poor health and achievement outcomes throughout the lifespan. Studies of broad-based outcomes indicate associations between socioeconomic disadvantage and lower academic achievement from early childhood through adolescence (Bradley & Corwyn, 2002; McLoyd, 1998; Reardon, 2011). Children and adolescents from low-SES backgrounds also show higher rates and levels of internalizing (e.g., depression, anxiety) and externalizing problems (e.g., conduct disorders) compared to those from higher SES backgrounds, and the risk of mental health problems increases with the duration of socioeconomic disadvantage (Goodman, Slap, & Huang, 2003; Merikangas et al., 2010; NICHD ECCRN, 2005; Shanahan, Copeland, Costello, & Angold, 2008; Tracy, Zimmerman, Gaius, McCauley, & Vander Stoep, 2008; Wadsworth & Achenbach, 2005). Similarly, children who have been maltreated or adopted from institutions are at elevated risk for multiple forms of psychopathology that persists into adulthood (Bos et al., 2011; Cohen, Brown, & Smalls, 2001; McLaughlin et al., 2012; Green et al., 2010).

This research has generated considerable interest in identifying the more specific underlying neural mechanisms that link adverse childhood experiences with a higher risk of negative long-term outcomes. Understanding these mechanisms is important in terms of informing the design of effective targeted interventions for at-risk children and their families and shaping policy that dictates the allocation of funding and resources for prevention and intervention programs. Describing the effects of adverse childhood experiences on neural development is also important for a basic scientific understanding of the role of experience in brain development.

As such, in this chapter we review the research on associations between adverse childhood experiences and brain development. We first present an overview of normative brain development and briefly describe theoretical perspectives linking early experience with brain development. We then review research in humans showing links between childhood adversity and neural structure and function. This section is focused on exposure to socioeconomic disadvantage during childhood but also highlights studies of child maltreatment and early institutionalization. We conclude by discussing topics and future directions relevant to researchers and practitioners interested in early experience.

**Normative Patterns of Brain Development**

In general, brain development consists of progressive and regressive changes, with neurons, glial cells, and synapses being initially overproduced and then pruned. Prenatally, neurons are produced through the process of neurogenesis and then migrate to their final position (Stiles & Jernigan, 2010). Neurons then decrease in number as they undergo apoptosis or programmed cell loss, prior to birth. Once neurons have migrated, their differentiation, including the development of dendrites and axons that allow them to communicate with other neurons, begins prenatally but continues postnatally. In contrast to neurons, glial cell production and migration continues for an extended period after birth, glial cell differentiation continues throughout childhood, and glial cells undergo naturally occurring cell death postnatally (Brown & Jernigan, 2012).
Postnatally, the brain develops most rapidly during early childhood, continues to develop through adolescence, with plateauing of some structures and circuits but ongoing age-related changes in others across the lifespan. The pruning of neuronal processes such as axons and dendrites occurs postnatally throughout childhood and adolescence. Myelin, which is an insulating layer or sheath (made out of glial cells), begins to form around axons in the third trimester, allowing signals to be transmitted quickly and efficiently. Although myelination is mostly complete by the end of the second postnatal year, it continues into adulthood in some cortical areas.

Synaptogenesis refers to the formation of synapses which allow electrochemical signals to be transmitted from one neuron to another. It begins during the third trimester, peaks about three months after birth, and ends before the second year of life (Huttenlocher & Dabholkar, 1997; Petanjek et al., 2011). During this early period of synaptic growth, there are rapid increases in synaptic density and the total number of synapses, to a final number that exceeds adult levels (Huttenlocher & de Courten, 1987; Innocenti & Price, 2005; Rakic, Bourgeois, Eckenhoff, Zecevic, & Goldman-Rakic, 1986). Synaptic pruning/elimination begins in early childhood and continues for an extended period through childhood and adolescence. The process of pruning is regulated by competitive interactions between neuronal connections (Courchesne, Ghisano, & Townsend, 1994). As two neurons co-activate, the association between the neurons strengthens, and it becomes more likely that this synaptic connection will persist. In contrast, synaptic connections that are infrequently activated become weaker over time and are likely to be pruned (Greenough, Black, & Wallace, 1987; Purves & Lichtman, 1980), leading to the common aphorism, "cells that fire together, wire together."

These processes at the cellular level underlie developmental changes in gray matter (neuron cell bodies, dendrites) and white matter (axons, glia) volumes. Total gray matter volume follows a nonlinear trend in which it initially increases in early life and then begins to decrease in middle childhood (Durston et al., 2001; Giedd et al., 1996a; Giedd et al., 1996b). However, cortical volume (gray matter volume) represents a composite of cortical surface area and cortical thickness, which show different developmental trajectories. Cortical thickness decreases rapidly in childhood and early adolescence, followed by a more gradual thinning, and ultimately plateauing in early adulthood (Giedd & Rapoport, 2010; Gogtay et al., 2004; Raznahan et al., 2011; Schnack et al., 2015; Sowell et al., 2004; Sowell et al., 2003; Sowell et al., 2007). This is likely due to both synaptic pruning and increases in white matter myelination. In contrast, cortical surface area expands through childhood and early adolescence and then shrinks in adulthood (Schnack et al., 2015). This is likely due to synaptic pruning and pressure from increased myelination expanding the brain surface outward. White matter volume increases rapidly during early childhood then continues to increase over childhood into adulthood (Durston et al., 2001).

The specific timing of these developmental processes varies by brain region. In general, subcortical structures (e.g., amygdala, hippocampus) develop earlier than cortical structures (Payne, Machado, Bliswal, & Bachevalier, 2010). Furthermore, primary sensory and motor cortices mature earlier than association cortices, such as prefrontal cortex (PFC); (Giedd & Rapoport, 2010; Gogtay et al., 2004; Gogtay & Thompson, 2010; Shaw et al., 2008). For example, synaptic elimination occurs earlier for primary sensory cortex and later for association cortex (Huttenlocher & Dabholkar, 1997; Huttenlocher & de Courten, 1987).
Theoretical Framework Linking Early Experience with Brain Development

Environmental experience is thought to play an important role in shaping brain development. Experience-expectant models of development propose that expected environmental input (e.g., species-typical care, such as adequate nutrition, social and linguistic stimulation, and the presence of an attachment figure) must be provided during certain timeframes or sensitive periods for typical neural development to proceed (Greenough, Black, & Wallace, 1987; Marshall & Kenney, 2009; Rutter & O'Connor, 2004). Thus, the lack of species-typical care during sensitive periods would be expected to lead to lasting alterations in brain development.

In contrast, experience-dependent models posit that variation in experience shapes brain development regardless of the timing of the experience (Greenough et al., 1987). These processes are more relevant to explaining individual differences in neural development due to variability in experience on a continuous scale closer to the normal range of experience. Experience-dependent processes also emphasize the adaptation of neural development to an individual's particular circumstances.

Experience-adaptive programming is a third concept linking experience and brain development which shares features with both experience-expectant and experience-dependent models (Marshall & Kenney, 2009). Experience-adaptive models specify that variability in experience during certain time frames will lead to persistent individual differences in neural development, with reduced plasticity outside of these time frames. Neural functioning is expected to adapt to the specific characteristics of the early environment.

Experience-expectant and experience-adaptive models are closely associated with the notion of "sensitive periods" in development, namely, times when neural systems exhibit increased plasticity and therefore vulnerability to environmental influences. Sensitive periods are thought to coincide with periods when the brain is rapidly developing, and thus early childhood may be a time of maximal neural plasticity and vulnerability to environmental effects (Lupien, McEwen, Gunnar, & Heim, 2009). Given that brain regions vary in the timing of their normative developmental trajectories, they likely vary in their sensitive periods. It has been argued that those with a more protracted period of postnatal development, such as the PFC, may be particularly vulnerable to postnatal experience.

Differences in Neural Structure Associated with Adverse Childhood Experiences

Exposure to adverse childhood experiences is associated with structural and functional alterations in the brain. Neuroimaging studies of brain structure (e.g., using magnetic resonance imaging [MRI] and diffusion tensor imaging [DTI]) have shown effects of early adversity on a number of brain regions and circuits underlying language, executive function (EF), memory, and social-emotional processing. These regions include left hemisphere
language cortex, PFC, hippocampus, and amygdala, as well as white matter pathways connecting these structures (Brito & Noble, 2014). Although we focus here on these regions, which have the broadest empirical support, we note that differences associated with adverse childhood experiences have also been observed in other areas of the brain.

Lower SES is associated with structural differences in the left temporal, temporo-occipital, and frontal cortices, which support language skills (Hanson et al., 2013; Jednoróg et al., 2012). In a study of SES effects with the largest sample size to date, lower family income and parental education were associated with reduced surface area of left hemisphere language areas (Noble et al., 2015). In another study, an interaction between parental education and age was found for the left superior temporal gyrus and left inferior frontal gyrus, such that SES differences increased with age in these regions. Specifically, at older ages, lower parental education was associated with smaller volume of these regions (Noble, Houston, Kan, & Sowell, 2012). Furthermore, a marginally significant correlation between SES and inferior frontal gyrus volume was observed in a small sample of 5-year-old children (Raizada, Richards, Meltzoff, & Kuhl, 2008).

The PFC, the anterior portion of the frontal lobe, is associated with EF (which includes inhibitory control, working memory, and cognitive flexibility) and emotion regulation. The anterior cingulate cortex (ACC) and lateral PFC areas, such as dorsolateral PFC (dlPFC), support EF and attention regulation (Bunge & Crone, 2009). Effortful emotion regulation processes also rely on the dorsal ACC and regions in the left PFC, which modulate amygdala activity (Buhle et al., 2014; Ochsner et al., 2004; Urry et al., 2006). Medial PFC areas, including the orbitofrontal cortex (OFC), modulate amygdala activity to support implicit or automatic emotion regulation processes (Milad & Quirk, 2012; Weinberg, Johnson, Bhatt, & Spencer, 2010; Etkin, Egner, Farza, Kandel, & Hirsch, 2006).

Neuroimaging studies have shown that childhood socioeconomic disadvantage is associated with changes in PFC structure. Specifically, lower parental education has been associated with reduced prefrontal cortical thickness in the left superior frontal gyrus and right anterior cingulate gyrus (Lawson, Duda, Avants, Wu, & Farah, 2013). Similarly, lower scores on an SES composite were associated with reduced volume of the superior and middle frontal gyri in a small sample of 8–10-year-old children (Jednoróg et al., 2012). In a study of over 1,000 children and adolescents, lower family income and parental education were associated with reduced surface area of prefrontal cortical regions, including the middle and superior frontal gyri. Differences in total cortical surface area were found to mediate links between family income and children's performance on certain EF tasks (Noble et al., 2015). Another study found SES-related differences in cortical thickness in areas that included PFC regions (Mackey et al., 2015), and these brain structural differences partially accounted for socioeconomic disparities in school achievement test scores. Another study reported that infants from lower income families had reduced frontal lobe volume, suggesting that SES-related differences in PFC structure may emerge early in life. Children from lower income families also had slower trajectories of brain growth during infancy and early childhood (Hanson et al., 2013). In addition, children from lower income families displayed structural differences in the frontal lobe, which partially explained their lower academic achievement (Hair, Hanson, Wolfe, & Pollak, 2015).

Childhood maltreatment and early institutionalization have also been associated with decreased PFC volume (De Brito et al., 2013; Kelly et al., 2013). For instance, children
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exposed to physical abuse had smaller OFC volume, which was associated with their behavioral functioning (Hanson et al., 2010), and 12-14-year-old post-institutionalized children had smaller prefrontal cortical volume (attributable to differences in surface area) compared to non-adopted children reared in their biological families (Hodel et al., 2015).

The hippocampus is part of the limbic system and is required for learning and memory (Jarrard, 1999). Lower family income (Hair, Hanson, Wolfe, & Pollak, 2015; Hanson, Chandra, Wolfe, & Pollak, 2011; Noble, Houston, Kan, & Sowell, 2012; Luby et al., 2013), lower parental education (Hanson et al., 2011; Noble et al., 2015), and lower scores on SES composites (Hanson et al., 2015; Jednoróg et al., 2012) have been associated with smaller hippocampal volumes in children. In one study of adults, childhood SES was positively associated with hippocampal volume, even after adjusting for adulthood SES, suggesting that early experience may have an effect on structural brain development over and above later experience (Staff et al., 2012). Maltreatment and early institutionalization have also been associated with differences in hippocampal volume, but findings are more mixed. For instance, childhood exposure to maltreatment is associated with reduced hippocampal volume in adulthood but not when measured in childhood, possibly because effects on the hippocampus emerge later in life even when exposure to adversity occurred early (Hart & Rubia, 2012; Tottenham & Sheridan, 2010). Similarly, previously institutionalized children have not been found to differ from control groups in the volume of the hippocampus (Mehra et al., 2009; Tottenham et al., 2010; Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012; McLaughlin, Sheridan, Winter, Fox, Zeanah, & Nelson, 2013).

The amygdala is part of the limbic system that supports emotional and social information processing (Adolphs, Tranel, Damasio, & Damasio, 1995). Findings for effects on the amygdala of childhood socioeconomic disadvantage, maltreatment, and early institutionalization have been inconsistent. In one study of SES, lower parental education (but not family income) was associated with larger amygdala volume (Noble, Houston, Kan, & Sowell, 2012), while in another study, lower family income was associated with smaller amygdala volume (Luby et al., 2013). One recent study found that socioeconomic disadvantage, physical abuse, and early institutionalization were each linked to smaller amygdala volumes (Hanson et al., 2015). However, other studies have failed to find significant SES-related differences in amygdala structure (Hanson et al., 2011; Noble et al., 2015). Findings among adolescents exposed to childhood maltreatment have been similarly mixed (Hart & Rubia, 2012). Although two studies of children exposed to early institutionalization found larger amygdala volume (Mehra et al., 2009; Tottenham et al., 2010), other studies of this population have not found group differences (Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012; McLaughlin, Sheridan, Winter, Fox, Zeanah, & Nelson, 2014). One possibility is that adverse childhood experiences result in an initial increase in amygdala volume, along with increased reactivity during emotion processing, which over time leads to “burnout” and diminished amygdala volume (Tottenham & Sheridan, 2010).

Studies using diffusion tensor imaging (DTI) to measure white matter tracts have also reported structural differences linked to early childhood adversity. Maltreated children have decreased volume of the corpus callosum, which connects the right and left hemispheres and is the largest white matter tract in the brain (Hart & Rubia, 2012). Early institutional rearing is associated with alterations in white matter integrity, including in limbic and
paralimbic pathways (e.g., uncinate fasciculus, which connects the frontal lobe (OFC) to the amygdala; Eluvathingal et al., 2006; Hanson et al., 2013; Kumar et al., 2014) and frontostriatal circuitry (Behen et al., 2009; Govindan, Rehen, Helder, Makki, & Chugani, 2010; Hanson et al., 2013). In one longitudinal study, early institutional rearing was associated with alterations in white matter microstructure throughout the brain, but institutionalized children randomly assigned to high quality foster care did not significantly differ from the control group for most white matter tracts, suggesting improvement in white matter integrity following removal from the depriving environment (Bick et al., 2015). Similarly, children randomly assigned to foster care did not differ from the control group in total white matter volume (Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012). In sum, the evidence to date from studies using structural neuroimaging techniques suggests that adverse childhood experiences are associated with reduced volume in a number of brain regions including left hemisphere language cortex, PFC, and hippocampus, and differences in white matter integrity. Results for the amygdala have been inconsistent, but one possibility is that early adversity affects amygdala structure differently at different points in development. Similar effects are found across different types of adversity, which range in severity. Although many studies report on cortical volume, some studies have distinguished between surface area and cortical thickness, and effects of early adversity on both have been found across studies (Brito & Able, 2014). Further research is needed to more fully elucidate the differences in neural structure associated with the type, timing, and duration of exposure to adversity.

Differences in Neural Function Associated with Adverse Childhood Experiences

Adverse childhood experiences have also been linked with differences in brain function in studies using functional MRI (fMRI) and electrophysiological methods. Studies of childhood SES have revealed differences in neural activation during language and EF tasks, and a few studies have examined SES-related disparities in neural function with regard to memory and social-emotional processing (Ursache & Noble, 2016). In contrast, studies of neural function in maltreated and post-institutionalized children have had more of a focus on social-emotional processing and EF (Hart & Rubia, 2012).

Language

In one fMRI study, SES was associated with the degree of hemispheric specialization in the left inferior frontal gyrus in 5-year-olds during an early literacy (phonological awareness) task. Higher SES was associated with higher left lateralization of language processing, which has been found to reflect the maturation of language-processing areas of the brain (Raizada et al., 2008). In another fMRI study, SES moderated the relation of neural function in the left fusiform gyrus to phonological skill (Noble, Wolmetz, Ochs, Firah, & McCandliss, 2006). Specifically, among lower SES struggling readers, phonological skill
differences were associated with large differences in brain activation during a reading task, primarily in the left fusiform gyrus region, an area of the brain that has been shown to be important for visual-orthographic aspects of reading. However, this brain-behavior relationship weakened as SES increased. One possible interpretation is that, among children who struggle with reading in the context of limited access to resources, difficulty reading might occur despite a typical underlying neurobiological profile. In contrast, among children who struggle with reading despite plentiful access to resources, reading difficulties might suggest an atypical neurobiological profile.

In one study of 6–9-month-old infants, recordings of baseline EEG activity showed that lower SES infants had lower frontal gamma power, which may indicate early risk for language problems (Tomalski et al., 2013). In adults, childhood SES has been associated with larger amplitude negativity to syntactic violations. Specifically, in response to syntactic violations, adults who were raised in lower SES families exhibited smaller negative event-related potential (ERP) responses in left anterior sites than did those who had grown up in higher SES environments (Pakulak & Neville, 2010). This effect was independent of adult education level.

**Executive function**

Several studies have reported evidence of SES-related disparities in EF using both fMRI and ERP methods. In one fMRI study, lower SES 8–12-year-old children performed worse than higher SES children on a nonverbal stimulus-response learning task. During completion of this EF task, low-SES children showed greater recruitment of the right middle frontal gyrus compared to higher SES children, which may reflect inefficient recruitment of neural resources during the task because this increased brain activation was not associated with improved task performance (Sheridan, Sarsour, Jutte, D’Esposito, & Boyce, 2012). In female adolescents, lower SES was associated with decreased inhibitory control and increased ACC activation (but no differences in dlPFC activation) over a two-year period. Female adolescents with lower SES may develop less efficient inhibitory control, requiring greater and relatively unsuccessful compensatory recruitment of ACC (Spielberg et al., 2015).

Several studies have also demonstrated SES-related differences in ERP activity during selective attention tasks associated with the PFC (D’Angiulli, Herdman, Stapells, & Hertzman, 2008; Kishiyama, Boyce, Jimenez, Perry, & Knight, 2009). For example, one study investigated SES-related disparities in neural indices of auditory selective attention in children. This study found that ERP responses to attended versus unattended auditory stimuli were reduced in lower SES compared to higher SES children (Stevens, Lauinger, & Neville, 2009).

Maltreatment and early institutionalization have also been associated with differences in neural function during EF tasks. An fMRI study showed that maltreated adolescents did not differ in their performance on an inhibitory control task from control adolescents. However, they had increased activation in ACC and mPFC and decreased activation of dlPFC while completing the task (Carrion, Garrett, Menon, Weems, & Reiss, 2008). Also, adolescents who were adopted following early maltreatment or institutionalization
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(i.e., adopted from US foster care or international orphanages) showed greater activation in PFC regions (left inferior frontal cortex and dorsal ACC) and the striatum while performing an inhibitory control task; yet they displayed worse performance on the task (Mueller et al., 2010).

Memory

Few studies have investigated socioeconomic disparities in the neural correlates of memory performance. One study found that maternal reports of higher subjective social status were related to greater hippocampal activation in children during a relational memory task, but subjective social status was unrelated to behavioral performance (Sheridan, How, Araujo, Schamberg, & Nelson, 2013).

Social-emotional processing

Functional neuroimaging studies measuring neural activity associated with emotional stimuli (e.g., happy, sad, or angry faces) have been conducted with adults exposed to socioeconomic disadvantage during childhood. For example, lower perceived parental social standing has been associated with greater amygdala reactivity to angry faces in a sample of college students (Gianaros et al., 2008). Similarly, adults with lower family income at age 9 had more difficulty suppressing amygdala activation and had reduced PFC activity during a task in which they had to use cognitive reappraisal to regulate their emotional responses to negative stimuli (Kim et al., 2013). Interestingly, these associations were specific to childhood SES as adulthood SES was not associated with brain activity. In a study of adults, lower parental education was related to activation in and connectivity among corticostriatal brain systems during a reward processing task. These associations remained significant even after controlling for participants’ own levels of education and household income (Gianaros et al., 2011).

Child maltreatment is also associated with differences in neural responses during social-emotional processing tasks. An fMRI study of 8–18-year-olds adopted following maltreatment or institutionalization (i.e., from US foster care or orphanages abroad) measured activation in the hippocampus and amygdala while subjects viewed emotional faces (Maheu et al., 2010). Compared to control children, maltreated children had faster reaction times to angry faces and they showed significantly greater amygdala and hippocampus activation when viewing angry or fearful faces. In another fMRI study, maltreated children exhibited significantly greater activation of the insula and amygdala in response to angry faces (McCroy et al., 2011; see also McCroy et al., 2013). Increased amygdala activation to negative facial cues has also been reported in an fMRI study investigating the impact of early institutionalization (Tottenham et al., 2011).

Children with a history of physical abuse or neglect also generated altered ERP response amplitudes compared to non-maltreated children when presented with angry or fearful stimuli compared to happy or neutral targets (Cicchetti & Curtis, 2005; Curtis & Cicchetti, 2011; Parker & Nelson, 2005; Pollak, Klorman, Thatcher, & Cicchetti, 2001; Shackman,
Together, these results suggest that exposure to maltreatment is associated with a pattern of altered brain activity to threatening stimuli. Maltreated children may be hyper-vigilant to perceived threat in the form of angry stimuli, which may be adaptive in the context of an abusive environment but maladaptive outside of this context.

In sum, there is a small but growing literature on neural function in children exposed to adverse childhood experiences. Studies of SES have found differences in neural activation associated with language, EF, memory, and social-emotional processing. In addition, maltreatment and early institutionalization have been linked with differences in the neural correlates of EF and social-emotional processing. Early adversity may alter patterns of neural activity used to complete these tasks. For certain domains, such as EF, this may mean greater neural activation despite equal or worse task performance. Studies of SES, maltreatment, and early institutionalization have reported greater amygdala reactivity to negative emotional stimuli, which may persist into adulthood.

Explaining Differences in Academic Achievement and Mental Health Outcomes

In this chapter, we have covered emerging neuroscience research providing insight into the links between early adversity and brain development. Results from this review indicate significant associations between adverse childhood experiences and changes to the neural systems supporting language, memory, EF, and social-emotional processing, including left hemisphere language cortex, PFC, hippocampus, and amygdala, and white matter tracts connecting these structures. Importantly, the findings of this review are consistent with neurocognitive studies showing links between childhood adversity and decreased performance on specific neurocognitive tasks, including language, memory, EF, and social-emotional processing tasks (Hart & Rubia, 2012; Merz, McCall, Wright, & Luna, 2013; Noble, McCandliss, & Farah, 2007; Noble, Norman, & Farah, 2005).

One limitation of this literature is that most studies have been correlational with cross-sectional designs, which does not allow for any inference into causality or the direction of associations. Future research is needed that builds on these findings using longitudinal designs in which early adversity and brain development are assessed over time. Another way to strengthen causal inference is through randomized control trials in which some families receive an intervention whereas others do not, and children's neural development is measured. For example, in terms of SES, such interventions can occur at the level of SES (e.g., income supplements), putative mediating factors (e.g., increasing linguistic stimulation in the home environment), or outcomes of interest (e.g., educational interventions). If children in the intervention group demonstrate improved brain development relative to those in the control group, then evidence for a causal role of experience is strengthened. Although interventions at these levels have been conducted to examine effects on behavioral outcomes (Costello, Compton, Keeler, & Angold, 2003; Raver et al., 2011), few studies have included neuroimaging measures (see later in the chapter for further discussion of this topic). Indeed, studies of behavioral outcomes have provided evidence of a causal
role for SES in children's academic and mental health outcomes (Hackman, Farah, & Meaney, 2016), suggesting that SES may impact the neural mechanisms underlying these outcomes.

The studies in this review have also elucidated the neural mechanisms that potentially underlie associations between adverse childhood experiences and higher risk of persistent mental health problems and lower academic achievement. Differences in the neural circuits underlying language, memory, and EF have been associated with academic achievement. Some evidence has supported a mediation model in which early adversity affects academic achievement via differences in neural structure. For example, lower family income was associated with widespread reductions in cortical thickness, which in turn were associated with lower performance on standardized academic tests (Mackey et al., 2015), and structural differences in the frontal and temporal lobes were found to partially explain socioeconomic disparities in academic achievement (Hair, Hanson, Wolfe, & Pollak, 2015). In addition, neural systems underlying social-emotional processing and EF have been associated with mental health. There is some empirical support for a mediation model in which early adversity influences mental health via differences in neural structure. For example, reduced prefrontal cortical thickness partially mediated the association of institutionalization with inattention and impulsivity, suggesting that atypical PFC structure may be partially responsible for the markedly elevated rates of ADHD found among post-institutionalized children (McLaughlin et al., 2014). However, further work, especially using longitudinal designs, is needed that examines mediation models which include associations between these neural measures and behavioral functioning.

**Mechanisms Linking Adverse Childhood Experiences and Neural Development**

Here we provide an overview of two pathways by which adverse childhood experiences have been hypothesized to influence neural development: stress and low levels of cognitive and linguistic stimulation.

**Stress**

Across separate literatures focused on childhood socioeconomic disadvantage, maltreatment, and early institutionalization, chronic stress is thought to be a primary mediator of effects on brain development. Indeed, these adverse environments represent stressful experiences for children and are often described as types of “early life stress” (McLaughlin, Sheridan, & Lambert, 2014; Petchel & Pizzagalli, 2011). Although the specific experiences differ, children exposed to any of these types of adversity often endure high levels of stress in their lives. Specific stressors that often characterize disadvantaged environments include crowding, dangerous neighborhoods, household chaos and unpredictability, and lower parental nurturance (Evans, 2004; Evans & Kim, 2013; Hackman, Farah, & Meaney,
Maltreated children experience extremely high levels of stress from trauma or attachment insecurity in the parent-child relationship (Shackman, Shackman, & Pollak, 2007). Institutionalized children frequently experience stress early in their lives from the lack of an attachment figure, exposure to frequent changes in caregivers, and low levels of responsive caregiving (Smyke et al., 2007).

Neuroendocrine stress system reactivity is hypothesized to be a primary neurobiological mechanism through which early adversity affects neural development. One of the most extensively studied systems is the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis response to a stressor comprises a cascade of events which prepare the body to deal with a threat. In brief, the hypothalamus secretes corticotrophin-releasing hormone (CRH), which signals the pituitary to release adrenocorticotropic hormone (ACTH). ACTH then binds to receptors in the adrenal glands leading to the release of cortisol. Circulating cortisol exerts negative feedback inhibition to shut down its own release when cortisol levels are high by acting on glucocorticoid receptors in the hippocampus.

Adverse childhood experiences are associated with disrupted development and functioning of the HPA axis (Gunnar & Quevedo, 2007). Higher basal cortisol levels and cortisol reactivity have been found following early exposure to socioeconomic disadvantage (Blair et al., 2011; Chen, Cohen, & Miller, 2010; Evans & Schatzberg, 2009; Lupien, King, Meaney, & McEwen, 2001), maltreatment (McCroy, De Brito, & Viding, 2010), and institutionalization (Hostinar, Sullivan, & Gunnar, 2014). However, exposure to these adverse experiences has also been associated with hypocortisolism, which is characterized by low cortisol, flat daytime production patterns, and blunted responses to stressors (Badanes, Watamura, & Hanks, 2011; Bruce, Fisher, Pears, & Levine, 2009; Fisher, Stoolmiller, Gunnar, & Buraston, 2007; Kraft & Luecken, 2009; Ouellet-Morin et al., 2011). Differences in the duration, timing, and type of adversity are thought to explain these discrepancies. In particular, extreme or chronic exposure to stressors may lead to higher cortisol reactivity in the short term but blunted cortisol reactivity in the long term (Carpenter, Shattuck, Tyrka, Geraciotti, & Price, 2011; MacMillan et al., 2009; Trickett, Gordis, Peckins, & Susman, 2014).

In turn, HPA axis dysregulation has been associated with changes to neural structure and function, especially in the hippocampus, amygdala, and PFC (Arnsten, 2009). These areas of the brain have been shown to be particularly vulnerable to stress-response system dysregulation because they play a role in mediating the HPA axis stress response and have high concentrations of glucocorticoid receptors (McEwen & Gianaros, 2010; Tottenham & Sheridan, 2010). For example, in rodent studies, chronic stress reduced the size of PFC dendrites, the parts of the neuron that receive input from neighboring brain cells. These structural differences in turn correlated with impaired performance on PFC-dependent EF tasks (Arnsten, 2009; Hains et al., 2009; Liston et al., 2006; Liston, McEwen, & Casey, 2009; McEwen & Morrison, 2013).

Parenting quality early in life is associated with variation in children’s HPA axis reactivity. Extensive research has shown that variations in licking and grooming of rat pups are associated with enduring differences in HPA axis reactivity (Gunnar & Quevedo, 2007; Liu et al., 1997; Weaver et al., 2004). Specifically, offspring of low licking and
grooming mothers show higher HPA responses to stress compared with the offspring of high licking and grooming mothers. Low licking and grooming has been found to cause a reduction in the number of glucocorticoid receptors in the hippocampus and thus disrupt negative feedback regulation of the HPA axis (Hackman, Farah, & Meaney, 2010). Parental buffering of HPA axis reactivity has also been observed in human research (Blair et al., 2011; Tottenham, 2012). For instance, in the presence of the attachment figure, toddlers who are in secure attachment relationships do not show elevations in cortisol to distress-eliciting events, whereas toddlers in insecure attachment relationships do (Gunnar & Quevedo, 2007; Hostinar, Sullivan, & Gunnar, 2014). Thus, lower parenting or caregiving quality whether occurring in the context of socioeconomic disadvantage, maltreatment, or institutionalization, may lead to HPA axis dysregulation, which in turn influences neural structure and function (Belsky & de Haan, 2011).

Low levels of cognitive and linguistic stimulation

Low levels of cognitive and linguistic stimulation are another hypothesized mechanism by which adverse childhood experiences may affect neural development (Brito & Noble, 2014; Hackman, Farah, & Meaney, 2010; McLaughlin, Sheridan, & Lambert, 2014). Children from disadvantaged families often experience lower quality and quantity of cognitive and linguistic input in both their home and school environments compared to their peers from more advantaged families (Bradley & Corwyn, 2002; Hart & Risley, 1995; Hoff, 2003; Rowe & Goldin-Meadow, 2009). They also experience lower exposure to enriching cognitive experiences in the home and school environments, including reduced access to books and extracurricular activities (Linner, Brooks-Gunn, & Kohen, 2002; NICHD ECCR, 2005; Sirie, 2005). In more extreme situations, children who are neglected by their parents or caregivers are not provided with adequate social interactions and physical resources, including books and toys (Hildyard & Wolfe, 2002). Children raised in institutions experience markedly lower exposure to interactions with adults, variation in daily routines and activities, and novel and age-appropriate enriching cognitive stimuli (Smyke et al., 2007).

Animal models have shown effects of variability in cognitive stimulation on brain development. Rodents assigned to rearing in “impoverished” environments (i.e., standard lab cage, without toys or littermates) have been compared to those reared in “enriched” environments (i.e., large cages with interesting and changing objects and multiple littermates). Such environmental “enrichment” is associated with increased cortical thickness due to greater dendritic branching, increased dendritic spine density, and more synapses per neuron in a number of brain areas (Davidson & McEwen, 2012; Kempermann, Kuhn, & Gage, 1997; Markham & Greenough, 2004; Sale, Berardi, & Maffei, 2009; van Praag, Kempermann, & Gage, 2000) as well as larger volume and greater myelination in the corpus callosum (Juraska & Kopcik, 1988; Sanchez, Hearn, Do, Rilling, & Herndon, 1998; though it has been pointed out that even such “enriched” environments are likely far less cognitively stimulating than the experience of growing
Regardless, it is notable that these effects follow differences in early experience and have not been observed following variation in later experiences (Markham, Herting, Luszpak, Juraska, & Greenough, 2009).

Lower levels of cognitive and linguistic stimulation may underlie differences in the development of left hemisphere language-supporting cortical regions associated with adverse childhood experiences. For example, differences in the quality and quantity of linguistic stimulation in the home have been associated with variability in the development of left hemisphere language cortex (Perkins, Finegood, & Swain, 2013).

Although we have emphasized their similarities, it is important to reiterate that different types of environmental experiences may influence brain development through different underlying mechanisms. In general, maltreatment and institutionalization are more severe forms of early adversity compared to socioeconomic disadvantage, and it is important to recognize that many socioeconomically disadvantaged families provide warm and nurturing homes for their children. By definition, maltreatment and early institutionalization also more narrowly refer to disruptions in the parenting or caregiving environment. In contrast, low SES often indicates lower quality of a broad range of environments including home, school, and neighborhood settings. Given that these different adverse experiences often co-occur, measuring the degree to which children face various mediating factors (e.g., stress, cognitive deprivation) is important for future research. It is likely that mediating mechanisms are better able to explain neural outcomes than are categorical characterizations of adverse experiences (McLaughlin, Sheridan, & Lambert, 2014).

**Developmental Timing of Adversity**

Adversity likely has the most deleterious effects when it occurs during sensitive periods of development. Early childhood may be one such period of heightened vulnerability to environmental effects on neural development. Animal studies suggest that early exposure to adversity may have enduring effects on neural development even when circumstances improve later in life, whereas later exposure to adversity is less likely to produce lasting effects (Tottenham & Sheridan, 2010). Studies of early institutionalization, in which the timing and duration of extreme adversity can be clearly delineated, allow insight into sensitive periods in humans. As reviewed earlier, children adopted from institutions who were exposed to a circumscribed period of early deprivation exhibit differences in neural structure and function even many years after removal from an institution (Hodel et al., 2015; Mehta et al., 2009; Tottenham et al., 2010). In studies of this population, older age at adoption has been associated with poorer behavioral outcomes, often in a step-like or threshold pattern rather than a linear association. Although age at adoption cut-offs vary widely across studies, children adopted from institutions before 6 months of age tend to not differ from non-adopted children reared in their birth families (Rutter et al., 2007) whereas those adopted after 18-24 months are generally at higher risk for a range of negative outcomes (Merz & McCall, 2010). Studies of SES have addressed timing effects as well and similarly found that childhood SES predicts neural
structure above and beyond adulthood SES (Gianaros et al., 2011; Kim et al., 2013; Staff et al., 2012).

Given that neural systems differ in their developmental trajectories, the specific timing of sensitive periods likely varies across neural systems. Therefore, depending on the timing of exposure, some neural processes may exhibit greater effects than others. For example, in the Bucharest Early Intervention Project (BEIP), institutionalized children who were randomly assigned to high-quality foster care did not differ from control children who were raised in their birth families in total white matter volume or white matter integrity of most circuits (Bick et al., 2015; Sheridan et al., 2012), whereas they did have reduced cortical thickness across prefrontal, parietal, and temporal regions compared to the control group (McLaughlin et al., 2014). These findings are consistent with the idea that neural processes vary in their plasticity and sensitive periods (Andersen et al., 2008) and underscore the need for future research to examine how neural plasticity varies across brain regions.

Leveraging Neuroimaging Tools in Prevention and Intervention Research

The studies reviewed here highlight a set of specific neurocognitive skills (e.g., language, EF, memory, and social-emotional processing) that early interventions should target in order to improve mental health and academic achievement trajectories in at-risk children. Indeed, early interventions targeting and improving EF skills have found subsequent gains in academic achievement (Bierman, Nix, Greenberg, Blair, & Domitrovich, 2008; Diamond, Barnett, Thomas, & Munro, 2007; Raver et al., 2011). These findings suggest that targeting specific neurocognitive skills may be important in reversing the negative effects of early adversity on the underlying neural systems. However, few prevention or intervention studies have integrated measures of neural development into their research designs.

Integrating neuroimaging measures into prevention and intervention research is important for a variety of reasons (Beauchaine, Neuhauß, Brenner, & Garzke-Kopp, 2008; Bryck & Fisher, 2012; Cicchetti & Gunnar, 2008). In particular, differences at the neural level can be found even in the absence of differences at the behavioral level. More specifically, interventions may be found to enhance neural functioning even when behavioral improvement is not immediately observed (Raizada & Kishiyama, 2010). Thus, without examining outcomes at the neural level, positive intervention effects may be missed. Neural data may also be especially important when examining the maintenance of intervention gains over time. While the positive behavioral effects of many interventions seem to decrease over time, it is possible that changes to neural systems persist. These changes could explain instances when the positive behavioral effects of interventions are seen years after the intervention has concluded (Raizada & Kishiyama, 2010).

Neuroimaging tools can also be used to measure the neural mechanisms by which interventions improve behavioral outcomes and thus elucidate the mechanisms linking experience and behavioral outcomes in an experimental context that strengthens causal
inferences. Only a few studies to date have examined the effects of interventions on neural development in at-risk children. In one such study, a combination of parent training sessions, which emphasized strategies to support children's attention and reduce family stress, and child attention training sessions enhanced ERP correlates of selective attention and cognitive development in preschoolers from lower SES backgrounds (Neville et al., 2013). In another ERP study, an intervention involving parent training and a therapeutic playgroup produced increased feedback-related ERP amplitudes in 5-7-year-old children in foster care (Bruce, McDermott, Fisher, & Fox, 2009). These studies suggest that neural development may be malleable to positive interventions following early adversity and extend findings from intervention studies showing improvements on attention and EF tasks by showing that the neural correlates of these cognitive processes are also amenable to improvement. Further research is needed to link changes in the neural underpinnings of neurocognitive skills (e.g., selective attention, EF) with improvement in children's mental health and academic achievement over time.

Conclusion

Consistent with theoretical perspectives linking experience with neural development, emerging neuroscience research has shown early adversity to be associated with changes to the structure and function of neural systems supporting language, EF, memory, and social-emotional processing. These findings provide insight into the neural mechanisms potentially underlying associations between adverse childhood experiences and a higher risk of persistent mental health problems and lower academic achievement. Although existing research hints that early adversity plays a causal role in shaping brain development, future research is needed to strengthen causal inference. For example, large, prospective and longitudinal studies can help rule out threats to validity. Stronger still are randomized control trials which examine whether children who experience an intervention demonstrate changes in brain development, thereby ruling out selection bias and providing evidence of a causal role for early adversity. Prevention and intervention services that are provided early in life and target the neural systems identified in this review may be the most effective in terms of reversing the effects of early adversity and promoting positive academic and mental health outcomes.

References


Neural Development in Context


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Neural Development in Context


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